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Effects of non-invasive brain stimulation on cognitive function in healthy aging and Alzheimer's disease: a systematic review and meta-analysis

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Abstract

The study aimed to evaluate the effects of non-invasive brain stimulation on cognitive function in healthy older adults and patients with Alzheimer's disease (AD). A comprehensive literature search was performed on non-invasive stimulation studies published from January 1990 to November 2014 in Pubmed and Web of Science. Fourteen articles with a total of 331 participants were identified as studies with healthy older adults and the mean effect size and 95% confidence interval were estimated. A significant effect size of 0.42 was found for the cognitive outcome. Further subgroup analyses demonstrated more prominent effects for studies delivering the stimulation before the execution of the task and studies applying multiple sessions of stimulation. To assess effects of stimulation on AD patients, eleven studies with a total of 200 patients were included in the analysis. A significant effect size of 1.35 was found for the cognitive outcomes. Subgroup analyses indicated more pronounced effects for studies applying the stimulation during the execution of the task compared to studies delivering the stimulation before the execution of the task. Non-invasive brain stimulation has a positive effect on cognitive function in physiological and pathological aging.

Keywords

meta-analysis; aging; Alzheiner's disease (AD); repetitive transcranial magnetic stimulation (rTMS); transcranial direct current stimulation (tDCS); cognitive function; neuronal plasticity

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Author's disclosure statement

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1. Introduction

Aging is associated with functional decline in a wide range of cognitive domains, including attention, memory, language, and executive functions (Celsis, 2000). These age-related cognitive deficits have a profound impact on older adults' activities of daily living and quality of life (Craik and Bialystok, 2006; Logsdon et al., 2002), and as a consequence, increases burden on societies (Christensen et al., 2009). As the older population continues to grow worldwide, strategies for optimizing and remediating age-associated cognitive decline have gained increasing attention.

Alzheimer's disease (AD) is a neurodegenerative disease manifested by cognitive impairment and behavioral derangement, and AD is the most common cause of dementia in older adults (Plassman et al., 2007). It is estimated that 4% of people under 65 years of age are affected by AD, and the prevalence rises between 40% and 50% by the age of 85 years (Geldmacher and Whitehouse, 1997). To date, cholinesterase inhibitors are the mainstream treatment for patients with AD. However, pharmacological treatments have limited efficacy and is accompanied by adverse side effects (Shafqat, 2008). Given this debilitating disease affects millions of people and the incidence keeps rising due to progressive population aging (Brookmeyer et al., 2007), it is of great importance to develop alternative therapeutic approaches.

Recently, different forms of non-invasive brain stimulation techniques have been applied to healthy older adults and patients with AD in order to improve physiological and pathological aging-related cognitive impairments (Boggio et al., 2011; Vallence and Goldsworthy, 2014; Zimerman and Hummel, 2010). Two main forms of non-invasive brain stimulation techniques are repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS). rTMS is a painless, non-invasive method that modulates cortical activities by delivering strong magnetic pulses to the cortex through the scalp. Depending on stimulation parameters (e.g., duration, stimulus intensity, frequency), rTMS can enhance or suppress cortical excitability in targeted cortical regions (Fregni and Pascual-Leone, 2007; Hallett, 2007; Rubens and Zanto, 2012). In general, high frequency rTMS facilitates cortical excitability (Pascual-Leone et al., 2005; Peinemann et al., 2004), whereas low frequency rTMS suppresses cortical excitability (Muellbacher et al., 2000). The facilitatory effects of high frequency rTMS on various cognitive functions have been documented in multiple studies (Grafman and Wassermann, 1999; Guse et al., 2010) and may be used to treat a variety of cognitive disorders (Anderkova and Rektorova, 2014; Nadeau et al., 2014; Wolwer et al., 2014). In addition to rTMS, tDCS may also be used in a therapeutic context (Kuo et al., 2014). tDCS delivers weak electrical currents to the scalp to modulate neuronal transmembrane potential towards hyperpolarization or depolarization (Creutzfeldt et al., 1962; Purpura and McMurtry, 1965), thereby altering plasticity in the stimulated brain regions (Fricke et al., 2011; Kidgell et al., 2013; Nitsche et al., 2007). Depending on whether anodal or cathodal stimulation is applied, tDCS increases or decreases cortical excitability, respectively (Lang et al., 2005; Nitsche et al., 2008), in turn affecting a wide range of cognitive and behavioral performance measures (Jacobson et al., 2012; Kuo and Nitsche, 2012).

