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 (HrTMS) 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%). HrTMS (1.08, 9.0, 3.5–8.1) and ctDCS (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, HrTMS (1.65, 0.77–2.5) 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, tRMS and tDCS were well tolerated.

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

INTRODUCTION

Alzheimer’s disease (AD) and mild cognitive impairment (MCI) are substantial healthcare challenges in the 21st century. The treatment of cognitive decline is key to managing AD and MCI; however, pharmacological interventions provide suboptimal benefits for AD and exhibit no effects on MCI, and curative or disease-modifying therapies are currently lacking. Accumulating evidence suggests that non-invasive electrical brain stimulation (NIBS) may be effective alternative treatments.

Repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS) are the two most widely investigated NIBS interventions. 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. In contrast, 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. Although clinical protocols are highly variable, tDCS and rTMS are generally applied daily for 20–40 min, over a period of 2–5 weeks. Both techniques have proven safety and tolerability, do not require sedation or anaesthesia, and have few contraindications. Although tRMS presents a low risk of seizures, the risk can be almost mitigated by adherence to published protocols. Clinical application of rTMS, including as a treatment for major depression, is more widespread compared with the use of tDCS. Conversely, tDCS is cheaper than rTMS, is portable and is relatively easy to use, making home-use of tDCS possible.

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 hyperactive, 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 tDCS15 and rTMS.16

Two recent pairwise meta-analyses of randomised controlled trials (RCTs) reported that rTMS improved global cognition in AD2 and MCI.18 Preliminary data on tDCS for MCI1 and AD19 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 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 TYC) extracted the data of included studies using a prespecified data extraction form. Duplicates were electronically removed, and only the most recent/completed 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
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.
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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; HfTMS, high-frequency repetitive transcranial magnetic stimulation; LfTMS, low-frequency repetitive transcranial magnetic stimulation; LL, lower limit; MD, mean difference; MMSE, Mini-Mental State Examination; NMA, network meta-analysis; UL, upper limit.

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; HfTMS, high-frequency repetitive transcranial magnetic stimulation; NMA, network meta-analysis; SMD, standardised mean difference.
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
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 supple-
mental figure S7).

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; cdTMS, cathodal transcranial direct
current stimulation; HiFrTMS, high-frequency repetitive transcranial magnetic stimulation; LL, lower limit; NMA, network meta-analysis; SMD, standardised
mean difference; UL, upper limit.

Figure 6  NMA estimates and SUCRA values. BS, brain stimulation; CT, cognitive training; HiFrTMS, 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 disorder. 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. 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. 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 and no positive effects reported. 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. 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 and atDCS, 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. 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). 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 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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Online supplementary data

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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Appendix 1. Detailed search strategy
Date: through Mar 5, 2020

(1). PubMed N=2366
Keyword: (non-invasive brain stimulation or theta-burst stimulation or transcranial magnetic stimulation or Transcranial Direct Current Stimulation or neuromodulation) AND (dementia or Alzheimer’s disease or cognitive impairment) AND (cognitive therapy or cognitive training or cognition or language or executive or memory or disease severity or apathy) With Filters applied: Clinical Trial

(2). Psychology and Behavioral Sciences Collection N=2694
Keyword: (non-invasive brain stimulation or theta-burst stimulation or transcranial magnetic stimulation or Transcranial Direct Current Stimulation or neuromodulation) AND (dementia or Alzheimer’s disease or cognitive impairment) AND (cognitive therapy or cognitive training or cognition or language or executive or memory or disease severity or apathy)

(3). Embase N=2884
Keyword: ('non-invasive brain stimulation' OR 'theta-burst stimulation' OR 'transcranial magnetic stimulation' OR 'transcranial direct current stimulation' OR neuromodulation) AND (dementia OR 'alzheimers disease' OR 'cognitive impairment') AND ('cognitive therapy' OR 'cognitive training' OR cognition OR language OR executive OR memory OR 'disease severity' OR apathy)

(4). ClinicalTrials.gov N=88
Keyword: Dementia and brain stimulation (k=67) and mild cognitive impairment and brain stimulation (k=21)

(5). Cochrane N=1143
Keyword: (non-invasive brain stimulation or theta-burst stimulation or transcranial magnetic stimulation or Transcranial Direct Current Stimulation or neuromodulation or brain stimulation) AND (dementia or Alzheimer’s disease or cognitive impairment) AND (cognitive therapy or cognitive training or cognition or language or executive or memory or disease severity or apathy)

Excluded studies with reasons Studies excluded: n=298
(1) Review/Meta-analysis articles n=51
(2) Not cognitively impaired population and/or not interventional study n=48
(3) Other subjects n=53 (study of subjects with other health related disease = 34; healthy population =19)
(4) Other trials n=88 (ongoing trials and study protocol = 24; open label trials = 9; depression trials = 10; DBS and other intervention = 22; case report/series = 16; animal study = 7)
(5) Outcome not related to cognition n=24
(6) Duplicated database from other studies n=9
(7) No detailed data available n=6
(8) No adequate control n=6
(9) Conference Abstract n=2
(10) Less than five sessions of rTMS/tDCS n=18

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study of subjects with other health related disease = 34

1. Evaluation of a Transcranial Stimulation With Direct Current on Language Disorders in Semantic Dementia [NCT03481933] → semantic dementia
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(4) Other trials n=86 [24+9+10+22]

ongoing trials and study protocol n = 24

1. A randomized controlled trial of Theta Burst Stimulation for the treatment of mild to moderate Alzheimer’s disease [ACTRN12615000992505]

2. Repetitive Transcranial Magnetic Stimulation for Apathy in Alzheimer’s Dementia [NCT02190084]

3. Enhancing Working Memory in Patients With Early Alzheimer's Disease Through the Use of rTMS [NCT02537496]

4. Repetitive Transcranial Magnetic Stimulation for Dementia (rTMS for dementia) [NCT02621424]

5. Investigating the Effect of Repetitive Transcranial Magnetic Stimulation (rTMS) as a Treatment for Alzheimer's Disease [NCT02908815]

6. Repetitive Transcranial Magnetic Stimulation in Patients With Alzheimer Disease (AD-EMTr) [NCT03270137]

7. Noninvasive Brain Stimulation for Mild Cognitive Impairment [NCT03331796]

8. Supporting Episodic Memory With Transcranial Direct Current Stimulation in Healthy Controls and Dementia Patients [NCT03227785]

9. Transcranial Direct Current Stimulation and Early Alzheimer's disease (tDCS-AD) (tDCS-AD) [NCT03283863]

10. MR Guided tDCS in Alzheimer's Disease [NCT03322505]

11. The Effects of Transcranial Direct Current Stimulation in Mild Cognitive Impairment [NCT03441152]

12. Cathodal tDCS in MCI: A Randomized, Double-Blind, Sham-Controlled Pilot Study [NCT03521089]

13. Non-invasive Brain Stimulation Using Transcranial Direct Current Stimulation for Neuropsychiatric Symptoms of Dementia [NCT03638284]

14. Transcranial Direct Current Stimulation for Depression in Alzheimer's Disease Patient - Preliminary Research (ADAPT) [NCT0351388]

15. Using fMRI-guided TMS to Increase Central Executive Function in Older Adults (MCI_Sub) (MCI_Sub) [NCT04176406]

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20. Brain stimulation, 2017, Conference: 2nd International Brain Stimulation Conference. Spain. Conference.
open label trials = 9

depression trials = 10

1. Effect of Repetitive Transcranial Magnetic Stimulation on Language in Alzheimer's Disease [NCT00814697]
2. Study of Repetitive Transcranial Magnetic Stimulation (rTMS) as add-on Treatment for Early Alzheimer's Disease (ALSTIMAG) [NCT01481961]
3. Home-Based CR and tDCS to Enhance Cognition in Persons With Mild Cognitive Impairment and Late Life Depression [NCT02959502]
4. Antczak J, Kowalska K, Klimekowicz-Mrowiec A, Wach B, Kasprzyk K, Banach M, Rzeźnicka-Brzegowy K, Kubica J, Słowiak A. Repetitive transcranial magnetic stimulation for the treatment of cognitive impairment in frontotemporal dementia: an open-label pilot study. Neuropsychiatr Dis Treat. 2018 Mar 13;14:749-755.
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10. Supplemental material

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**DBS and other intervention = 22**

1. Deep Brain Stimulation for Patients With Dementia With Lewy Bodies [NCT02263937]

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(6) Duplicated database from other studies n=9

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(7) No detailed data available n=6
1. Repetitive transcranial magnetic stimulation for apathy treatment in Alzheimer's disease: a randomised, double-blind, controlled study [NCT01885806] → Complete but unknown status in ClinicalTrial.gov
2. Therapeutic Role of Transcranial DCS in Alzheimer [NCT03313518] → Complete but unknown results in the ClinicalTrial.gov
3. A Pilot Study of rDCS for Mild to Moderate Alzheimer's Disease [NCT02227953] → unknown status in ClinicalTrial.gov
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1. Alcalá-Lozano R, Morelos-Santana E, Cortés-Sotres JF, Garza-Villarreal EA, Sosa-Ortiz AL, González-Olvera JJ. Similar clinical improvement and maintenance after rTMS at 5 Hz using a simple vs. complex protocol in Alzheimer's disease. Brain Stimul. 2018 May-Jun;11(3):625-627.
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(9) Conference Abstract n=2
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(10) Less than five sessions of rTMS/DCS n=18
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Supplemental material

The study selection process

The study selection process is shown in Figure 1. We identified 7482 potential records and considered 36 studies eligible. Of these studies, three were identified from The study selection process is shown in Figure 1. We identified 7482 potential records used tDCS [Boggio PS et al., 2012; Cotelli M et al., 2014; Khedr EM et al., 2014; BMJ Publishing Group Limited (BMJ) disclaims all liability and responsibility arising from any reliance placed on this supplemental material which has been supplied by the author(s) 

and because the study subjects were the same as those of another study [Rutherford G et al., 2015; Lee J et al., 2016; Zhao J et al., 2017; Koch G et al., 2018; Sabbagh M et al., 2019; Zhang F et al., 2019] and 14 trials was excluded because of apparently dissimilar data [Coppi E et al., 2016; Pini L et al., 2017; Zhang M et al., 2017]. Two clinical trials (viz., NCT01504958 and NCT01894620) identified from ClinicalTrial.gov were excluded because the results were unavailable [NCT01885806 and NCT01894620] and because the study subjects were the same as those of another study [Rutherford G et al., 2015]. Consequently, 27 RCTs satisfied all inclusion criteria, among which 13 trials used rTMS [NCT01504958; Cotelli M et al., 2011; Ahmed MA et al., 2012; Rabey JM et al., 2013; Drumond Marra HL et al., 2015; Wu Y et al., 2015; Rutherford G et al., 2015; Lee J et al., 2016; Zhao J et al., 2017; Koch G et al., 2018; Padala PR et al., 2018; Sabbagh M et al., 2019; Zhang F et al., 2019] and 14 trials used tDCS [Boggio PS et al., 2012; Cotelli M et al., 2014; Khedr EM et al., 2014;
Suemoto CK et al., 2014; Bystad M et al., 2016; Yun K et al., 2016; Das N et al., 2019; Gomes MA et al., 2019; Im JJ et al., 2019; Inagawa T et al., 2019; Khedr EM et al., 2019; Lu H et al., 2019; Manor B et al., 2019; Martin DM et al., 2019].

