Research Paper

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

Samuel J. Westwood, PhD; Joaquim Radua, PhD; Katya Rubia, PhD

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.[1] 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.[2]

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.[3,4]

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;[5,6] the right dorsolateral prefrontal cortex (dlPFC) and striatal and parietal regions during attention;[6] the bilateral superior prefrontal regions during working memory;[7] the inferior frontal, parietal and cerebellar regions during timing processes;[8] and the ventromedial frontostriatal areas during reward-related functions.[9]

The most effective short-term treatment for ADHD is with psychostimulant medications,[10] but they have side effects and limited longer-term efficacy.[11] Alternative treatments, including behavioural therapies, cognitive training, neurofeedback or dietary interventions, have shown limited efficacy.[12–14]

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.[9] They are also relatively safe, with minimal side effects; they are cheaper than long-term drug treatments or

Correspondence to: S.J. Westwood, Department of Child and Adolescent Psychiatry PO46, Social, Genetic and Developmental Psychiatry (SGDP) Centre, Institute of Psychiatry, Psychology and Neuroscience, King's College London, 16 De Crespigny Park, London, SE5 8AF, United Kingdom; samuel.westwood@kcl.ac.uk

Submitted Oct. 28, 2019; Revised Feb. 6, 2020; Accepted Feb. 29, 2020; Early-released Oct. 1, 2020

DOI: 10.1503/jpn.190179

fMRI neurofeedback, for example; and, more importantly, they can induce neuroplasticity,[15] providing hope for longer-term effects, which drugs do not offer.[9]

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 after-effects. In general, high-frequency rTMS (5 to 20 Hz) promotes cortical excitability, and low-frequency rTMS (1 Hz) inhibits cortical excitability.[15] 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;[16] 4 months in schizophrenia when stimulating temporoparietal regions;[17] and 12 months in major depressive disorder when stimulating the dlPFC,[18–20] supporting its neuroplastic potential. Relative to tDCS, rTMS has greater specificity in targeting neural regions,[21] but it is more expensive because of device costs and extensive user-training requirements.[22–24] The most common adverse effects are transient scalp discomfort underneath the coil as a result of stimulation of the pericranial muscles and peripheral nerves.[25,26]

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.[27] Although tDCS is a relatively new form of noninvasive brain stimulation, there is evidence that it can enhance cognitive functions in healthy controls,[28] with longer-term effects of up to 9 or 12 months.[29,30] In psychiatric disorders, positive clinical effects have been observed typically up to 1 month after stimulation (for reviews, see Moffa and colleagues,[31] Tortella and colleagues[32] and Kekic and colleagues),[33] 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.[34,35] 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.[36]

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.[20] 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.[9,37] 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 neuroethical concerns about potential costs to nontargeted functions.[38] Despite these shortcomings, however, noninvasive brain stimulation is already offered in private clinics in several countries and is available commercially and online.[39,40]

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).[41] However, effect size estimates may have been inflated, because 2 studies reporting mostly null effects were not included;[42,43] multiple dependent effects were clustered in the meta-analyses, unduly reducing variation between effect sizes and overestimating statistical significance;[44,45] 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[46] (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 > 65[47] or the Kiddie Schedule for Affective Disorders and Schizophrenia[48]). 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,"

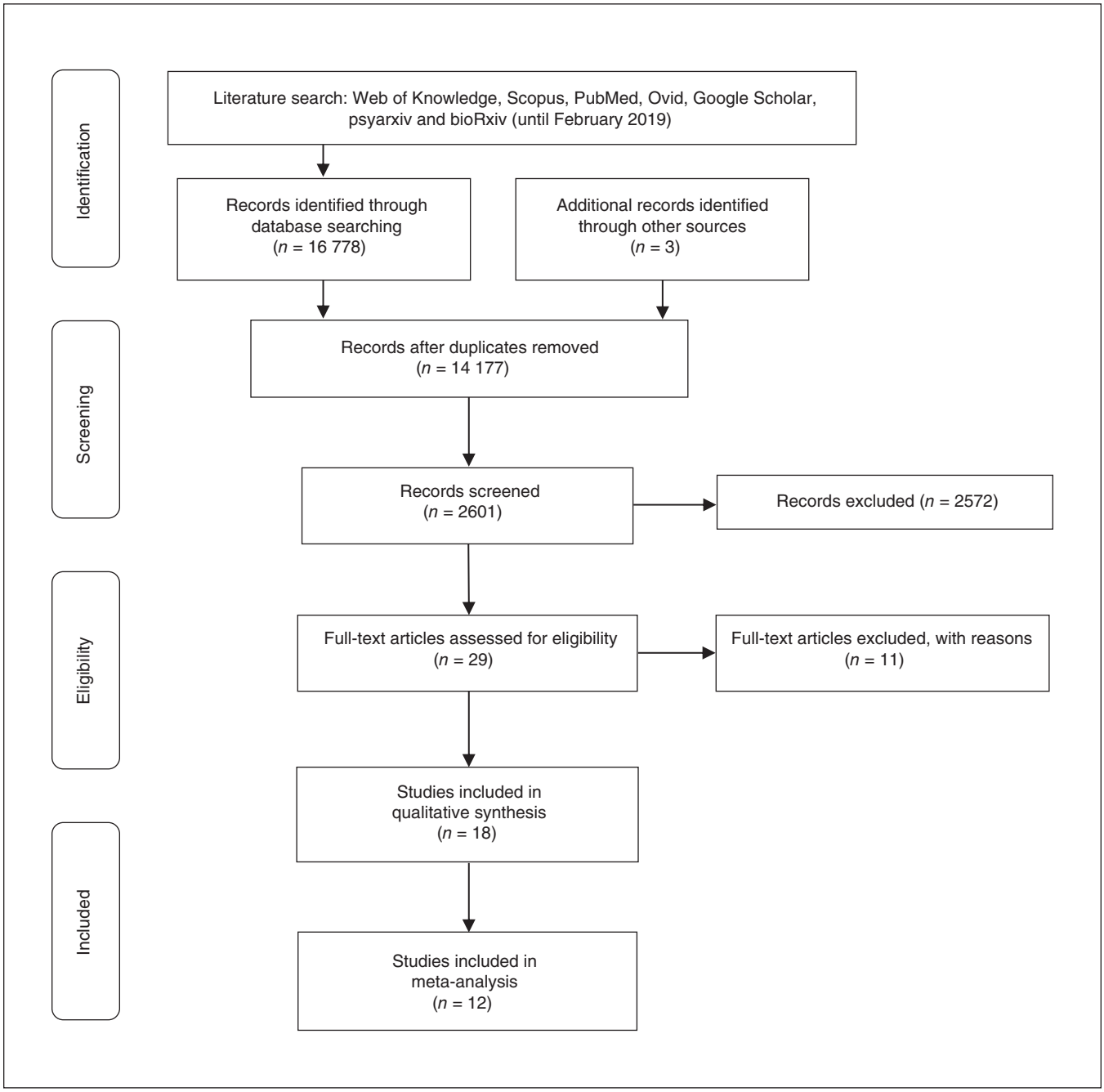

Fig. 1: Preferred Reporting Items in Systematic Reviews and Meta-Analyses (PRISMA) flow diagram of study selection.