Previous studies have suggested that rTMS (Ahmed et al., 2012; Cotelli et al., 2006, 2008, 2011; Eliasova et al., 2014; Kim et al., 2012; Rabey et al., 2013; Sole-Padulles et al., 2006) or tDCS (Berryhill and Jones, 2012; Boggio et al., 2009, 2012; Cotelli et al., 2014; Ferrucci et al., 2008; Fertonani et al., 2014; Floel et al., 2012; Harty et al., 2014; Holland et al., 2011; Khedr et al., 2014; Manenti et al., 2013; Meinzer et al., 2013, 2014; Park et al., 2014; Ross et al., 2011; Sandrini et al., 2014) may have beneficial effects on various cognitive functions in healthy older adults and patients with AD. By applying a single session of rTMS or tDCS, studies have demonstrated that both of these techniques are capable of positively influencing cognitive functions among older participants (Berryhill and Jones, 2012; Fertonani et al., 2014; Floel et al., 2012; Harty et al., 2014; Kim et al., 2012; Manenti et al., 2013; Meinzer et al., 2013, 2014; Park et al., 2014; Ross et al., 2011; Sandrini et al., 2014; Sole-Padulles et al., 2006) and patients with AD (Ahmed et al., 2012; Boggio et al., 2009, 2012; Cotelli et al., 2006, 2008, 2011; Eliasova et al., 2014; Ferrucci et al., 2008; Khedr et al., 2014). With multiple sessions of stimulation, long-term after-effects of these techniques have been found (Ahmed et al., 2012; Boggio et al., 2012; Cotelli et al., 2011; Khedr et al., 2014). For example, Boggio et al. (2012) demonstrated that 5-days of multiple sessions of anodal tDCS had a long-lasting (4 weeks) favorable effect on visual recognition memory. Similarly, Ahmed et al. (2012) showed that 5-days of high-frequency rTMS improves the mini-mental state exam (MMSE) score in patients with AD at a 3-month follow-up assessment. However, beneficial effects of non-invasive stimulation are not always observed. A randomized-double blind control study revealed that tDCS over prefrontal cortex increases high-risk behavior in older adults (Boggio et al., 2010). Additionally, Cotelli et al. (2014) utilized a 2-week tDCS protocol and did not show measurable differences in a face-name association task between anodal and placebo conditions 3 months after stimulation (Cotelli et al., 2014). Thus, the overall efficacy of non-invasive neural stimulation as a therapeutic is still under debate.

A recent systematic review showed that tDCS can modulate various cognitive functions in different domains; however, the results were inconsistent (Tremblay et al., 2014). Previous studies have revealed that the effects of non-invasive brain stimulation critically depend on the prevailing brain-states (Bullard et al., 2011; Neuling et al., 2013). As the majority of the articles included in this prior review were focused on cognitive performance in healthy young adults, the relatively better baseline performance may have limited the beneficial effects of non-invasive brain stimulation on cognitive function (i.e. ceiling effect). It is possible that the effects of non-invasive brain stimulation on cognitive function may be more prominent in older adults and in patients with Alzheimer's disease since physiological and pathological aging show structural and functional alterations related to neural plasticity (Gutchess, 2014; Oberman and Pascual-Leone, 2013). Supporting this hypothesis, it appears that many studies have exhibited significant enhancement of cognitive function when non-invasive stimulation is applied in older adults (Ahmed et al., 2012; Boggio et al., 2012; Eliasova et al., 2014; Fertonani et al., 2014; Floel et al., 2012; Harty et al., 2014; Khedr et al., 2014; Manenti et al., 2013; Meinzer et al., 2013; Ross et al., 2011; Sandrini et al., 2014), whereas fewer studies have exhibited little to no beneficial effects (Boggio et al., 2010; Cotelli et al., 2014). The conflicting results along with differences in quality and methods across the studies make it difficult to reach a consensus regarding the effects of non-invasive

brain stimulation on physiological and pathological aging-associated cognitive impairments. A systematic review and a meta-analysis of the available data should help us reach a more definitive conclusion about this issue. The primary goal of the present study is to evaluate the potentially favorable effects of rTMS and tDCS on cognitive function in healthy older adults and patients with AD. In addition, we aim to further clarify the variables that may influence the results of stimulation and contribute to a better cognitive outcome.