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NCT01504958. Effects of a Combined Transcranial Magnetic Stimulation (TMS) and Cognitive Training in Alzheimer Patients. In: https://ClinicalTrials.gov/show/NCT01504958.
NCT01885806. Repetitive Transcranial Magnetic Stimulation for Apathy Treatment in Alzheimer's Disease. In: https://ClinicalTrials.gov/show/NCT01885806.
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### Appendix 2. PRISMA

**PRISMA checklist of current network meta-analysis**

| Section/Topic       | # | Checklist Item                                                                 | Reported on Page # |
|---------------------|---|--------------------------------------------------------------------------------|-------------------|
| **TITLE**           |   |                                                                                |                   |
| Title               | 1 | Identify the report as a systematic review incorporating a network meta-analysis (or related form of meta-analysis) | 1                 |
| **ABSTRACT**        |   |                                                                                |                   |
|                     |   | Provide a structured summary including, as applicable:                        |                   |
|                     |   | Background: main objectives Methods: data sources; study eligibility criteria, participants, and interventions; study appraisal; and synthesis methods, such as network meta-analysis. Results: number of studies and participants identified; summary estimates rankings may also be discussed. Authors may choose to summarize pairwise comparisons against a chosen treatment included in their analyses for brevity. Discussion/Conclusions: limitations; conclusions and implications of findings. Other: primary source of funding; systematic review registration number with registry name | 4-5               |
| Structured summary  | 2 | with corresponding confidence/credible intervals; treatment                  |                   |
| **INTRODUCTION**    |   |                                                                                |                   |
| Rationale           | 3 | already known, including mention of why a network meta-analysis has been conducted | 7–9               |
|                     |   | Provide an explicit statement of questions being addressed, with               |                   |
| Objectives          | 4 | reference to participants, interventions, comparisons, outcomes, and study design (PICOS) | 7–9               |
| **METHODS**         |   |                                                                                |                   |
| Protocol and        | 5 | Indicate whether a review protocol exists and if and where it can be accessed (e.g., Web address); and, if available, provide registration information, including registration number. | 10                |
| registration        |   | Specify study characteristics (e.g., PICOS, length of follow-up) and          |                   |
|                     |   | report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale. Clearly describe eligible treatments included in the treatment network, and note whether any have been clustered or merged into the same node (with justification). | 10-11             |
| Eligibility criteria| 6 | Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched. | 10-11 and appendix 1 and 3 |
| Information sources | 7 |                                                                                |                   |
| Topic                                      | Page |
|--------------------------------------------|------|
| Search                                    | 8    |
| Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated | 10-11 and appendix 1 and 3 |
| State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis). | 10-11 and appendix 1 and 3 |
| Study selection                           | 9    |
| Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators | 11 |
| Data collection process                    | 10   |
| List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made | 11 |
| Data items                                 | 11   |
| Describe methods used to explore the geometry of the treatment network under study and potential biases related to it. This should include how the evidence base has been graphically summarized for presentation, and what characteristics were compiled and used to describe the evidence base to readers. | 12-14, figure 1 and appendix 5 |
| Geometry of the network                    | S1   |
| Risk of bias in individual studies         | 12   |
| Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis. | 12-14 and appendix 11 |
| Summary measures                           | 13   |
| State the principal summary measures (e.g., risk ratio, difference in means). Also describe the use of additional summary measures assessed, such as treatment rankings and surface under the cumulative ranking curve (SUCRA) values, as well as modified approaches used to present summary findings from meta-analyses. | 12-14, figure 2-6, and appendices 6-8 |
| Planned methods of analysis                | 14   |
| Describe the methods of handling data and combining results of studies for each network meta-analysis. This should include, but not be limited to: Handling of multigroup trials; Selection of variance structure; Selection of prior distributions in Bayesian analyses; and Assessment of model fit | 12-14 |
| Assessment of inconsistency                | S2   |
| Describe the statistical methods used to evaluate the agreement of direct and indirect evidence in the treatment network(s) studied. Describe efforts taken to address its presence when found. | 12-14 and appendix 12 |
| Risk of bias across studies                | 15   |
| Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies). | 12-14 and appendix 13 |
| Additional analyses                        | 16   |
| Describe methods of additional analyses if done, indicating which were prespecified. This may include, but not be limited to, the | 12-14 and appendix 14 and 15 |

Chu C-S, et al. J Neurol Neurosurg Psychiatry 2020;0:1–9. doi: 10.1136/jnnp-2020-323870
following: Sensitivity or subgroup analyses; Meta-regression analyses; Alternative formulations of the treatment network; and Use of alternative prior distributions for Bayesian analyses (if applicable).

## RESULTS

| Section                        | Description                                                                                                                                                                                                 | References       |
|--------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------|
| Study selection                | Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.                                                                 | 15 and appendix 1 and 3. |
| Presentation of network structure | Provide a network graph of the included studies to enable visualization of the geometry of the treatment network.                                                                                       | 15-17, Figure 1 and appendix 5. |
| Summary of network geometry    | Provide a brief overview of characteristics of the treatment network. This may include commentary on the abundance of trials and randomized patients for the different interventions and pairwise comparisons in the network, gaps of evidence in the treatment network, and potential biases reflected by the network structure. | 15–17 and appendix 4 and 10. |
| Study characteristics          | For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.                                                               | 15-17 and appendix 4, 9, 10 and 16. |
| Risk of bias within studies    | Present data on risk of bias of each study and, if available, any outcome level assessment.                                                                                                                 | 20-21 and appendix 11. |
| Results of individual studies  | For all outcomes considered (benefits or harms), present, for each study: 1) simple summary data for each intervention group, and 2) effect estimates and confidence intervals. Modified approaches may be needed to deal with information from larger networks. | 15–19, figure 2-5, and appendix 6-8 and 10. |
| Synthesis of results           | Present results of each meta-analysis done, including confidence/credible intervals. In larger networks, authors may focus on comparisons versus a particular comparator (e.g., placebo or standard care), with full findings presented in an appendix. League tables and forest plots may be considered to summarize pairwise comparisons. If additional summary measures were explored (such as treatment rankings), these should also be presented. | 15–19, figure 2-6, and appendix 6-8. |
| Exploration for inconsistency  | Describe results from investigations of inconsistency. This may include such information as measures of model fit to compare consistency and inconsistency models, P values from statistical tests, or summary of inconsistency estimates from different parts of the treatment network. | 20-21 and appendix 12. |
| Risk of bias across studies    | Present results of any assessment of risk of bias across studies for the evidence base being studied.                                                                                                       | 20-21 and appendix 11. |
Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression analyses, alternative network geometries studied, alternative choice of prior distributions for Bayesian analyses, and so forth).

**DISCUSSION**

**Summary of evidence**
Summarize the main findings, including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., health care providers, researchers, and policymakers).

Discuss limitations at study and outcome level (e.g., risk of bias), and at review level (e.g., incomplete retrieval of identified research, reporting bias). Comment on the validity of the assumptions, such as transitivity and consistency. Comment on any concerns regarding network geometry (e.g., avoidance of certain comparisons).

**Limitations**

**Conclusions**
Provide a general interpretation of the results in the context of other evidence, and implications for future research.

**FUNDING**
Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review. This should also include information regarding whether funding has been received from manufacturers of treatments in the network and/or whether some of the authors are content experts with professional conflicts of interest that could affect use of treatments in the network.

From: Hutton B, Salanti G, Caldwell DM, et al. The PRISMA extension statement for reporting of systematic reviews incorporating network meta-analyses of health care interventions: checklist and explanations. Ann Intern Med. 2015;162(11):777-784.
Appendix 3 (eFigure S1). Flow diagram of trial selection

Records identified through database searching (n = 9175)

Duplicate records excluded (n = 395)

Records after duplicates removed (n = 8780)

Excluded by title and abstract (n = 8437)

Full-text articles assessed for eligibility (n = 343)

Articles excluded according to (n = 298)
1. Review/Meta-analysis
2. Not cognitively impaired population and/or not interventional study
3. Other subjects (study of subjects with other health related diseases; healthy population)
4. Other trials (ongoing trials and study protocol; open label trials; depression trials; DBS and other intervention; case report series; animal study)
5. Outcome not related to cognition
6. Duplicated database from other studies
7. No detailed data available
8. No adequate control
9. Conference abstract
10. Less than five sessions of rTMS/DCS

Studies with potential eligibility (n = 36)

Articles excluded according to (n = 9)
1. Dissimilar study subjects
2. Lack of detailed data
3. Results were unavailable from ClinicalTrials.gov
4. Same population from other study

Studies included in current network meta-analysis (n = 27)
### Appendix 4 (eTable S1). The characteristics of the included studies

