ORIGINAL RESEARCH

Cognitive effects and acceptability of non-invasive brain stimulation on Alzheimer's disease and mild cognitive impairment: a component network meta-analysis

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ABSTRACT

Objectives To compare cognitive effects and acceptability of repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS) in patients with Alzheimer's disease (AD) or mild cognitive impairment (MCI), and to determine whether cognitive training (CT) during rTMS or tDCS provides additional benefits.

Methods Electronic search of PubMed, Medline, Embase, the Cochrane Library and PsycINFO up to 5 March 2020. We enrolled double-blind, randomised controlled trials (RCTs). The primary outcomes were acceptability and pre–post treatment changes in general cognition measured by Mini-Mental State Examination, and the secondary outcomes were memory function, verbal fluency, working memory and executive function. Durability of cognitive benefits (1, 2 and ≥3 months) after brain stimulation was examined.

Results We included 27 RCTs (n=1070), and the treatment components included high-frequency rTMS (HFrTMS) and low-frequency rTMS, anodal tDCS (atDCS) and cathodal tDCS (ctDCS), CT, sham CT and sham brain stimulation. Risk of bias of evidence in each domain was low (range: 0%–11.1%). HFrTMS (1.08, 9, 0.35–1.80) and atDCS (0.56, 0.03–1.09) had short-term positive effects on general cognition. CT might be associated with negative effects on general cognition (−0.79, −2.06 to 0.48) during rTMS or tDCS. At 1-month follow-up, HFrTMS (1.65, 0.77–2.54) and ctDCS (2.57, 0.20–4.95) exhibited larger therapeutic responses. Separate analysis of populations with pure AD and MCI revealed positive effects only in individuals with AD. rTMS and tDCS were well tolerated.

Conclusions HFrTMS is more effective than atDCS for improving global cognition, and patients with AD may have better responses to rTMS and tDCS than MCI.

INTRODUCTION

Alzheimer's disease (AD) and mild cognitive impairment (MCI) are substantial healthcare challenges in the 21st century.[1] The treatment of cognitive decline is key to managing AD and MCI[1]; however,

pharmacological interventions provide suboptimal benefits for AD and exhibit no effects on MCI, and curative or disease-modifying therapies are currently lacking.[1] Accumulating evidence suggests that non-invasive electrical brain stimulation (NIBS) may be effective alternative treatments.[2]

Repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS) are the two most widely investigated NIBS interventions.[2 3] rTMS is applied to the scalp using a coil, and uses strong but brief electromagnetic pulses to modify underlying brain activity. Usually, rTMS is considered excitatory when using high-frequency (HF) protocols (≥10 Hz) or intermittent theta-burst stimulation, and inhibitory when using low-frequency (LF) (≤1 Hz) protocols or continuous theta-burst stimulation.[4] In contrast, in tDCS, a low-intensity electric current (usually 1–2 mA) is injected into the brain through electrodes placed over the scalp. Electrons flow from the cathode to the anode, in the radial direction. The electric current does not generate action potentials per se, but facilitates or inhibits synaptic transmission; this is mediated by an increase or decrease in the frequency of action potentials in endogenous neuronal firing, usually induced by anodal or cathodal stimulation, respectively.[5] Although clinical protocols are highly variable, tDCS and rTMS are generally applied daily for 20–40 min, over a period of 2–5 weeks.[6] Both techniques have proven safety and tolerability, do not require sedation or anaesthesia, and have few contraindications.[6] Although rTMS presents a low risk of seizures, the risk can be almost mitigated by adherence to published protocols.[7] Clinical application of rTMS, including as a treatment for major depression, is more widespread compared with the use of tDCS.[8–10] Conversely, tDCS is cheaper than rTMS, is portable and is relatively easy to use, making home-use of tDCS possible.[11]

Although the mechanisms of action of NIBS techniques remain elusive, both seem to induce long-term potentiation and depotentiation-like phenomena via several molecular and cellular mechanisms, such

as induction of synaptic strengthening and neurogenesis.[12][13] Anodal tDCS (atDCS) and HFrTMS are considered 'excitatory' NIBS modalities, whereas cathodal tDCS (ctDCS) and LFrTMS are considered inhibitory. Both rTMS and tDCS could enhance brain activity in areas that are hypoactive, leading to changes in functional outcomes. Indeed, when targeting the dorsolateral prefrontal cortex (DLPFC), these techniques were shown to enhance working memory,[14] and, regarding cognitive enhancement, promising findings have been observed for both tDCS[15] and rTMS.[16]

Two recent pairwise meta-analyses of randomised controlled trials (RCTs) reported that rTMS improved global cognition in AD[17] and MCI.[18] Preliminary data on tDCS for MCI[5] and AD[19] have also been promising. Several studies have reported positive results on cognitive function when combining cognitive training (CT) with rTMS.[20][21] However, there is also evidence suggesting negative effects of tDCS plus CT on cognitive function.[22][23] To date, an in-depth comparison of the effects of direct rTMS and tDCS in RCTs, as well as the effects of CT during rTMS or tDCS interventions, is lacking.

