Noninvasive brain stimulation in children and adults with attention-deficit/hyperactivity disorder: a systematic review and meta-analysis

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Background: Repetitive transcranial magnetic stimulation (rTMS) or transcranial direct current stimulation (tDCS) could provide treatment alternatives to stimulant medication for attention-deficit/hyperactivity disorder (ADHD), given some evidence for improvements in cognition and clinical symptoms. However, despite a lack of solid evidence for their use, rTMS and tDCS are already offered clinically and commercially in ADHD. This systematic review and meta-analysis aimed to critically appraise rTMS and tDCS studies in ADHD to inform good research and clinical practice. Methods: A systematic search (up to February 2019) identified 18 studies (rTMS 4, tDCS 14; 311 children and adults with ADHD) stimulating mainly the dorsolateral prefrontal cortex (dlPFC). We included 12 anodal tDCS studies (232 children and adults with ADHD) in 3 random-effects meta-analyses of cognitive measures of attention, inhibition and processing speed. Results: The review of rTMS and tDCS showed positive effects in some functions but not others, and little evidence for clinical improvement. The meta-analyses of 1 to 5 sessions of anodal tDCS over mainly the left or bilateral dlPFC showed trend-level improvements in inhibition and processing speed, but not in attention. Limitations: Heterogeneity in stimulation parameters, patient age and outcome measures limited the interpretation of findings. Conclusion: The review and meta-analysis showed limited evidence that 1 to 5 sessions of rTMS and tDCS, mostly of the dlPFC, improved clinical or cognitive measures of ADHD. These findings did not support using rTMS or tDCS of the dlPFC as an alternative neurotherapy for ADHD as yet. Larger, multi-session stimulation studies identifying more optimal sites and stimulation parameters in combination with cognitive training could achieve larger effects.

Introduction

Attention-deficit/hyperactivity disorder (ADHD) is defined by age-inappropriate and impairing symptoms of inattention, hyperactivity and impulsivity. It is one of the most common childhood disorders, with a prevalence of approximately 7%; problems persist into adulthood in the majority of cases, and ADHD is associated with poor academic and social outcomes. Patients with ADHD have cognitive deficits, most prominently in executive functions, such as motor and interference inhibition, selective and sustained attention, working memory and switching, as well as in timing processes and reward-based decision-making.

Furthermore, meta-analyses of functional MRI (fMRI) studies in ADHD show underactivation in different cognitive-domain-dependent frontostriatal and frontocerebellar systems, such as the right inferior and medial prefrontal and striatal regions during cognitive control; the right dorsolateral prefrontal cortex (dlPFC) and striatal and parietal regions during attention; the bilateral superior prefrontal regions during working memory; the inferior frontal, parietal and cerebellar regions during timing processes; and the ventromedial frontostriatal areas during reward-related functions.

The most effective short-term treatment for ADHD is with psychostimulant medications, but they have side effects and limited longer-term efficacy. Alternative treatments, including behavioural therapies, cognitive training, neurofeedback or dietary interventions, have shown limited efficacy. Noninvasive brain stimulation treatments, such as repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS), are promising because they can stimulate key brain dysfunctions that have been established in ADHD over the last 2 decades of fMRI research. They are also relatively safe, with minimal side effects; they are cheaper than long-term drug treatments or
In rTMS, rapid magnetic pulses are delivered to the scalp with a wire coil to generate an electric current in the brain via electromagnetic induction. The induced electrical current can trigger action potentials in a focal cortical region under the coil, and when pulses are administered at a particular frequency, rTMS can modulate neural activity with longer-lasting aftereffects. In general, high-frequency rTMS (5 to 20 Hz) promotes cortical excitability, and low-frequency rTMS (1 Hz) inhibits cortical excitability. Longer-term clinical improvements with rTMS have been demonstrated in several psychiatric disorders: up to 3 months in obsessive–compulsive disorder when stimulating prefrontal, orbitofrontal and supplementary motor regions; 4 months in schizophrenia when stimulating temporoparietal regions; 12 months in major depressive disorder when stimulating the dlPFC, supporting its neuroplasticity. Relative to tDCS, rTMS has greater specificity in targeting neural regions, but it is more expensive because of device costs and extensive user-training requirements. The most common adverse effects are transient scalp discomfort underneath the coil as a result of stimulation of the pericranial muscles and peripheral nerves.

In tDCS, a weak direct electric current is passed between 2 electrodes (a positive anode and a negative cathode) placed on the scalp. The current modulates spontaneous discharge rates and therefore neuronal network activity by causing subthreshold polarity-dependent shifts in resting membrane potentials, with net increases (anodal stimulation) or decreases (cathodal stimulation) in the excitability of underlying neurons, leading to respective increases or decreases in cortical function and synaptic strength. Although tDCS is a relatively new form of noninvasive brain stimulation, there is evidence that it can enhance cognitive functions in healthy controls, with longer-term effects of up to 9 or 12 months. In psychiatric disorders, positive clinical effects have been observed typically up to 1 month after stimulation (for reviews, see Moffa and colleagues, Tortella and colleagues, and Kekic and colleagues), although it is possible that effects are longer-term. However, overall, tDCS effects are often small, especially when administered in single sessions in healthy controls. Relative to rTMS, tDCS is cheaper, easier to use and produces relatively less discomfort; the most common adverse effects are mild transient tingling, itching and reddening of the skin underneath the electrodes.

Both rTMS and tDCS potentiate cellular and molecular mechanisms involved in use-dependent local and distant synaptic plasticity (e.g., γ-aminobutyric acid [GABA] and glutamate-mediated long-term potentiation), which may lead to longer-term effects. This systematic review and meta-analysis focuses on the clinical and cognitive benefits of rTMS and tDCS, because they are the most investigated noninvasive brain stimulation methods in ADHD. To our knowledge, other methods have not been as well investigated or applied in clinical settings in ADHD (e.g., intermittent or continuous theta burst stimulation, transcranial alternating current stimulation or transcranial random noise stimulation).

There has been an increase over the last decade of 18 rTMS and tDCS studies in ADHD. Studies have used relatively heterogenous stimulation protocols, as well as clinical and cognitive outcome measures, and have reported mixed positive and negative effects on cognition and ADHD symptoms. Furthermore, knowledge is lacking with respect to optimal stimulation protocols for children with ADHD (such as stimulation frequency, intensity or stimulation site), and there are neuro-ethical concerns about potential costs to nontargeted functions. Despite these shortcomings, however, noninvasive brain stimulation is already offered in private clinics in several countries and is available commercially and online.

A recent meta-analysis of 10 tDCS studies in ADHD (n = 201) found that predominantly anodal tDCS of the dlPFC led to a significant but small improvement in measures of inhibitory control (Hedges’ g = 0.12, 95% confidence interval [CI] 0.01–0.24), and to a significant but moderate improvement in reaction times in n-back tasks in a smaller meta-analysis of 7 effect sizes derived from 3 studies (Hedges’ g = 0.66, 95% CI 0.17–1.25). However, effect size estimates may have been inflated, because 2 studies reporting mostly null effects were not included; multiple dependent effects were clustered in the meta-analyses, unduly reducing variation between effect sizes and overestimating statistical significance; and the analysis of inhibitory control measures included noninhibitory measures, such as inattention (e.g., omission errors), processing speed (e.g., reaction times to go trials) and reaction time variability, calling into question the specificity of the positive tDCS effects to the domain of inhibitory control.

We therefore considered it paramount and timely to conduct a systematic review of rTMS and tDCS studies and a meta-analysis of tDCS studies in ADHD that included all available empirical studies and controlled for multiple dependent effects and potential bias; that clustered cognitive effects into clearly separated cognitive domains of inhibitory control, attention and processing speed to elucidate effects of tDCS on specific cognitive domains; that tested the replicability of meta-analysis results with jackknife sensitivity analyses; and that included further sensitivity analyses to reduce heterogeneity caused by studies with designs that deviated from the majority.

This review and meta-analysis aimed to provide a critical appraisal of the most consistent clinical and cognitive effects of rTMS and tDCS in ADHD, scrutinizing the quality of the studies, outlining limitations in the field and discussing neuroethical concerns and future directions, with the ultimate aim of guiding clinical practice.