2. Material and Methods

2.1. Data source and study selection

In order to collect pertinent studies, computerized searches were performed in Pubmed and Web of Science. The search terms were aging/elder/older adult, Alzheimer's disease/AD, repetitive transcranial magnetic stimulation/rTMS, and transcranial direct current stimulation/tDCS. In addition, manual searches of the reference list of retrieved articles and relevant reviews were also conducted. Our search was limited to human studies that were written in English and published from January 1990 to November 2014. For healthy older adult studies, articles that met the following criteria were included: (1) the main goal was to study rTMS or tDCS effects on cognitive function in elders; (2) reports of ≥10 participants receiving non-invasive brain stimulation; (3) outcome measures were quantitatively reported; (4) the study included experimental (real stimulation) and control (sham stimulation) conditions. For studies with AD patients, an additional criterion was added: the participants were diagnosed as AD. We reviewed the full text of articles that appeared to be relevant.

2.2. Quality assessment

To assess the methodological quality of studies included, a modified checklist derived from a quality screening form revised by Moher et al. was used (Moher et al., 2001). The quality of each study was evaluated according to the following criteria: (1) randomization; (2) blinding procedure; (3) drop-out number; (4) statistical comparisons between interventions; (5) point estimates and measures of variability; and (6) description of adverse effects. Randomization was recorded as 1 when the study pointed out that participants were randomly allocated into different groups. Regarding the blinding procedure, the rating ranged from 0 to 2, in which 0 indicated the non-described or non-blinded procedure and 1 and 2 represented single-blind and double-blind design, respectively. Drop-outs were recorded as the number of participants withdrawn from the study. Statistical comparisons as well as point estimates and measures of variability were denoted as 1 when provided. Adverse effects were recorded as the number of participants who exhibited an adverse event as well as the type of event. The quality of the included studies is summarized in the results section (3.4. Quality assessment).

2.3. Quantitative analyses

In order to obtain relevant information from each study, one reviewer (WY.H.) extracted data by using a standard data recording form that included number of participants, study design, mean age, mean mini-mental state examination (MMSE) score, mean years of education, stimulation protocol (i.e., stimulation tool, frequency of rTMS, intensity, numbers

of rTMS pulses, duration of tDCS, target brain region stimulated, method of sham stimulation), outcome measures, and post-stimulation mean as well as standard deviation (SD) for each outcome measure in the experimental (real stimulation) and control (sham stimulation) groups. The data was based on the first measurement taken after the stimulation period for studies with "offline" design (Ahmed et al., 2012; Berryhill and Jones, 2012; Boggio et al., 2012; Cotelli et al., 2011, 2014; Eliasova et al., 2014; Ferrucci et al., 2008; Fertonani et al., 2014; Floel et al., 2012; Khedr et al., 2014; Kim et al., 2012; Rabey et al., 2013; Sandrini et al., 2014; Sole-Padulles et al., 2006). For studies that applied stimulation while the participants were engaged in the task, the data were based on the cognitive performance score from the task (Boggio et al., 2009, 2010; Cotelli et al., 2006, 2008; Fertonani et al., 2014; Harty et al., 2014; Holland et al., 2011; Manenti et al., 2013; Meinzer et al., 2013, 2014; Park et al., 2014; Ross et al., 2011). Various cognitive outcome measures were found across the studies, and some studies evaluated multiple measures. In this meta-analysis, the data used to assess each study was the explicitly declared primary outcome measure. When the primary outcome was not clearly defined, the first outcome reported in the results section was used. For the studies that did not report the mean and SD of their outcome measures, the data were estimated from the figures (Berryhill and Jones, 2012; Boggio et al., 2009, 2010, 2012; Cotelli et al., 2006, 2008, 2014; Holland et al., 2011; Khedr et al., 2014; Kim et al., 2012; Meinzer et al., 2013, 2014). Six of the studies with healthy older adults contributed more than one trial to the analyses due to different stimulation sites (Berryhill and Jones, 2012; Boggio et al., 2010; Manenti et al., 2013; Meinzer et al., 2014; Ross et al., 2011) or protocols (Fertonani et al., 2014). For studies with AD patients, five articles contributed more than one trial because they employed different stimulation protocols (Ahmed et al., 2012; Khedr et al., 2014), applied the stimulation over different brain regions (Boggio et al., 2009; Cotelli et al., 2006, 2008), or they divided the patients into subgroups based on severity of the disease (Ahmed et al., 2012; Cotelli et al., 2008). After one of the authors (WY. H.) extracted relevant data from the included studies, another author (Y.K.) confirmed that the data were accurately retrieved from the included studies.

