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Winning over ADHD by charging the brain non-invasive stimulation methods in ADHD: A systematic review

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Abstract
Attention Deficit Hyperactivity Disorder (ADHD) is a neurodevelopmental disorder characterized primarily by either hyperactivity or inattention or both. Non-Invasive brain stimulation techniques including Transcranial direct current stimulation (tDCS) and Repetitive Transcranial magnetic stimulation (rTMS) act by altering brain activity and modulating neuronal networks. Both rTMS and tDCS have been previously used in pediatric population and now being used as an intervention for ADHD. The aim of this study was to review the existing literature on Non-Invasive stimulation in ADHD as a means of treatment. An English Language Literature search using Google Scholar, Scopus, PubMed and Pedro was done to identify the data. PRISMA guidelines were followed and those studies which fulfilled the specific requirements were selected. Methodological quality of these studies was assessed using PEDro scale. In accordance with the inclusion criteria; eight studies done between 2010 and 2019 were reviewed. Studies were grouped according to intervention given: rTMS and tDCS. Our findings reveal that both rTMS and tDCS have positive effects on improving inhibitory control, executive function as well as the impulsive symptoms in ADHD. It was concluded that Non-invasive stimulation is a promising and upcoming tool for improving executive functions and inhibitory control in ADHD. More number of high quality randomized control trials are required to strengthen the evidence and incorporation of these tools in clinical practice.

Keywords: ADHD, non-invasive stimulation, TDCS, RTMS, TMS, TES

1. Introduction

According to DSM-5 criteria, Attention Deficit Hyperactivity Disorder (ADHD) is a neurodevelopmental disorder characterized primarily by either hyperactivity or inattention or both. It is classified into three types on the basis of presenting symptoms, that are; Inattentive type (ADHD-I), Hyperactive type (ADHD-H) or the Combined type (ADHD-C) [1]. Symptoms have been reported to be persistent in adulthood as well [2]. The existing literature has reports the global prevalence of ADHD to be 5-9% with an estimate that about 67% of these children continue to exhibit symptoms in adulthood as well [3]. The prevalence of ADHD in India is reported to be 11.33% supporting the global finding of boys (66.7%) being more affected than the girls (33.3%) being highest in the age group of 9-10 years [4]. Individuals with ADHD (children as well as adolescents) experience impairments in their school life as well as social life including low tolerance, difficult relationship with family, frustration, poor academic performance, punishments and repetition of classes in school [5]. It has also been reported that children with ADHD have cognitive deficits, mainly in the executive functions which are higher cortical abilities responsible for efficient neuropsychological functioning and cognitive flexibility of the individual [6]. They are the higher level cognitive functions which regulate the lower level cognitive behavior of future oriented and goal-directed behavior and are dependent upon the brain function, mainly of the prefrontal cortex (PFC) [4]. Deficits in executive functioning, including working memory (WM), response inhibition, and temporal processing, have been suggested to play an important role in ADHD [7]. In adults, inhibitory control which is the skill to inhibit and limit the responses to any distracting stimuli, has been described to be the most commonly affected executive function. The existing literature suggests that there is a reduced activation of the prefrontal region of brain in individuals with ADHD causing the compromised inhibitory control, clinically seen as inattentiveness [3]. Hyperactivity on the other hand has been stated to be a consequence of imbalance between intra-cortical facilitation and intra-cortical inhibition [8]. Impulsivity is another core symptom of ADHD as a result of impaired cognitive control [9]. The available evidence suggests that deficits in attention, impulsivity and hyperactivity cause impairments in executive function. A multimodal treatment approach for ADHD is recommended internationally including Cognitive behavioral therapy, task oriented training and psycho-education [10]. Despite the availability of these, there is a need for an approach which can modulate cortical excitability and augment in treating undertreated or inadequately treated patients. Non-Invasive brain stimulation techniques including Transcranial direct current stimulation (tDCS) and Repetitive Transcranial magnetic stimulation (rTMS) act by altering brain activity and modulating neuronal networks [14]. tDCS is a non-invasive electric brain stimulation which involves the use of an electric current of low amplitude applied via electrodes placed on the scalp [11]. rTMS is another non-invasive brain stimulation includes the use of a magnetic coil placed over a specific area of the brain and is useful in inducing long term changes in cortical excitability [8, 12]. Both rTMS and tDCS have been previously used in pediatric population and now being used as an intervention for ADHD. This review study is an attempt to retrieve literature on non-invasive stimulation methods in ADHD.