Methods

Eligibility criteria

The systematic review followed Preferred Reporting Items in Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Fig. 1; PRISMA checklist, Appendix 1, available at jpn.ca/190179-a1). Inclusion criteria were as follows: empirical studies with sufficient method details that applied rTMS or tDCS in children and/or adults with ADHD confirmed by...
either a clinical diagnosis (as defined by DSM/ICD criteria) or by meeting cut-off criteria for ADHD on validated ADHD rating scales or research diagnosis questionnaires (e.g., Conners’ Adult ADHD Rating Scale t score > 6547 or the Kiddie Schedule for Affective Disorders and Schizophrenia48). To avoid language bias, we did not exclude studies published in a language other than English, unless the paper could not be accessed and/or translated by the authors of the article. Relevant outcome measures included clinical measures of ADHD and performance measures on cognitive tasks.

**Search strategy**

We searched Web of Knowledge, Scopus, PubMed, Ovid, Google Scholar, psyarxiv and bioRxiv (up to the end of February 2019) using the following keywords: “noninvasive brain stimulation,” “transcranial electric stimulation,” “transcranial direct current stimulation,” “tDCS,” “transcranial magnetic stimulation,” “rTMS” or “transcranial electric stimulation,” each in combination with “hyperkinetic disorder,” “attention-deficit/hyperactivity disorder,” “ADHD,”

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**Fig. 1:** Preferred Reporting Items in Systematic Reviews and Meta-Analyses (PRISMA) flow diagram of study selection.
Brain stimulation in ADHD

“inattention,” “hyperactivity” or “impulsivity.” We also hand-searched the reference lists of retrieved articles and reviews. One author (S.J.W.) and an additional reviewer (S.W.H.) carried out the search separately; another author (K.R.) crosschecked the results.

Study selection

After removing all duplicates, 1 author (S.J.W.) and an additional reviewer (S.W.H.) independently screened titles and abstracts. The full text of the remaining studies determined final inclusion in accordance with our eligibility criteria. Of the 16,778 studies identified, 14,177 duplicates and 2,572 irrelevant papers were excluded after screening titles and abstracts. A full-text review of the remaining 29 studies resulted in the exclusion of a further 11 studies, including 1 rTMS study written in Arabic, because the paper could not be accessed and a translation could not be obtained from the authors48 (Appendix 1, Table S1). This resulted in 18 peer-reviewed, published studies (4 rTMS and 14 tDCS; total ADHD sample = 312), of which 12 anodal tDCS studies (total n = 232) were eligible for meta-analysis (for the list of excluded studies, see Appendix 1, Table S1). The final list of included studies was agreed upon by consensus; any disagreements were resolved by another author (K.R.).

Risk of bias assessment

We assessed risk of bias using the Cochrane Collaboration’s risk of bias tool,50 which rates risk of bias across 5 domains: selection bias, performance bias, detection bias, attrition bias and other biases. Using this tool, S.J.W. and K.R. assessed risk of bias for all sham-controlled studies and resolved any disagreements by consensus. Because the tool is designed for randomized controlled trials, we excluded open-label trials51,52 to avoid undue inflation of bias across domains. We included open-label trials in the systematic review for a complete overview of available empirical studies.

Meta-analysis

Because of the small number of included studies, neither the clinical effects of rTMS and tDCS (n = 2 for each) nor the cognitive effects of rTMS studies (n = 2) and cathodal tDCS (n = 3) could be subjected to meta-analysis. Therefore, we conducted a meta-analysis only on the cognitive effects of anodal tDCS (12 studies) in ADHD. We calculated effect sizes from reported means and standard deviations or t and F values where possible. All data were extracted by S.J.W. We used Plot Digitizer to convert plotted data to numerical values (for an example, see Westwood and Romani35), and we obtained any unreported data by personal communication. All extracted data were cross-checked by K.R.

To reduce large heterogeneity, we clustered cognitive outcome measures into 3 domains and analyzed them in 3 separate meta-analyses. Such clustering of outcome measures into cognitive domains was informed by factor analyses of executive-function measures of ADHD, which typically cluster into factors that comprise measures of attention, inhibition and processing speed.53–56 Accordingly, for attention measures, we included the numbers or percentages of errors or omission errors (or the inversely reported number or percentage of correct trials) and intrasubject reaction time variability or intrasubject coefficient of variation (intrasubject reaction time variability divided by mean reaction time) to go/congruent/target trials in go/no-go tasks, flanker tasks, Stroop colour and word tasks (Stroop), working memory tasks and the Wisconsin Card Sorting Task (WCST). For inhibition measures, we included the numbers or percentages of commission errors (or the inversely reported number or percentage of correct trials) to no-go trials in the go/no-go task; the number of percentage errors or reaction time to incongruent trials in flanker or Stroop tasks; the number of commission errors in continuous performance tasks (CPTs) or MOXO tasks; stop signal reaction times in the stop task; perseverative errors in the WCST; and multi-button responses in the MOXO task. For processing speed, we included mean reaction times to go/congruent/target trials in alertness, CPT, go/no-go and MOXO tasks, and completion time in the WCST.

We estimated effect sizes using small-sample-corrected standardized mean differences (i.e., Hedges’ g).57 which calculated the difference in performance under sham versus anodal tDCS divided by pooled standard deviation to standardize the effect. We reported effects as positive if a cognitive outcome measure showed improvement with anodal tDCS relative to sham stimulation, and as negative if it showed deterioration. We conducted all meta-analyses using random-effects models to account for heterogeneity (i.e., effect size variation between studies beyond that expected for sampling error alone).58 To provide a measure of heterogeneity, we report the I² value; I² values of 75%, 50% and 25% reflect high, moderate and low heterogeneity, respectively.59

When estimating Hedges’ g in crossover designs, we accounted for the correlation between pre and post measures (otherwise, there would have been an underestimation of the effect sizes).60 Where multiple effects were reported from the same sample, we created composite effect sizes by averaging effect sizes and decreasing variances, assuming correlation across the different effects. Because tDCS studies did not report these correlations, we estimated the crossover correlation from reported t values (25 of 60 reported outcomes) derived from analyses comparing anodal tDCS with sham stimulation, and we estimated the correlation across multiple dependent outcomes from an ongoing neurotherapy intervention study in our laboratory with a sample of 74 adolescents with ADHD tested before and after intervention in the Maudsley Attention and Response Suppression task battery, including go/no-go tasks, CPTs, Simon tasks, time estimation tasks61 and the WCST. Specifically, we assumed a correlation of 0.629 between outcome measures for studies with crossover designs, and a correlation of 0.3 between the different effects for composite effects. In addition, we conducted sensitivity analyses assuming crossover correlation of 0.407 and 0.780 (the upper and low 95% CIs of the estimated correlation) and composite correlation of 0.1 and 0.5 to test whether findings depended on our estimates.
Finally, we used jackknife sensitivity analyses (i.e., repeating the same analysis and excluding a different study each time) to establish the replicability of findings. To improve homogeneity, we carried out additional sensitivity analyses that excluded studies with overlapping samples,60–63 or studies with methods that deviated from the majority of studies, such as those including community participants with high ADHD symptoms on validated ADHD ratings scales but without a clinical ADHD diagnosis; those including adult samples with ADHD,42,65,66 those targeting the right inferior frontal cortex (IFC);43,64 those reporting change scores (i.e., post minus pre differences) rather than post scores only;66 those using multi-stimulation sessions;60–62,65 those with effect sizes based on working memory or WCST tasks;61,68 or those using parallel rather than crossover designs.62,66,67 Lastly, given that effect-size estimates might be inflated in studies with a high risk of bias, we conducted meta-regression analyses to compare the effect sizes of studies with high versus low or unclear risk of bias for each risk of bias domain (i.e., selection bias, performance bias, detection bias, attrition bias and other biases). All analyses were conducted by J.R.; meta-analysis calculations were conducted using the function “rma” of the “metafor” package version 2.1 in R version 3.6.69,70

Results

Literature review

rTMS studies
Two double-blind, crossover studies targeted the right dlPFC. In 13 adults with ADHD, 1 session of 20 Hz rTMS relative to sham significantly improved overall self-rated inattention but not hyperactivity symptoms.71 In 9 adults with ADHD, 10 daily sessions of 10 Hz rTMS relative to sham showed no effect on self-rated clinical symptoms, nor on electroencephalography or executive-function measures.72 In a single-blind study in 21 adolescents with ADHD, 20 daily sessions of 18 Hz deep rTMS over the bilateral dlPFC (n = 13) compared with sham (n = 9) showed no effect on self-rated clinical or cognitive measures of sustained attention.73 An open-label trial in 10 children with ADHD showed fewer teacher-rated inattention and parent-rated hyperactivity/impulsivity symptoms 1 week after 5 daily sessions of 1 Hz rTMS of the left dlPFC compared with baseline.52 However, without sham control conditions, placebo effects could not be ruled out (Table 1).

tDCS studies
Fourteen studies tested tDCS in ADHD; 9 studies were double-blind, 4 studies were single-blind and 1 study was open-label. Ten studies tested children, and 4 studies tested adults. Only 2 studies combined tDCS with cognitive training (Table 2 and Table 3).