In order to clarify variables that may influence cognitive outcomes, a planned subgroup analysis was performed by grouping the data according to the stimulation timing ("online" vs. "offline"), session numbers (single session vs. multiple sessions), and rTMS stimulus frequency ("high" vs. "low"). We also attempted to compare the effects of anodal and cathodal tDCS. However, none of the studies with healthy older adults and only one study with AD patients applied cathodal tDCS. Therefore, comparing anodal to cathodal stimulation effects was not feasible with the current data.

The meta-analysis was conducted with Comprehensive Meta Analysis 2.0 software (Biostat Inc, Englewood, NJ) to test the results of different data sets. The effect size and 95 % confident interval (CI) were calculated according to the differences between post-stimulation evaluations (Ahmed et al., 2012; Berryhill and Jones, 2012; Boggio et al., 2012; Cotelli et al., 2011, 2014; Eliasova et al., 2014; Ferrucci et al., 2008; Fertonani et al., 2014; Floel et al., 2012; Khedr et al., 2014; Kim et al., 2012; Sandrini et al., 2014), changes relative to the baseline (Rabey et al., 2013; Sole-Padulles et al., 2006), or "online" performance (Boggio et al., 2009, 2010; Cotelli et al., 2006, 2008; Fertonani et al., 2014; Harty et al., 2014; Holland et al., 2011; Manenti et al., 2013; Meinzer et al., 2013, 2014;

Park et al., 2014; Ross et al., 2011) in the experimental (real stimulation) and control (sham stimulation) groups divided by pooled SD. Because the effect size from each study may overestimate the effect in the studies with a small sample size, a weighting factor was applied to give more weight to effect sizes from studies with a larger sample size. The mean effect sizes were obtained after combining the weighted effect size of each study. An effect size of 0.2 to 0.49 were considered to be small (Cohen, 1992), a value of 0.5 was likely to be clinically meaningful, and the effect size over 0.8 was considered to be large (Sloan et al., 2005). The heterogeneity across effect sizes was assessed with Q-statistics (Cochran, 1954) and the I^2 index (Higgins and Thompson, 2002), which is useful for assessing consistency between studies (Higgins et al., 2003). When heterogeneity was found by Q-statistics or when I^2 >50%, a random effects model was applied. If not, a fixed effects model was used. To address the possibility of publication bias, a funnel plot (Egger and Smith, 1995) was generated. The funnel plot is a scatter plot where effect sizes from individual trials are plotted against the standard error. It assumes that studies with larger sample sizes appear toward the top of the plot and near the mean effect size, whereas studies with smaller sample sizes would be spread on both sides of the average effect size and appear toward the bottom of the plot, indicating more variation in these smaller studies. The plot generates a roughly funnel-shaped distribution. In the absence of publication bias, results from small studies will scatter widely at the bottom of the graph and the plot may show a symmetrical distribution. Conversely, in the presence of publication bias, studies with smaller sample size showing no statistically significant effects may remain unpublished, and so the publication bias may lead to an asymmetrical appearance of the funnel plot. A Begg and Mazumdar rank correlation (Begg and Mazumdar, 1994) was also applied to assess a publication bias. A Trim and Fill procedure (Duval and Tweedie, 2000) was applied to correct for any publication bias. Trim and Fill is a funnel plot-derived approach aimed at identifying publication bias and adjusting the results. There are three steps of the approach. First, it trims off the asymmetric outlying part of the funnel after estimating how many studies are in the asymmetric domain. Second, it estimates an adjusted mean effect size considering only the symmetric part of the funnel, and replaces the trimmed studies as well as imputes the potential missing studies. In a final step, it re-evaluates the adjusted mean effect size with the filled funnel plot. The statistical significance level was set at 0.05.