1.1 Purpose of the review
The present study intends to review the existing literature on Non-Invasive stimulation in ADHD as a means of treatment.

2. Methodology
2.1 Type of Studies
All prospective RCT's, crossover trials, Quasi Experimental studies (Pre/Post design, Cohort studies) meeting the inclusion criteria were considered eligible for the entry.

2.2 Inclusion Criteria
Studies were included if they were Randomized Clinical Trials with the primary focus of using non-invasive stimulation (rTMS and tDCS) in individuals with ADHD.

2.3 Exclusion Criteria
Those studies which focused on techniques other than non-invasive brain stimulation were not included in this review. An English language limitation was another exclusion criteria. Further the articles for which full text articles were not available and studies with participants not having ADHD were excluded.

2.4 Primary Search Terms and Data Sources
For this review study, an electronic search was conducted of the literature published from the databases: Pedro, Scopus and search engines: PubMed, Research Gate and Google Scholar. The following search terms were used: adhd; non-invasive stimulation; tdcs; rtms; tms; tes.

2.5 Types of Participants
Children and Adults diagnosed with ADHD, irrespective of the gender and age above 8 years. Participants with history of any other neurological diseases like epilepsy, CP, neuropsychiatric disorders such as depression, autism, tics, schizophrenia were excluded.

2.6 Types of Interventions
Articles with Non-Invasive stimulation (rTMS and tDCS) as an intervention in individuals with ADHD were included in this review.

2.7 Data collection and analysis
2.7.1 Selection of Studies
Firstly, the articles which fulfilled the search criteria were identified following which abstracts were screened to determine if they fulfilled the inclusion criteria. Full texts of all the identified articles were retrieved. In the situations where it could not be established from the abstract whether article satisfies the inclusion and exclusion criteria, full text were retrieved and screened for trial eligibility. Then, the reference lists of these full text articles were exclusively searched to identify any publication which could have been missed out during database searching. The whole procedure of abstract screening and scrutinizing full text articles was then repeated. Finally, a list of all the selected articles was made and methodological steps for data extraction were followed.

2.7.2 Data Extraction
Data relevant to the aims of the review was extracted from the selected full text articles. Information about the number of participants, study design, type of intervention given, outcome measures used and the results of various studies were extracted.

2.7.3 Assessment of Risk of Bias in included studies
To evaluate the risk of bias in included studies The Physiotherapy Evidence Database (PEDro) scale was used which is a 10 point scale to assess the methodological quality of studies. The maximum score any research article could be awarded was 10. All articles were analyzed for their quality as per the PEDro scale guidelines, a score of 0-3 indicates poor, 4-5 indicates fair, 6-8 indicates well, 9-10 indicates excellent quality. Based on the available literature, intra-rater reliability of PEDro scale is reported to be 0.55 (95% CI, 0.41-0.72) [13]. No particular cut-off limit for PEDro scales was included as an inclusion criteria for this review.