Table 1: Clinical and cognitive effects of rTMS

| Study            | Design                    | Outcome measures                                                                 || Clinical* | Cognitive |
|------------------|---------------------------|----------------------------------------------------------------------------------|-----------|----------|
| Bloch et al. 71  | Single-blind, sham-controlled cross-over | 1680 pulses (12 s on, 60 s off) within 20 s of MT | Not tested | Not tested |
| Gomez et al. 52  | Double-blind, crossover    | 2000 pulses (14 s on, 20 s off) within 20 s of MT | Not tested | Not tested |
| Paz et al. 73    | Double-blind, sham-controlled | 2000 pulses (14 s on, 20 s off) within 20 s of MT | Not tested | Not tested |
| Weaver et al. 72 | Single-blind, sham-controlled | 2000 pulses (14 s on, 20 s off) within 20 s of MT | Not tested | Not tested |

*Plus sign [+] = statistically significant improvement.
†5 cm forward to MT point.
‡Small change from baseline of 0.25 and 1.16 on 5-point Likert scales.
§6 cm rostral to motor cortex.

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### Table 2: Clinical and cognitive effects of tDCS (part 1 of 2)

| Study                  | Design                      | N   | Mean age, yr | Anode/ cathode | mA   | Sessions, n | Timing* | Duration, min | Clinical† | Cognitive† |
|------------------------|-----------------------------|-----|--------------|----------------|------|--------------|---------|---------------|-----------|------------|
| *Children*             |                             |     |              |                |      |              |         |               |           |            |
| Bandeira et al.51‡     | Open-label                  | 9   | 11           | Left dlPFC/ right SOA | 2    | 5            | Online | 28            | PGH       | Visual Attention Test (TAVIS-3; omission errors [+]); NEPSY-II-inhibition (switch errors [+]); digit span task; Corsi cube task |
| Breitling et al.67     | Single-blind, sham-controlled, crossover | 21  | 14           | Right IFC/ left cheek; Left cheek/ right IFC | 1    | 1            | Online | 20            | Not tested | Flanker task (incongruent trials: errors [+]; ICV [+]; Flanker task) |
| Munz et al.50          | Double-blind, sham-controlled, crossover | 14  | 12           | Left dlPFC/ right cheek; right dlPFC/ left cheek | 0.25 | 1            | Offline | 25 (5 on, 1 off) | Not tested | Go/no-go task (go RT [+]; n-back; WCST (total categories completed [+], total errors [+], perseverative errors [+]) |
| Nejati et al.68 (experiment 1) | Double-blind, sham-controlled, crossover | 15  | 10           | Left dlPFC/ right dlPFC | 1    | 1            | Offline | 15            | Not tested | Go/no-go task (go RT [+]; n-back; WCST (total categories completed [+], total errors [+], perseverative errors [+]) |
| Nejati et al.68 (experiment 2) | Double-blind, sham-controlled, crossover | 10  | 9            | Left dlPFC/ right SOA | 1    | 1            | Offline | 15            | Not tested | Go/no-go task (go RT [+]; n-back; WCST (total categories completed [+], total errors [+], perseverative errors [+]) |
| Prehn-Kristensen et al.61 | Double-blind, sham-controlled, parallel | 12  | 12           | Left dlPFC/ right cheek; right dlPFC/ left cheek | 0.25 | 1            | Offline | 25 (5 on, 1 off) | Not tested | Declarative memory task (accuracy [+]); alertness task; digit span task |
| Soff et al.62          | Double-blind, sham-controlled, crossover | 15  | 14           | Left dlPFC/ vertex | 1    | 5            | Online | 20            | FBB-AHDH (inattention [+]; hyperactivity [+]) |
| Soltaninejad et al.43§ | Single-blind, sham-controlled, crossover | 20  | 16           | Left dlPFC/ right SOA | 1.5  | 1            | Online | 15            | Not tested | Go/no-go task (go RT [+]; Stroop task) |
| Soltaninejad et al.43§ | Single-blind, sham-controlled, crossover | 20  | 16           | Right IFC/ left SOA | 1.5  | 1            | Online | 15            | Not tested | Go/no-go task (go RT [+]; Stroop task) |
| Soltaninejad et al.43§ | Double-blind, sham-controlled, crossover | 13  | 14           | Left dlPFC/ vertex | 1    | 1            | Online | 20            | Not tested | QbTest (RT [+], RT [+]; omission errors [-]; accuracy [-]) |
Table 2: Clinical and cognitive effects of tDCS (part 2 of 2)

| Study                  | Design                        | N   | Age, yr | Mean | Sessions, n | Timing* | Duration, min | Clinical† | Cognitive† |
|------------------------|-------------------------------|-----|---------|------|-------------|---------|---------------|-----------|------------|
| Adults                 |                               |     |         |      |             |         |               |           |            |
| Allenby et al.         | Double-blind, sham-controlled, crossover | 37  | 32      |      | 2           | Online  | 20            | Not tested|            |
| Cachoeira et al.       | Double-blind, sham-controlled, crossover | Active: 9 | Active: 31 | Sham: 8 | Sham: 34 | Right dlPFC/ left SOA | 2          | 5          | Offline 20 | ADHD checklist (inattention [+], total [+])****, SDS (after tDCS only [+]) | Not tested |
| Cosmo et al.           | Double-blind, sham-controlled, parallel | Active: 30 | Active: 32 | Sham: 30 | Sham: 33 | Left dPFC/ right dlPFC | 1          | 1          | Offline 20 | Go/no-go task |            |
| Jacoby et al.          | Single-blind, sham-controlled, crossover | 20  | 23      |      | 1.8         | Offline | 20            | Not tested| CPT (multi-button presses [+]) |            |

ADHD = attention deficit/hyperactivity disorder; CPT = continuous performance task; dPFC = dorsolateral prefrontal cortex; FBB-ADHD = parents' version of a German adaptive diagnostic checklist for ADHD; ICV = intrasubject coefficient of variation; IFC = inferior frontal cortex; NEPSY-II = Neuropsychological Development Assessment, Second Edition; PG1-I = Patient Global Impression of Improvement; QbTest = Quantitative Behaviour Test; RT = reaction time; RTV = reaction time variability or standard deviation of reaction times; SDS = Sheehan Disability Scale; SOA = supraorbital area; Stroop = Stroop colour and word task; tDCS = transcranial direct current stimulation; WCST = Wisconsin Card Sorting Task.