In the current study, we used a systematic review and component network meta-analysis (NMA) approach to assess the cognitive effects and acceptability of different rTMS and tDCS modalities in patients with MCI or AD. We sought to investigate the effects of rTMS and tDCS on general cognitive function and specific cognitive domains; whether CT provides additional effects when combined with rTMS or tDCS; whether the treatment effects of rTMS and tDCS are sustained, and finally, whether some cognitive domains have late onset responses.

METHODS

This study protocol is registered in PROSPERO (CRD42018104591). We followed the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) extension statement for NMA.[24]

Search strategy

Two investigators (C-SC and C-SL) independently searched PubMed, Embase and the Cochrane Library from the inception of each through to 5 March 2020. Additional unpublished and ongoing trials were identified from ClinicalTrials.gov. When data were unavailable in the articles, we contacted the authors to request the unreported data. A search algorithm was developed and adapted for each database, with no restrictions on age, setting, sex, ethnicity, language or publication year. The full search strategy with search terms (online supplemental appendix 1) and PRISMA checklist (online supplemental appendix 2) are available in the online supplemental data.

Eligibility criteria

Double-blind RCTs that made comparisons with sham treatment in patients with MCI, probable AD or AD were included. The criteria for MCI and AD are compatible with international guidelines and are listed in online supplemental table S1. Trials with fewer than five treatment sessions were excluded, as they would not be considered a therapeutic course for any brain-stimulation modality.[25] LF was defined as ≤1 Hz, and HF was defined as ≥5 Hz.[26]

Data extraction

Two of the authors (P-TT and T-YC) extracted the data of included studies using a prespecified data extraction form. Duplicates were electronically removed, and only the most recent/complete report was included.

Primary and secondary outcomes

The primary outcomes were treatment efficacy for general cognitive function and acceptability. As most of the included studies used the Mini-Mental State Examination (MMSE) to examine general cognitive function, the treatment efficacy of global cognition was based on pre–post changes in MMSE scores. If different instruments were used to measure general cognitive function, the scores were converted to MMSE scores using suggested methods.[27] Acceptability referred to all-cause discontinuation, defined as premature discontinuation of treatment for any reason.

The secondary outcomes were pre–post changes in memory function, verbal fluency, working memory and executive function. In studies using several cognitive instruments to examine the same cognitive subdomain, we selected the most reliable instrument.[28] For trials with follow-up outcomes, long-lasting effects were examined at 1 month, 2 months and ≥3 months after the last session of NIBS.

Quality assessment

Two independent authors (T-CY and C-KT) assessed the methodological quality of the included trials using the revised Cochrane risk of bias (ROB V.2.0) tool.[29] In cases of discrepancy, a third investigator (C-SC) was consulted to obtain a consensus.

Statistical analysis

Several studies combined CT or sham CT (sham_CT) with NIBS interventions; such combination treatments can be considered a sum of two component parts. We employed an additive component NMA model for the data synthesis. A component NMA model is an extension of the standard NMA, which can analyse the relative efficacy of specific components or combinations of components. Therefore, the effect sizes of CT and sham_CT can be calculated when CT or sham_CT is combined with NIBS or sham brain stimulation (sham_BS). The current NMA had seven components: atDCS, CT, ctDCS, HFrTMS, LFrTMS, sham_BS and sham_CT.

Mean differences with 95% CIs were calculated for the primary outcomes, and standardised mean differences with 95% CIs for the secondary outcomes. For interpretation of effect sizes, we followed the rules of classifying $<|0.2|$ as very small, $|0.2|–|0.5|$ as small, $|0.5|–|0.8|$ as moderate and $>|0.8|$ as large.[30] We calculated the relative ranking probabilities of all treatments for the target primary and secondary outcomes.

The surface under the cumulative ranking curve (SUCRA) indicated the mean rank of each treatment relative to an imaginary intervention that was the best without uncertainty. A larger area under the curve indicated a higher rank of treatment benefit on cognitive effects.

Potential inconsistencies between direct and indirect evidence were examined by the node-splitting method and the design-by-treatment model. Publication bias was investigated using Egger's tests and comparison-adjusted funnel plots. Meta-regression analyses were conducted to examine potential effect modifiers, and the differences in effect sizes between AD and MCI were analysed. Finally, we assessed the efficacy of sham rTMS stimulation versus sham tDCS stimulation for the primary outcome as an additional proof of transitivity.