| Study | Diagnosis | Diagnostic criteria | Intervention (combined with medications) | Subjects, total (intervention vs control) | Mean age | Gender (female) | Study design, follow-up | Cognitive assessment | Cognitive assessment | Others |
|-------|-----------|---------------------|------------------------------------------|-----------------------------------------|----------|----------------|-------------------------|----------------------|----------------------|---------|
| Sabbath et al., 2019 | AD | MMSE = 18 to 26, ADAS-Cog > 17, CDR = 1 or 2, DSM-IV | HFtMS-six regions + CT vs sham (ADM) | 109 (59 vs 50) | 76.8 | 45.3% | Parallel, 1 month | ADAS-Cog | N/A | N/A |
| Zhang et al., 2019 | Probable AD | NINCDS-ADRDA | HFtMS-Lt DLPFC + CT vs sham + CT (ADM) | 28 (15 vs 13) | 68.8 ± 8.1 | 78.6% | Parallel, 1 month | MMSE | ACE III-memory | N/A | VF: MMSE-verbal fluency, WM: MMSE-attention |
| Zhao et al., 2017 | AD | MMSE = 18 to 26, CDR = 1 or 2, DSM-IV | HFtMS-parietal and posterior TL vs sham (ADM) | 30 (17 vs 13) | 70.2 ± 5.6 | 57.1% | Parallel, six weeks | MMSE | ADAS-Cog-memory | ADAS-Cog-EF | LANG: ADAS-Cog-LANG |
| Lee et al., 2016 | Probable AD | MMSE = 18 to 26, CDR = 1 or 2, DSM-IV | HFtMS-six regions + CT vs sham + sham CT | 26 (18 vs 8) | 70.9 ± 5.9 | 60.4% | Parallel, six weeks | MMSE | ADAS-Cog-memory | ADAS-Cog-EF | LANG: ADAS-Cog-LANG |
| Author, year | Diagnosis | Diagnostic criteria | Intervention (combined with medications) | Subjects, total (intervention vs control) | Mean age | Gender (female) | Study design, follow-up | Cognitive assessment | Gender | Study design, follow-up | Cognitive assessment |
|--------------|-----------|---------------------|-------------------------------------------|------------------------------------------|----------|----------------|------------------------|---------------------|--------|------------------------|---------------------|
| Rutherford et al., 2015, | Probable AD | MoCA = 5 to 26, MADRS < 20 | HFrTMS-bilateral DLPFC vs sham (ADM) | 10 | range: 40 to 90 | N/A | Crossover, no f/u | ADAS-Cog | WIA-memory | WIA | N/A |
| Wu et al., 2015 | Probable AD | MMSE < 24, BEHAVE-AD > 8, NINCDS-ADRDA | HFrTMS-Lt DLPFC vs sham (risperidone) | 52 (26 vs 26) | 71.7 ± 4.9 | 59.6% | Parallel, 1 month | ADAS-Cog | ADAS-Cog | ADAS-Cog-Attention | LANG: ADAS-Cog-LANG |
| Rabey et al., 2013 | Probable mild to moderate AD | MMSE = 18 to 24, CDR = 1, DSM-IV | HFrTMS-six brain regions + CT vs sham + sham CT (AchEIs) | 15 (7 vs 8) | 74.1 ± 9.1 | 33.3% | Parallel, no f/u | ADAS-Cog | N/A | N/A |
| Ahmed et al., 2012 | Probable AD | NINCDS-ADRDA | HFrTMS-bilateral DLPFC vs LF-rTMS-bilateral DLPFC vs sham | 45 (15 vs 15 vs 15) | 67.6 ± 6 | 64.5% | parallel, 3-armed study, 1 and 3 months | MMSE | N/A | N/A |
| Cotelli et al., 2015 | Probable | MMSE = 16 | HFrTMS-Lt | 10 (5 vs 5) | 72.8 ± 5.3 | N/A | Parallel | MMSE | SCP | CET | LANG: |
| Author, year | Diagnosis | Diagnostic criteria | Intervention (combined with medications) | Subjects, total (intervention vs control) | Gender (female) | Study design, follow-up | Cognitive assessment | GCF | Memory | EXE | Others |
|--------------|-----------|---------------------|-------------------------------------------|------------------------------------------|----------------|------------------------|----------------------|-----|--------|-----|--------|
| 2011         | moderate  | NINCDS-ADRDA        | DLPFC vs sham (AchEIs)                     | 16 (10 vs 6)                             | 69.4           | Parallel, 1 month      | SC-BADA             | f/u | N/A    | N/A |        |
| NCT01504958, 2010 | AD       | NINCDS-ADRDA and DSM-IV | HFrTMS-five brain regions + CT vs sham + sham CT | 16 (10 vs 6) | 69.4 | Parallel, 1 month | ADAS-Cog | N/A | N/A    | N/A |        |
| rTMS in MCI (k=3) |          |                     |                                           |                                          |                |                        |                      |     |        |     |        |
| Koch et al., 2018 | Prodromal | AD                    | HFrTMS-precuneus vs sham (N/A)          | 14                                        | 70 ± 5.1       | Crossover, no f/u     | MMSE                | MMSE | N/A    | Exit-25 | WM: DSST |
| Padala et al., 2018 | MCI      | MMSE > 23, Petersen criteria | HFrTMS-Lt DLPFC vs sham (antidepressants) | 9                                         | 65.6 ± 9.3     | Crossover, 1 month    | 3MS      | N/A    | Exit-25 | WM: TMT-A |
| Drumond et al., 2015 | MCI      | MoCA ≤ 24; CDR = 0; GDS < 5; HAMD-17 < 7, HAMA-14 < 8 | HFrTMS-Lt DLPFC vs sham (N/A) | 34 (15 vs 19) | 65.2 ± 3.8 | Parallel, 1 month | N/A      | RBMT   | TMT-B | VF/AN | WM: LNST |
| tDCS in AD (k=8)   |           |                      |                                           |                                          |                |                        |                      |      |        |     |        |
| Inagawa et al., 2019 | Major or neurocognitive disorder | MMSE≥18, CDR≤2, DSM-V | atDCS-Lt DLPFC + CT vs sham + CT (ADM) | 19 (7 vs 12) | 76.3 ± 7.0 | Parallel, 2 weeks | MMSE | N/A    | FAB | N/A    |
| Author, year | Diagnosis | Diagnostic criteria | Intervention (combined with medications) | Subjects, total (intervention vs control) | Mean age | Gender (female) | Study design, follow-up | Cognitive assessment | GCF | Memory | EXE | Others |
|-------------|-----------|---------------------|------------------------------------------|------------------------------------------|----------|----------------|-----------------------|-------------------|-----|--------|-----|--------|
| Khedr et al., 2019 | Probable AD | NINCDS-ADRDA | atDCS-bil TL vs sham (memantine) | 46 (23 vs 23) | 64.7 ± 4.1 | 40.8% | Parallel, no f/u | MMSE | N/A | CDT | N/A |
| Im et al., 2019 | Probable AD | CDR = 0.5 or 1, DSM-IV or NINCDS-ADRDA | atDCS-Lt DLPFC vs sham (AchEIs) | 20 (12 vs 8) | 73.1 ± 7.9 | 83.1% | Parallel, no f/u | MMSE | SVLT-delayed recall | Stroop test | LANG: BNT, WM: SVLT-immediate recall |
| Bystad et al., 2016 | Probable AD | MMSE ≥ 18, NINCDS-ADRDA | atDCS-Lt TL vs sham (AchEIs) | 25 (12 vs 13) | 72.6 ± 8.7 | 44.6% | Parallel, no f/u | MMSE | CVLT-II delayed recall | CDT | WM: TMT-A |
| Cotelli et al., 2014 | Probable mild to moderate AD | NINCDS-ADRDA | atDCS-Lt DLPFC + CT vs sham + CT (AchEIs) | 24 (12 vs 12) | 75.7 ± 5.5 | 79.2% | Parallel, 3 and 6 months | MMSE | RAVLT-delayed recall | TMT-B | LANG: PNT-action |
| Khedr et al., 2014 | Probable AD | NINCDS-ADRDA | atDCS-Lt DLPFC vs sham (memantine) | 34 (11 vs 12) | 68.9 ± 6.4 | 44.1% | Parallel, 1 and 2 months | MMSE | WAIS-III Digit span | WAIS-III-block design | LANG: WAIS-III vocabulary, WM: WAIS-III |
| Author, year      | Diagnosis         | Diagnostic criteria       | Intervention (combined with medications) | Subjects, total (intervention vs control) | Mean age | Gender (female) | Study design, follow-up | Cognitive assessment | Others    |
|-------------------|-------------------|---------------------------|------------------------------------------|------------------------------------------|----------|-----------------|--------------------------|---------------------|-----------|
| Suemoto et al., 2014 | Probable or possible AD | MMSE = 10 to 20, NINCDS-ADRDA | atDCS-Lt DL-PFC vs sham (ADM) | 40 (20 vs 20) | 80.4 ± 7.7 | 70% | Parallel, no f/u | ADAS-Cog | GCF, Memory, EXE, Digit symptom coding |
| Boggio et al., 2012 | AD                | MMSE > 15, NINCDS-ADRDA and DSM-IV | atDCS-bilateral TL vs sham (AChEIs) | 30 (15 vs 15) | 78.9 ± 8.4 | 46.7% | Crossover, 1 month | ADAS-Cog | VAT, N/A |
| Gomes et al., 2019 | MCI               | Petersen criteria         | atDCS-Lt DPFC vs sham (N/A) | 58 (29 vs 29) | 72.3 ± 8.6 | 72.5% | Parallel, 90 days but no raw data available | MMSE | G-CAMCOG, O-CAMC, LANG: CAMCOG-LANG; VF: CAMCOG-VF; WM: TMT-A |
| Martin et al., 2019 | MCI               | NIAAA criteria            | atDCS-Lt DPFC + CT vs sham + CT (no AChEIs) | 68 (33 vs 35) | 71.7 ± 6.4 | 66.2% | Parallel, 3 months | N/A | CVLT-II, N/A |

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| Author, year | Diagnosis | Diagnostic criteria | Intervention (combined with medications) | Subjects, total (intervention vs control) | Mean age | Gender (female) | Study design, follow-up | Cognitive assessment | EXE | Others |
|-------------|-----------|---------------------|------------------------------------------|-----------------------------------------|----------|----------------|------------------------|---------------------|-----|--------|
| Das et al., 2019 | MCI | CDR = 0.5, MMSE = 24 to 30, Petersen Criteria | atDCS-IFG + CT vs sham + CT (N/A) | 22 (12 vs 10) | 62.9 ± 8.0 | 72.7% | Parallel, 3 months | N/A | CVLT | DKEFS Card Sort |
| Lu et al., 2019 | MCI | CDR ≤ 0.5, MMSE = 22 to 27, DSM-V | atDCS-Lt LTC + CT vs sham + CT vs atDCS-Lt LTC + sham CT (no ADM) | 201 (69 vs 64 vs 68) | 74.0 ± 6.5 | 53.8% | Parallel, 1 and 2 months | MMSE WLLT-delay recall | CVFT WMC |
| Manor et al., 2018 | MCI | MMSE ≥ 18; Walking speed and TMT-B | atDCS-Lt DLPFC vs sham (N/A) | 19 (9 vs 10) | 80.4 ± 4.3 | 52.7% | Parallel, 1 month | N/A | N/A | TMT-B/TMT -A |
| Yun et al., 2016 | MCI | Petersen criteria | atDCS-Lt DLPFC vs sham (N/A) | 16 (8 vs 8) | 73.9 ± 6.2 | 68.8% | Parallel, no f/u | N/A | HVLT N/A N/A |

Brief summary:

(i) The 27 trials were published between 2011 and 2019, and 9 trials used MCI population. Two studies had three arms, and the remaining had two arms. There were four crossover trials.

(ii) For the rTMS trials (n = 455), the mean age was 70.6 ± 3.8 years, percentage of women participants was 53.4% ± 16.3%, MMSE score was 20.9 ± 4.0, and study duration was 3.6 ± 2.0 weeks.