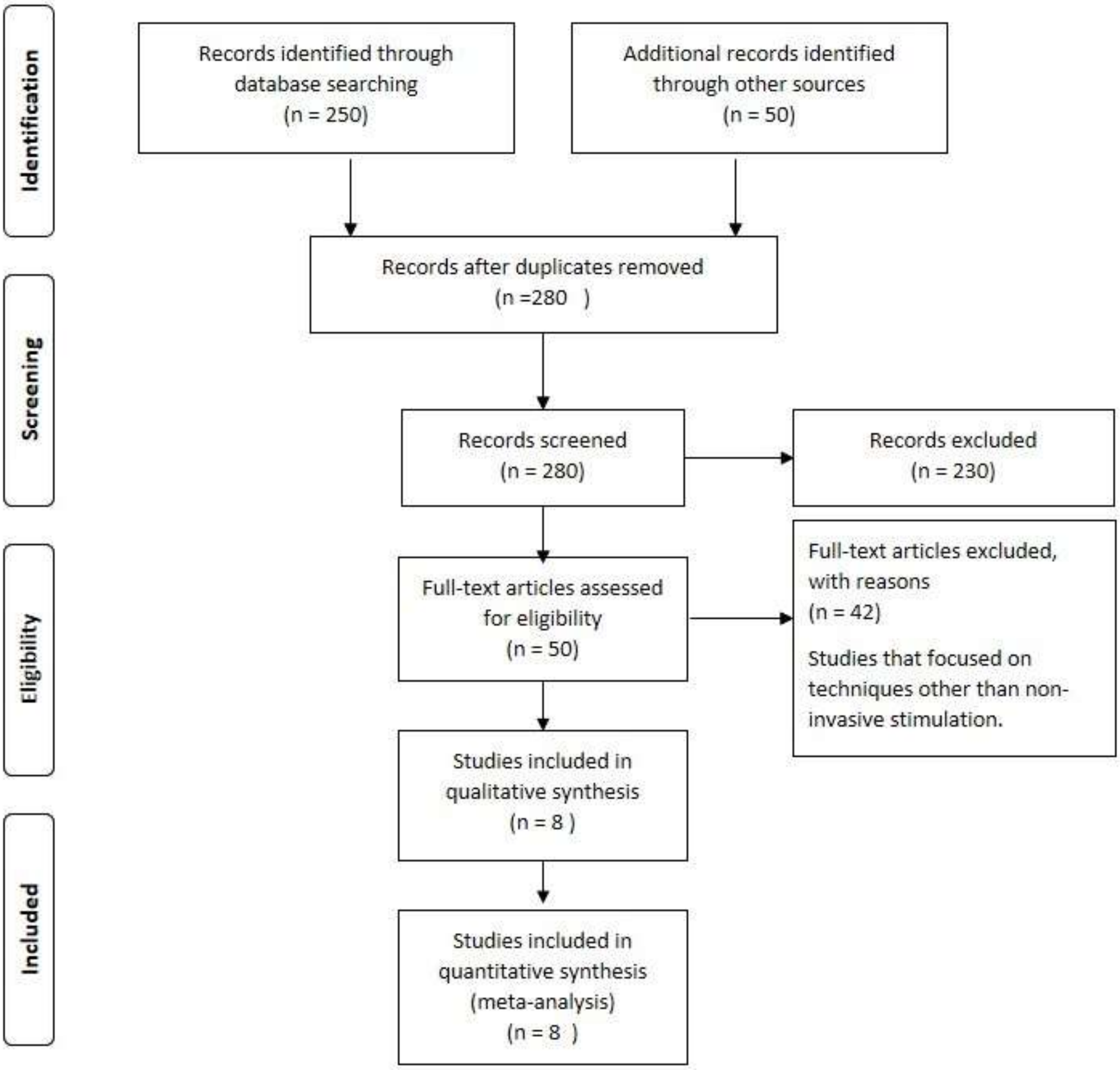

Fig 1: PRISMA Flow Diagram

3. Results

3.1 Description of Studies

A total of 8 studies with 250 participants, meeting the selection criteria could be retrieved and included in this review. Three articles used Transcranial Magnetic Stimulation (TMS) as an intervention while the remaining five studies used Transcranial Direct Current Stimulation (tDCS). A detailed description of various studies including study design, study participants, intervention, outcome measures and results is given in Table 1.

3.2 Risk of bias in Included Studies

Risk of bias was evaluated for each study using PEDro scale. The included articles were of fair to excellent quality with the PEDro scores ranging from 6-9. The detailed description of satisfied criteria for each study has been outlined in Table 2.

3.3 Effect of Interventions

3.3.1 Repetitive Transcranial Magnetic Stimulation (rTMS)

Repetitive transcranial magnetic stimulation (rTMS) is a noninvasive tool which involves the application of powerful pulsed magnetic fields with help of a stimulator and the electrodes placed on scalp. It acts by altering the neuronal excitability and can be used to both stimulate as well as inhibit specific areas of brain. It works on neuronal networks and depolarizes the neurons by inducing local electrical current in cerebral cortex.