The NMA was performed using intention-to-treat analysis in R-Project (V.3.5.3, R Foundation). The p values for all

(A) Short-term effects
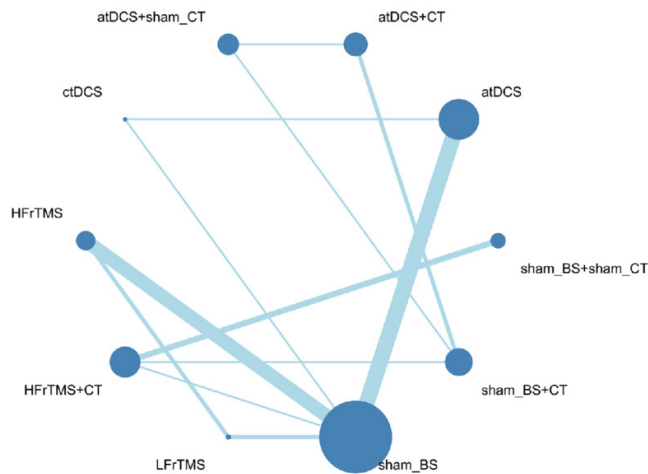
(B) Long-lasting effects after 1 month
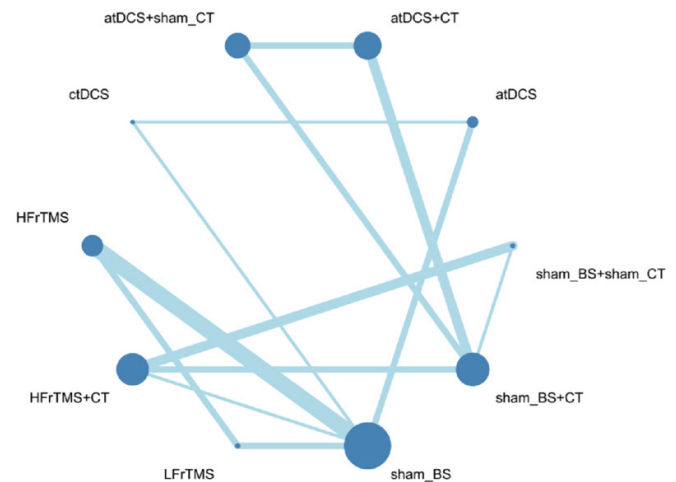
Figure 1 (A) Network of eligible comparisons for general cognition: short-term effects. (B) Network of eligible comparisons for general cognition: long-lasting effects after 1 month. atDCS, anodal transcranial direct current stimulation; ctDCS, cathodal transcranial direct current stimulation; HFrTMS, high-frequency repetitive transcranial magnetic stimulation; LFrTMS, low-frequency repetitive transcranial magnetic stimulation; sham_BS, sham brain stimulation; sham_CT, sham cognitive training.

comparisons were two-tailed, and a cut-off point of 0.05 was considered statistically significant.

RESULTS
Study characteristics
The study selection process is shown in online supplemental figure S1. These 27 RCTs were published between 2011 and 2019. For the 13 rTMS trials (n=436, AD=375, MCI=61), the mean age, percentage of women and MMSE score were 70.5±4.0 years, 53.1%±16.9% and 21.1±4.2, respectively. For the 14 tDCS trials (n=634, AD=250, MCI=384), the mean age, percentage of women and MMSE score were 73.3±5.0 years, 60.5%±14.5% and 21.7±4.3, respectively. The characteristics of the included studies are summarised in online supplemental table S1).

Network plots of eligible comparisons
Figure 1A illustrates the network of eligible comparisons for the short-term effects on general cognitive function. The recruited trials generated 10 nodes contributing to 12 pairs of comparisons. There were three sham treatments (sham_BS, sham_BS+CT and sham_BS+sham_CT), and sham_BS was used as the common comparator. No study directly compared rTMS with tDCS. The network plot of long-lasting effects of NIBS is illustrated in figure 1B. The supplementary data show the network plots for the secondary outcomes (online supplemental figure S2).

Primary outcomes
Short-term effects
Figure 2A shows the short-term effects of the 10 treatments on general cognitive function. The effect size for each treatment was compared with sham_BS, and the mean pre–post MMSE changes ranged from 1.08 (95% CI, 0.35 to 1.80) for HFrTMS to −1.57 (95% CI, −3.05 to −0.09) for sham_BS+sham_CT. Statistical significance was observed for HFrTMS, atDCS and sham_BS+sham_CT. Combining CT with HFrTMS and atDCS did not result in larger effect sizes than were observed when

using HFrTMS or atDCS alone. The mean pre–post MMSE changes of each component ranged from 1.08 (95% CI, 0.37 to 1.79) for HFrTMS to −1.13 for sham_CT (95% CI, −2.59 to 0.33), with statistical significance for HFrTMS and atDCS.

Long-lasting effects at 1-month follow-up
MMSE scores were increased with ctDCS, HFrTMS, HFrTMS+CT and atDCS compared with that with sham_BS, while changes for HFrTMS+CT and atDCS did not reach statistical significance (figure 2B). Both ctDCS and HFrTMS reached statistical significance and had larger effects at this time point. As observed for short-term effects, combining CT with HFrTMS and atDCS did not have larger effect sizes compared with those observed using HFrTMS or atDCS alone. Only ctDCS and HFrTMS significantly increased MMSE scores compared with those with sham_BS.