"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 2572 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 authors[49] (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 trials[51,52] 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 Romani[35]), 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 I^2 value; I^2 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).[57] 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 tasks[54] 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;[43,64] those including adult samples with ADHD;[42,65,66] those targeting the right inferior frontal cortex (IFC);[43,67] 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).

tDCS studies in children with ADHD

Two single-blind, sham-controlled crossover studies in 20 high school students who scored above the clinical cut-off

Table 1: Clinical and cognitive effects of rTMS

Study	Design	*N*	Age, yr	Region	Stimulation protocol				Outcome measures	
					Sessions, *n*	Frequency, Hz	Intensity, % of MT	Duration	Clinical*	Cognitive
Bloch et al.[71]	Single-blind, sham-controlled, crossover	13	Adults (age not reported)	Right dlPFC†	1	20	100	1680 pulses (2 s on, 30 s off)	PANAS (inattention [+], total score [+]); VAS (inattention [+])‡	Not tested
Gomez et al.[52]	Open-label	10	7–12	Left dlPFC	5	1	90	1500 pulses (on/off not reported)	DSM-IV ADHD symptom checklist (parent-rated hyperactivity/impulsivity [+], teacher-rated inattention [+])	Not tested
Paz et al.[73]	Double-blind, sham-controlled, parallel	Active: 9 Sham: 13	Active: 32 Sham: 30	Bilateral dlPFC§	20	18	120	1980 pulses (2 s on, 20 s off)	CAARS	TOVA
Weaver et al.[72]	Single-blind, sham-controlled, crossover	9	18	Right dlPFC†	10	10	100	2000 pulses (4 s on, 26 s off)	CGI-I scale; ADHD-RS-IV scale	WASI/WISC-IV; Conners' CPT; D-KEFS; Buschke Selective Reminding Test; digit symbol coding test; finger oscillation tasks

ADHD = attention-deficit/hyperactivity disorder; ADHD-RS-IV = ADHD Rating Scale, Fourth Edition; CAARS = Conners' Adult ADHD Rating Scales; CGI-I = Clinical Global Impression–Improvement scale; CPT = continuous performance task; D-KEFS = Delis–Kaplan Executive Function System; dlPFC = dorsolateral prefrontal cortex; DSM-IV = *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition; MT = motor threshold; PANAS = Positive and Negative Affect Schedule; rTMS = repetitive transcranial magnetic stimulation; TOVA = Test of Variables of Attention; VAS = visual analogue scale; WASI = Wechsler Abbreviated Scale of Intelligence (selected subtests from the Wechsler Adult Intelligence Scale); WISC-IV = Wechsler Intelligence Scale for Children, Fourth Edition.
*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.

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

Study	Design	*N*	Mean age, yr	Stimulation protocol: Anode/ cathode	mA	Sessions, *n*	Timing*	Duration, min	Outcome measures: Clinical†	Cognitive†
Children										
Bandeira et al.[51]‡	Open-label	9	11	Left dlPFC/ right SOA	2	5	Online	28	PGI-I	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	1	1	Online	20	Not tested	Flanker task (incongruent trials: errors [+]¶,** and ICV [+]¶,††)
				Left cheek/ right IFC	1	1	Online	20	Not tested	Flanker task
Munz et al.[60]	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 [+] and intrasubject RTV [+]); motor memory task; alertness task
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; n-back (accuracy, RT [+]); Stroop task (incongruent trials: errors [+] and RT [+]); WCST (completion time [+])
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; n-back (accuracy [+],¶ RT [+]**); WCST (total categories completed [+], total errors [+], perseverative errors [+])**
				Right SOA/ left dlPFC	1	1	Offline	15	Not tested	Go/no-go task (no-go accuracy [+])**; n-back; WCST (total categories completed [+], total errors [+] and 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-ADHD (inattention [+])‡‡,§§,¶¶	QbTest (inattention [+]††; hyperactivity [+]***)§§,¶¶
Soltaninejad et al.[64]	Single-blind, sham-controlled, crossover	20	16	Left dlPFC/ right SOA	1.5	1	Online	15	Not tested	Go/no-go task (go accuracy [+])¶,**; Stroop task
				Right SOA/ left dlPFC	1.5	1	Online	15	Not tested	Go/no-go task (no-go accuracy [+])¶,†††; Stroop task
Soltaninejad et al.[43]§	Single-blind, sham-controlled, crossover	20	16	Right IFC/ left SOA	1	1	Online	15	Not tested	Go/no-go task (go accuracy [+]); Stroop task
Sotnikova et al.[63]	Double-blind, sham-controlled, crossover	13	14	Left dlPFC/ vertex	1	1	Online	20	Not tested	QbTest (RT [+], RTV [+],‡‡‡ omission errors [–], accuracy [–])§§§

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

Study	Design	*N*	Mean age, yr	Stimulation protocol					Outcome measures	
				Anode/ cathode	mA	Sessions, *n*	Timing*	Duration, min	Clinical†	Cognitive†
Adults										
Allenby et al.[65‡]	Double-blind, sham-controlled, crossover	37	32	Left dlPFC/ right SOA	2	3	Online	20	Not tested	Conners' CPT (commission errors [+]¶¶¶); stop task
Cachoeira et al.[74]	Double-blind, sham-controlled, parallel	Active: 9 Sham: 8	Active: 31 Sham: 34	Right dlPFC/ left dlPFC	2	5	Offline	20	ADHD checklist (inattention [+], total [+])****; SDS (after tDCS only [+])	Not tested
Cosmo et al.[66]	Double-blind, sham-controlled, parallel	Active: 30 Sham: 30	Active: 32 Sham: 33	Left dlPFC/ right dlPFC	1	1	Offline	20	Not tested	Go/no-go task
Jacoby et al.[42]	Single-blind, sham-controlled, crossover	20	23	Left and right dlPFC/ cerebellum	1.8	1	Offline	20	Not tested	CPT (multi-button presses [+])

ADHD = attention deficit/hyperactivity disorder; CPT = continuous performance task; dlPFC = 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; PGI-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.

‡Combined stimulation with cognitive training.

§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 and 7 days later.

†††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.

****Inattention improved immediately after anodal tDCS and after 2 weeks; total score improved only after 2 weeks.

for ADHD on validated ADHD questionnaires applied a single session of anodal tDCS over the left dlPFC[64] or the right IFC.[43] Anodal relative to cathodal tDCS of the left dlPFC improved go accuracy, and cathodal tDCS improved no-go accuracy compared with anodal tDCS and sham treatment, but none improved performance on the Stroop task.[64] Right IFC anodal tDCS relative to sham treatment improved go accuracy, but there were no equivalent improvements on any other go/no-go or Stroop task measures.[43]

Two double-blind, sham-controlled, crossover studies applied single-session stimulation over the dlPFC. In 15 adolescents with ADHD, tDCS over the bilateral dlPFC (anode left/cathode right) improved WCST completion time and n-back and Stroop reaction times and errors to incongruent trials, but had no effects on n-back accuracy or go/no-go measures. Furthermore, errors and reaction times to incongruent trials in the Stroop task were used as main outcome measures, rather than the Stroop interference or error effect (reaction time/errors on Stroop – reaction time/errors on congruent trials) — the established key outcome measure of the Stroop task. In 10 adolescents with ADHD, anodal tDCS of the left dlPFC improved n-back working memory accuracy and reaction times compared to both sham treatment and cathodal tDCS. Both anodal and cathodal tDCS over the left dlPFC improved WCST performance; anodal tDCS had stronger effects. Cathodal tDCS of the left dlPFC also improved no-go accuracy, presumably via interhemispheric inhibition increasing right prefrontal regions,[68] which have been associated with motor response inhibition in children and adults.[54,75] This explanation is partly supported by a single-blind crossover study in 21 adolescents with ADHD, which found that 1 session of anodal (but not cathodal) tDCS over the right IFC versus sham treatment reduced errors (trend level) and reaction time variability in a flanker task.[67] However, as in the previous paper,[68] findings were based on flanker incongruent trials rather than on flanker interference reaction time or error effect, and the analysis included only the first session to remove a practice effect, reducing the sample size to 7 participants per condition.