(iii) For the tDCS trials (n = 634), the mean age was 73.3 ± 5.0 years, percentage of women participants was 60.5% ± 14.5%, MMSE score was 21.7 ± 4.3, and study duration was 4.1 ± 5.5 weeks.
Abbreviation: ACE III: Addenbrooke’s Cognitive Examination III; AChEIs: acetylcholinesterase inhibitors; AD: Alzheimer’s disease; ADAS-Cog: Alzheimer’s Disease Assessment Scale-cognitive subscale; ADM: Anti-dementia Medication; AES: Apathy Evaluation Scale; AN: Animal Naming; AVLT: Auditory Verbal Learning Test; BEHAVE-AD: Behavioral Pathology in Alzheimer’s disease rating scale; BNT: Boston Naming Test; CAMCOG: The Cambridge Cognitive Examination; CDR: Clinical Dementia Rating; CDS: Cornell Depression Scale; CDT: Clock Drawing Test; CFT: Cognitive Estimation Test; COWAT: Controlled Oral Word Association Test; CVFT: Category Verbal Fluency Test; CVLT: California Verbal Learning Test; DCT: Digit Cancellation Task; DKEFS: Delis–Kaplan Executive Function System; DLPFC: Dorsolateral Prefrontal Cortex; DSM: Diagnostic and Statistical Manual of Mental Disorders; DSST: Digit Symbol Substitution Test; EXE: executive function; EXIT-25: Executive interview; FAB: Frontal Assessment Battery; GDS: Geriatric Depression Scale; HAMA: Hamilton Anxiety Rating Scale; HAMD: Hamilton Depression Rating Scale; HFrTMS: high frequency rTMS; HVLT: Hopkins Verbal Learning Test; IFG: Inferior Frontal Gyrus; LANG: language function; LFrTMS: low frequency rTMS; LNST: Letter-number Sequencing Test; LTC: Lateral Temporal Cortex; MADRS: Montgomery-Asberg Depression Rating Scale; MCI: Mild Cognitive Impairment; MMSE: Mini-Mental State Examination; MoCA: Montreal Cognitive Assessment; N/A: not available; NIAAA: National Institute on Aging-Alzheimer's Association workgroups; NINCDS-ADRDA: National Institute of Neurological and Communicative Diseases and Stroke/Alzheimer’s Disease and related disorders association; NPI: Neuropsychiatric Inventory; NPS: Neuropsychiatric Symptoms; PIQ: performance IQ; PNT: Picture Naming Task; RAVLT: Rey Auditory Verbal Learning Test; RBMT: Rivermead Behavioral Memory Test; Ref: reference area; SAS: Starkstein Apathy Scale; SC-BADA: Subtest from the Battery for Analysis of Aphasic Deficits; SCP: Serial Curve Position; SVLT: Seoul Verbal Learning Test; TL: Temporal Lobe; TMT-B: Trail Making Test part B; VAT: Visual Attention Task; VF/AN: verbal fluency/animal naming; VRT: Visual Recognition Task; WAIS-III: Wechsler adult intelligent scale-third edition; WMM: Working Memory; WMC: Working Memory Capacity; WIA: Word Image Association; WRT: Word Recognition Task; 3MS: Modified Mini-Mental State Examination; atDCS: anodal transcranial direct current stimulation; ctDCS: cathodal transcranial direct current stimulation; rTMS: repetitive transcranial magnetic stimulation.

a Not including stimulation sessions in the maintenance period.

b Dubois B et al., Preclinical Alzheimer’s disease: Definition, natural history, and diagnostic criteria. Alzheimers Dement. 2016 Mar;12(3):292–323.

c Petersen RC et al., Mild cognitive impairment: clinical characterization and outcome. Arch. Neurol. 1999;56,303–308.

d Whiteside DM et al., Verbal Fluency: Language or Executive Function Measure? Appl Neuropsychol Adult. 2016;23(1):29–34.

Six regions included: Broca’s area, Wernicke’s area, bilateral DLPFC, and bilateral parietal somatosensory association cortex.

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After two weeks RCT, all patients received true stimulation during 2 to 4 weeks. All patients received follow-up evaluation at week 12.

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Five regions include: left and right parietal cortex (somatosensory association cortex), left and right DLPFC (dorsolateral prefrontal cortex), and left superior temporal gyrus (Broca’s area).
Appendix 5 (eFigure S2). Network plots for the secondary outcome

| Immediate evaluation after last session | Follow-up assessment after 1 month |
|-----------------------------------------|-----------------------------------|
| **Memory function**                     |                                   |
|                                         | ![Network Plot](image1)            |
|                                         | ![Network Plot](image2)            |
| **Verbal fluency**                      |                                   |
|                                         | ![Network Plot](image3)            |
|                                         | ![Network Plot](image4)            |
| **Working memory**                      |                                   |
|                                         | ![Network Plot](image5)            |
|                                         | ![Network Plot](image6)            |
| **Executive function**                  |                                   |
|                                         | ![Network Plot](image7)            |
|                                         | ![Network Plot](image8)            |
Appendix 6 (eFigure S3). Short-term effects on general cognition divided by AD and MCI

(a) AD population

| Treatment          | vs. sham_BS (MMSE Changes from Baseline) | MD    | 95% CI        |
|--------------------|----------------------------------------|-------|---------------|
| HFrTMS             | -0.15 [-1.23; 0.93]                    | 0.00  |               |
| ctDCS              | 0.00                                   |       |               |
| atDCS              | -0.31 [-2.14; 1.53]                    | 0.00  |               |
| sham_BS + CT       | 0.10 [-0.22; 0.42]                     | 0.00  |               |
| sham_BS + sham_CT  | -1.65 [-3.06; -0.25]                   | 0.00  |               |

(b) MCI population

| Treatment          | vs. sham_BS (MMSE Changes from Baseline) | MD    | 95% CI        |
|--------------------|----------------------------------------|-------|---------------|
| atDCS + CT         | -0.50 [-1.74; 0.74]                    | 0.00  |               |
| atDCS              | 0.00                                   |       |               |
| atDCS + sham_CT    | 0.29 [-0.23; 0.82]                     | 0.00  |               |
| sham_BS + CT       | 0.10 [-0.22; 0.42]                     | 0.00  |               |
| sham_BS            | 0.00                                   |       |               |
| HFrTMS             | 0.49 [-0.25; 1.22]                     | 0.00  |               |

Forest Plot for Components

| Components         | MD    | 95% LL | 95% UL |
|--------------------|-------|--------|--------|
| HFrTMS             | 1.50  | 0.63   | 2.39   |
| ctDCS              | 1.09  | -0.79  | 2.97   |
| atDCS              | 0.61  | -0.06  | 1.28   |
| LFrTMS             | -0.31 | -2.06  | 1.44   |
| CT                 | -1.07 | -2.43  | 0.29   |
| sham_CT            | -1.15 | -3.22  | 0.92   |

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Appendix 7 (eFigure S4). Long-lasting effects on general cognition at 1-month follow-up divided by AD and MCI

(a) AD population

| Treatment                  | vs. sham_BS (MMSE Changes from Baseline) | MD     | 95%–CI     |
|----------------------------|----------------------------------------|--------|------------|
| cDCS                       | 2.70 [0.67; 4.73]                      |        |            |
| HF/TMS                     | 1.71 [0.86; 2.56]                      |        |            |
| HF/TMS+CT                  | 0.68 [-0.54; 1.90]                     |        |            |
| atDCS                      | 0.30 [-0.64; 1.25]                     |        |            |
| sham_BS                    | 0.00                                   |        |            |
| LF/TMS                     | -0.08 [-2.06; 1.90]                    |        |            |
| atDCS+CT                   | -0.72 [-2.51; 1.07]                    |        |            |
| atDCS+sham_CT              | -0.84 [-2.72; 1.04]                    |        |            |
| sham_BS+CT                 | -1.03 [-2.52; 0.46]                    |        |            |
| sham_BS+sham_CT            | -1.14 [-2.84; 0.56]                    |        |            |

(b) MCI population

| Treatment                  | vs. sham_BS (MMSE Changes from Baseline) | MD     | 95%–CI     |
|----------------------------|----------------------------------------|--------|------------|
| HF/TMS                     | 3.50 [-0.62; 7.62]                     |        |            |
| atDCS                      | 1.47 [-2.44; 5.38]                     |        |            |
| atDCS+CT                   | 1.12 [-1.74; 3.97]                     |        |            |
| atDCS+sham_CT              | 0.76 [-1.92; 3.45]                     |        |            |
| sham_BS+CT                 | 0.35 [-1.41; 2.11]                     |        |            |
| sham_BS                    | 0.00                                   |        |            |

Forest Plot for Components

| Components                  | MD     | 95% LL | 95% UL |
|-----------------------------|--------|--------|--------|
| cDCS                        | 2.70   | 0.76   | 4.64   |
| HF/TMS                      | 1.71   | 0.88   | 2.54   |
| atDCS                       | 0.31   | -0.62  | 1.24   |
| sham_BS (Ref.)              | 0.00   | -1.58  | 1.38   |
| CT                          | -0.10  | -1.58  | 1.38   |
| sham_CT                     | -0.21  | -1.91  | 1.49   |
| LF/TMS                      | -0.44  | -2.08  | 1.20   |

Pre-Post Changes in MMSE Scores

Forest Plot for Components

| Components                  | MD     | 95% LL | 95% UL |
|-----------------------------|--------|--------|--------|
| HF/TMS                      | 3.50   | -0.62  | 7.62   |
| CT                          | 1.89   | -0.51  | 4.30   |
| sham_CT                     | 1.19   | -0.73  | 3.11   |
| CT                          | 1.12   | -1.40  | 3.65   |
| sham_BS (Ref.)              | 0.00   | 0.00   | 0.00   |

Pre-Post Changes in MMSE Scores
Appendix 8 (eFigure S5). Forest plots for the executive function

(a) Immediate effects

(b) Long-lasting effects after 1 month
Appendix 9 (eTable S2). The effect sizes (SMD) for studies with follow-up data longer than 1 month

| Source      | Protocol          | General cognition | Memory function | Verbal fluency | Working memory | Executive function |
|-------------|-------------------|-------------------|-----------------|----------------|----------------|--------------------|
| Lu 2019     | atDCS+CT          | 0.11 (0.10)       | 0.34 (0.10)     | 0.39 (0.10)    | 0.43 (0.10)    |                    |
|             | sham_BS+CT        | 0.04 (0.10)       | 0.22 (0.10)     | 0.19 (0.10)    | 0.22 (0.10)    |                    |
|             | atDCS+sham_CT     | 0.27 (0.10)       | 0.18 (0.10)     | 0.35 (0.10)    | 0.17 (0.10)    |                    |
| Khedr 2014  | atDCS             | 1.12 (0.30)       | 0.21 (0.24)     | 0.82 (0.27)    | 0.22 (0.24)    | 0.61 (0.26)        |
|             | ctDCS             | 1.70 (0.35)       | 1.72 (0.35)     | 1.43 (0.32)    | 0.96 (0.27)    | 1.04 (0.28)        |
|             | sham_BS           | 0.16 (0.24)       | 0.00 (0.23)     | 0.00 (0.23)    | -0.14 (0.24)   | 0.39 (0.24)        |
| ≥ 3 month   |                   |                   |                 |                |                |                    |
| Source      | Protocol          | General cognition | Memory function | Verbal fluency | Working memory | Executive function |
| Ahmed 2012  | HFrTMS            | 1.29 (0.27)       |                 |                |                |                    |
|             | LFrTMS            | 0.16 (0.20)       |                 |                |                |                    |
|             | sham_BS           | -0.26 (0.20)      |                 |                |                |                    |
| Cotelli 2014| atDCS+CT          | -0.16 (0.23)      | 0.00 (0.22)     | -0.09 (0.22)   | 0.35 (0.23)    | -0.03 (0.22)       |
|             | sham_BS+CT        | -0.06 (0.22)      | 0.34 (0.23)     | 0.48 (0.24)    | 0.00 (0.22)    | 0.24 (0.23)        |
|             | atDCS+sham_CT     | -0.47 (0.24)      | 0.00 (0.22)     | 0.09 (0.22)    | 0.14 (0.23)    | 0.07 (0.22)        |

Abbreviation: CT, cognitive training; ctDCS, cathodal transcranial direct current stimulation; HF, high-frequency; LF, low-frequency; rTMS, repetitive transcranial magnetic stimulation; tDCS, transcranial direct current stimulation; sham_BS, sham brain stimulation; sham_CT, sham cognitive training; SMD, standardized mean difference
### Appendix 10 (eTable S3). The reported adverse effects of the included studies.