Comparison of pure AD and MCI groups
Online supplemental figure S3 illustrates the short-term pre–post MMSE changes in pure AD and MCI groups. Online supplemental appendix figure S4 depicts the long-lasting effects at 1-month follow-up. HFrTMS had both short-term (1.50, 0.61–2.40) and long-lasting (1.71, 0.86–2.56) positive effects on the population with AD. None of the treatments or components reached statistical significance in the population with MCI. Benefits of ctDCS were observed in the population with AD at 1-month follow-up.

Secondary outcomes

Memory function
HFrTMS was the only treatment and component that significantly improved memory function after the last rTMS session, with a moderate effect size (figure 3). However, this memory improvement did not persist after 1-month follow-up. atDCS was the only treatment and component that significantly impaired memory function at 1-month follow-up, with a large effect size.
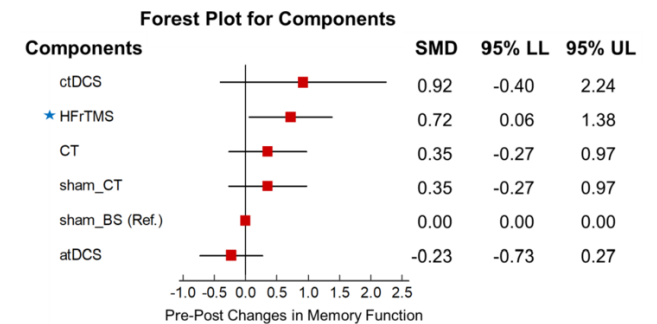
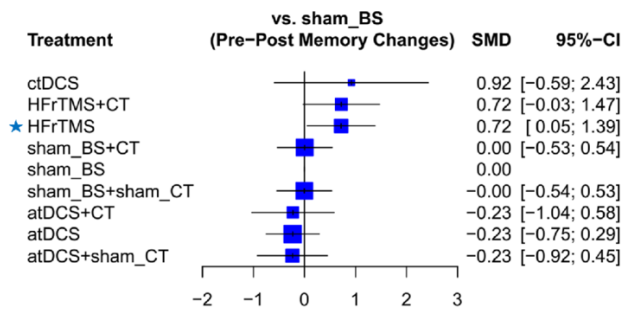## (A) Short-term effects
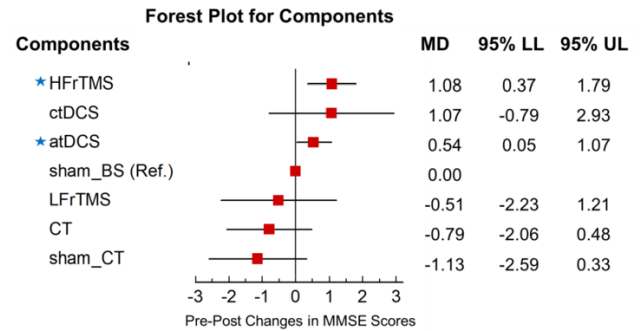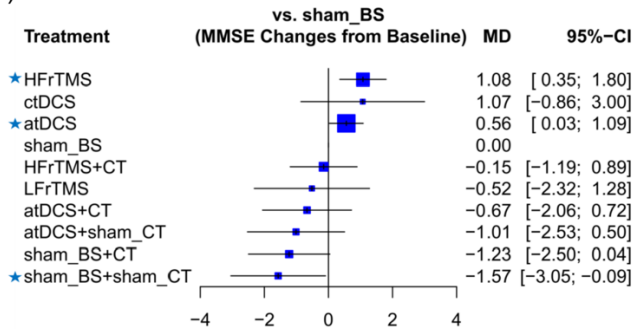
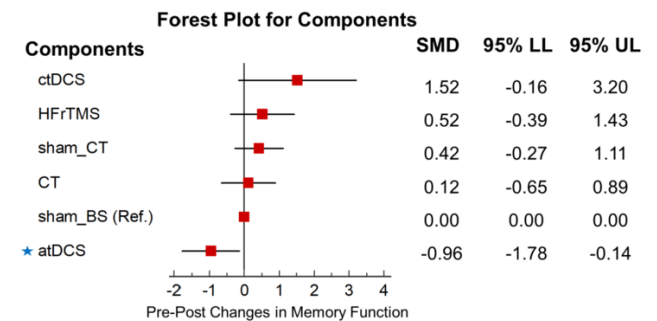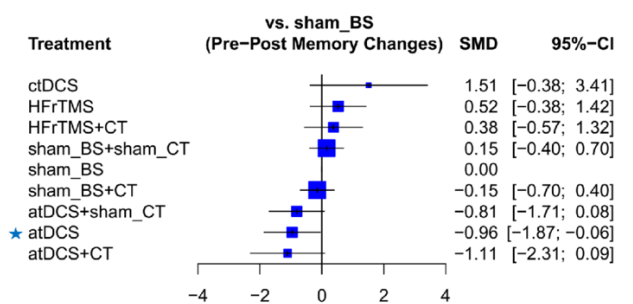## (B) Long-lasting effects after 1 month
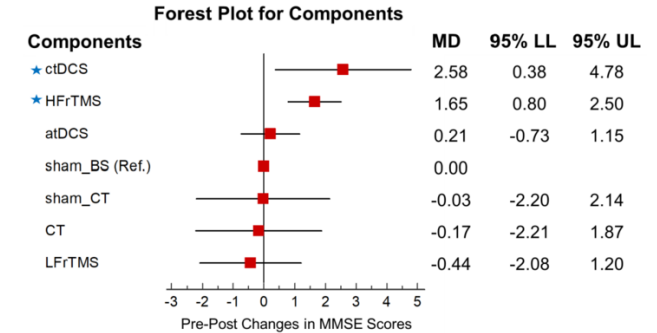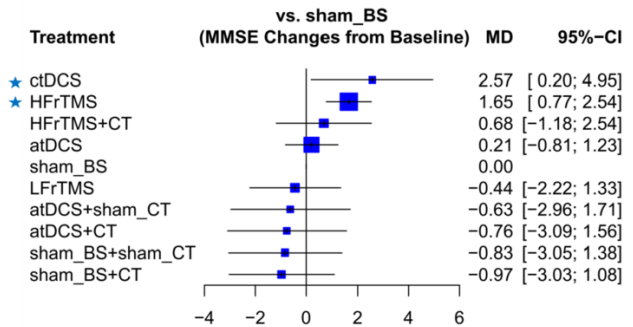
Figure 2 (A) Forest plot of NMA of changes of general cognition: short-term effects. (B) Forest plot of NMA of changes of general cognition: long-lasting effects after 1 month. atDCS, anodal transcranial direct current stimulation; BS, brain stimulation; CT, cognitive training; ctDCS, cathodal transcranial direct current stimulation; HFrTMS, high-frequency repetitive transcranial magnetic stimulation; LFrTMS, low-frequency repetitive transcranial magnetic stimulation; LL, lower limit; MD, mean difference; MMSE, Mini-Mental State Examination; NMA, network meta-analysis; UL, upper limit.
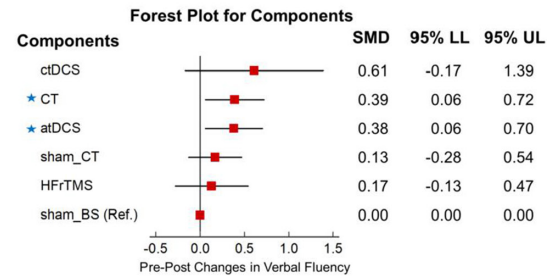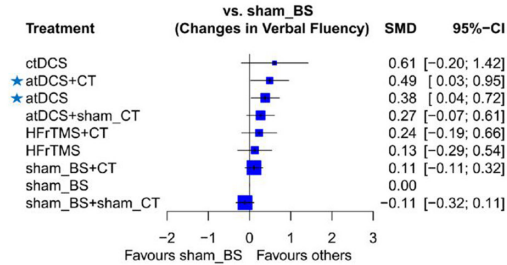
(A) Short-term effects