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)	Intraindividual 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
	Go/no-go task (go trials)	Intrasubject RTV (ms)	225.2 ± 246.9	379.4 ± 425.3	
	Go/no-go task (go trials)	No. omission errors	3.0 ± 3.0	4.3 ± 4.4	
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)	No. 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 (go trials)	% Correct	100 ± 0.0	98.5 ± 3.2	Composite
	N-back task (1-back)	No. 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 intrasubject 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.[43]	Go/no-go task (go trials)§	% Correct	—	—	Single
Sotnikova et al.[63]	QbTest (overall)	Intrasubject RTV (ms)	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 ± 68.1	
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)	No. commission errors	15.7 ± 10.3	12.6 ± 8.2	Single
Nejati et al.[68] (experiment 1)	Go/no-go task (no-go trials)	% correct	19.9 ± 7.6	19.0 ± 7.8	Composite
	Stroop task (incongruent trials)	RT (ms)	2870 ± 2210	1390 ± 440	
	Stroop task (incongruent trials)	% Errors	24.9 ± 12.0	34.9 ± 15.5	
	WCST	No. perseverative errors	17.6 ± 3.6	18.0 ± 9.0	
Nejati et al.[68] (experiment 2)	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	
Soff et al.[62]	QbTest (impulsivity)	z-scores (commission errors, multi-button press per stimulus, anticipatory button press)	0.2 ± 1.2	−0.2 ± 0.7	Single
Soltaninejad et al.[64]	Go/no-go task (no-go trials)	% Correct	96.2 ± 8.2	95.8 ± 6.9	Composite
	Stroop task (incongruent trials)	% Correct	98.3 ± 2.9	96.4 ± 3.6	
	Stroop task (incongruent trials)	RT (ms)	1080 ± 180	1130 ± 220	

Table 3: Cognitive task measures (mean ± SD) extracted from studies (part 2 of 2)

Study	Cognitive task	Cognitive outcome measure	tDCS, mean ± SD	Sham, mean ± SD	Effect*
Soltaninejad et al.[43]	Go/no-go task (no-go trials)§	% Correct	—	—	Composite
	Stroop task (incongruent trials)§	% Correct	—	—	
	Stroop task (incongruent trials)§	RT (ms)	—	—	
Sotnikova et al.[63]	QbTest (overall)	No. commission errors	6.0 ± 5.1	6.0 ± 4.2	Single
Measures of processing speed					
Allenby et al.[65]	CPT	RT (ms) to target	420.9 ± 63.3	419.7 ± 73.0	Single
Jacoby et al.[42]	MOXO task	RT (ms) to target	541.5 ± 50.8	547.0 ± 53.5	Composite
Munz et al.[60]	Alertness task	RT (ms)	309.6 ± 51.8	302.4 ± 44.3	Composite
	Go/no-go task (go trials)	RT (ms)	453.2 ± 131.3	566.9 ± 234.1	
Nejati et al.[68] (experiment 1)	Go/no-go task (go trials)	RT (ms)	1080 ± 210	1030 ± 170	Composite
	N-back task (1-back)	RT (ms)	120.2 ± 22.5	175.7 ± 55.4	
	WCST	Completion time (ms)	237 300 ± 79 800	291 100 ± 106 700	
Nejati et al.[68] (experiment 2)	Go/no-go task (go trials)	RT (ms)	1330 ± 900	1230 ± 120	Composite
	N-back task (1-back)	RT (ms)	103.4 ± 24.2	162.9 ± 94.4	
	WCST	Completion time (ms)	123 200 ± 16 900	170 300 ± 85 900	
Soltaninejad et al.[64]	Go/no-go task (go trials)	RT (ms)	830 ± 290	910 ± 350	Single
Soltaninejad et al.[43]	Go/no-go task (go trials)§	RT (ms)	—	—	Single
Sotnikova et al.[63]	QbTest (overall)	RT (ms)	555.3 ± 116.2	564.2 ± 130.8	Single

CPT = continuous performance task; QbTest = Quantitative Behaviour Test; RT = reaction time; RTV = reaction time variability; SD = standard deviation of the mean; Stroop = Stroop colour word task; WCST = Wisconsin Card Sorting Task.
*For multiple effects from the sample, we created composite effect-size estimates; single effects otherwise.
†Intrasubject reaction time variability divided by mean reaction time.
‡Only change scores (post – pre/baseline) were reported.
§The author could not provide raw means and standard deviations for each stimulation condition, so to calculate Hedges' *g* we converted the reported *t*-statistics.[57]
¶The % correct was reported as: hits (total no. of target trials – no. of omission errors errors) + correct rejections (total no. of no-go trials – no. of commissions errors)/total number of stimuli[63]

One double-blind, crossover study applied 5 daily sessions of anodal versus sham 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.[62] 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.[63]

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[61] and go reaction time and its intrasubject variability in 14 children with ADHD,[60] 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.[51]

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.[66] 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 not omission errors or reaction times.[42] 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.[65] 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[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 dlPFC, which persisted in a milder form the following day.[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.[63] Moreover, 7 sham-controlled studies did not correct for multiple comparisons,[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 dlPFC 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 (Hedge's 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,[66] Munz and colleagues[60] and Soltaninejad and colleagues[43]) and in processing speed (excluding Allenby and colleagues[65] and Soltaninejad and colleagues;[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

Table 4: Side effects and adverse effects reported in studies using rTMS and tDCS

Study	Side and adverse effects
rTMS studies	
Bloch et al.[71]	Not tested, but authors observed differences in the somatosensory experience of real rTMS and sham, which limited true blinding
Gomez et al.[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.[73]	Not tested
Weaver et al.[72]	Minority reported transient mild headaches and scalp discomfort
tDCS studies	
Allenby et al.[65]	Burning, itching, pain and tingling were rated significantly higher during anodal tDCS compared with sham
Bandeira et al.[51]	Majority reported mild to moderate headache, tingling, itching, 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.[67]	Skin sensations were rated higher during cathodal tDCS relative to sham
Cachoeira et al.[74]	Comparable reports of headache, tingling, itching, 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.[66]	None reported
Jacoby et al.[42]	Not tested, but authors reported that stimulation was well tolerated and no side effects were reported
Munz et al.[60]	Not tested, but no side effects were reported
Nejati et al.[68]	Reports of mild itching or tingling under electrodes
Prehn-Kristensen et al.[61]	Not tested. No side effects reported
Soff et al.[62]	About half of participants reported tingling and itching sensations under electrode during sham and anodal tDCS
Soltaninejad et al.[64]*	Not reported
Soltaninejad et al.[43]*	Several participants dropped out because of tingling sensation and headache
Sotnikova et al.[63]	About half of participants reported tingling and itching sensations under electrode during sham and anodal tDCS

rTMS = repetitive transcranial magnetic stimulation; tDCS = transcranial direct current stimulation.
*Personal communication, 2019.