In a study by Bloch *et al.*, (2010), it was reported that single session high frequency rTMS applied on the right prefrontal cortex has a significant effect on improving attention when compared with the attention scores pre-rTMS, as measured by PANAS (t=2.235; p<0.01) and VAS (t=2.934; p<0.05) scores for attention. Furthermore, it was observed that real rTMS (t=3.746; p<0.0.1) had a significant impact on ADHD score while there was no impact of sham stimulation. However, there was no effect on mood, hyperactivity or anxiety PANAS scores as well as the neuropsychological tests (CANTAB) between the real and sham stimulation groups.

In a study by Helfrich *et al.*, (2012) it was established that there was a reduction in N100 amplitude post a single session of low frequency rTMS (p=0.335).

Weaver *et al.*, (2012) reported a highly significant change in score of CGI-I scale (p<0.005), ADHD-IV scale (p<0.05). However, there was no differences found on the neuropsychological parameters between active and sham stimulation groups which is consistent with findings of Bloch *et al.*, (2010).

As stated by Cao *et al.*, (2019) there was a significant improvement in attention deficit, hyperactive impulse and oppositional defiance (p=0.000) observed on the SNAP-IV scale after six weeks (6 sessions/week; each session lasting 30 minutes) of rTMS treatment applied at right dorsolateral prefrontal cortex (DLPFC).

3.3.2 Transcranial Direct Current Stimulation (tDCS)

tDCS is a non-invasive stimulation which involves the use of a weak electric current (1-2 mA) applied on the scalp with help of saline soaked electrodes. When applied over the prefrontal cortex, tDCS can be used to modulate cognitive control circuits which are impaired in ADHD.

Cosmo, C. *et al.* (2015) found that there are no significant differences in correct responses of Go/No-Go fruits (0.71) and letters (p= 0.78) tasks between participants from tDCS group and sham stimulation group.

In a study by Cachoeira, C. T. *et al.* (2016), it was reported that there is a significant decrease in ASRS as well as SDS scores after the application of 2mA tDCS for 5 days.

Nejati, V. *et al.* (2017) reported that anodal lDLPFC/ cathodal rDLPFC tDCS did not have any significant effect on inhibitory control, cognitive flexibility, task switching executive functions while a significant improvement was seen in interference as measured by Stroop test. Furthermore, it was established that cathodal lDLPFC/ anodal rOFC tDCS was more effective than lDLPFC/ cathodal rDLPFC tDCS in improving all measures of executive function which were tested.

Allenby, C. *et al.* (2018) reported that there was a significant effect of active tDCS stimulation on false positive scores of CPT (p= 0.013) whille the results were not significant for true positive errors in CPT, SSRT and concurrent tDCS task performance (*p*>0.05).

3.4 Safety of Non Invasive Stimulation in ADHD

The available evidence has established that non-invasive stimulation (rTMS and tDCS) are well tolerated and have minimal side effects.18 In our current review we found that 75% reviewed studies reported the adverse reactions from stimulation while 25% studies did not report any. Out of the 122 participants who received rTMS, only seven (0.05%) complained of having mild transient headaches. As for tDCS, the frequent complaints were that of tingling, itching, burning sensations under the areas where electrodes were placed and mild headache post the stimulation. No serious fatal adverse effects have been reported in our review as well as the previous studies. Thus, it can be inferred that non-invasive stimulation techniques are well tolerated and safe for therapeutic use keeping the appropriate safety guidelines in mind.