3. Results

3.1. Evidence base

For studies with healthy older adults, the searches yielded 569 articles. After exclusion based on the title and abstract, 23 potentially eligible articles remained. After full-text review, 14 articles met the meta-analysis inclusion criteria (Berryhill and Jones, 2012; Boggio et al., 2010; Fertonani et al., 2014; Floel et al., 2012; Harty et al., 2014; Holland et al., 2011; Kim et al., 2012; Manenti et al., 2013; Meinzer et al., 2013, 2014; Park et al., 2014; Ross et al., 2011; Sandrini et al., 2014; Sole-Padulles et al., 2006). The other 9 articles were excluded due to the following reasons: the main goal of the study was not to enhance cognitive function (8 studies) or the article was a review article (1 study). Table 1 summarizes the characteristics of the studies with healthy older adults. A total of 331 participants were included. Only 1 drop-out was reported by Sole-Padulles et al. (2006).

For studies with AD patients, the searches resulted in 353 articles, and 28 of them were potentially relevant. After full-text review, 11 articles (Ahmed et al., 2012; Boggio et al., 2009, 2012; Cotelli et al., 2006, 2008, 2011, 2014; Eliasova et al., 2014; Ferrucci et al., 2008; Khedr et al., 2014; Rabey et al., 2013) were identified based on inclusion criteria. The other 17 articles were excluded due to the following reasons: they were review articles (13 studies), a case study (2 articles), the main goal of the study was not to enhance cognitive function (1 study), or the study did not include a control (sham stimulation) condition (1 study). Table 2 presents detailed characteristics of each study. In total, 200 patients with AD were included, and 3 drop-outs were reported (Rabey et al., 2013).

3.2. Intervention

Most of the studies with healthy older adults used tDCS as their stimulation tool (Berryhill and Jones, 2012; Boggio et al., 2010; Fertonani et al., 2014; Floel et al., 2012; Harty et al., 2014; Holland et al., 2011; Manenti et al., 2013; Meinzer et al., 2013, 2014; Park et al., 2014; Ross et al., 2011; Sandrini et al., 2014). Only two studies applied rTMS (Kim et al., 2012; Sole-Padulles et al., 2006). Eight studies delivered the stimulation while the participants were engaged in the cognitive task (Boggio et al., 2010; Harty et al., 2014; Holland et al., 2011; Manenti et al., 2013; Meinzer et al., 2013, 2014; Park et al., 2014; Ross et al., 2011) and five studies utilized an “offline” design (Berryhill and Jones, 2012; Floel et al., 2012; Kim et al., 2012; Sandrini et al., 2014; Sole-Padulles et al., 2006). One study employed both “online” and “offline” conditions (Fertonani et al., 2014). Two studies applied multiple sessions of stimulation (Kim et al., 2012; Park et al., 2014). Additional add-on training was reported in two articles (Floel et al., 2012; Park et al., 2014).

For studies with AD patients, five studies employed tDCS as the stimulation tool (Boggio et al., 2009, 2012; Cotelli et al., 2014; Ferrucci et al., 2008; Khedr et al., 2014). The other six studies applied rTMS (Ahmed et al., 2012; Cotelli et al., 2006, 2008, 2011; Eliasova et al., 2014; Rabey et al., 2013). Three studies reported that the stimulation was delivered online during the cognitive task (Boggio et al., 2009; Cotelli et al., 2006, 2008). Six studies were designed as multiple session trials (Ahmed et al., 2012; Boggio et al., 2012; Cotelli et al., 2011, 2014; Khedr et al., 2014; Rabey et al., 2013). Cognitive training combined with stimulation was present in two studies (Cotelli et al., 2014; Rabey et al., 2013).