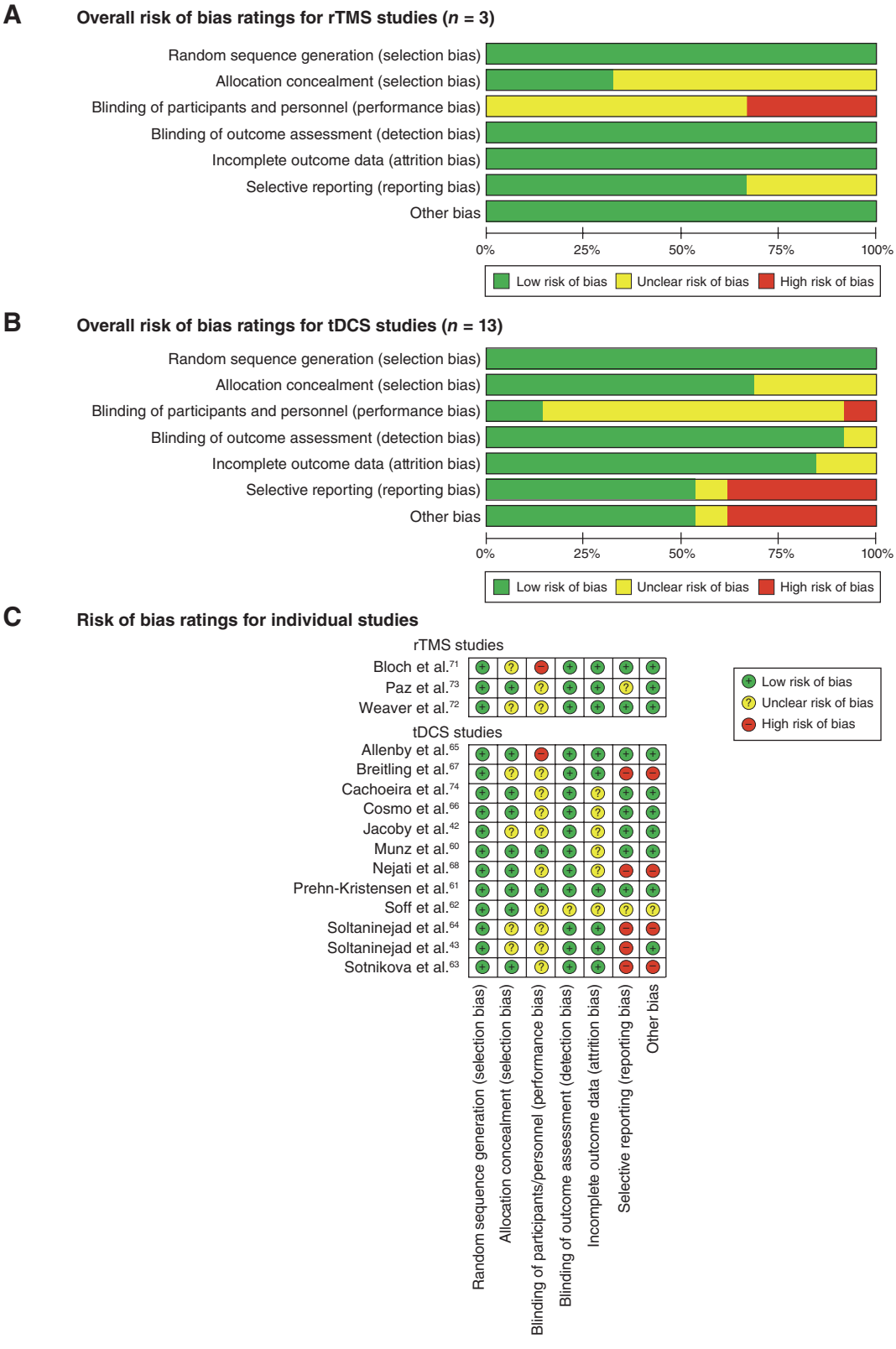

Fig. 2: Risk of bias ratings for (A) repetitive transcranial magnetic stimulation (rTMS), (B) transcranial direct current stimulation (tDCS) and (C) individual studies. Note: risk of bias ratings were the same for both studies reported in Nejati et al.[68]

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

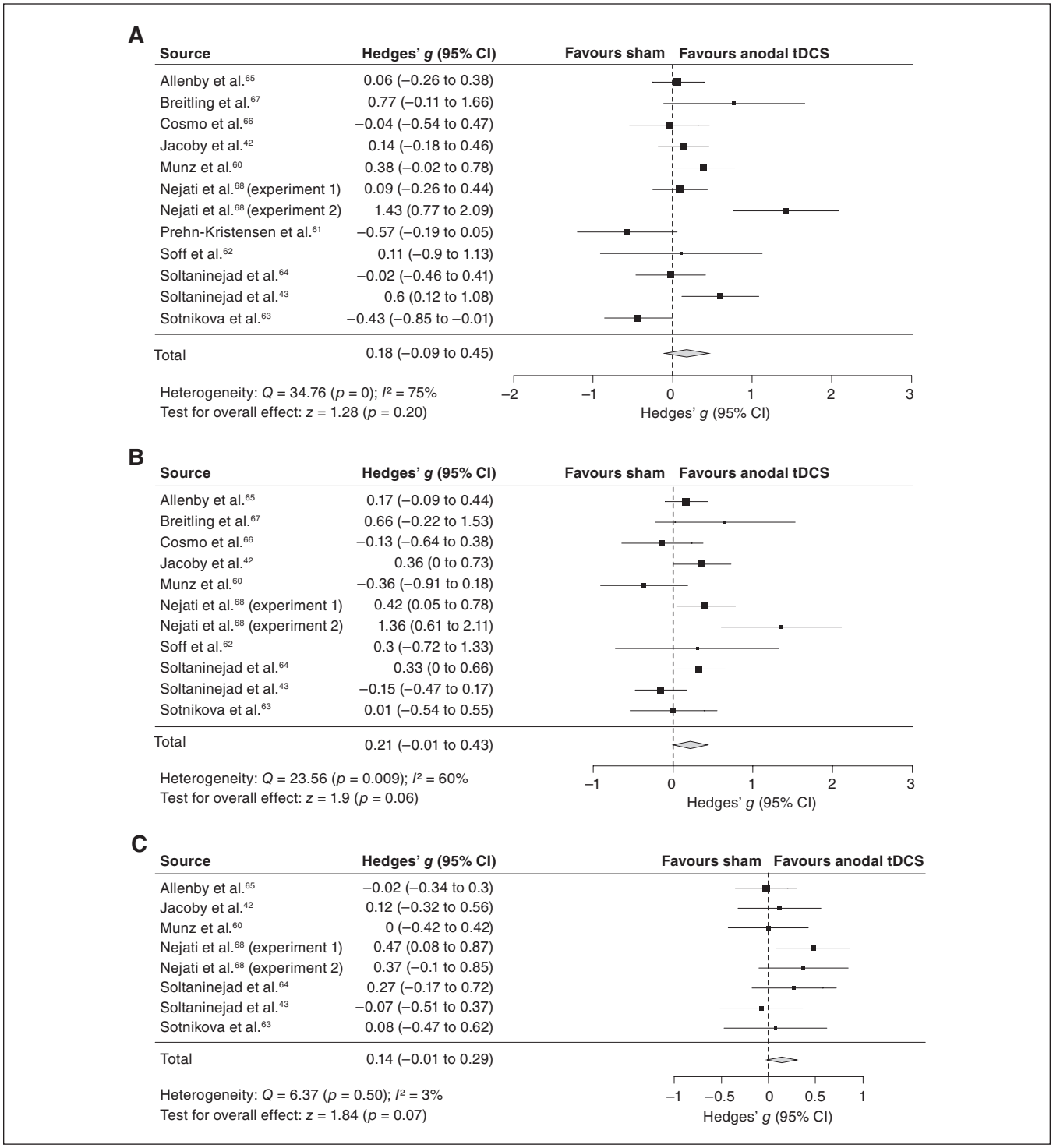

Fig. 3: Meta-analysis of measures of (A) attention, (B) inhibition and (C) processing speed. CI = confidence interval; tDCS = transcranial direct current stimulation.

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 α 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

		Effect size			Heterogeneity	
Meta-analysis	Studies excluded	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 0.49	0.24	77	< 0.001
	Munz et al.[60]	0.16	−0.14 to 0.46	0.30	77	< 0.001
	Nejati et al.[68] (experiment 1)	0.19	−0.12 to 0.50	0.22	77	< 0.001
	Nejati et al.[68] (experiment 2)	0.08	−0.12 to 0.27	0.43	49	0.040
	Prehn-Kristensen et al.[61]	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.[64]	0.20	−0.10 to 0.50	0.19	77	< 0.001
	Soltaninejad et al.[43]	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.[68] (experiment 1)	0.19	−0.06 to 0.43	0.13	63	0.010
	Nejati et al.[68] (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.[68] (experiment 1)	0.09	−0.08 to 0.25	0.29	0	0.79
	Nejati et al.[68] (experiment 2)	0.12	−0.04 to 0.28	0.15	2	0.50
	Soltaninejad et al.[64]	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.

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

			Effect sizes			Heterogeneity	
Included studies	Excluded studies	Studies	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.[65]; Breitling et al.[67]*; Soff et al.[62]	9	0.17	−0.17 to 0.50	0.32	82	< 0.001
Patients with clinical ADHD diagnosis	Soltaninejad et al.[43]; Soltaninejad et al.[64]†	10	0.16	−0.16 to 0.48	0.33	78	< 0.001
No WCST and working memory tasks	Nejati et al.[68]‡; Prehn-Kristensen et al.[61]	11	0.14	−0.04 to 0.32	0.13	39	0.12
No overlapping samples§	Munz et al.[60]; Soff et al.[62]	10	0.16	−0.16 to 0.49	0.32	80	< 0.001
	Munz et al.[60]; Sotnikova et al.[63]	10	0.22	−0.08 to 0.53	0.15	74	0.002
	Prehn-Kristensen et al.[61]; Soff et al.[62]	10	0.24	−0.04 to 0.52	0.09	76	< 0.001
	Prehn-Kristensen et al.[61]; Sotnikova et al.[63]	10	0.29	0.05 to 0.54	0.020	62	0.010
Only single-session tDCS	Allenby et al.[65]¶; Munz et al.[60]; Prehn-Kristensen et al.[61]; Soff et al.[62]	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.[67]††; Soltaninejad et al.[43]	10	0.10	−0.19 to 0.39	0.51	76	0.001
Only studies in children	Allenby et al.[65]; Cosmo et al.[66]‡‡; 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.[67]*; Cosmo et al.[66]; Soff et al.[62]	8	0.22	−0.04 to 0.48	0.09	71	0.004
Patients with clinical ADHD diagnosis	Soltaninejad et al.[43]; Soltaninejad et al.[64]†	9	0.26	−0.02 to 0.53	0.07	62	0.02
No WCST and working memory tasks	Nejati et al.[68]‡	11	0.17	0.00 to 0.35	0.06	41	0.09
Only single-session tDCS	Allenby et al.[65]¶; Munz et al.[60]; Soff et al.[62]	8	0.28	0.01 to 0.56	0.040	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.[67]††; Soltaninejad et al.[43]	9	0.24	0.01 to 0.47	0.040	56	0.02
Studies in children only	Allenby et al.[65]; Cosmo et al.[66]‡‡; 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.[43]; Soltaninejad et al.[64]†	6	0.16	−0.02 to 0.34	0.09	13	0.40
No WCST and working memory tasks	Nejati et al.[68]‡	8	0.00	−0.16 to 0.16	1.00	0	0.78
Only single-session tDCS	Cosmo et al.[66]¶; Munz et al.[60]	6	0.22	0.04 to 0.41	0.020	0	0.51
Target site of dlPFC	Soltaninejad et al.[43]††	7	0.17	0.01 to 0.33	0.040	5	0.50
Studies in children	Allenby et al.[65]‡‡; 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 sudies 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.