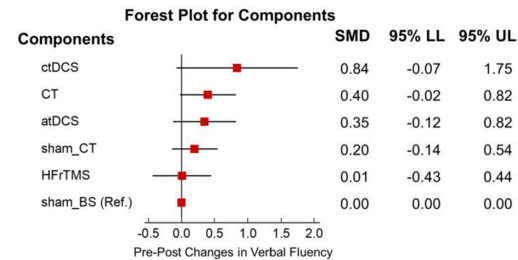## (B) Long-lasting effects after 1 month

Figure 3 (A) Forest plot of NMA of changes of memory function: short-term effects. (B) Forest plot of NMA of changes of memory function: long-lasting effects after 1 month. atDCS, anodal transcranial direct current stimulation; BS, brain stimulation; CT, cognitive training; ctDCS, cathodal transcranial direct current stimulation; HFrTMS, high-frequency repetitive transcranial magnetic stimulation; NMA, network meta-analysis; SMD, standardised mean difference.
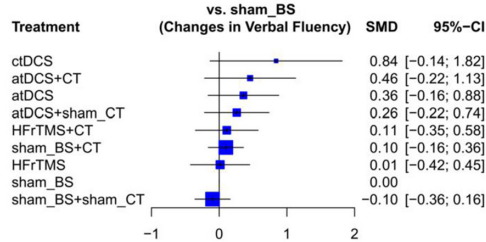
Figure 4 (A) Forest plot of NMA of changes of verbal fluency: short-term effects. (B) Forest plot of NMA of changes of verbal fluency: long-lasting effects after 1 month. atDCS, anodal transcranial direct current stimulation; BS, brain stimulation; CT, cognitive training; ctDCS, cathodal transcranial direct current stimulation; HFrTMS, high-frequency repetitive transcranial magnetic stimulation; LL, lower limit; NMA, network meta-analysis; SMD, standardised mean difference; UL, upper limit.