3.3. Outcome measures

Various outcome measures had been used in the selected studies. In studies with healthy older adults, picture naming (Fertonani et al., 2014; Holland et al., 2011), two-back working memory (Berryhill and Jones, 2012; Park et al., 2014), verbal episodic memory (Manenti et al., 2013; Sandrini et al., 2014) and semantic word retrieval (Meinzer et al., 2013, 2014) were assessed in at least two articles. Other outcome measures included associative memory (Sole-Padulles et al., 2006), a gambling risk task (Boggio et al., 2010), a face naming task (Ross et al., 2011), the Stroop test (Kim et al., 2012), an object-location memory task (Floel et al., 2012), and an error awareness task (Harty et al., 2014). For studies with AD patients, picture naming (Cotelli et al., 2006, 2008), visual recognition memory (Boggio et al., 2009, 2012) and MMSE (Ahmed et al., 2012; Khedr et al., 2014) were reported in at least two studies. Other cognitive measurements included word recognition (Ferrucci et al., 2008),

auditory sentence comprehension (Cotelli et al., 2011), Alzheimer's Disease Assessment Scale-cognitive subsection (Rabey et al., 2013), a trail making test (Eliasova et al., 2014), and a face-name association task (Cotelli et al., 2014).

3.4. Quality assessment

The quality of the methods of the included studies is detailed in Table 3. Random allocation was pointed out in most of the trials (Ahmed et al., 2012; Boggio et al., 2009, 2010, 2012; Cotelli et al., 2006, 2008, 2011, 2014; Eliasova et al., 2014; Ferrucci et al., 2008; Floel et al., 2012; Harty et al., 2014; Khedr et al., 2014; Kim et al., 2012; Manenti et al., 2013; Meinzer et al., 2014; Park et al., 2014; Rabey et al., 2013; Ross et al., 2011; Sandrini et al., 2014; Sole-Padulles et al., 2006). Most of the studies were double-blind (Ahmed et al., 2012; Boggio et al., 2010, 2012; Cotelli et al., 2014; Ferrucci et al., 2008; Khedr et al., 2014; Meinzer et al., 2013; Park et al., 2014; Rabey et al., 2013; Sole-Padulles et al., 2006) or single-blind (Cotelli et al., 2011; Fertonani et al., 2014; Floel et al., 2012; Harty et al., 2014; Kim et al., 2012; Manenti et al., 2013; Meinzer et al., 2014; Sandrini et al., 2014) design. Only two studies had drop-out(s) (Rabey et al., 2013; Sole-Padulles et al., 2006). Three studies did not compare the differences across stimulation conditions (Eliasova et al., 2014; Kim et al., 2012; Park et al., 2014). Eleven studies did not provide point estimates and measures of variability (Boggio et al., 2009, 2010, 2012; Cotelli et al., 2006, 2008, 2014; Holland et al., 2011; Khedr et al., 2014; Kim et al., 2012; Meinzer et al., 2013, 2014).

3.5. Adverse effects

For studies with healthy older adults, ten of the 14 studies reported information about adverse effects. Four studies found adverse events, including itching, irritation, and burning sensation caused by tDCS (Fertonani et al., 2014; Harty et al., 2014; Manenti et al., 2013; Sandrini et al., 2014). For studies with AD patients, ten of them reported information about adverse effects, and only two trials showed 3 participants with painful scalp sensation and 2 subjects with itching, headache and dizziness after rTMS (Eliasova et al., 2014) or tDCS (Khedr et al., 2014) stimulation, respectively.