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

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,[42,43,60–65,67,68] 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[43,62–64,67,68] 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,[74,76–84] and that meta-analyses of fMRI studies in ADHD show underactivation of the right IFC during inhibition tasks.[5,6] 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.[85–88] The meta-analysis of Salehinejad and colleagues[41] 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[41] included multiple dependent effects in their meta-analyses, which could have reduced variation between effect sizes and therefore overestimated significance.[44,45] 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,[41] 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,[41] 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[89] — in particular the Stroop task.[90–93] Further, tDCS studies in healthy adults have reported improved performance on interference inhibition tasks following anodal tDCS of the left dlPFC.[94–97] 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[76,78,79,81,82,98–101] and evidence of its underactivation in ADHD,[5,6,9] as well as with tDCS studies in healthy adults showing that right IFC stimulation improves motor inhibitory performance.[85–88]

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.[102–104] Interestingly, when the processing speed analysis excluded the only study stimulating the right IFC[43] — 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,[41] which showed that predominantly anodal tDCS over the left dlPFC improved reaction times and its intrasubject 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,[77–79,84,105–107] and in meta-analyses of fMRI studies in ADHD, which show functional underactivation of the right dlPFC/IFC during attention tasks.[6] 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[63] and another study reported a hypobulia episode in 1 patient,[74] raising neuroethical concerns of potential costs to nontargeted functions.[38,108] 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.[109,110]

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.[108,111] In healthy adults, multi-session stimulation combined with cognitive training may lead to longer-term effects,[30,112] 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[113] 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.[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,[115] transcranial alternating current stimulation,[116,117] transcranial random noise stimulation[118,119] or trigeminal nerve stimulation (TNS).[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[66,68] and bifrontal (anode left and right) in 3 studies.[42,60,61] 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.[122] In fact, it has been shown that bilateral electrode montage over the primary motor cortex can have neurologically neutral effects.[123] With regards to low power, only 2 studies[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/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.[64,67,68] Blinding integrity was not reported in 2 studies,[43,64] failed in 3 studies[65,67,71] and was potentially compromised in 3 studies, where at least 60% of participants correctly identified the stimulation type;[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;[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[43,62–64,67,68]) 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;[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.[40] Given the neuroethical concerns of brain stimulation with respect to potential negative effects on nontargeted functions,[38,108,114] future researchers are duty-bound to report results to the highest possible standard.[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),[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.

Acknowledgements: The authors thank Sophie Wallace Hanlon (S.W.H.) for assisting S.J.W. with the literature search and study identification. We also thank Zahra Soltaninejad[43,64] for providing additional and original data from her study for the meta-analysis, and for translating her paper into English.

Affiliations: From the Department of Child & Adolescent Psychiatry, Institute of Psychiatry, Psychology & Neuroscience, King's College London, London, United Kingdom (Westwood, Rubia); the Institut d'Investigacions Biomèdiques August Pi i Sunyer, Barcelona, Spain (Radua); the Mental Health Research Networking Centre (CIBERSAM), Madrid, Spain (Radua); the Department of Clinical Neuroscience, Centre for Psychiatric Research and Education, Karolinska Institutet, Tomtebodavägen 18A, Stockholm, Sweden (Radua); and the Department of Psychosis Studies, Institute of Psychiatry, Psychology and Neuroscience, King's College London, De Crespigny Park, London, United Kingdom (Radua).

Competing interests: K. Rubia has received a grant from Shire pharmaceuticals (now Takeda) for another project not relevant to this work on the effects of guanfacine and lisdexamfetamine on fMRI brain function in ADHD. No other competing interests were declared.

Funding: S. Westwood is supported by Action Medical Research (GN2426), the Garfield Weston Foundation and the National Institute for Health Research (NIHR) Biomedical Research Centre at South London and the Maudsley NHS Foundation Trust and King's College London. K. Rubia receives research support from the Medical Research Council (MR/P012647/1) and the National Institute for Health Research (NIHR) Biomedical Research Centre at South London and the Maudsley NHS Foundation Trust and King's College London. The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health and Social Care. J. Radua is supported by Miguel Servet Research Contract MS14/00041 and CPII19/00009, and Research Projects PI14/00292 and PI19/00394 from the Plan Nacional de I+D+i 2013–2016 and and 2017–2020, the Instituto de Salud Carlos III-Subdirección General de Evaluación y Fomento de la Investigación and the European Regional Development Fund (FEDER).

Contributors: S. Westwood, J. Radua and K. Rubia designed the study. S. Westwood and K. Rubia acquired the data, which all authors analyzed. S. Westwood and K. Rubia wrote the article, which all authors reviewed. All authors approved the final version to be published and can certify that no other individuals not listed as authors have made substantial contributions to the paper.

Meeting presentations: An oral presentation of this systematic review and meta-analysis was given by S. Westwood at the European Network for Hyperkinetic Disorders (Eunethydis) International Conference, Edinburgh on Sept. 23, 2018, and at the 3rd International Brain Stimulation Conference, Vancouver, Canada, and the World Federation of ADHD (WFA) 2019. In 2019, the meta-analysis results were presented by K. Rubia at the WFA in Lisbon, at the Eunethydis conference in Nijmegen and with S. Westwood at the National Institute for Health Research Maudsley Biomedical Research Council Conference in London.