Combining CT with HFrTMS or atDCS did not significantly increase the effect sizes, and therefore did not provide additional effects.

Verbal fluency

Both atDCS and atDCS+CT were significantly associated with short-term improvement in verbal fluency, with small effect sizes (figure 4). Combining CT with atDCS had a larger effect size than atDCS alone, and therefore provided additional effects to atDCS on verbal fluency. Considering the effect size for each component relative to sham_BS, both CT and atDCS were significantly associated with beneficial effects on verbal fluency, with small effect sizes. However, at 1-month follow-up, the beneficial effects of atDCS and CT were not significant.

Working memory

Later responses on working memory were observed for both rTMS and tDCS, as none of the treatments resulted in significant short-term effects (figure 5). Three treatments (ctDCS, HFrTMS+CT and HFrTMS) showed statistically significant effects at 1-month follow-up. Combining CT with HFrTMS had a larger effect size than HFrTMS alone, and therefore CT provided additional effects to HFrTMS on working memory. ctDCS, CT and HFrTMS were significantly associated with beneficial effects on working memory, with moderate-to-large effect sizes, when compared with sham_BS.

Executive function

None of the treatments or components reached statistical significance for short-term or long-lasting effects on executive function (online supplemental figure S5).

Longer durable effects (2 months and ≥3 months)

Due to the limited number of trials that followed up participants for longer than 1 month after the last NIBS session, NMA was not conducted to examine longer durable effects. Online supplemental table S2 summarises the effect sizes of long-lasting effects for each study on the primary and secondary outcomes. The effect sizes for each study arm ranged from −0.47 for atDCS+sham_CT in general cognitive function to 1.72 for ctDCS in memory function.

SUCRA for short-term and long-lasting effects on outcomes

Figure 6 illustrates the SUCRA of each component's (a) short-term effects and (b) long-lasting effects at 1-month follow-up on the primary and secondary outcomes, with sham_BS as reference treatment.

For the short-term effects, HFrTMS was ranked as the best intervention for general cognitive function, and its effect size reached statistical significance. ctDCS was ranked as the best intervention for memory function, verbal fluency and working memory; however, this effect size did not reach statistical significance. CT was ranked as the best intervention for executive function, although its effect size did not reach statistical significance.

For the long-lasting effects at 1-month follow-up, ctDCS was ranked as the best intervention for all primary and secondary outcomes, although statistically significant effects were only observed for general cognitive function and working memory.

Acceptability, adverse events, and dropout

Both rTMS and tDCS were safe and well tolerated. Of the 27 studies, 8 reported no adverse events (AEs) on both active arm and sham arms, and 6 did not report any AEs during the study period. Headaches and scalp pain were the most common AEs in rTMS protocols. Scalp burning sensation and tingling were common in tDCS protocols. Detailed AEs of the 27 studies are summarised in the online supplemental table S3. The dropout rates were 5.1% (31/599) and 6.1% (29/471) in the intervention and sham treatment groups, respectively; this between-group difference was not significant ($\chi^2=0.48$, p=0.49).
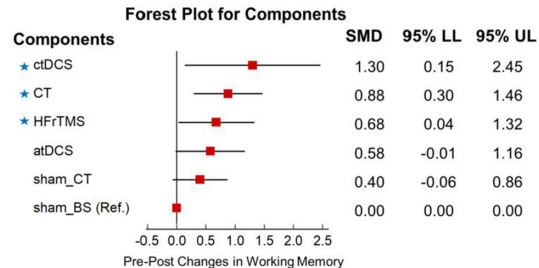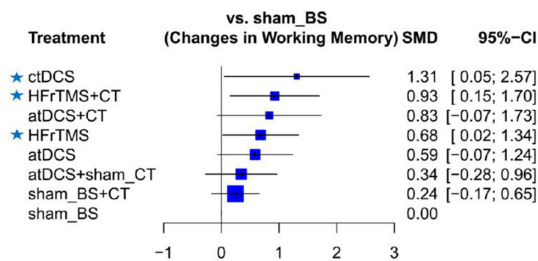
ROB, inconsistency, publication bias, and sensitivity analysis

Based on the Cochrane ROB criteria, six studies were judged as having a high ROB, with random sequence generation being the

A Short-term effects
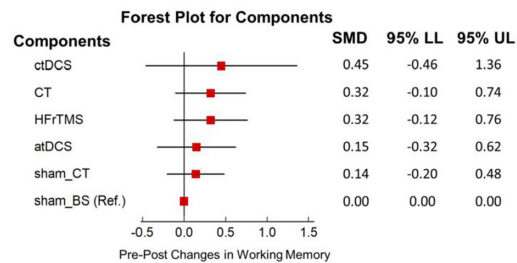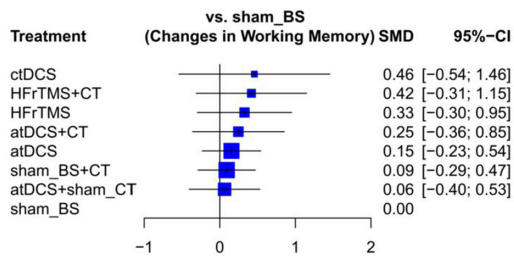