*Refers to whether cognitive performance was during stimulation (online) or after stimulation (offline).
†Plus sign [+]= statistically significant improvement; minus sign [−]= statistically significant impairment.
‡Originally published in Persian; translated by the lead author (ZS).
§Would likely not survive multiple comparison correction.
**Comparisons between stimulation conditions based on post-hoc least significant difference tests, which do not correct for multiple comparisons.
††Based on underpowered analysis focusing on the first session, with 7 participants per condition.
†‡ Improvement seen only 7 days after the fifth anodal tDCS session.
†§ Did not survive correction for multiple comparisons.
§§ Based on underpowered analysis focusing on the first 5 sessions, with 7/8 participants per condition.
¶¶ Improvement seen immediately after the fifth anodal tDCS session.
††† Significant in comparison to cathodal tDCS only.
‡‡‡ Based on a crossover interaction; tDCS reduced RT and RTV in 1 of 4 conditions (2-back tasks), but this did not survive correction for multiple comparisons.
§§§ Included carryover effect raised by Soff et al. 62.
¶¶¶ Significant only immediately after anodal tDCS; not significant 3 days later.
***Improvement seen immediately after anodal tDCS and after 2 weeks; total score improved only after 2 weeks.
†††† Significant in comparison to cathodal tDCS and sham treatment in 21 adolescents with ADHD, which found that 1 session of anodal tDCS over the left dlPFC 64 or the right dlPFC also improved no-go accuracy.
†††‡ Based on a crossover interaction; tDCS reduced RT and RTV in 1 of 4 conditions (2-back tasks), but this did not survive correction for multiple comparisons.
†††§ Based on underpowered analysis focusing on the first session to remove a practice effect, and the analysis included time or error scores on n-back and Stroop task measures, rather than the Stroop interference or error effect (reaction time/errors on congruent vs. incongruent trials) — the established key outcome measures. Furthermore, errors and reaction times to incongruent trials but not to congruent trials were used as main outcome measures. Further adjustment for age made no difference. Most statistical analyses were performed on any other go/no-go or go/pace measures; if not otherwise stated.
†††¶ Based on underpowered analysis focusing on the first session with 7 participants per condition.
‡‡‡§ Based on underpowered analysis focusing on the first session with 7 participants per condition.
§§§§ Based on underpowered analysis focusing on the first 5 sessions with 7/8 participants per condition.
¶¶¶¶ Significant in comparison to cathodal tDCS and sham treatment in 21 adolescents with ADHD, which found that 1 session of anodal tDCS over the left dlPFC 64 or the right dlPFC also improved no-go accuracy.
††††† Significant in comparison to cathodal tDCS and sham treatment in 21 adolescents with ADHD, which found that 1 session of anodal tDCS over the left dlPFC 64 or the right dlPFC also improved no-go accuracy.
‡‡‡‡ Based on underpowered analysis focusing on the first 5 sessions with 7/8 participants per condition.
§§§§§ Based on underpowered analysis focusing on the first session with 7 participants per condition.
¶¶¶¶¶ Significant in comparison to cathodal tDCS and sham treatment in 21 adolescents with ADHD, which found that 1 session of anodal tDCS over the left dlPFC 64 or the right dlPFC also improved no-go accuracy.
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### Table 3: Cognitive task measures (mean ± SD) extracted from studies (part 1 of 2)

| Study | Cognitive task | Cognitive outcome measure | tDCS, mean ± SD | Sham, mean ± SD | Effect* |
|-------|----------------|---------------------------|-----------------|-----------------|---------|
| **Measures of attention** | | | | | |
| Allenby et al.65 | CPT | No. omission errors | 1.9 ± 4.3 | 2.1 ± 2.4 | Single |
| Breitling et al.67 | Flanker task (incongruent trials) | % Omission errors | 2.2 ± 4.6 | 5.8 ± 7.6 | Composite |
| Flanker task (incongruent trials) | Intra-individual coefficient of variation (ms)† | 0.2 ± 0.1 | 0.3 ± 0.1 | |
| Cosmo et al.66 | Go/no-go task (fruits) | No. omission errors (post/pre)‡ | −2.9 ± 24.5 | −3.7 ± 21.2 | Single |
| Jacoby et al.42 | MOXO task | RT (ms) with 1 distractor | 552.2 ± 53.9 | 558.9 ± 52.1 | Composite |
| MOXO task | RT (ms) with 2 distractors | 556.5 ± 54.4 | 568.9 ± 53.5 | |
| MOXO task | No. omission errors | 4.2 ± 4.1 | 4.3 ± 4.0 | |
| Munz et al.60 | Alertness task | Intrasubject RTV (ms) | 69.5 ± 25.1 | 76.1 ± 31.2 | Composite |
| Nejati et al.68 (experiment 1) | Go/no-go task (go trials) | % Correct | 93.3 ± 11.4 | 90.9 ± 19.6 | Composite |
| N-back task (1-back) | % Correct | 15.3 ± 8.3 | 14.4 ± 7.4 | |
| WCST | No. of categories completed | 2.5 ± 0.8 | 2.4 ± 1.1 | |
| WCST | No. total errors | 29.7 ± 8.3 | 30.7 ± 9.3 | |
| Nejati et al.68 (experiment 2) | Go/no-go task (no-go trials) | % Correct | 100.0 ± 0.0 | 98.5 ± 3.2 | Composite |
| N-back task (1-back) | % Correct | 21.0 ± 2.3 | 17.9 ± 2.9 | |
| WCST | No. of categories completed | 5.1 ± 0.7 | 3.9 ± 0.7 | |
| WCST | No. total errors | 11.0 ± 2.9 | 21.6 ± 5.4 | |
| Prehn-Kristensen et al.61 | Digit span task | No. correct | 9.6 ± 2.4 | 10.8 ± 2.1 | Single |
| Soff et al.62 | QbTest (inattention) | z-scores (omission errors, RT and insubject RTV) | 0.1 ± 1.2 | −0.1 ± 0.4 | Single |
| Soltaninejad et al.64 | Go/no-go task (go trials) | % Correct | 98.8 ± 3.6 | 98.9 ± 1.9 | Single |
| Soltaninejad et al.63 | Go/no-go task (go trials)§ | % Correct | — | — | Single |
| Sotnikova et al.63 | QbTest (overall) | % Correct | 214.3 ± 97.2 | 235.2 ± 122.7 | Composite |
| QbTest (overall) | No. omission errors | 38.6 ± 22.8 | 22.5 ± 15.3 | |
| QbTest (overall) | % Correct¶ | 31.7 ± 5.1 | 43.5 ± 6.9 | |
| **Measures of inhibition** | | | | | |
| Allenby et al.65 | CPT | No. commission errors | 17.1 ± 9.1 | 19.8 ± 10.9 | Composite |
| Stop task | Stop signal RT | 288.4 ± 76.0 | 291.5 ± 66.1 | |
| Breitling et al.67 | Flanker task (incongruent trials) | RT (ms) | 581.0 ± 43.0 | 585.0 ± 38.0 | Composite |
| Flanker task (incongruent trials) | % Errors | 9.8 ± 7.2 | 20.6 ± 9.2 | |
| Cosmo et al.66 | Go/no-go task (fruits) | No. commission errors (post/pre)‡ | −5.5 ± 10.0 | −6.9 ± 10.4 | Single |
| Jacoby et al.42 | MOXO task | Multi-button responses | 4.7 ± 4.9 | 7.0 ± 6.3 | Composite |
| MOXO task | No. commission errors | 11.3 ± 11.2 | 11.7 ± 12.1 | |
| Munz et al.60 | Go/no-go task (no-go trials) | % correct | 19.9 ± 7.6 | 19.0 ± 7.8 | Composite |
| Go/no-go task (no-go trials) | % Errors | 24.9 ± 12.0 | 34.9 ± 15.5 | |
| Stromar task (incongruent trials) | RT (ms) | 2870 ± 1220 | 1390 ± 440 | |
| Stromar task (incongruent trials) | No. perseverative errors | 17.6 ± 3.6 | 18.0 ± 9.0 | |
| Nejati et al.68 (experiment 1) | Go/no-go task (no-go trials) | % Correct | 22.7 ± 1.3 | 20.7 ± 4.4 | Composite |
| WCST | No. perseverative errors | 7.8 ± 2.4 | 14.8 ± 3.7 | |
| Nejati et al.68 (experiment 2) | QbTest (impulsivity) | z-scores (commission errors, multi-button press per stimulus, anticipatory button press) | 0.2 ± 0.1 | −0.2 ± 0.7 | Single |
| Soff et al.62 | Go/no-go task (no-go trials) | % Correct | 96.2 ± 8.2 | 95.8 ± 6.9 | Composite |
| Go/no-go task (no-go trials) | % Correct | 98.3 ± 2.9 | 96.4 ± 3.6 | |
| Sotnikova et al.63 | QbTest (overall) | % Correct | 214.3 ± 97.2 | 235.2 ± 122.7 | Composite |
| QbTest (overall) | No. omission errors | 38.6 ± 22.8 | 22.5 ± 15.3 | |
| QbTest (overall) | % Correct¶ | 31.7 ± 5.1 | 43.5 ± 6.9 | |
One double-blind, crossover study applied 5 daily sessions of anodal tDCS over the left dlPFC in 15 adolescents with ADHD. The results showed improvements relative to sham treatment in parent-rated clinical measures of inattention and on cognitive measures of attention (as assessed using the QbTest, a combined working memory and go/no-go task) 7 days after anodal tDCS but not immediately after, and improvements in QbTest measures of hyperactivity both immediately after anodal tDCS and 7 days later. Clinical and QbTest impulsiveness measures showed no effects. However, findings were based on the first 5 sessions to remove a carryover effect, reducing the sample to 7 or 8 participants per condition. In the same study, 13 of the 15 adolescents with ADHD showed reduced reaction time variability but increased errors on the QbTest after a single session of anodal tDCS. However, this analysis included a carryover effect.