References

1. American Psychiatric Association. *Diagnostic and statistical manual of mental disorders*. American Psychiatric Association. 4th ed. Washington (DC); 2000.
2. Cazzoli D, Jung S, Nyffeler T, et al. The role of the right frontal eye field in overt visual attention deployment as assessed by free visual exploration. *Neuropsychologia* 2015;74:37-41.
3. Noreika V, Falter CM, Rubia K. Timing deficits in attention-deficit/hyperactivity disorder (ADHD): evidence from neurocognitive and neuroimaging studies. *Neuropsychologia* 2013;51:235-66.
4. Coghill D, Toplak M, Rhodes S, et al. Cognitive functioning in ADHD: inhibition, memory, temporal discounting, decision-making, timing and reaction time variability. In: Banaschewski T, Coghill D, Zuddas A, editors. *Oxford textbook of attention deficit hyperactivity disorder*. Oxford, United Kingdom: Oxford University Press; 2018: chapter 10.
5. Norman LJ, Carlisi C, Lukito S, et al. Structural and functional brain abnormalities in attention-deficit/hyperactivity disorder and obsessive-compulsive disorder: a comparative meta-analysis. *JAMA Psychiatry* 2016;73:815-25.
6. Hart H, Radua J, Nakao T, et al. Meta-analysis of functional magnetic resonance imaging studies of inhibition and attention in attention-deficit/hyperactivity disorder: exploring task-specific, stimulant medication, and age effects. *JAMA Psychiatry* 2013; 70:185-98.
7. McCarthy H, Skokauskas N, Frodl T. Identifying a consistent pattern of neural function in attention deficit hyperactivity disorder: a meta-analysis. *Psychol Med* 2014;44:869-80.
8. Hart H, Radua J, Mataix-Cols D, et al. Meta-analysis of fMRI studies of timing in attention-deficit hyperactivity disorder (ADHD). *Neurosci Biobehav Rev* 2012;36:2248-56.
9. Rubia K. Cognitive neuroscience of attention deficit hyperactivity disorder (ADHD) and its clinical translation. *Front Hum Neurosci* 2018;12:100.
10. Cortese S, Adamo N, Del Giovane C, et al. Comparative efficacy and tolerability of medications for attention-deficit hyperactivity disorder in children, adolescents, and adults: a systematic review and network meta-analysis. *Lancet Psychiatry* 2018;5:727-38.
11. Swanson JM, Arnold LE, Jensen PS, et al. Long-term outcomes in the Multimodal Treatment study of children with ADHD (the MTA): from beginning to end. In: Banaschewski T, Coghill D, Zuddas A, editors. *Oxford textbook of attention deficit hyperactivity disorder*. Oxford, United Kingdom: Oxford University Press; 2018: chapter 34.
12. Catala-Lopez F, Hutton B, Nunez-Beltran A, et al. The pharmacological and non-pharmacological treatment of attention deficit hyperactivity disorder in children and adolescents: a systematic review with network meta-analyses of randomised trials. *PLoS One* 2017;12:e0180355.
13. Sonuga-Barke EJ, Brandeis D, Cortese S, et al. Nonpharmacological interventions for ADHD: systematic review and meta-analyses of randomized controlled trials of dietary and psychological treatments. *Am J Psychiatry* 2013;170:275-89.
14. Cortese S, Ferrin M, Brandeis D, et al. Cognitive training for attention-deficit/hyperactivity disorder: meta-analysis of clinical and neuropsychological outcomes from randomized controlled trials. *J Am Acad Child Adolesc Psychiatry* 2015;54:164-74.
15. Dayan E, Censor N, Buch ER, et al. Noninvasive brain stimulation: from physiology to network dynamics and back. *Nat Neurosci* 2013;16:838-44.
16. Cocchi L, Zalesky A, Nott Z, et al. Transcranial magnetic stimulation in obsessive-compulsive disorder: a focus on network mechanisms and state dependence. *Neuroimage Clin* 2018;19:661-74.
17. Cole JC, Green Bernacki C, Helmer A, et al. Efficacy of transcranial magnetic stimulation (TMS) in the treatment of schizophrenia: a review of the literature to date. *Innov Clin Neurosci* 2015;12:12-9.
18. Perera T, George MS, Grammer G, et al. The Clinical TMS Society consensus review and treatment recommendations for TMS therapy for major depressive disorder. *Brain Stimul* 2016;9:336-46.
19. Janicak PG, Dokucu ME. Transcranial magnetic stimulation for the treatment of major depression. *Neuropsychiatr Dis Treat* 2015; 11:1549-60.
20. Demirtas-Tatlidede A, Vahabzadeh-Hagh AM, Pascual-Leone A. Can noninvasive brain stimulation enhance cognition in neuropsychiatric disorders? *Neuropharmacology* 2013;64:566-78.
21. Parkin BL, Ekhtiari H, Walsh VF. Non-invasive human brain stimulation in cognitive neuroscience: a primer. *Neuron* 2015;87:932-45.
22. Sauvaget A, Tostivint A, Etcheverrigaray F, et al. Hospital production cost of transcranial direct current stimulation (tDCS) in the treatment of depression. *Neurophysiol Clin* 2019;49:11-8.
23. Etcheverrigaray F, Bulteau S, Machon LO, et al. [Hospital production cost of repetitive transcranial magnetic stimulation (rTMS) in the treatment of depression]. *Rev Epidemiol Sante Publique* 2015;63: 268-74.
24. Zaghi S, Heine N, Fregni F. Brain stimulation for the treatment of pain: a review of costs, clinical effects, and mechanisms of treatment for three different central neuromodulatory approaches. *J Pain Manag* 2009;2:339-52.

25. Meteyard L, Holmes NP. TMS SMART—scalp mapping of annoyance ratings and twitches caused by transcranial magnetic stimulation. *J Neurosci Methods* 2018;299:34-44.
26. Rossi S, Hallett M, Rossini PM, et al. Safety of TMSCG. Safety, ethical considerations, and application guidelines for the use of transcranial magnetic stimulation in clinical practice and research. *Clin Neurophysiol* 2009;120:2008-39.
27. Ashkan K, Shotbolt P, David AS, et al. Deep brain stimulation: a return journey from psychiatry to neurology. *Postgrad Med J* 2013;89:323-8.
28. Dedoncker J, Brunoni AR, Baeken C, et al. A systematic review and meta-analysis of the effects of transcranial direct current stimulation (tDCS) over the dorsolateral prefrontal cortex in healthy and neuropsychiatric samples: influence of stimulation parameters. *Brain Stimul* 2016;9:501-17.
29. Ruf SP, Fallgatter AJ, Plewnia C. Augmentation of working memory training by transcranial direct current stimulation (tDCS). *Sci Rep* 2017;7:876.
30. Katz B, Au J, Buschkuehl M, et al. Individual differences and long-term consequences of tDCS-augmented cognitive training. *J Cogn Neurosci* 2017;29:1498-508.
31. Moffa AH, Brunoni AR, Nikolin S, et al. Transcranial direct current stimulation in psychiatric disorders: a comprehensive review. *Psychiatr Clin North Am* 2018;41:447-63.
32. Tortella G, Casati R, Aparicio LVM, et al. Transcranial direct current stimulation in psychiatric disorders. *World J Psychiatry* 2015; 5:88-102.
33. Kekic M, Boysen E, Campbell IC, et al. A systematic review of the clinical efficacy of transcranial direct current stimulation (tDCS) in psychiatric disorders. *J Psychiatr Res* 2016;74:70-86.
34. Horvath JC, Forte JD, Carter O. Quantitative review finds no evidence of cognitive effects in healthy populations from single-session transcranial direct current stimulation (tDCS). *Brain Stimul* 2015;8:535-50.
35. Westwood SJ, Romani C. Transcranial direct current stimulation (tDCS) modulation of picture naming and word reading: a meta-analysis of single session tDCS applied to healthy participants. *Neuropsychologia* 2017;104:234-49.
36. Krishnan C, Santos L, Peterson MD, et al. Safety of noninvasive brain stimulation in children and adolescents. *Brain Stimul* 2015;8:76-87.
37. Rubia K. ADHD brain function. In: Banaschewski T, Coghill D, Zuddas A, editors. *Oxford textbook of attention deficit hyperactivity disorder*. Oxford, United Kingdom: Oxford University Press; 2018: chapter 7.
38. Brem AK, Fried PJ, Horvath JC, et al. Is neuroenhancement by noninvasive brain stimulation a net zero-sum proposition? *Neuroimage* 2014;85:1058-68.
39. Fitz NS, Reiner PB. The Perils of using electrical stimulation to change human brains. In: Cohen Kadosh R, editor. *The stimulated brain*. San Diego (CA): Academic Press; 2014: 61-83.
40. Steenbergen L, Sellaro R, Hommel B, et al. "Unfocus" on foc.us: commercial tDCS headset impairs working memory. *Exp Brain Res* 2016;234:637-43.
41. Salehinejad MA, Wischnewski M, Nejati V, et al. Correction. Transcranial direct current stimulation in attention-deficit hyperactivity disorder: a meta-analysis of neuropsychological deficits. *PLoS One* 2019;14:e0221613.
42. Jacoby N, Lavidor M. Null tDCS effects in a sustained attention task: the modulating role of learning. *Front Psychol* 2018;9:476.
43. Soltaninejad Z, Nejati V, Ekhtiari H. Effect of transcranial direct current stimulation on remediation of inhibitory control on right inferior frontal gyrus in attention deficit and hyperactivity symptoms. *J Rehabil Med* 2015;3:1-9.
44. Becker BJ. Multivariate meta-analysis. In: *Handbook of applied multivariate statistics and mathematical modeling*. San Diego (CA): Academic Press; 2000: 499-525.
45. Lipsey MW, Wilson DB. *Practical meta-analysis*. Thousand Oaks, (CA): Sage Publications, Inc; 2001.
46. Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *J Clin Epidemiol* 2009;62:1006-12.
47. Conners CK, Pitkanen J, Rzepa SR. Conners, 3rd edition (Conners 3; Conners 2008). In: Kreutzer JS, DeLuca J, Caplan B, editors. *Encyclopedia of clinical neuropsychology*. New York: Springer New York; 2011: 675-678.
48. Kaufman J, Birmaher B, Brent D, et al. Schedule for affective disorders and schizophrenia for school-age children — present and lifetime version (K-SADS-PL): initial reliability and validity data. *J Am Acad Child Adolesc Psychiatry* 1997;36:980-8.
49. Bayoumy IM, Khaleel SH, Nada M, et al. Efficacy and attributes of repetitive transcranial magnetic stimulation (rTMS) in treatment of a sample of children with attention deficit hyperactivity disorder (ADHD). *Egypt J Neurol Psychiat Neurosurg* 2014;51:361-7.
50. Higgins JPT, Altman DG, Gøtzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ* 2011;343:d5928.
51. Bandeira ID, Guimaraes RS, Jagersbacher JG, et al. Transcranial direct current stimulation in children and adolescents with attention-deficit/hyperactivity disorder (ADHD): a pilot study. *J Child Neurol* 2016;31:918-24.
52. Gomez L, Vidal B, Morales L, et al. Low frequency repetitive transcranial magnetic stimulation in children with attention deficit/hyperactivity disorder: preliminary results. *Brain Stimul* 2014;7:760-2.
53. Kuntsi J, Wood AC, Rijsdijk F, et al. Separation of cognitive impairments in attention-deficit/hyperactivity disorder into 2 familial factors. *Arch Gen Psychiatry* 2010;67:1159-67.
54. Rubia K, Smith A, Taylor E. Performance of children with attention deficit hyperactivity disorder (ADHD) on a test battery of impulsiveness. *Child Neuropsychol* 2007;13:276-304.
55. Coghill DR, Seth S, Matthews K. A comprehensive assessment of memory, delay aversion, timing, inhibition, decision making and variability in attention deficit hyperactivity disorder: advancing beyond the three-pathway models. *Psychol Med* 2014;44:1989-2001.
56. Cheung CH, Rijsdijk F, McLoughlin G, et al. Cognitive and neurophysiological markers of ADHD persistence and remission. *Br J Psychiatry* 2016;208:548-55.
57. Lakens D. Calculating and reporting effect sizes to facilitate cumulative science: a practical primer for t-tests and ANOVAs. *Front Psychol* 2013;4:863.
58. Higgins JPT, Thompson SG, Spiegelhalter DJ. A re-evaluation of random-effects meta-analysis. *J R Stat Soc Ser A Stat Soc* 2009; 172:137-59.
59. Borenstein M, Higgins JPT, Hedges LV, et al. Basics of meta-analysis: I^2 is not an absolute measure of heterogeneity. *Res Synth Methods* 2017;8:5-18.
60. Munz MT, Prehn-Kristensen A, Thielking F, et al. Slow oscillating transcranial direct current stimulation during non-rapid eye movement sleep improves behavioral inhibition in attention-deficit/hyperactivity disorder. *Front Cell Neurosci* 2015;9:307.
61. Prehn-Kristensen A, Munz M, Goder R, et al. Transcranial oscillatory direct current stimulation during sleep improves declarative memory consolidation in children with attention-deficit/hyperactivity disorder to a level comparable to healthy controls. *Brain Stimul* 2014; 7:793-9.
62. Soff C, Sotnikova A, Christiansen H, et al. Transcranial direct current stimulation improves clinical symptoms in adolescents with attention deficit hyperactivity disorder. *J Neural Transm (Vienna)* 2017;124:133-44.
63. Sotnikova A, Soff C, Tagliazucchi E, et al. Transcranial direct current stimulation modulates neuronal networks in attention deficit hyperactivity disorder. *Brain Topogr* 2017;30:656-72.
64. Soltaninejad Z, Nejati V, Ekhtiari H. Effect of anodal and cathodal transcranial direct current stimulation on DLPFC on modulation of inhibitory control in ADHD. *J Atten Disord* 2019;23:325-32.
65. Allenby C, Falcone M, Bernardo L, et al. Transcranial direct current brain stimulation decreases impulsivity in ADHD. *Brain Stimul* 2018;11:974-81.