| Author, year, study design | Population, diagnostic criteria | Intervention (medications, cognitive training) | Protocol (frequency, intensity, pulses per condition, total stimulation sessions) for the brain area(s) | Adverse events |
|----------------------------|--------------------------------|-----------------------------------------------|-----------------------------------------------------------------------------------------------|----------------|
| Sabbagh et al., 2019, parallel | AD (MMSE = 18 to 26, CDR = 1 or 2, DSM-IV) | HF-rTMS + CT vs sham (anti-dementia medications) | HF-rTMS (10 Hz, 110% MT, 1300 pulses, 30 sessions) for the Bil DLPFC, Bil inferior parietal lobe, Broca’s and Wernicke’s areas | There are 13 participants reporting adverse events, with 11 in the active and 2 in the sham group. The side effects included headache (5.4%), scalp/skin discomfort (3.1%), neck pain/stiffness (1.5%), and fatigue (0.7%). All were mild and most resolved on the day of occurrence with either minor or no action. |
| Zhang et al., 2019, parallel | Probable AD, NINCDS-ADRDA | HF-rTMS + CT vs sham + CT (anti-dementia medications) | HF-rTMS (10 Hz, 100% MT, 1000 pulses, 20 sessions) for the Lt DLPFC and Lt lateral temporal lobe | At the first treatment, some participants slight tingling in the scalp or mild muscle contraction around the area of stimulation. All discomfort disappeared when the stimulus was paused. No other adverse effects occurred during the treatment. |
| Koch et al., 2018, crossover | Prodromal AD (CDR = 0.3 ± 0.3, Dubois’s diagnostic criteria) | HF-rTMS vs sham | HF-rTMS (20 Hz, 100% MT, 1600 pulses, 10 sessions) for the precuneus | Unreported |
| Padala et al., 2018, crossover | MCI (MMSE > 23) Petersen criteria | HF-rTMS vs sham (antidepressants) | HF-rTMS (10 Hz, 120% MT, 3000 pulses, 10 sessions) for the Lt DLPFC | There were 16 adverse events in 9 subjects, and most adverse events were experienced while receiving rTMS (14 events in 8 subjects) compared to only 2 events with sham treatment (neck discomfort and ER visit for unrelated wrist pain). The most common adverse event was discomfort at the treatment site (8 events in 6 subjects) with 4 subjects rating the discomfort as mild, 1 as moderate, and 1 as severe. One subject who experienced severe pain was discontinued from the study. The remaining adverse events related to rTMS were shock sensation at treatment site (n = 1) or to eye (2 events in 1 subject), facial twitching (n = 1), insomnia (n = 1), and dizziness upon standing (n = 1); all of which were mild. |
| Author, year, study design | Population, diagnostic criteria | Intervention (medications, cognitive training) | Protocol (frequency, intensity, pulses per condition, total stimulation sessions*) for the brain area(s) | Adverse events |
|---------------------------|--------------------------------|-----------------------------------------------|-------------------------------------------------------------------------------------------------|---------------|
| Zhao et al., 2017, parallel | AD (MMSE = 18 to 26, CDR = 1 or 2), DSM-IV | HF-rTMS vs sham (anti-dementia medications) | HF-rTMS (20 Hz, N/A, 4000 pulses, 30 sessions) for the Bil temporal and parietal lobes | Two patients in the rTMS treatment group and one in the sham group had the adverse effect, and they had the mild headache and fatigue after the first treatment. |
| Lee et al., 2016, parallel | Probable AD (MMSE = 18 to 26, CDR = 1 or 2), DSM-IV | HF-rTMS + CT vs sham + CT (AchEIs) | HF-rTMS (10 Hz, 90% MT for bilateral DLPFC and Broca’s area, 110% MT for bilateral pSAC and Wernicke’s area, 1200 pulses, 30 sessions) for the Bil DLPFC, Bil pSAC, Broca’s and Wernicke’s areas | One patient in the sham group complained of mild headache and fatigability at the first visit. That patient withdrew. |
| Drumond et al., 2015, parallel | MCI (MoCA ≤ 24), CDR = 0, GDS < 5, HAMD-17 < 7, HAMA-14 < 8, unknown criteria | HF-rTMS vs sham | HF-rTMS (10 Hz, 110% MT, 2000 pulses, 10 sessions) for the Lt DLPFC | rTMS group: Headache (n = 10), scalp pain (n = 9). Sham group: Headache (n = 5), cervical pain (n = 1), scalp pain (n = 2), burning scalp (n = 1). |
| Rutherford et al., 2015, crossover | Probable AD (MoCA = 5 to 26, MADRS < 20), unknown criteria | HF-rTMS vs sham (anti-dementia medications) | HF-rTMS (20 Hz, 90 to 100% MT, 2000 pulses, 10 sessions) for the Bil DLPFC | Unreported |
| Wu et al., 2015, parallel | Probable AD (MMSE < 24, BEHAVE-AD > 8), NINCDS-ADRAD (risperidone) | HF-rTMS vs sham | HF-rTMS (20 Hz, 80% MT, 1200 pulses, 20 sessions) for the Lt DLPFC | Transient headache (4 cases in the intervention group and 5 cases in the control group). These side effects were mild and well tolerated. Overall, 30.8% (8/26) of the participants in the intervention group experienced an adverse event during the study while 26.9% (7/26) in the control group experienced an adverse event (X^2 =0.09, p=0.760). |
| Author, year, study design | Population, diagnostic criteria | Intervention (medications, cognitive training) | Protocol (frequency, intensity, pulses per condition, total stimulation sessions*) for the brain area(s) | Adverse events |
|---------------------------|---------------------------------|-----------------------------------------------|-------------------------------------------------------------------------------------------------|---------------|
| Rabey et al., 2013, parallel | Probable mild to moderate AD (MMSE = 18 to 24, CDR = 1), DSM-IV | HF-rTMS+ CT vs sham + sham CT (AchEIs) | HF-rTMS: 10 Hz, 90% MT for Bil DLPFC and Broca’s area, 110% MT for Bil pSAC and Wernicke’s area, 1300 pulses (max: 1500 pulses), 30 sessions for the Bil DLPFC, Bil pSAC, Broca’s and Wernicke’s areas | No patients experienced side effects or adverse events. |
| Ahmed et al., 2012, parallel, 3-armed study | Probable AD, NINCDS-ADRDA | HF-rTMS vs LF-rTMS vs sham | HF-rTMS (20 Hz, 90% MT, 2000 pulses, 5 sessions) vs LF-rTMS (1Hz, 100% MT, 2000 pulses, 5 sessions) for the Bil DLPFC | All the patients tolerated rTMS well without any adverse effects. |
| Cotelli et al., 2011, parallel | Probable moderate AD (MMSE = 16), NINCDS-ADRDA | HF-rTMS vs sham (AchEIs) | HF-rTMS: 20 Hz, 110% MT, 2000 pulses, 10 sessions for the Lt DLPFC | All participants tolerated rTMS well and did not report any adverse effects. |
| NCT01504958, 2010, parallel | AD, NINCDS-ADRDA and DSM-IV | HF-rTMS + CT vs sham | HF-rTMS (20 Hz, N/A, 1800 pulses, 30 sessions) for the Bil DLPFC, Bil pSAC, and Broca’s areas | One subject experienced serious adverse events in the sham rTMS with sham cognitive training group (a 5cm contusion and subtle rib fracture resulting from a fall at home). Five subjects experienced adverse events in the rTMS with cognitive training group. These adverse events included hearing impairment (n = 1), blurry vision (n = 1), neck pain (n = 3), scalp pain (n = 3), soreness (n = 1), achiness (n = 1), muscle heaviness (n = 1), headache (n = 5), tiredness (n = 3), dizziness (n = 1), and anxiousness (n = 1). |
| Author, year, study design | Population, diagnostic criteria | Intervention (medications, cognitive training) | Protocol (frequency, intensity, pulses per condition, total stimulation sessions*) for the brain area(s) | Adverse events |
|---------------------------|---------------------------------|-----------------------------------------------|-------------------------------------------------------------------------------------------------|---------------|
| Das et al., 2019, parallel | MCI (CDR = 0.5, MMSE = 24 to 30), Petersen criteria | atDCS + CT vs sham + CT, 22 (atDCS, 12), 62.9 ± 8.0, 72.7% | atDCS (2 mA, 20 mins, 8, 20 s) for the inferior frontal gyrus (Ref: contralateral shoulder) | Unreported |
| Gomes et al., 2019, parallel | MCI, Petersen criteria | atDCS vs sham, 58 (atDCS, 29), 72.3 ± 8.6, 72.5% | atDCS (2 mA, 30 mins, 10, 30 s) for the Lt DLPFC (Ref: Rt supraorbital area) | Unreported |
| Im et al., 2019, parallel | Probable AD (CDR = 0.5 or 1), NINCDS-ADRDA or DSM-IV | atDCS vs sham (AchEIs), 20 (atDCS, 12), 73.1 ± 7.9, 83.1% | atDCS (2 mA, 30 mins, 180, 30 s) for the Lt DLPFC (Ref: Rt DLPFC) | Unreported |
| Inagawa et al., 2019, parallel | Mild or major neurocognitive disorder (MMSE ≥ 18, CDR ≤ 2), DSM-V | atDCS + CT vs sham + CT (anti-dementia medications), 19 (atDCS, 7), 76.3 ± 7.0, 50.0% | atDCS (2 mA, 20 mins, 10, 30 s) for the Lt DLPFC (Ref: Rt supraorbital area) | Adverse events were reported 11 in tDCS and 33 in sham group without significant difference. Neither severe adverse events nor the need for medications by adverse events were reported in each group. |
| Khedr et al., 2019, parallel | Probable AD, NINCDS-ADRDA ADRDA | atDCS vs sham (memantine), 46 (atDCS, 23), 64.7 ± 4.1, 40.8% | atDCS (2 mA, 20 mins, 10, 30 s) for the Bil temporal-parietal region (Ref: deltoid muscle) | All the patients tolerated tDCS well without major adverse effects. Minor effects were observed in 2 patients in the active tDCS group who recorded itching, headache, and dizziness that disappeared after a few hours after the first session, but not in subsequent sessions. |