A double-blind, sham-controlled crossover study found that relative to sham treatment, overnight slow-wave oscillatory anodal tDCS over the left and right dlPFC improved declarative memory in 12 children with ADHD and go reaction time and its intrasubject variability in 14 children with ADHD, but had no effects on no-go accuracy, or on measures of alertness, digit span or motor memory.

The only open-label trial in 9 children with ADHD found that 5 daily sessions of anodal tDCS to the left dlPFC combined with a picture association cognitive training task reduced errors on attention (omission) and switch tasks but did not improve working memory. Parents reported improvements in some of their children’s behaviour except for one, who reported their child was “much worse.” However, without a sham control condition, findings could have been confounded by placebo, test–retest or cognitive training effects.

### tDCS studies in adults with ADHD

A double-blind, parallel study found no effects of a single session of anodal tDCS over the left dlPFC relative to sham treatment on go/no-go performance in 60 adults with ADHD. A single-blind, crossover study in 20 undergraduates with ADHD found that 1 session of bifrontal anodal tDCS over the left and right dlPFC relative to sham treatment improved hyperactivity measures in a sustained attention task (i.e., multiple/random responses), but no omission errors or reaction times. A double-blind, crossover study in 37 adults with ADHD found that 3 sessions over alternate days of visual working memory training combined with anodal tDCS relative to sham tDCS of the left dlPFC reduced commission errors in a sustained attention task immediately after anodal tDCS, but not at the 3-day follow-up; there were no effects on omission errors, reaction times or stop task performance immediately after anodal tDCS or 3 days later. Finally, a double-blind, parallel study in 17 adults with ADHD reported that 5 daily sessions of anodal right tDCS (n = 9) relative to sham treatment (n = 8) improved inattention but not hyperactivity/impulsive symptoms immediately after stimulation and 2 weeks later, at which point the total ADHD score was also improved.

### Safety in tDCS studies

Brain stimulation was well tolerated overall; the most commonly reported side effects were mild tingling and itching.
One study reported dropouts because of tingling sensations and headache\textsuperscript{43} (Table 4). There was 1 case of an adverse effect, where 1 patient reported hypobulia after a single session of anodal tDCS over the right dIPFC, which persisted in a milder form the following day.\textsuperscript{74}

**Summary of findings of tDCS studies**

Findings were mixed. With respect to the clinical effects of tDCS, only 2 sham-controlled studies tested and found improvement in behavioural symptoms of inattention but not in impulsiveness/hyperactivity symptoms, and an open-label trial found improvements in parent-rated impression of improvement in global functioning. Of 14 studies that tested cognitive effects, 13 observed positive effects on some cognitive functions but not others, and 1 reported worse performance in a sustained attention task.\textsuperscript{63} Moreover, 7 sham-controlled studies did not correct for multiple comparisons,\textsuperscript{43,62–64,67,68} and the majority of their findings would not have survived correction.

**Risk of bias**

A minority of studies indicated unclear bias for selection (\(n = 6\)), detection (\(n = 1\)) and attrition (\(n = 2\)), but on balance bias was low in these domains. Performance bias (i.e., blinding participants and personnel) was unclear in 11 studies and high in 2 studies; selective reporting bias and other biases (e.g., nonstandard outcome measures, no correction for multiple testing, lenient significance threshold) were high in 4 studies (Fig. 2; Appendix 1, Table S2).

**Meta-analysis of anodal tDCS studies**

The majority of the studies included in the meta-analysis (10 of 12) used anodal stimulation of mostly left dIPFC regions (unilateral left, \(n = 5\); bifrontal anode left and right, \(n = 3\); bilateral anode left/cathode right, \(n = 2\)); only 2 studies involved unilateral stimulation of the right IFC (Table 2). The meta-analyses showed no significant effect in measures of attention (Hedges’ \(g = 0.18\), 95% CI \(-0.19\) to 0.45, \(p = 0.20\)) with high heterogeneity (\(I^2 = 75\%\), \(p < 0.001\)) and trend-level improvements in measures of inhibition (Hedges’ \(g = 0.21\), 95% CI \(-0.01\) to 0.43, \(p = 0.06\)) with moderate heterogeneity (\(I^2 = 60\%\), \(p = 0.01\)) and of processing speed (Hedges’ \(g = 0.14\), 95% CI \(-0.01\) to 0.29, \(p = 0.07\)) with low heterogeneity (\(I^2 = 3\%\), \(p = 0.50\); Fig. 3). Sensitivity analyses confirmed that these findings did not systematically rely on our estimated correlations for effects from crossover studies or for composite effect-size estimates (Appendix 1, Table S3). Further, we replicated these findings in the jackknife sensitivity analyses (i.e., repeating the main analyses but excluding a different study with each repetition), with only minor exceptions: excluding a minority of individual studies led to a significant but still small effect in measures of inhibition (excluding Cosmo and colleagues,\textsuperscript{46} Munz and colleagues\textsuperscript{60} and Soltaninejad and colleagues\textsuperscript{43}) and in processing speed (excluding Allenby and colleagues\textsuperscript{43} and Soltaninejad and colleagues,\textsuperscript{43} Table 5).

To improve homogeneity, we carried out additional sensitivity analyses to exclude studies with overlapping samples, methods that departed from the majority of studies or studies

| Study | Side effects and adverse effects |
|-------|----------------------------------|
| Bloch et al.\textsuperscript{71} | Not tested, but authors observed differences in the somatosensory experience of real rTMS and sham, which limited true blinding |
| Gomez et al.\textsuperscript{52} | Majority reported transient mild headache and scalp discomfort; a minority reported neck pain. No seizure-like cortical activity was found. One case of slight and brief dizziness |
| Paz et al.\textsuperscript{73} | Not tested |
| Weaver et al.\textsuperscript{72} | Minority reported transient mild headaches and scalp discomfort |

| tDCS studies | Side effects and adverse effects |
|----------------|----------------------------------|
| Allenby et al.\textsuperscript{43} | Burning, itching, pain and tingling were rated significantly higher during anodal tDCS compared with sham |
| Bandeira et al.\textsuperscript{51} | Majority reported mild to moderate headache, tingling, burning sensation and redness of the skin. Minority reported mild neck pain, sleepiness and static shock. One parent reported child was “much worse” after stimulation |
| Breitling et al.\textsuperscript{57} | Skin sensations were rated higher during cathodal tDCS relative to sham |
| Cachoeira et al.\textsuperscript{74} | Comparable reports of headache, tingling, burning sensation and tiredness were found in both sham and anodal tDCS. One patient withdrew after the first sessions because of an “acute mood change, feeling sad, hypobulia, tension … 5 hours after stimulation and persisted in a milder form into the next day” |
| Cosmo et al.\textsuperscript{43} | None reported |
| Jacoby et al.\textsuperscript{42} | Not tested, but authors reported that stimulation was well tolerated and no side effects were reported |
| Munz et al.\textsuperscript{60} | Not tested, but no side effects were reported |
| Nejati et al.\textsuperscript{58} | Reports of mild itching or tingling under electrodes |
| Prehn-Kristensen et al.\textsuperscript{61} | Not tested. No side effects reported |
| Soft et al.\textsuperscript{62} | About half of participants reported tingling and itching sensations under electrode during sham and anodal tDCS |
| Soltaninejad et al.\textsuperscript{44} | Not reported |
| Soltaninejad et al.\textsuperscript{54} | Several participants dropped out because of tingling sensation and headache |
| Sotnikova et al.\textsuperscript{63} | About half of participants reported tingling and itching sensations under electrode during sham and anodal tDCS |

\textsuperscript{rTMS = repetitive transcranial magnetic stimulation; tDCS = transcranial direct current stimulation.}

\textsuperscript{*Personal communication, 2019.}
Fig. 2: Risk of bias ratings for (A) repetitive transcranial magnetic stimulation (rTMS), (B) transcranial direct current stimulation (tDCS) and (C) individual studies. Note: risk of bias ratings were the same for both studies reported in Nejati et al.68
that were of lower methodological quality (Table 6). For inhibition measures, these analyses revealed significant but small effects when the analysis was limited to studies using single-session tDCS (Hedges’ $g = 0.28$, 95% CI 0.01 to 0.56, $p = 0.04$; reported only post-stimulation scores (Hedges’ $g = 0.24$, 95% CI 0.01 to 0.48, $p = 0.04$); or stimulated mainly the left dlPFC (Hedges’ $g = 0.24$, 95% CI 0.01 to 0.47, $p = 0.04$), all of which were associated with significant moderate heterogeneity ($I^2 = 66$, $p = 0.01$; $I^2 = 63$, $p = 0.01$; $I^2 = 56$, $p = 0.02$, respectively). For processing speed measures, we found significant but small

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**Fig. 3:** Meta-analysis of measures of (A) attention, (B) inhibition and (C) processing speed. CI = confidence interval; tDCS = transcranial direct current stimulation.
effects when the analysis was limited to studies that used single-session tDCS (Hedges’ $g = 0.22$, 95% CI 0.04 to 0.41, $p = 0.02$), used child samples (Hedges’ $g = 0.20$, 95% CI 0.01 to 0.39, $p = 0.04$) or stimulated mainly the left dlPFC (Hedges’ $g = 0.17$, 95% CI 0.01 to 0.33, $p = 0.04$), all of which were associated with low heterogeneity ($I^2 = 0$, $p = 0.51$; $I^2 = 9$, $p = 0.41$; $I^2 = 5$, $p = 0.50$, respectively).