66. Cosmo C, Baptista AF, de Araujo AN, et al. A randomized, double-blind, sham- controlled trial of transcranial direct current stimulation in attention-deficit/hyperactivity disorder. *PLoS One* 2015; 10:e0135371.
67. Breitling C, Zaehle T, Dannhauer M, et al. Improving interference control in ADHD patients with transcranial direct current stimulation (tDCS). *Front Cell Neurosci* 2016;10:72.
68. Nejati V, Salehinejad MA, Nitsche MA, et al. Transcranial direct current stimulation improves executive dysfunctions in ADHD: implications for inhibitory control, interference control, working memory, and cognitive flexibility. *J Atten Disord* 2017; 1087054717730611.
69. Viechtbauer W. Conducting meta-analyses in R with the metafor package. *J Stat Softw* 2010;1:2010.
70. *RStudio: integrated development for R.* Version 3.6. Boston (MA): RStudio, Inc.; 2015.
71. Bloch Y, Harel EV, Aviram S, et al. Positive effects of repetitive transcranial magnetic stimulation on attention in ADHD subjects: a randomized controlled pilot study. *World J Biol Psychiatry* 2010; 11:755-8.
72. Weaver L, Rostain AL, Mac EW, et al. Transcranial magnetic stimulation (TMS) in the treatment of attention-deficit/hyperactivity disorder in adolescents and young adults: a pilot study. *J ECT* 2012;28:98-103.
73. Paz Y, Friedwald K, Levkovitz Y, et al. Randomised sham-controlled study of high-frequency bilateral deep transcranial magnetic stimulation (dTMS) to treat adult attention hyperactive disorder (ADHD): negative results. *World J Biol Psychiatry* 2018;19:561-6.
74. Cachoeira CT, Leffa DT, Mittelstadt SD, et al. Positive effects of transcranial direct current stimulation in adult patients with attention-deficit/hyperactivity disorder: a pilot randomized controlled study. *Psychiatry Res* 2017;247:28-32.
75. Rubia K, Smith AB, Brammer MJ, et al. Right inferior prefrontal cortex mediates response inhibition while mesial prefrontal cortex is responsible for error detection. *Neuroimage* 2003;20:351-8.
76. Rubia K, Lim L, Ecker C, et al. Effects of age and gender on neural networks of motor response inhibition: from adolescence to mid-adulthood. *Neuroimage* 2013;83:690-703.
77. Sebastian A, Jung P, Neuhoff J, et al. Dissociable attentional and inhibitory networks of dorsal and ventral areas of the right inferior frontal cortex: a combined task-specific and coordinate-based meta-analytic fMRI study. *Brain Struct Funct* 2016;221:1635-51.
78. Manly T, Owen AM, McAvinue L, et al. Enhancing the sensitivity of a sustained attention task to frontal damage: convergent clinical and functional imaging evidence. *Neurocase* 2003;9:340-9.
79. Smith AB, Halari R, Giampetro V, et al. Developmental effects of reward on sustained attention networks. *Neuroimage* 2011;56:1693-704.
80. Zhang R, Geng X, Lee TMC. Large-scale functional neural network correlates of response inhibition: an fMRI meta-analysis. *Brain Struct Funct* 2017;222:3973-90.
81. Rae CL, Hughes LE, Weaver C, et al. Selection and stopping in voluntary action: a meta-analysis and combined fMRI study. *Neuroimage* 2014;86:381-91.
82. Dambacher F, Sack AT, Lobbestael J, et al. A network approach to response inhibition: dissociating functional connectivity of neural components involved in action restraint and action cancellation. *Eur J Neurosci* 2014;39:821-31.
83. Criaud M, Boulinguez P. Have we been asking the right questions when assessing response inhibition in go/no-go tasks with fMRI? A meta-analysis and critical review. *Neurosci Biobehav Rev* 2013; 37:11-23.
84. Corbetta M, Patel G, Shulman GL. The reorienting system of the human brain: from environment to theory of mind. *Neuron* 2008;58:306-24.
85. Campanella S, Schroder E, Vanderhasselt MA, et al. Short-term impact of tDCS over the right inferior frontal cortex on impulsive responses in a go/no-go task. *Clin EEG Neurosci* 2018;49:398-406.
86. Cunillera T, Brignani D, Cucurell D, et al. The right inferior frontal cortex in response inhibition: a tDCS–ERP co-registration study. *Neuroimage* 2016;140:66-75.
87. Jacobson L, Javitt DC, Lavidor M. Activation of inhibition: diminishing impulsive behavior by direct current stimulation over the inferior frontal gyrus. *J Cogn Neurosci* 2011;23:3380-7.
88. Hogeveen J, Grafman J, Aboseria M, et al. Effects of high-definition and conventional tDCS on response inhibition. *Brain Stimul* 2016; 9:720-9.
89. Christakou A, Halari R, Smith AB, et al. Sex-dependent age modulation of frontostriatal and temporo-parietal activation during cognitive control. *Neuroimage* 2009;48:223-36.
90. van't Ent D, van Beijsterveldt CEM, Derks EM, et al. Neuroimaging of response interference in twins concordant or discordant for inattention and hyperactivity symptoms. *Neuroscience* 2009; 164:16-29.
91. Hwang S, White SF, Nolan ZT, et al. Executive attention control and emotional responding in attention-deficit/hyperactivity disorder: a functional MRI study. *Neuroimage Clin* 2015;9:545-54.
92. Chou T-L, Chia S, Shang C-Y, et al. Differential therapeutic effects of 12-week treatment of atomoxetine and methylphenidate on drug-naïve children with attention deficit/hyperactivity disorder: a counting Stroop functional MRI study. *Eur Neuropsychopharmacol* 2015;25:2300-10.
93. Peterson BS, Potenza MN, Wang Z, et al. An FMRI study of the effects of psychostimulants on default-mode processing during Stroop task performance in youths with ADHD. *Am J Psychiatry* 2009;166:1286-94.
94. Loftus AM, Yalcin O, Baughman FD, et al. The impact of transcranial direct current stimulation on inhibitory control in young adults. *Brain Behav* 2015;5:e00332.
95. Frings C, Brinkmann T, Friehs MA, et al. Single session tDCS over the left DLPFC disrupts interference processing. *Brain Cogn* 2018;120:1-7.
96. Jeon SY, Han SJ. Improvement of the working memory and naming by transcranial direct current stimulation. *Ann Rehabil Med* 2012;36:585-95.
97. Baumert A, Buchholz N, Zinkernagel A, et al. Causal underpinnings of working memory and Stroop interference control: testing the effects of anodal and cathodal tDCS over the left DLPFC. *Cogn Affect Behav Neurosci* 2020;20:34-48.
98. Dambacher F, Schuhmann T, Lobbestael J, et al. Reducing proactive aggression through non-invasive brain stimulation. *Soc Cogn Affect Neurosci* 2015;10:1303-9.
99. Dambacher F, Schuhmann T, Lobbestael J, et al. No effects of bilateral tDCS over inferior frontal gyrus on response inhibition and aggression. *PLoS One* 2015;10:e0132170.
100. Rubia K, Smith AB, Brammer MJ, et al. Right inferior prefrontal cortex mediates response inhibition while mesial prefrontal cortex is responsible for error detection. *Neuroimage* 2003;20:351-8.
101. Sebastian A, Jung P, Neuhoff J, et al. Dissociable attentional and inhibitory networks of dorsal and ventral areas of the right inferior frontal cortex: a combined task-specific and coordinate-based meta-analytic fMRI study. *Brain Struct Funct* 2016;221:1635-51.
102. Motes MA, Biswal BB, Rypma B. Age-dependent relationships between prefrontal cortex activation and processing efficiency. *Cogn Neurosci* 2011;2:1-10.
103. Motes MA, Yezhuvath US, Aslan S, et al. Higher-order cognitive training effects on processing speed–related neural activity: a randomized trial. *Neurobiol Aging* 2018;62:72-81.
104. Jacobs HI, Leritz EC, Williams VJ, et al. Association between white matter microstructure, executive functions, and processing speed in older adults: the impact of vascular health. *Hum Brain Mapp* 2013;34:77-95.
105. Lawrence NS, Ross TJ, Hoffmann R, et al. Multiple neuronal networks mediate sustained attention. *J Cogn Neurosci* 2003;15:1028-38.
106. Hampshire A, Chamberlain SR, Monti MM, et al. The role of the right inferior frontal gyrus: inhibition and attentional control. *Neuroimage* 2010;50:1313-9.