Table 1: Description of Studies

Study	Study Design	Study Subjects	Intervention	Outcome Measures	Results
Bloch *et al.*, (2010)	RCT with a crossover design	n=13 Adults who fulfilled ADHD criteria according to DSM-IV criteria confirmed by clinical interview by a psychiatrist assisted by ASRS and WUAAS	Single real or sham rTMS session and crossover 1 week apart. Evaluations were conducted prior to treatment and 10 minutes after real/sham stimulation	PANAS, VAS, CANTAB	There was significant improvement in overall ADHD scores, VAS scores for attention and attention as evaluated by PANAS score post real rTMS sessions relative to sham stimulation. However, there were no statistically significant differences in VAS scores for mood.
Weaver *et al.*, (2012)	RCT with a crossover design	n=9 Young adults (14-21 years) with a primary diagnosis of ADHD by clinical evaluation based on DSM-IV criteria.	Transcranial Magnetic stimulation applied to right prefrontal cortex at 10hz, at 100% of observed motor threshold, 2000 pulses per session, 5 sessions per week for 2 weeks.	Electroencephalogram, Audiometry, CGI-I, Neuropsychological battery of tests: WAIS, CPT, DKEFS, Buschke Selective Reminding Test, Symbol Digit Coding Test, Finger Oscillation Tasks	TMS was well tolerated with no serious adverse events reported. A statistically significant improvement in scores of CGI-I was reported, however no significant differences were found between active and sham stimulation groups on the neuropsychological parameters.
Helfrich *et al.*, (2012)	Quasi Experimental (Pre-Post Design)	n=25 Children aged 8-14 years diagnosed with ADHD verified by Diagnostic Interview for Psychiatric Disorders in Children with parents.	Sham stimulation or Sub-threshold 1Hz rTMS at an intensity of 80% participant's RMT applied to left primary motor cortex for fifteen minutes	Electroencephalogram (EEG) Surface Electromyography (EMG)	A significant effect of real rTMS stimulation relative to sham stimulation was reported on cortical excitability in children with ADHD.
Cosmo *et al.*, (2015)	RCT	n= 60 Adults aged 18-65 years diagnosed with ADHD as confirmed by a psychiatrist based on DSM-IV criteria.	Single session of active or sham tDCS with anode at F3 and cathode at F4 at an intensity of 1.0 mA for 20 minutes. The intensity was increased for initial 30 seconds and then the current was turned off in case of sham stimulation.	Go/No-Go task before and after the stimulation session	There were no statistically significant differences observed in scores of Go/No-Go task before and after the stimulation in tDCS vs. sham group.

Cachoeira *et al.*, (2016)	RCT	n=17 Adults between 18-45 years diagnosed with ADHD as per DSM-5 criteria.	tDCS was applied at an intensity of 2mA for 20 minutes per session for 5 consecutive days. In sham stimulation, tDCS device was turned off after 1 minute of active stimulation.	Primary: ASRS Secondary: SDS	The scores for both ASRS as well as SDS were found to be significantly reduced in active stimulation group relative to the individuals who received sham stimulation.
Nejati *et al.*, (2017)	RCT	n= 25 Children with ADHD diagnosed by a child psychiatrist according to DSM-5 criteria.	ADHD children received left anodal/ right cathodal DLPFC tDCS and sham stimulation in experiment 1 and left anodal DLPFC/right cathodal OFC tDCS and left cathodal DLPFC/right anodal OFC tDCS in experiment 2.	Go/No-Go task N-back test WCST Stroop test	Anodal DLPFC appeared to improve executive functions while cathodal DLPFC tDCS improved inhibitory control.
Allen *et al.*, (2018)	RCT with a crossover design	n=37 Healthy Adults aged 18-65 years with a prior diagnosis confirmed by brief history and Structured Clinical Interview based on DSM-5 criteria.	Anodal tDCS or sham stimulation for three sessions two weeks apart were given at an intensity of 2.0 mA applied over left DLPFC and right supra-orbital area for 20 minutes.	Primary: CPT Secondary: SSRT	It was reported that stimulation of left DLPFC with tDCS helps to improve impulsive symptoms in ADHD.
Cao *et al.*, (2019)	RCT	n=107 75 ADHD patients diagnosed as per DSM-5 criteria	Real or Sham rTMS group were stimulated at a frequency of 10 Hz, 100% intensity, 30 min per session with 2400 pulses, five sessions/week for 6 weeks	SNAP-IV scale Expression of miRNA-107	There was no significant difference between ADHD patients and healthy children before and after rTMS sessions.

(Abbreviations: Wender-Utah adult ADHD scale (WUAAS); Positive and Negative Affect Schedule (PANAS); Visual Analogue Scales (VAS); Neuropsychological battery of tests using Cambridge Neuropsychological Test Automated Battery (CANTAB) testing system; Neuropsychological Testing Clinical Global Impression- Improvement Scale (CGI-I); Wechsler Adult Intelligence Scale (WAIS); Connors Continuous Performance Test (CPT); Delis-Kaplan Executive Function System (DKEFS); Electroencephalogram (EEG); Surface Electromyography (EMG); Adult ADHD self-Report Scale Symptom Checklist (ASRS), Sheehan Disability Scale (SDS); Continuous Performance Test (CPT); Stop Signal Reaction Time (SSRT).