Finally, meta-regression analyses compared the effect sizes from studies with a high risk of reporting bias versus the effect sizes from studies with low or unclear risk of such bias. At a descriptive level, the effect sizes from studies with high risk of reporting bias or “other” biases (e.g., no correction to multiple testing, lenient $\alpha$ level) were larger than the effect sizes from studies with low or unclear risk. These differences were not statistically significant in any of the outcomes for reporting bias (lowest $p = 0.14$), but “other” biases yielded a significant effect in measures of inhibition ($p = 0.03$) and processing speed ($p = 0.03$). Because none of the studies showed high risk of selection, detection or attrition bias, and only 1 study showed high risk of performance bias, we did not carry out meta-regression analyses for these biases.

**Discussion**

There has been a recent proliferation of noninvasive brain stimulation studies in ADHD, with large heterogeneity in methodology and outcome measures. We therefore conducted a systematic review of rTMS and tDCS studies. Furthermore, we conducted a rigorous meta-analysis of tDCS studies in ADHD that clustered cognitive effects into clearly separated cognitive domains to increase homogeneity, controlled for multiple dependent effects and potential bias of studies, and tested the replicability of meta-analysis results with jackknife and other sensitivity analyses. The meta-analysis of tDCS studies of mostly the dlPFC showed only trend-level effects on improvement of inhibition and processing speed, but not on attention, suggesting limited effects of tDCS on cognition in children and adults with ADHD.

| Table 5: Results of jackknife sensitivity analysis |
|-----------------------------------------------|
| **Meta-analysis** | **Studies excluded** | **Effect size** | **Heterogeneity** |
|                 |                           | Hedges’ $g^*$ | 95% CI | $p$ value | $I^2$ | $p$ value |
| **Attention**   | Allenby et al. [65]       | 0.19         | -0.11 to 0.50 | 0.22 | 77 | < 0.001 |
|                 | Breitling et al. [67]     | 0.14         | -0.13 to 0.42 | 0.31 | 76 | < 0.001 |
|                 | Cosmo et al. [66]         | 0.20         | -0.10 to 0.50 | 0.19 | 78 | < 0.001 |
|                 | Jacoby et al. [42]        | 0.19         | -0.12 to 0.48 | 0.24 | 77 | < 0.001 |
|                 | Munz et al. [60]          | 0.16         | -0.14 to 0.46 | 0.30 | 77 | < 0.001 |
|                 | Nejati et al. [56] (experiment 1) | 0.19 | -0.12 to 0.50 | 0.22 | 77 | < 0.001 |
|                 | Nejati et al. [56] (experiment 2) | 0.08 | -0.12 to 0.27 | 0.43 | 49 | 0.040 |
|                 | Prehn-Kristensen et al. [31] | 0.23 | -0.03 to 0.50 | 0.09 | 72 | 0.001 |
|                 | Soff et al. [62]          | 0.18         | -0.11 to 0.47 | 0.22 | 78 | < 0.001 |
|                 | Soltaninejad et al. [54]  | 0.20         | -0.10 to 0.50 | 0.19 | 77 | < 0.001 |
|                 | Soltaninejad et al. [51]  | 0.14         | -0.15 to 0.42 | 0.35 | 75 | 0.001 |
|                 | Sotnikova et al. [63]     | 0.24         | -0.03 to 0.50 | 0.08 | 70 | 0.002 |
| **Inhibition**  | Allenby et al. [65]       | 0.22         | -0.04 to 0.48 | 0.09 | 65 | 0.010 |
|                 | Breitling et al. [67]     | 0.19         | -0.03 to 0.41 | 0.10 | 62 | 0.010 |
|                 | Cosmo et al. [66]         | 0.24         | 0.01 to 0.48  | 0.040 | 63 | 0.010 |
|                 | Jacoby et al. [42]        | 0.20         | -0.05 to 0.44 | 0.12 | 65 | 0.010 |
|                 | Munz et al. [60]          | 0.25         | 0.05 to 0.46  | 0.020 | 53 | 0.020 |
|                 | Nejati et al. [56] (experiment 1) | 0.19 | -0.06 to 0.43 | 0.13 | 63 | 0.010 |
|                 | Nejati et al. [56] (experiment 2) | 0.15 | -0.03 to 0.32 | 0.10 | 37 | 0.12 |
|                 | Soff et al. [62]          | 0.21         | -0.02 to 0.44 | 0.07 | 65 | 0.010 |
|                 | Soltaninejad et al. [64]  | 0.20         | -0.05 to 0.45 | 0.12 | 65 | 0.010 |
|                 | Soltaninejad et al. [43]  | 0.26         | 0.04 to 0.48  | 0.020 | 52 | 0.030 |
|                 | Sotnikova et al. [63]     | 0.23         | -0.01 to 0.47 | 0.06 | 66 | 0.010 |
| **Processing speed** | Allenby et al. [65]       | 0.19         | 0.02 to 0.35  | 0.030 | 0  | 0.53 |
|                 | Jacoby et al. [42]        | 0.15         | -0.02 to 0.32 | 0.09 | 13 | 0.38 |
|                 | Munz et al. [60]          | 0.16         | 0.00 to 0.33  | 0.06 | 10 | 0.44 |
|                 | Nejati et al. [56] (experiment 1) | 0.09 | -0.08 to 0.25 | 0.29 | 0 | 0.79 |
|                 | Nejati et al. [56] (experiment 2) | 0.12 | -0.04 to 0.28 | 0.15 | 2 | 0.50 |
|                 | Soltaninejad et al. [54]  | 0.13         | -0.04 to 0.29 | 0.14 | 9  | 0.42 |
|                 | Soltaninejad et al. [43]  | 0.17         | 0.01 to 0.33  | 0.040 | 5  | 0.50 |
|                 | Sotnikova et al. [63]     | 0.15         | -0.02 to 0.31 | 0.08 | 11 | 0.40 |

CI = confidence interval.

*Effect size estimates assumed a correlation of 0.629 for crossover studies and a correlation of 0.3 for multiple dependent effects.
The findings of the systematic review revealed that for rTMS, of the 4 included studies, only 2 measured and found clinical effects, while the other 2 measured and found no effects on cognitive functions. For tDCS, 12 of the 14 studies included in the systematic review stimulated the dlPFC with anodal tDCS, mostly over the left hemisphere (unilateral left, \( n = 6 \); bilateral anode left/cathode right, \( n = 2 \); bifrontal left and right, \( n = 3 \)), and 1 study applied bilateral cathodal tDCS over the left dlPFC (anode right/ cathode left), and 2 studies used unilateral anodal tDCS over the right IFC. Only 2 sham-controlled tDCS studies measured clinical outcomes and found that anodal tDCS over the left or right dlPFC improved ADHD inattention, but not impulsiveness/hyperactivity symptoms, immediately after tDCS and 1 week\(^{62,74}\) or 2 weeks later.\(^ {74}\) This could suggest that dlPFC stimulation can improve clinical inattention in ADHD, but this finding will need to be confirmed by future, larger studies.