107. Langner R, Eickhoff SB. Sustaining attention to simple tasks: a meta-analytic review of the neural mechanisms of vigilant attention. *Psychol Bull* 2013;139:870-900.
108. Davis NJ. Transcranial stimulation of the developing brain: a plea for extreme caution. *Front Hum Neurosci* 2014;8:600.
109. Iuculano T, Cohen Kadosh R. The mental cost of cognitive enhancement. *J Neurosci* 2013;33:4482.
110. Cohen Kadosh R, Levy N, O'Shea J, et al. The neuroethics of noninvasive brain stimulation. *Curr Biol* 2012;22:R108-11.
111. Kessler SK, Minhas P, Woods AJ, et al. Dosage considerations for transcranial direct current stimulation in children: a computational modeling study. *PLoS One* 2013;8:e76112.
112. Berryhill ME. Longitudinal tDCS: Consistency across working memory training studies. *AIMS Neuroscience* 2017;4:71-86.
113. Knudsen EI. Sensitive periods in the development of the brain and behavior. *J Cogn Neurosci* 2004;16:1412-25.
114. Baldwin T, Cole J, Fitzgerald M, et al. *Novel neurotechnologies.* London: Nuffield Council on Bioethics; 2013.
115. Lowe CJ, Manocchio F, Safati AB, et al. The effects of theta burst stimulation (TBS) targeting the prefrontal cortex on executive functioning: a systematic review and meta-analysis. *Neuropsychologia* 2018;111:344-59.
116. Alexander ML, Alagapan S, Lugo CE, et al. Double-blind, randomized pilot clinical trial targeting alpha oscillations with transcranial alternating current stimulation (tACS) for the treatment of major depressive disorder (MDD). *Transl Psychiatry* 2019;9:106.
117. Iuculano T, Cohen Kadosh R. Preliminary evidence for performance enhancement following parietal lobe stimulation in developmental dyscalculia. *Front Hum Neurosci* 2014;8:38.
118. Mulquiney PG, Hoy KE, Daskalakis ZJ, et al. Improving working memory: exploring the effect of transcranial random noise stimulation and transcranial direct current stimulation on the dorsolateral prefrontal cortex. *Clin Neurophysiol* 2011;122:2384-9.
119. Terney D, Chaieb L, Moliadze V, et al. Increasing human brain excitability by transcranial high-frequency random noise stimulation. *J Neurosci* 2008;28:14147-55.
120. McGough JJ, Loo SK, Sturm A, et al. An eight-week, open-trial, pilot feasibility study of trigeminal nerve stimulation in youth with attention-deficit/hyperactivity disorder. *Brain Stimul* 2015;8:299-304.
121. McGough JJ, Sturm A, Cowen J, et al. Double-blind, sham-controlled, pilot study of trigeminal nerve stimulation for attention-deficit/hyperactivity disorder. *J Am Acad Child Adolesc Psychiatry* 2019;58:403-411.e3.
122. Faria P, Hallett M, Miranda PC. A finite element analysis of the effect of electrode area and inter-electrode distance on the spatial distribution of the current density in tDCS. *J Neural Eng* 2011;8:066017-066017.
123. Parkin BL, Bhandari M, Glen JC, et al. The physiological effects of transcranial electrical stimulation do not apply to parameters commonly used in studies of cognitive neuromodulation. *Neuropsychologia* 2019;128:332-9.
124. Walsh VQ. Ethics and social risks in brain stimulation. *Brain Stimul* 2013;6:715-7.
125. Amad A, Jardri R, Rousseau C, et al. Excess significance bias in repetitive transcranial magnetic stimulation literature for neuropsychiatric disorders. *Psychother Psychosom* 2019;88:363-70.
126. Sathappan AV, Luber BM, Lisanby SH. The dynamic duo: combining noninvasive brain stimulation with cognitive interventions. *Prog Neuropsychopharmacol Biol Psychiatry* 2019;89:347-60.