B Long-lasting effects after 1 month

Figure 5 (A) Forest plot of NMA of changes of working memory: short-term effects. (B) Forest plot of NMA of changes of working memory: long-lasting effects after 1 month. atDCS, anodal transcranial direct current stimulation; BS, brain stimulation; CT, cognitive training; ctDCS, cathodal transcranial direct current stimulation; HFrTMS, high-frequency repetitive transcranial magnetic stimulation; LL, lower limit; NMA, network meta-analysis; SMD, standardised mean difference; UL, upper limit.

most frequent (online supplemental table S4). The high ROB in each domain ranged from 0% to 11.1%.
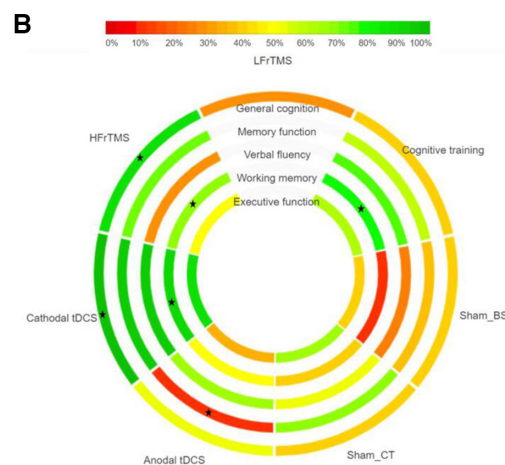
The design-by-treatment interaction model and node-splitting method did not detect any inconsistencies in the primary outcome (online supplemental table S5). Visual inspection of funnel plots and Egger's tests (online supplemental table S6) did not identify any risk of publication bias in the primary outcome.

Meta-regression analyses did not identify any potential effect modifiers (online supplemental tables S6 and S7). Finally, the pre–post changes in MMSE scores between sham rTMS and sham tDCS stimulation were not significant (online supplemental figure S7).
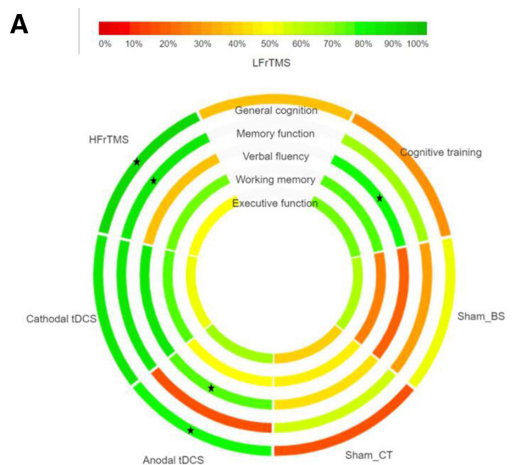
A	Anodal tDCS	Cognitive training	Cathodal tDCS	HFrTMS	LFrTMS	Sham BS	Sham CT
General cognition	79	30.2	85.13	93.67	40.23	53.53	18.3
Memory function	17.28	66.86	87.3	86.06		33.72	58.82
Verbal fluency	76.58	79.48	86.58	40.54		20.18	46.66
Working memory	50.48	76.96	77.12	72.18		26.04	47.26
Executive function	66.82	72.7	53.2	52.54		63.1	41.66

B	Anodal tDCS	Cognitive training	Cathodal tDCS	HFrTMS	LFrTMS	Sham BS	Sham CT
General cognition	54.07	41.25	96.97	90.12	30.97	43.38	43.28
Memory function	11.94	59.82	96.56	72.06		38.8	70.84
Verbal fluency	67.72	76.38	94.36	30.58		25.66	55.34
Working memory	51.18	81.02	92.84	69.16		12.46	43.38
Executive function	37.48	63.7	90.56	50.5		40.9	66.88

★ : reaching statistical significance on point estimate compared with sham_BS

BS, brain stimulation; CT, cognitive training; HF, high-frequency; LF, low-frequency; rTMS, repetitivetranscranial magnetic stimulation; tDCS, transcranial direct current stimulation; SUCRA, surface under the cumulative ranking curve.

Figure 6 NMA estimates and SUCRA values. BS, brain stimulation; CT, cognitive training; HFrTMS, high-frequency repetitive transcranial magnetic stimulation; LFrTMS, low-frequency repetitive transcranial magnetic stimulation; NMA, network meta-analysis; SUCRA, surface under the cumulative ranking curve; tDCS, transcranial direct current stimulation.

DISCUSSION

We found the following primary outcomes: (1) HFrTMS and atDCS had short-term positive effects on general cognitive function; (2) HFrTMS and ctDCS revealed late larger therapeutic responses on general cognitive function; (3) CT did not provide additional effects; (4) only populations with pure AD, but not populations with MCI, significantly responded to HFrTMS and ctDCS based on subgroup analysis; and (5) all NIBS treatments were well tolerated.