Importantly, the rigorous meta-analysis of 12 tDCS studies applying 1 to 5 sessions of anodal tDCS of mostly left or bilateral/bifrontal dlPFC (with the exception of Soltaninejad and colleagues\(^ {43} \) and Breitling and colleagues\(^ {67} \)) showed only

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### Table 6: Results for sensitivity analysis of the meta-analyses of attention, inhibition and processing speed

| Included studies | Excluded studies | Studies | Effect sizes | Heterogeneity |
|------------------|-----------------|---------|--------------|---------------|
|                  |                 |         | Hedges' \( g \) | 95% CI         | \( p \) value | \( I^2 \) | \( p \) value |
| **Attention**    |                 |         |              |               |            |          |               |
| All              | None            | 12      | 0.18         | -0.19 to 0.45 | 0.20       | 75        | < 0.001      |
| Studies with crossover design | Allenby et al.\(^ {56} \); Breitling et al.\(^ {57} \); Soff et al.\(^ {52} \) | 9       | 0.17         | -0.17 to 0.50 | 0.32       | 82        | < 0.001      |
| Patients with clinical ADHD diagnosis | Soltaninejad et al.\(^ {41} \); Soltaninejad et al.\(^ {51} \) | 10      | 0.16         | -0.16 to 0.48 | 0.33       | 78        | < 0.001      |
| No WCST and working memory tasks | Nejati et al.\(^ {52} \); Prehn-Kristensen et al.\(^ {51} \) | 11      | 0.14         | -0.04 to 0.32 | 0.13       | 39        | 0.12         |
| No overlapping samples\(^ {6} \) | Munz et al.\(^ {52} \); Soff et al.\(^ {52} \) | 10      | 0.16         | -0.16 to 0.49 | 0.32       | 80        | < 0.001      |
|                   | Munz et al.\(^ {52} \); Sotnikova et al.\(^ {53} \) | 10      | 0.22         | -0.08 to 0.53 | 0.15       | 74        | 0.002        |
|                   | Prehn-Kristensen et al.\(^ {51} \); Soff et al.\(^ {52} \) | 10      | 0.24         | -0.04 to 0.52 | 0.09       | 76        | < 0.001      |
|                   | Prehn-Kristensen et al.\(^ {51} \); Sotnikova et al.\(^ {53} \) | 10      | 0.29         | 0.05 to 0.54  | 0.020      | 62        | 0.010        |
| Only single-session tDCS | Allenby et al.\(^ {60} \); Munz et al.\(^ {52} \); Prehn-Kristensen et al.\(^ {51} \); Soff et al.\(^ {52} \) | 8       | 0.26         | -0.11 to 0.64 | 0.17       | 81        | < 0.001      |
| Report of post scores only | Cosmo et al.\(^ {66} ** \) | 11      | 0.20         | -0.10 to 0.50 | 0.19       | 78        | < 0.001      |
| Target site of dlPFC only | Breitling et al.\(^ {51} \); Soltaninejad et al.\(^ {43} \) | 10      | 0.10         | -0.19 to 0.39 | 0.51       | 76        | 0.001        |
| Only studies in children | Allenby et al.\(^ {50} \); Cosmo et al.\(^ {51} \); Jacoby et al.\(^ {42} \) | 9       | 0.24         | -0.16 to 0.63 | 0.24       | 80        | < 0.001      |
| **Inhibition**   |                 |         |              |               |            |          |               |
| All              | None            | 11      | 0.21         | -0.01 to 0.43 | 0.06       | 60        | 0.01         |
| Studies with crossover design | Breitling et al.\(^ {51} \); Cosmo et al.\(^ {50} \); Soff et al.\(^ {52} \) | 8       | 0.22         | -0.04 to 0.48 | 0.09       | 71        | 0.004        |
| Patients with clinical ADHD diagnosis | Soltaninejad et al.\(^ {51} \); Soltaninejad et al.\(^ {51} \) | 9       | 0.26         | -0.02 to 0.53 | 0.07       | 62        | 0.02         |
| No WCST and working memory tasks | Nejati et al.\(^ {52} \) | 11      | 0.17         | 0.00 to 0.35  | 0.06       | 41        | 0.09         |
| Only single-session tDCS | Allenby et al.\(^ {60} \); Munz et al.\(^ {52} \); Soff et al.\(^ {52} \) | 8       | 0.28         | 0.01 to 0.56  | 0.046      | 66        | 0.01         |
| Report of post scores only | Cosmo et al.\(^ {66} ** \) | 10      | 0.24         | 0.01 to 0.48  | 0.040      | 63        | 0.01         |
| Target site of dlPFC only | Breitling et al.\(^ {51} \); Soltaninejad et al.\(^ {43} \) | 9       | 0.24         | 0.01 to 0.47  | 0.040      | 56        | 0.02         |
| Studies in children only | Allenby et al.\(^ {50} \); Cosmo et al.\(^ {51} \); Jacoby et al.\(^ {42} \) | 8       | 0.26         | -0.08 to 0.60 | 0.13       | 72        | 0.004        |
| **Processing speed** |               |         |              |               |            |          |               |
| All              | None            | 8       | 0.14         | -0.01 to 0.29 | 0.07       | 3         | 0.50         |
| Patients with clinical ADHD diagnosis | Soltaninejad et al.\(^ {51} \); Soltaninejad et al.\(^ {51} \) | 6       | 0.16         | -0.02 to 0.34 | 0.09       | 13        | 0.40         |
| No WCST and working memory tasks | Nejati et al.\(^ {52} \) | 8       | 0.00         | -0.16 to 0.16 | 1.00       | 0         | 0.78         |
| Only single-session tDCS | Cosmo et al.\(^ {60} \); Munz et al.\(^ {50} \) | 6       | 0.22         | 0.04 to 0.41  | 0.020      | 0         | 0.51         |
| Target site of dlPFC | Soltaninejad et al.\(^ {41} \) | 7       | 0.17         | 0.01 to 0.33  | 0.040      | 5         | 0.50         |
| Studies in children | Allenby et al.\(^ {41} \); Jacoby et al.\(^ {42} \) | 6       | 0.20         | 0.01 to 0.39  | 0.040      | 9         | 0.41         |

ADHD = attention deficit/hyperactivity disorder; CI = confidence interval; dlPFC = dorsolateral prefrontal cortex; IFC = inferior frontal cortex; tDCS = transcranial direct current stimulation; WCST = Wisconsin Card Sorting Task.

*These studies used a parallel design; all others used crossover designs.
†Participants did not have a clinical diagnosis of ADHD.
‡Only WCST and working memory data excluded.
§To remove overlapping samples, we excluded 1 study at a time.
¶These studies applied tDCS over multiple sessions; all others used one session.
**The only studies to use change scores (post/pre stimulation scores), all other used post-tDCS scores.
††The only studies stimulated the right IFC; all other targeted the dlPFC.
‡‡Included adults; all others included children and adolescents.
trend-level improvements with small effect sizes in inhibition and processing speed, but no effects on attention.

This systematic review of tDCS and rTMS studies showed that there is very limited evidence that rTMS and tDCS can have an effect on clinical symptoms based on a small sample of 3 sham-controlled studies. The meta-analyses showed — albeit with small effect sizes — that 1 to 5 sessions of anodal tDCS over mostly the left (but also bilateral and bifrontal) dlPFC improved performance on cognitive measures of inhibition and processing speed, but there was no evidence for improvement in attention measures.

Given that 11 of 12 sham-controlled studies in the systematic review tested and found tDCS-induced improvement in 1 or more executive-function measures, it was the findings of the meta-analysis may seem disappointing. However, the lack of positive overall findings, despite positive findings in individual studies, was likely due to underpowered small study effects that were uncorrected for multiple testing and did not survive the scrutiny of meta-analysis. The decision to cluster cognitive outcome measures into domains for the meta-analysis introduced additional heterogeneity, particularly in the attention and inhibition domains; the processing speed domain was more homogeneous.

The relatively small trend-level effect on inhibition may have been related to the fact that predominantly the right hemispheric IFC mediates inhibitory functions in children and adults, and that meta-analyses of fMRI studies in ADHD show underactivation of the right IFC during inhibition tasks. Stimulation of the right IFC may be more effective for improving inhibitory functions in ADHD. This hypothesis is supported by studies in healthy adults showing that right IFC stimulation improves inhibitory performance.

The meta-analysis of Salehinejad and colleagues reported a similarly small, albeit significant, benefit (Hedges’ g = 0.12) with anodal tDCS of mostly the dlPFC on inhibitory measures, which survived when the analysis focused on accuracy measures or only on studies stimulating the dlPFC. However, Salehinejad and colleagues included multiple dependent effects in their meta-analyses, which could have reduced variation between effect sizes and therefore overestimated significance. Further, their meta-analysis included noninhibitory measures of attention (e.g., CPT omission errors), processing speed (e.g., reaction times to go trials) and reaction time variability, and therefore was not specific to inhibitory control, which could explain the differences in findings compared to our meta-analysis.