Abbreviations: MCI = mild cognitive impairment; CDR = Clinical Dementia Rating; MMSE = Mini-Mental State Examination; atDCS = anodal tDCS; CT = cognitive training; tDCS = transcranial direct current stimulation; DLPFC = dorsolateral prefrontal cortex; AchEIs = acetylcholinesterase inhibitors; Lt = left; Rt = right; C時の = 76.3 ± 7.0, 50.0%; Bil = bilateral.
| Author, year, study design | Population, diagnostic criteria | Intervention (medications, cognitive training) | Protocol (frequency, intensity, pulses per condition, total stimulation sessions*) for the brain area(s) | Adverse events |
|---------------------------|-------------------------------|---------------------------------|-------------------------------------------------|----------------|
| Lu et al., 2019, parallel, 3-armed study | Mild neurocognitive disorder (CDR ≤ 0.5, MMSE = 22 to 27), DSM-V | atDCS + CT vs sham + CT vs atDCS + sham CT, 201 (atDCS + CT, 69; sham + CT, 64), 74.0 ± 6.5, 53.8% | atDCS (2 mA, 10 mins, 12, 30 s) for Lt lateral temporal cortex (Ref: contralateral upper limb) | Three cases had skin lesions under the cathodal electrode during repeated sessions of tDCS. No differences between tDCS + CT group (2/69) and tDCS + sham CT (1/68). |
| Martin et al., 2019, parallel | MCI, NIAAA criteria | atDCS + CT vs sham + CT (no AChEIs), 68 (atDCS, 33), 71.7 ± 6.4, 66.2% | atDCS (2 mA, 30 mins, 15, 30 s) for the Lt DLPFC (Ref: Rt DLPFC) | No serious adverse effects were reported. All minor adverse effects without significant difference between groups were reported, including redness, tingling, mild burning, pain, nausea, light headedness, headache, blurred vision, and fatigue. For the ITT sample, the most common adverse events reported across all sessions were: tingling (25.9%), redness (16.2%), mild burning (11%), and itching (10.5%). |
| Manor et al., 2018, parallel | MCI (MMSE ≥ 18), unknown criteria | atDCS vs sham, 19 (atDCS, 9), 80.4 ± 4.3, 52.7% | atDCS (2 mA, 20 mins, 10, 60 s) for the Lt DLPFC (Ref: Rt supraorbital area) | No significant differences were found between groups. |
| Bystad et al., 2016, parallel | Probable AD (MMSE ≥ 18), unknown criteria | atDCS vs sham (AchEIs), 25 (atDCS, 13), 72.6 ± 8.7, 44.6% | atDCS (2 mA, 30 mins, 6, 30 s) for the Lt temporal cortex (Ref: Rt frontal cortex) | The tDCS intervention was both safe and well-tolerated, so no adverse effects were reported. |
| Cotelli et al., 2014, parallel | Probable mild to moderate AD, NINCDS-ADRDA | atDCS + CT vs sham + CT (AchEIs), 24 (atDCS, 12), 75.7 ± 5.5, 79.2% | atDCS (2 mA, 25 mins, 10, 40 s) for the Lt DLPFC (Ref: Rt deltoid) | Unreported |
| Author, year, study design | Population, diagnostic criteria | Intervention (medications, cognitive training) | Protocol (frequency, intensity, pulses per condition, total stimulation sessions*) for the brain area(s) | Adverse events |
|-----------------------------|--------------------------------|-----------------------------------------------|-------------------------------------------------|---------------|
| Khedr et al., 2014, parallel | Probable AD, NINCDS-ADRDA | atDCS vs ctDCS vs sham (memantine), 34 (atDCS, 11; ctDCS, 12); 68.9 ± 6.4, 44.1% | atDCS (2 mA, 30 mins, 6, 30 s) for the Lt temporal cortex (Ref: Rt supraorbital region) | All the patients tolerated tDCS well without any adverse effects except two patients under active stimulation recorded itching, headache, and dizziness that were disappear after few hours. |
| Suemoto et al., 2014, parallel | Probable or possible AD (MMSE = 10 to 20), NINCDS-ADRDA | atDCS vs sham (anti-dementia medications), 40 (atDCS, 20), 80.4 ± 7.7, 70% | atDCS (2 mA, 20 mins, 6, 20 s) for the Lt DLPFC (Ref: Rt orbit) | Some minor side effects, namely scalp burning sensation and tingling, were more common in the tDCS patients compared to sham group (P ¼ 0.03 and P ¼ 0.003, respectively). Other side effects were similar in both groups of stimulation. |
| Yun et al., 2016, parallel | MCI, Petersen criteria | atDCS vs sham, 16 (tDCS 8), 73.9 ± 6.2, 68.8% | atDCS (2 mA, 30 mins, 9, 20 s) for the Lt DLPFC | No patient reported adverse effects. |
| Boggio et al., 2012, crossover | AD (MMSE > 15), NINCDS-ADRDA and DSM-IV | atDCS vs sham (AChEIs), 15, 78.9 ± 8.4, 46.7% | atDCS (2 mA, 30 mins, 5, 30 s) for the Bil temporal cortex (Ref: Rt deltoid) | All 15 patients tolerated tDCS therapy well and none of them reported adverse effects. |

AChEIs: acetylcholinesterase inhibitors; AD: Alzheimer’s disease; ADAS-Cog: Alzheimer’s Disease Assessment Scale-cognitive subscale; AVLT: Auditory Verbal Learning Test; BEHAVE-AD: Behavioral Pathology in Alzheimer’s disease rating scale; CDR: Clinical Dementia Rating; CDT: Clock Drawing Test; CET: Cognitive Estimation Test; CVLT: California Verbal Learning Test; DCT: Digit Cancellation Task; DLPFC: dorsolateral prefrontal cortex; DSM: Diagnostic and Statistical Manual of Mental Disorders; EXE: executive function; EXIT-25: Executive interview; FAB: Frontal Assessment Battery; GDS: Geriatric Depression Scale; HAMA: Hamilton Anxiety Rating Scale; HAMD: Hamilton Depression Rating Scale; HF-rTMS: high frequency rTMS; LANG: language function; LF-rTMS: low frequency rTMS; MADRS: Montgomery–Asberg Depression Rating Scale; MEM: memory function; MMSE: Mini-Mental State Examination; MoCA: Montreal Cognitive Assessment; N/A: not available; NINCDS-ADRDA: National Institute of Neurological and Communicative Diseases and Stroke/Alzheimer’s Disease and related disorders association; NPS: neuropsychiatric symptoms; PIQ: performance IQ; PNT: Picture Naming Task; RAVLT: Rey Auditory Verbal Learning Test; RBMT: Rivermead Behavioral Memory Test; Ref: reference area; SCP: Serial Curve Position; TMT-B: Trail
Making Test part B; VF/AN: verbal fluency/animal naming; VRT: Visual Recognition Task; WAIS-III: Wechsler adult intelligent scale-third edition; WIA: Word Image Association; 3MS: Modified Mini-Mental State Examination; aDCS: anodal transcranial direct current stimulation; cDCS: cathodal transcranial direct current stimulation; rTMS: repetitive transcranial magnetic stimulation; pSAC: parietal somatosensory association cortex.

a Not including stimulation sessions in the maintenance period.

b Dubois B et al., Preclinical Alzheimer's disease: Definition, natural history, and diagnostic criteria. Alzheimers Dement. 2016 Mar;12(3):292-323.

c Petersen RC et al., Mild cognitive impairment: clinical characterization and outcome. Arch. Neurol. 1999;56,303–308.

d Whiteside DM et al., Verbal Fluency: Language or Executive Function Measure? Appl Neuropsychol Adult. 2016;23(1):29-34.
Appendix 11 (eTable S4). Risk of bias of the included studies

| Domain                                      | Low risk of bias | Unclear risk of bias | High risk of bias |
|---------------------------------------------|------------------|----------------------|-------------------|
| Random sequence generation (selection bias)| 11.1%            |                      |                   |
| Allocation concealment (selection bias)     | 0%               |                      |                   |
| Blinding of participants and personnel (performance bias) | 7.4%            |                      |                   |
| Blinding of outcome assessment (detection bias) | 3.7%            |                      |                   |
| Incomplete outcome data (attrition bias)    | 0%               |                      |                   |
| Selective reporting (reporting bias)        | 0%               |                      |                   |
| Other bias                                  | 0%               |                      |                   |

The proportion of high risk of bias in each domain

| Year  | Random sequence generation (selection bias) | Allocation concealment (selection bias) | Blinding of participants and personnel (performance bias) | Blinding of outcome assessment (detection bias) | Incomplete outcome data (attrition bias) | Selective reporting (reporting bias) | Other bias |
|-------|---------------------------------------------|-----------------------------------------|----------------------------------------------------------|-------------------------------------------------|---------------------------------------|-------------------------------------|------------|
| 2017  | 2                                           | 2                                       | 2                                                        | 2                                               | 2                                     | 2                                   |            |
| 2016  | 2                                           | 2                                       | 2                                                        | 2                                               | 2                                     | 2                                   |            |
| 2015  | 2                                           | 2                                       | 2                                                        | 2                                               | 2                                     | 2                                   |            |
| 2014  | 2                                           | 2                                       | 2                                                        | 2                                               | 2                                     | 2                                   |            |
| 2013  | 2                                           | 2                                       | 2                                                        | 2                                               | 2                                     | 2                                   |            |
| 2012  | 2                                           | 2                                       | 2                                                        | 2                                               | 2                                     | 2                                   |            |
| 2011  | 2                                           | 2                                       | 2                                                        | 2                                               | 2                                     | 2                                   |            |
| 2010  | 2                                           | 2                                       | 2                                                        | 2                                               | 2                                     | 2                                   |            |
| 2009  | 2                                           | 2                                       | 2                                                        | 2                                               | 2                                     | 2                                   |            |
| 2008  | 2                                           | 2                                       | 2                                                        | 2                                               | 2                                     | 2                                   |            |
| 2007  | 2                                           | 2                                       | 2                                                        | 2                                               | 2                                     | 2                                   |            |
| 2006  | 2                                           | 2                                       | 2                                                        | 2                                               | 2                                     | 2                                   |            |
| 2005  | 2                                           | 2                                       | 2                                                        | 2                                               | 2                                     | 2                                   |            |
| 2004  | 2                                           | 2                                       | 2                                                        | 2                                               | 2                                     | 2                                   |            |
| 2003  | 2                                           | 2                                       | 2                                                        | 2                                               | 2                                     | 2                                   |            |
| 2002  | 2                                           | 2                                       | 2                                                        | 2                                               | 2                                     | 2                                   |            |
| 2001  | 2                                           | 2                                       | 2                                                        | 2                                               | 2                                     | 2                                   |            |
| 2000  | 2                                           | 2                                       | 2                                                        | 2                                               | 2                                     | 2                                   |            |
| 1999  | 2                                           | 2                                       | 2                                                        | 2                                               | 2                                     | 2                                   |            |
| 1998  | 2                                           | 2                                       | 2                                                        | 2                                               | 2                                     | 2                                   |            |
| 1997  | 2                                           | 2                                       | 2                                                        | 2                                               | 2                                     | 2                                   |            |
| 1996  | 2                                           | 2                                       | 2                                                        | 2                                               | 2                                     | 2                                   |            |
| 1995  | 2                                           | 2                                       | 2                                                        | 2                                               | 2                                     | 2                                   |            |
| 1994  | 2                                           | 2                                       | 2                                                        | 2                                               | 2                                     | 2                                   |            |
| 1993  | 2                                           | 2                                       | 2                                                        | 2                                               | 2                                     | 2                                   |            |
| 1992  | 2                                           | 2                                       | 2                                                        | 2                                               | 2                                     | 2                                   |            |

Chu C-S, et al. J Neurol Neurosurg Psychiatry 2020;0:1–9. doi: 10.1136/jnnp-2020-323870
Appendix 12 (eTable S5). Inconsistency tests for general cognitive function