Table 2: PEDro Scores of Included Studies

Authors	**Eligibility Criteria Specified**	**Randomization performed**	**Concealed allocation to groups**	**Baseline similarity**	**Patient Blinded**	**Therapist Blinded**	**Observer Blinded**	**Withdrawals/ Dropouts <15%**	**Intention to treat analysis**	**Between groups difference tested statistically**	**Total Score**
Bloch *et al.*, (2010)	0	1	0	1	1	0	0	1	1	1	6
Weaver *et al.*, (2012)	1	1	0	1	1	0	1	1	1	0	7
Cosmo *et al.*, (2015)	1	1	1	1	1	0	1	1	1	1	9
Cachoeira *et al.*, (2016)	1	1	0	1	1	1	1	1	1	1	9
Nejati *et al.*, (2017)	1	1	0	1	1	1	0	1	1	1	8
Allen *et al.*, (2018)	1	1	1	0	1	1	0	0	1	1	7
Cao *et al.*, (2019)	1	1	0	1	1	1	0	1	0	1	7

4. Discussion

This review intended to gather available literature on non-invasive stimulation techniques in ADHD and evaluate their potential efficacy over the conventional methods of treatment. We reviewed those studies which were focused on the therapeutic effects of rTMS and tDCS in ADHD. There was a variability observed in frequency used for rTMS application in the different studies. Two studies used 10Hz as stimulation frequency while one study used 20Hz and another study used sub-threshold frequency of 1Hz. This variability is consistent with findings of previous systematic reviews [14, 15]. It has been established by previous studies that low frequency rTMS (less than or equal to 1Hz) has an inhibitory effect while high frequency rTMS (20Hz) will have a stimulatory effect [16]. Three out of the four studies on rTMS in this review gave high frequency stimulation at right dorsolateral prefrontal cortex (rDLPFC) while one study gave low frequency stimulation over the left motor cortex. It is evident from our review that rTMS has beneficial effects on improving attention in individuals with ADHD which matches with the findings of previous studies which report improvement in clinical symptoms as well [16, 17]. As per our review, rDLPFC (F4) has been consistently used as the anodal site of stimulation for tDCS in all the studies while cathodal stimulation site was found to be variable lDLPFC (F3) and right supra-orbital area (Fp2). In a study by Nejati *et al.*, (2017), a comparison was done between two placements of tDCS (F3 and F4 vs F4 and Fp2), it was found that using right supra-orbital area as the cathodal site produced better outcomes than on lDLPFC. According to the review of literature, it can be inferred that tDCS is efficacious in reducing impulsive symptoms as well as improving inhibitory control and executive function. These findings are similar to those of Bandeira *et al*., 2016, who reported a significant improvement in visual attention as well as inhibitory control after 5 consecutive sessions of anodal tDCS. It is evident that both rTMS and tDCS are efficacious in treatment of ADHD. However, tDCS has certain advantages over rTMS owing to its inexpensive, ease of applicability and lesser adverse effects [16].

5. Limitations of the current review

There are some limitations of the current review which should be discussed. While the pooled sample size is 250, there are only a limited number of randomized control trials available. Furthermore, some relevant studies might have been missed due to unavailability of the full text articles. The included studies were variable in the sample size and outcome measures which presented a possible difficulty in comparing them. Also, there is a prospective language bias because only English language literature was included. However, irrespective of the mentioned limitations, the review was successful in comparing and analyzing the previous studies. It is recommended that these limitations must be considered while interpreting the results of this review.

6. Conclusion

It can be concluded from the present review that non-invasive stimulation is a promising and upcoming tool for improving executive functions and inhibitory control in ADHD. However, there is a dearth of evidence available for the same. Thus, more number of high quality randomized control trials are required to strengthen the evidence and incorporation of these tools in clinical practice.

Conflict of interest

The authors declare that there is no conflict of interest.

Ethical approval

The authors declare that there is no ethical approval required for this review study.

Highlights

- Non-Invasive brain stimulation techniques used in ADHD include tDCS and rTMS.
- These act by altering brain activity and modulating neuronal networks.
- tDCS modulates cognitive control circuits which are impaired in ADHD.
- rTMS works on neuronal networks by inducing local electrical current in cerebral cortex.
- It is a promising tool for improving executive functions in ADHD.

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