Although right IFC has been more clearly implicated in motor response inhibition, the small, trend-level improvement in inhibition in our meta-analyses, in line with the small significant effect of Salehinejad and colleagues, may have been due to the fact that a majority of inhibitory measures were derived from interference inhibition tasks, which have been shown to be co-mediated by the left dlPFC and IFC — in particular the Stroop task. Further, tDCS studies in healthy adults have reported improved performance on interference inhibition tasks following anodal tDCS of the left dlPFC. Given that only 2 studies stimulated the right IFC, future studies will have to test whether inhibition functions can be enhanced with anodal tDCS over the right IFC, which would be in line with neuroimaging evidence of a role of the right IFC in inhibitory control and evidence of its underactivation in ADHD, as well as with tDCS studies in healthy adults showing that right IFC stimulation improves motor inhibitory performance.

The trend-level positive effect of tDCS of mostly the left dlPFC on processing speed is in line with fMRI evidence indicating that the left dlPFC is a key mediating region of processing speed. Interestingly, when the processing speed analysis excluded the only study stimulating the right IFC — and therefore included only studies stimulating mainly the left dlPFC (unilateral left, n = 5; bilateral, n = 1; bifrontal anodal left and right, n = 2) — the improvement in processing speed became significant, in line with neuroimaging evidence that the left dlPFC mediates processing speed and suggesting that the left dlPFC is an optimal site for enhancing processing speed in ADHD. These findings are partly in line with those of the meta-analysis by Salehinejad and colleagues, which showed that predominantly anodal tDCS over the left dlPFC improved reaction times and its intra-subject variability in n-back tasks.

The lack of systematic positive effects on attention measures may have been because predominantly the right dlPFC and IFC mediate attention, as evidenced by individual studies and meta-analyses of fMRI studies in children and adults, and in meta-analyses of fMRI studies in ADHD, which show functional underactivation of the right dlPFC/IFC during attention tasks. It is therefore possible that stimulation of the right dlPFC and/or right IFC may be more effective for improving attention functions in ADHD.

This meta-analysis of tDCS studies shows that anodal tDCS of mostly left dlPFC has only very limited, trend-level effects on improving inhibition and processing speed, with no evidence for attention improvement. However, we cannot rule out the possibility that stimulation of other prefrontal regions (such as the right hemispheric IFC or dlPFC or parietal regions), multiple session tDCS or tDCS in combination with cognitive training could improve clinical or cognitive functions in ADHD.

With respect to safety, stimulation was well tolerated overall, but 1 tDCS study reported higher errors on a sustained attention task and another study reported a hypobulia episode in 1 patient, raising neuroethical concerns of potential costs to nontargeted functions. It has been shown that stimulation of a particular region could impair functions mediated by other regions such as the homologue contralateral region via interhemispheric inhibition or other regions that are top-down controlled by the stimulated region.

Future studies need to address the lack of knowledge about optimal stimulation protocols for children with ADHD. Current knowledge about stimulation effects on the brain and standard protocols are largely derived from adult samples and are therefore not appropriate for children. In healthy adults, multi-session stimulation combined with cognitive training may lead to longer-term effects, but we do not know whether this protocol can lead to maladaptive plasticity in the developing brain, especially during “sensitivity periods,” where use-dependent plasticity changes are strongest and
the possibility of longer-term side effects when using noninvasive brain stimulation in pediatric samples needs more empirical investigation. Future studies should heed recommendations to comprehensively assess effects in children to capture possible unintended outcomes.\textsuperscript{110,114}

It should also be noted that the current findings refer only to studies using 1 to 20 Hz rTMS and conventional tDCS of dLPFC in ADHD. Other noninvasive brain stimulation protocols may be effective in ADHD, such as theta burst stimulation,\textsuperscript{115} transcranial alternating current stimulation,\textsuperscript{116,117} transcranial random noise stimulation\textsuperscript{118,119} or trigeminal nerve stimulation (TNS).\textsuperscript{120,121}

**Limitations**

Conclusive evidence of this systematic review of rTMS and tDCS and meta-analysis of anodal tDCS in ADHD is limited by the large heterogeneity between studies with respect to stimulation protocols (coil/electrode placement, number of sessions, stimulation intensity, crossover/parallel design), sample age and cognitive outcome measures.

Furthermore, limitations in individual studies were also present, such as tDCS electrode placement, low power, small effect sizes, biased reporting or insufficient blinding. Specifically, although all but 2 of 12 tDCS studies included in the meta-analysis stimulated the left dLPFC, electrode placement was bilateral (anode left/cathode right) in 2 studies\textsuperscript{66,68} and bifrontal (anode left and right) in 3 studies.\textsuperscript{2,60,61} Bilateral or bifrontal tDCS could have had a neutral effect, given that the short inter-electrode distance causes greater current shunting across the scalp and cerebral spinal fluid, resulting in only an estimated 35% of current reaching the brain.\textsuperscript{122} In fact, it has been shown that bilateral electrode montage over the primary motor cortex can have neurologically neutral effects.\textsuperscript{123} With regards to low power, only 2 studies\textsuperscript{65,66} had more than 30 participants; the sample size across all other studies was relatively small, with an average of 14 participants (with an \( n \) range of 7 to 20). Key outcome measures in interference inhibition tasks such as the Stroop and flanker reaction time or error interference effects (incongruent – congruent reaction times/\( \text{errors} \)) were not reported; instead, reaction times to incongruent trials were used to measure cognitive effects, meaning that effects on interference inhibition measures were confounded by processing speed.\textsuperscript{64,67,68}

Blinding integrity was not reported in 2 studies,\textsuperscript{43,64} failed in 3 studies\textsuperscript{65,67,71} and was potentially compromised in 3 studies, where at least 60% of participants correctly identified the stimulation type.\textsuperscript{62,63,74} Thus, placebo effects cannot be excluded. The meta-analysis of tDCS studies was hampered by the fact that only a minority of included studies controlled for baseline differences by analyzing change scores (i.e., post-treatment minus baseline),\textsuperscript{62,65,66} while other studies analyzed only post-measurement scores to establish effects. Finally, the meta-regression analysis showed that studies with a high risk of “other” biases (e.g., no correction for multiple testing, selective reporting of outcome measures or using a lenient significance threshold)\textsuperscript{63,62-64,67,68} reported larger effect sizes than studies with low or unclear risk of this bias, meaning that summary effect size estimates might have been overestimated. In early rTMS studies, the same research practices unduly inflated positive effects and slowed its uptake as an effective treatment of depression;\textsuperscript{124,125} the field risks doing the same with rTMS and tDCS in ADHD. Moreover, with tDCS there is an added danger that children and parents — faced with apparent positive findings — will self-administer given the widely available “do-it-yourself tDCS” material online or commercial devices, one of which has been shown to impair working memory.\textsuperscript{40} Given the neuroethical concerns of brain stimulation with respect to potential negative effects on nontargeted functions,\textsuperscript{38,108,114} future researchers are duty-bound to report results to the highest possible standard.\textsuperscript{114}

A final limitation of this meta-analysis is that it was not preregistered.

**Conclusion**

Based on current evidence, neither rTMS nor tDCS of the dLPFC can be recommended as an alternative neurotherapy for ADHD as yet. More studies are needed to assess clinical efficacy, and the demonstrated cognitive effects have been small and nonsignificant. However, we cannot rule out the possibility that rTMS or tDCS or other stimulation modalities of other regions — or even of the same region but using a larger number of sessions, different amplitude or other parameters, or combined with cognitive training — may be more effective. Furthermore, conclusive evidence from this systematic review of rTMS and tDCS studies and meta-analysis of tDCS studies in ADHD was hampered by heterogeneity in stimulation protocols, sample age and cognitive outcome measures. Larger, double-blind, randomized controlled trials with homogeneous protocols testing systematically for more optimal designs (e.g., multi-session stimulation combined with cognitive training, targeting right dorsal and ventral frontal or inferior parietal regions),\textsuperscript{9,126} and testing both clinical and cognitive outcomes, are needed to provide better insights into clinical and cognitive effects, and to provide clear guidance on optimal stimulation protocols. Future studies should also be wary of overstating positive effects and account for possible cognitive costs of tDCS and rTMS in children.

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