**Node-splitting model**

| Comparison | Number of Studies | Direct Evidence | Random effects model | MD 95% CI | Immediate effects on general cognition | Long-lasting effects on general cognition |
|------------|-------------------|-----------------|----------------------|-----------|----------------------------------------|------------------------------------------|
| atDCS=atDCS | 1 0.66           |                 |                      |           | –0.63 [−2.07; 1.19]                    | –0.83 [−3.29; 1.63]                     |
| Indirect estimate |                |                 |                      |           | −0.41 [−3.79; 2.79]                    | −0.35 [−3.75; 3.06]                     |
| Network estimate |                 |                 |                      |           | −0.40 [−2.47; 1.69]                    | −1.80 [−4.17; 0.58]                     |
| atDCS+CT-atDCS+sham_CT | 1 0.94 |                 |                      |           | 0.20 [−1.08; 1.48]                     | 0.18 [−1.12; 1.40]                      |
| Direct estimate |                |                 |                      |           | 0.22 [−1.06; 1.50]                     | 2.80 [−2.84; 8.45]                      |
| Indirect estimate |                |                 |                      |           | 0.20 [−1.04; 1.44]                     | 0.31 [−0.96; 1.58]                      |
| Network estimate |                 |                 |                      |           | –0.01 [−1.20; 1.22]                    | –6.19 [−29.86; 42.06]                   |
| atDCS+sham_BT-atDCS+sham_BT+CT | 1 0.94 |                 |                      |           | 0.20 [−1.11; 1.51]                     | 0.02 [−1.25; 1.23]                      |
| Direct estimate |                |                 |                      |           | 0.22 [−1.77; 3.21]                     | 0.74 [−1.24; 2.62]                      |
| Indirect estimate |                |                 |                      |           | 0.20 [−1.06; 1.47]                     | 0.72 [−1.25; 2.69]                      |
| Network estimate |                 |                 |                      |           | –0.00 [−1.34; 1.34]                    | –1.59 [−3.50; 0.39]                     |
| atDCS+sham_BT | 1 0.84           |                 |                      |           | 1.08 [−0.08; 3.00]                     | 1.96 [−0.26; 4.16]                      |
| Direct estimate |                |                 |                      |           | 1.21 [−0.52; 3.95]                     | 1.96 [−0.26; 4.16]                      |
| Indirect estimate |                |                 |                      |           | 1.00 [−0.87; 3.04]                     | 0.27 [−1.48; 1.91]                      |
| Network estimate |                 |                 |                      |           | 0.20 [−1.12; 1.54]                     | 0.20 [−1.12; 1.54]                      |
| HYFTMS+HYFTMS | 1 0.84           |                 |                      |           | 2.05 [−0.04; 4.06]                     | 2.20 [−0.08; 4.48]                      |
| Direct estimate |                |                 |                      |           | 1.92 [−0.47; 5.30]                     | 1.96 [−0.77; 4.59]                      |
| Indirect estimate |                |                 |                      |           | 1.40 [−0.44; 3.24]                     | 2.79 [0.75; 4.87]                       |
| Network estimate |                 |                 |                      |           | –0.08 [−2.08; 1.92]                    | –1.95 [−7.77; 3.85]                     |
| HYFTMS+sham_BT | 1 0.85           |                 |                      |           | –0.08 [−2.08; 1.92]                    | 0.20 [−0.05; 0.45]                      |
| Direct estimate |                |                 |                      |           | –0.10 [−2.08; 1.88]                    | 0.26 [−0.06; 0.58]                      |
| Indirect estimate |                |                 |                      |           | –0.70 [−2.54; 1.14]                    | –0.92 [−3.38; 1.54]                     |
| Network estimate |                 |                 |                      |           | –0.40 [−2.39; 1.59]                    | –1.40 [−3.50; 0.70]                     |

All P-values for the differences between direct and indirect estimates were > 0.05

**Design-by-treatment**

| Comparison | Number of Studies | Direct Evidence | Random effects model | MD 95% CI | Immediate effects on general cognition | Long-lasting effects on general cognition |
|------------|-------------------|-----------------|----------------------|-----------|----------------------------------------|------------------------------------------|
| atDCS=atDCS | 1 0.73           |                 |                      |           | –0.83 [−3.29; 1.63]                    | –0.83 [−3.29; 1.63]                     |
| Direct estimate |                |                 |                      |           | –1.80 [−4.17; 0.58]                    | –3.50 [−6.30; 2.30]                     |
| Indirect estimate |                |                 |                      |           | 0.20 [−1.08; 1.48]                     | 0.18 [−1.12; 1.40]                      |
| Network estimate |                 |                 |                      |           | 0.22 [−1.06; 1.47]                     | 2.80 [−2.84; 8.45]                      |
| atDCS+CT-atDCS+sham_CT | 2 0.96 |                 |                      |           | 0.18 [−1.12; 1.40]                     | 0.31 [−0.96; 1.58]                      |
| Direct estimate |                |                 |                      |           | 2.80 [−2.84; 8.45]                     | 6.19 [−29.86; 42.06]                    |
| Indirect estimate |                |                 |                      |           | 0.31 [−0.96; 1.58]                     | 0.02 [−1.25; 1.23]                      |
| Network estimate |                 |                 |                      |           | 0.04 [−1.20; 1.22]                     | 0.04 [−1.20; 1.22]                      |
| atDCS+sham_BT+CT | 3 1.00 |                 |                      |           | 6.19 [−29.86; 42.06]                    | 6.19 [−29.86; 42.06]                    |
| Direct estimate |                |                 |                      |           | 6.19 [−29.86; 42.06]                    | 6.19 [−29.86; 42.06]                    |
| Indirect estimate |                |                 |                      |           | –1.95 [−7.77; 3.85]                    | –1.95 [−7.77; 3.85]                     |
| Network estimate |                 |                 |                      |           | 2.96 [0.35; 5.57]                      | 2.96 [0.35; 5.57]                       |

All P-values for the differences between direct and indirect estimates were > 0.05

**Q** = 2.4, df = 3, p = 0.49

**Q** = 5.4, df = 5, p = 0.37
Appendix 13 (eFigure S6). Funnel plots for the primary outcome

**Immediate effect**

\[ p = 0.8381 \text{ (Egger)} \]

**Long-lasting effect**

\[ p = 0.9572 \text{ (Egger)} \]
### Appendix 14 (eTable S6). Network meta-regression of immediate effect on general cognition

| Effect modifier | Protocol          | Coef. | SE   | Z    | P     | 95% LL  | 95% UL  |
|-----------------|-------------------|-------|------|------|-------|---------|---------|
| MCI             | HFrTMS            | -1.56 | 0.99 | -1.57| 0.12  | -3.50   | 0.39    |
|                 | atDCS             | -0.29 | 0.84 | -0.35| 0.72  | -1.93   | 1.34    |
|                 | atDCS+CT          | 2.45  | 651.41| 0.00 | 1.00  | -1274.28| 1279.19 |
|                 | sham_BS+CT        | 2.46  | 651.40| 0.00 | 1.00  | -1274.27| 1279.20 |
| Sample size     | HFrTMS            | 0.05  | 0.06 | 0.85 | 0.39  | -0.07   | 0.17    |
|                 | HFrTMS+CT         | -0.02 | 3.39 | 0.00 | 1.00  | -6.67   | 6.63    |
|                 | LFrTMS            | -0.02 | 0.09 | -0.23| 0.82  | -0.20   | 0.16    |
|                 | atDCS             | -0.01 | 0.04 | -0.23| 0.82  | -0.08   | 0.06    |
|                 | atDCS+CT          | 0.01  | 4.03 | 0.00 | 1.00  | -7.89   | 7.90    |
|                 | sham_BS+CT        | 0.01  | 4.03 | 0.00 | 1.00  | -7.89   | 7.90    |
|                 | sham_BS+sham_CT   | 1.01  | 3.42 | 0.30 | 0.77  | -5.68   | 7.71    |
| Age             | HFrTMS            | -0.38 | 0.25 | -1.49| 0.14  | -0.88   | 0.12    |
|                 | HFrTMS+CT         | -0.06 | 25.03| 0.00 | 1.00  | -49.12  | 49.00   |
|                 | atDCS             | -0.08 | 0.04 | -1.83| 0.07  | -0.17   | 0.01    |
|                 | atDCS+CT          | 0.25  | 141.34| 0.00 | 1.00  | -276.78 | 277.28  |
|                 | sham_BS+CT        | 0.25  | 141.37| 0.00 | 1.00  | -276.83 | 277.33  |
|                 | sham_BS+sham_CT   | 0.08  | 25.04| 0.00 | 1.00  | -48.99  | 49.16   |
| Female          | HFrTMS            | 0.15  | 0.09 | 1.65 | 0.10  | -0.03   | 0.32    |
|                 | HFrTMS+CT         | 0.02  | 18.60| 0.00 | 1.00  | -36.44  | 36.48   |
|                 | atDCS             | 0.00  | 0.03 | 0.94 | 0.36  | -0.05   | 0.05    |
|                 | atDCS+CT          | -0.07 | 34.59| 0.00 | 1.00  | -67.86  | 67.72   |
|                 | sham_BS+CT        | -0.07 | 34.58| 0.00 | 1.00  | -67.85  | 67.71   |
|                 | sham_BS+sham_CT   | 0.00  | 18.60| 0.00 | 1.00  | -36.46  | 36.46   |
| MMSE            | HFrTMS            | -0.06 | 0.08 | -0.76| 0.45  | -0.22   | 0.09    |
|                 | HFrTMS+CT         | -0.24 | 128.62| 0.00 | 1.00  | -252.34 | 251.85  |
|                 | LFrTMS            | -0.17 | 0.23 | -0.73| 0.47  | -0.62   | 0.28    |
|                 | atDCS             | -0.06 | 0.07 | -0.83| 0.41  | -0.21   | 0.08    |
|                 | atDCS+CT          | 0.47  | 111.07| 0.00 | 1.00  | -217.22 | 218.16  |
|                 | sham_BS+CT        | 0.48  | 111.06| 0.00 | 1.00  | -217.20 | 218.16  |
|                 | sham_BS+sham_CT   | 0.59  | 128.62| 0.00 | 1.00  | -251.51 | 252.69  |
| AchEI           | HFrTMS            | 1.02  | 0.39 | 1.75 | 0.08  | -0.13   | 2.17    |
|                 | atDCS             | -0.30 | 0.82 | -0.36| 0.72  | -1.91   | 1.32    |
|                 | atDCS+CT          | -2.45 | 649.78| 0.00 | 1.00  | -1276.01| 1271.10 |
|                 | sham_BS+CT        | -2.46 | 649.78| 0.00 | 1.00  | -1276.02| 1271.09 |