For the secondary outcomes, we observed that: (1) HFrTMS had short-term positive effects on memory function, which were absent at 1-month follow-up; (2) atDCS was associated with short-term positive effects on verbal fluency, and CT provided additional effects; and (3) benefits on working memory were only observed in ctDCS and HFrTMS, and CT provided additional effects to those of HFrTMS.

Our study is the first to demonstrate that HFrTMS may have better efficacy for general cognition than atDCS, which is consistent with the treatment effects on major depressive disorders.[9] Although the reasons underpinning the different effects of HFrTMS and atDCS on general cognitive function remain unclear, distinct pathophysiological mechanisms may indirectly influence our findings. Generally, HFrTMS stimulates gyri immediately under the coil at more localised areas, and directly triggers neuronal firing, whereas atDCS modulates resting neuronal membrane potential without neuronal firing, and stimulates less focal and more diffuse brain regions.[31] HFrTMS and atDCS also differ substantially in terms of the effective distribution of the electric field on the cortical surface. Relative to rTMS, tDCS is more strongly influenced by skull anatomical features, with up to 50% of the electric field strength affected. Furthermore, the temporal resolution and spatial focality of rTMS are more precise than that of tDCS.[2] Therefore, rTMS may have been more focal in the target areas, resulting in potentiation of local and distributed neuromodulatory effects.

The use of combined CT with NIBS is controversial, and evidence for an additional positive effect of CT in combination with NIBS on cognitive function remains insufficient. Previous meta-analyses have shown both positive[32 33] and no positive effects reported.[34 35] However, traditional meta-analyses or NMA did not specifically evaluate the cognitive effects of CT when combined with NIBS. The present study used component NMA, which enabled evaluation of each component's effect. We observed that combining NIBS and CT had no additional positive effects on global cognition; indeed, the outcomes seemed to be poorer. The interaction between NIBS and CT on global cognition may be influenced by the complexity of functional networks in the human brain, whereby the topology, synchronisability, and other dynamic properties of functional networks are strongly affected by small-worldness and other metrics of structural connectivity.[36] Patients with AD and MCI exhibit brain network dysfunction at both structural and functional levels; thus, the combination of NIBS and CT may not exert synergistically beneficial effects on global cognition. Other confounding factors may influence the protective effects of NIBS on cognition, such as heterogeneity of participants' characteristics, selection of targeted brain regions, and standard CT or tailored/individualised CT. Although we did not identify potential effect modifiers based on meta-regression analyses, it is well established that CT is more effective at the earliest stage of AD.

With regards to cognition subdomain, we detected additional effects of CT on working memory and verbal fluency when combined with HFrTMS and atDCS, respectively. These findings were mainly derived from studies of HFrTMS[37] and atDCS,[38] which both applied individualised and tailored CT, and may therefore direct modulation of cortical areas or promote residual brain plasticity mechanisms related to specific cognitive abilities. In addition, both studies selected the left DLPFC as the single target site, as clinical and experimental findings have uniformly indicated the critical role of the DLPFC in both 'cold' (eg, working memory, inhibition and shifting) and 'hot' (eg, motivational, emotional or reward-based) executive functions.[39] Based on our findings, stimulating a single brain area (left DLPFC) with adjunctive tailored CT may be an effective protocol for enhancing compensatory mechanisms for a specific subdomain of cognitive dysfunction in MCI or AD.

Several limitations of the study should be considered. First, the overall ROB was 22.2% in the included studies, although the ROB was unclear for random sequence generation and allocation concealment. Second, ctDCS showed efficacy for various outcomes, including immediate working memory, general cognition and working memory at 1-month follow-up. However, these findings were derived from a single study with small sample size (n=12).[40] Third, we combined AD with MCI as our study subjects, which may increase the statistical power and generalisability of our study findings. However, AD and MCI are distinct clinical stages of neurocognitive disorders, suggesting that these conditions may respond differently to treatment. Indeed, subgroup analysis of pure AD versus MCI subgroups revealed that only the population with AD responded positively to NIBS for general cognition. Finally, sham tDCS and sham rTMS were grouped based on the assumption that they would have similar placebo responses, despite the differences in the methods.

The present study is the first systematic review and NMA to investigate the effects of NIBS on cognition in individuals with AD or MCI, and to combine direct and indirect evidence to delineate the efficacy of head-to-head comparisons of rTMS versus tDCS with/without combining CT on cognitive functions. We also conducted component NMA to strengthen treatment evaluation and increase the precision for assessing component effects of complex interventions; thus, enhancing the utility of the results for clinical practice.

CONCLUSION

Our data suggest that HFrTMS is more effective than atDCS for improving global cognition, and patients with AD may have better responses to rTMS and tDCS than MCI. Combining CT with NIBS, particularly tailored CT and single stimulation site of left DLPFC, may be beneficial for specific cognitive subdomain. Sustained cognitive protective effects were observed at 1-month follow-up. Overall, NIBS is well tolerated.

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