*: P-value < 0.05

Abbreviation: AchEi, acetylcholine esterase inhibitor; ctDCS, cathodal transcranial direct current stimulation; Coef., coefficient; CT, cognitive training; HF, high-frequency; LF, low-frequency; LL, lower limit; MCI, mild cognitive impairment; MMSE, mini-mental status examination; rTMS, repetitive transcranial magnetic stimulation; SE, standard error; sham_BS, sham brain stimulation; sham_CT, sham cognitive training; SMD, standardized mean difference; tDCS, transcranial direct current stimulation; UL, upper limit.
### Appendix 15 (eTable S7). Network meta-regression of 1-month F/U effect on general cognition

| Effect modifier | Protocol          | Coef  | SE   | Z    | P    | 95% LL | 95% UL |
|-----------------|-------------------|-------|------|------|------|--------|--------|
| MCI             | atDCS+CT          | 0.37  | 652.64 | 0.00 | 1.00 | -1278.78 | 1279.52 |
|                 | atDCS+sham_CT     | 0.93  | 652.64 | 0.00 | 1.00 | -1278.22 | 1280.08 |
|                 | sham_BS+CT        | 0.65  | 652.64 | 0.00 | 1.00 | -1278.49 | 1279.80 |
| Sample size     | HF/TMS            | 0.05  | 0.05  | 0.86 | 0.39 | -0.06  | 0.15   |
|                 | HF/TMS+CT         | 0.07  | 2.99  | 0.02 | 0.98 | -5.78  | 5.93   |
|                 | LF/TMS            | 0.09  | 0.13  | 0.70 | 0.49 | -0.16  | 0.34   |
|                 | atDCS             | 0.87  | 0.64  | 1.36 | 0.17 | -0.38  | 2.11   |
|                 | atDCS+CT          | -0.15 | 3.00  | -0.05 | 0.96 | 2.60  | 5.72   |
|                 | atDCS+sham_CT     | -0.15 | 3.00  | -0.05 | 0.96 | 2.60  | 5.72   |
|                 | sham_BS+CT        | -0.15 | 3.00  | -0.05 | 0.96 | -6.02  | 5.72   |
|                 | sham_BS+sham_CT   | 0.64  | 3.01  | 0.21 | 0.83 | -5.26  | 6.54   |
| Age             | HF/TMS            | -0.16 | 0.48  | -0.34 | 0.74 | -1.11  | 0.79   |
|                 | HF/TMS+CT         | 0.25  | 22.88 | 0.01 | 0.99 | -44.59 | 45.08  |
|                 | atDCS             | -0.35 | 0.26  | -1.34 | 0.18 | -0.85  | 0.16   |
|                 | atDCS+CT          | 1.86  | 23.15 | 0.08 | 0.94 | -43.52 | 47.23  |
|                 | atDCS+sham_CT     | 1.64  | 23.15 | 0.07 | 0.94 | -43.75 | 47.02  |
|                 | sham_BS+CT        | 1.75  | 23.14 | 0.08 | 0.94 | -43.60 | 47.11  |
|                 | sham_BS+sham_CT   | 0.53  | 22.91 | 0.02 | 0.98 | -44.38 | 45.43  |
| Female          | HF/TMS            | 0.12  | 0.26  | 0.48 | 0.63 | -0.38  | 0.62   |
|                 | HF/TMS+CT         | 0.02  | 12.26 | 0.00 | 1.00 | -24.00 | 24.05  |
|                 | atDCS             | -1.33 | 0.92  | -1.45 | 0.15 | -3.13  | 0.47   |
|                 | atDCS+CT          | -0.05 | 12.26 | 0.00 | 1.00 | -24.08 | 23.97  |
|                 | atDCS+sham_CT     | -0.05 | 12.26 | 0.00 | 1.00 | -24.08 | 23.97  |
|                 | sham_BS+CT        | -0.02 | 12.26 | 0.00 | 1.00 | -24.04 | 24.01  |
|                 | sham_BS+sham_CT   | 0.47  | 12.34 | 0.04 | 0.97 | -23.71 | 24.66  |
| MMSE            | HF/TMS            | -0.06 | 0.08  | -0.76 | 0.45 | -0.22  | 0.09   |
|                 | HF/TMS+CT         | -0.24 | 128.62 | 0.00 | 1.00 | -252.34 | 251.85 |
|                 | LF/TMS            | -0.17 | 0.23  | -0.73 | 0.47 | -0.62  | 0.28   |
|                 | atDCS             | -0.06 | 0.07  | -0.83 | 0.41 | -0.21  | 0.08   |
|                 | atDCS+CT          | 0.47  | 111.07 | 0.00 | 1.00 | -217.22 | 218.16 |
|                 | sham_BS+CT        | 0.48  | 111.06 | 0.00 | 1.00 | -217.20 | 218.16 |
|                 | sham_BS+sham_CT   | 0.59  | 128.62 | 0.00 | 1.00 | -251.51 | 252.69 |
| AchE1           | HF/TMS            | 0.86  | 1.96  | 0.44 | 0.66 | -2.98  | 4.69   |
|                 | HF/TMS+CT         | 0.00  | 407.58 | 0.00 | 1.00 | -798.84 | 798.83 |
|                 | atDCS+CT          | -0.62 | 407.58 | 0.00 | 1.00 | -799.47 | 798.23 |
|                 | atDCS+sham_CT     | -1.19 | 407.59 | 0.00 | 1.00 | -800.04 | 797.66 |
|                 | sham_BS+CT        | -0.91 | 407.58 | 0.00 | 1.00 | -799.75 | 797.93 |
| sham_BS+sham_C | 0.50 | 407.58 | 0.00 | 1.00 | -798.34 | 799.34 |

*: P-value < 0.05

Abbreviation: AchEI, acetylcholine esterase inhibitor; ctDCS, cathodal transcranial direct current stimulation; Coef., coefficient; CT, cognitive training; HF, high-frequency; LF, low-frequency; LL, lower limit; MCI, mild cognitive impairment; MMSE, mini-mental status examination; rTMS, repetitive transcranial magnetic stimulation; SE, standard error; sham_BS, sham brain stimulation; sham_CT, sham cognitive training; SMD, standardized mean difference; tDCS, transcranial direct current stimulation; UL, upper limit.
Appendix 16 (eFigure S7). Efficacy of sham rTMS vs sham tDCS in general cognitive function

Immediate Effect: Sham_rTMS vs Sham_tDCS in General Cognition

| Group by study name | Statistics for each study | Std diff in means | Std error | Variance | Lower limit | Upper limit | Z-Value | p-Value |
|---------------------|---------------------------|------------------|-----------|----------|-------------|------------|---------|---------|
| rTMS                |                           |                  |           |          |             |            |         |         |
| Koch 2018           |                           | 0.367            | 0.271     | 0.467    | 0.314       | 0.389      | 1.252   | 0.215   |
| rTMS                |                           | 0.250            | 0.201     | 0.297    | -0.224      | -0.029     | 1.245   | 0.215   |
| Lee 2016            |                           | 0.265            | 0.278     | 0.296    | 0.265       | 0.289      | 1.265   | 0.215   |
| Rufford 2015        |                           | 0.311            | 0.251     | 0.326    | -0.385      | 0.004      | 1.421   | 0.156   |
| Patey 2013          |                           | 0.111            | 0.275     | 0.428    | 0.049       | 0.403      | 1.386   | 0.087   |
| Cobelli 2011        |                           | 0.060            | 0.346     | 0.426    | 0.009       | 0.559      | 1.001   | 0.312   |
| Ahmed 2012          |                           | 0.089            | 0.200     | 0.394    | 0.034       | 0.402      | 1.048   | 0.297   |
| Zhang 2019          |                           | 0.238            | 0.221     | 0.369    | -0.010      | 0.760      | 1.377   | 0.169   |
| Sabrakh 2019        |                           | 1.245            | 0.146     | 0.201    | 0.889       | 1.531      | 5.530   | 0.000   |
| ICDIS               |                           | 0.349            | 0.186     | 0.292    | 0.023       | 0.674      | 2.101   | 0.036   |
| Gomes 2019          |                           | 0.000            | 0.144     | 0.201    | 0.002       | 0.000      | 1.000   | 0.300   |
| Inagami 2019        |                           | 0.010            | 0.224     | 0.050    | -0.449      | 0.282      | 0.000   | 1.000   |
| Lu 2019             |                           | 0.246            | 0.058     | 0.101    | 0.056       | 0.438      | 2.508   | 0.012   |
| Chen 2018           |                           | 0.000            | 0.205     | 0.246    | 0.000       | 0.000      | 1.000   | 0.300   |
| Khare 2019          |                           | 0.173            | 0.163     | 0.208    | 0.042       | 0.329      | 1.000   | 0.300   |
| Im 2019             |                           | -0.332           | 0.281     | 0.284    | 0.079       | 0.279      | -1.180  | 0.238   |
| ICDS               |                           | 0.077            | 0.215     | 0.246    | 0.046       | 0.399      | 0.380   | 0.719   |
| Khare 2014          |                           | 0.465            | 0.246     | 0.260    | 0.017       | 0.947      | 1.891   | 0.059   |
| Somarco 2014        |                           | -0.122           | 0.174     | 0.203    | 0.030       | 0.463      | 0.218   | 0.804   |
| Baggio 2012         |                           | 0.258            | 0.203     | 0.241    | -0.140      | 0.657      | 1.270   | 0.224   |
| ICDIS               |                           | 0.058            | 0.066     | 0.075    | 0.190       | 0.848      | 0.596   |         |

Group Difference: P-value = 0.106

1-Month F/U Effect: Sham_rTMS vs Sham_tDCS in General Cognition

| Group by study name | Statistics for each study | Std diff in means | Std error | Variance | Lower limit | Upper limit | Z-Value | p-Value |
|---------------------|---------------------------|------------------|-----------|----------|-------------|------------|---------|---------|
| rTMS                |                           |                  |           |          |             |            |         |         |
| Pettles 2018        |                           | -0.217           | 0.391     | 0.568    | -0.729      | 0.295      | -0.831  | 0.406   |
| rTMS                |                           | 0.204            | 0.244     | 0.266    | 0.286      | 1.343      | -0.239  | 0.632   |
| NCT01509058         |                           | -0.030           | 0.346     | 0.120    | 0.709      | 0.949      | -0.096  | 0.931   |
| NCT01509059         |                           | -0.174           | 0.319     | 0.102    | 0.798      | 0.451      | -0.545  | 0.586   |
| Lee 2016            |                           | 0.804            | 0.315     | 0.199    | 0.396      | 1.421      | 2.952   | 0.011   |
| Yu 2015             |                           | 0.273            | 0.150     | 0.052    | -0.301     | 0.756      | 1.763   | 0.078   |
| Ahmed 2012          |                           | 0.050            | 0.230     | 0.040    | -0.392     | 0.262      | 0.300   | 1.000   |
| Zhang 2019          |                           | 0.212            | 0.217     | 0.047    | -0.214     | 0.638      | 0.977   | 0.329   |
| Sabirakh 2019       |                           | 0.452            | 0.115     | 0.013    | -0.226     | 0.677      | 3.029   | 0.0030  |
| ICDIS               |                           | 0.253            | 0.108     | 0.012    | -0.042     | 0.405      | 2.300   | 0.019   |
| Inagami 2019        |                           | 0.098            | 0.224     | 0.050    | -0.341     | 0.538      | 0.439   | 0.680   |
| Lu 2019             |                           | 0.246            | 0.098     | 0.010    | 0.054      | 0.439      | 2.508   | 0.012   |
| Chen 2018           |                           | 0.000            | 0.246     | 0.060    | -0.460     | 0.460      | 0.000   | 1.000   |
| ICDS               |                           | 0.341            | 0.230     | 0.053    | -0.110     | 0.792      | 1.462   | 0.158   |
| Khare 2014          |                           | 0.310            | 0.239     | 0.057    | -0.159     | 0.778      | 1.296   | 0.185   |
| Baggio 2012         |                           | 0.172            | 0.201     | 0.041    | -0.223     | 0.697      | 0.654   | 0.533   |
| ICDIS               |                           | 0.217            | 0.071     | 0.005    | 0.078      | 0.395      | 3.073   | 0.002   |

Group Difference: P-value = 0.775