3.6. Meta-analysis

3.6.1. Healthy older adults—Table 4 describes outcome measures, mean and SD, number of participants, as well as the effect size of each study. Based on 13 articles with 18 effect sizes, the meta-analysis of cognitive outcomes revealed a statistically significant mean effect size of 0.42 (95% CI, 0.09–0.74, $p<0.05$) (Figure 1). Heterogeneity was observed across studies ($Q=64.02$, $I^2=73.45$, $p<0.001$). Berryhill et al. (2012) reported a favorable effect of tDCS on working memory performance in older adults with more education. However, they did not provide an appropriate sample number for their subgroup analyses. Thus the effect size could not be determined.

In order to determine variables that may influence the cognitive outcomes, planned subgroup analyses were conducted. The subgroup analysis for timing of the stimulation ("online" vs. "offline") revealed a mean effect size of 0.92 (95% CI, 0.30–1.54, $p<0.05$) for trials with an "offline" design. The mean effect size for trials with an "online" design was 0.23 (95% CI, −0.14–0.61, $p=0.22$). A subgroup analysis for session numbers (single session vs. multiple

sessions) showed the mean effect size for studies with multiple sessions was 0.89 (95% CI, 0.32–1.45, p<0.05). Studies with a single session showed a mean effect size of 0.44 (95% CI, 0.27–0.61, p<0.001). In the studies with healthy older adults, all of the studies that applied rTMS only used a high frequency protocol, therefore, a subgroup analysis of TMS stimulus frequency ("high" vs. "low") was not applicable to this group.

3.6.2. Alzheimer's disease—Table 5 summarizes outcome measures, mean and SD, number of participants, and, the effect size of studies with AD patients. Twenty effect sizes were obtained from 11 articles involving 200 patients with AD. The meta-analysis of cognitive outcomes showed a significant mean effect size of 1.35 (95% CI, 0.86–1.84, p<0.001) (Figure 2). Heterogeneity was found across studies (Q=93.02, I^2=79.57, p<0.001).

Again, planned subgroup analyses were performed. For the timing of the stimulation ("online" vs. "offline"), trials with an "offline" design showed a mean effect size of 1.04 (95% CI, 0.43–1.65, p<0.001). Mean effect size for trials with an "online" design was 1.79 (95% CI, 1.06–2.51, p<0.001). Subgroup analysis for session numbers (single session vs. multiple sessions) revealed that the mean effect size for studies with multiple sessions was 1.20 (95% CI, 0.46–1.94, p<0.05). Studies with single session showed a mean effect size of 1.49 (95% CI, 0.82–2.17, p<0.001). For the TMS stimulus frequency ("high" vs. "low"), studies that applied high frequency rTMS showed a mean effect size of 1.64 (95% CI, 1.03–2.27, p<0.001). Mean effect size for studies that employed low frequency rTMS was 0.23 (95% CI, −0.49–0.95, p=0.53).

3.7. Publication Bias

For studies with healthy older adults, the funnel plot (Fig 3A) resembles an inverted symmetrical funnel, which indicated that publication bias is absent (Egger et al., 1997). Rank correlation (tau=0.00, p=0.50) also confirmed that publication bias does not seem to affect the validity of the overall effect size obtained by the current meta-analysis. For studies with AD, the publication bias was discovered by the asymmetrical funnel plot (Fig 3B), in which the bottom of the plot showed a higher concentration of studies on one side of the mean than the other. Rank correlation (tau=0.53, p<0.001) also indicated that publication bias may exist. Thus, a Trim and Fill procedure (Duval and Tweedie, 2000) was applied to impute missing studies. After adjusting for missing studies, a mean effect size of 0.78 was found.

4. Discussion

The results of the present study suggest that rTMS and tDCS have beneficial effects on healthy aging and AD-associated cognitive decline.

The meta-analysis of studies with healthy older adults revealed a significant main effect size of 0.42, which is close to being clinically meaningful (0.5) (Sloan et al., 2005). No statistical evidence was found for publication bias. To determine what factors may lead to a better cognitive outcome, subgroup analyses were performed. The mean effect size for "offline" stimulation study designs (mean effect size, 0.92) was larger than that of "online" designs (mean effect size, 0.23). It is well known that rTMS can produce changes of cortical activity

that outlast the duration of the stimulus train *per se* (Hayashi et al., 2004). Similarly, tDCS studies have confirmed the presence of favorable effects on cognitive tasks with both "offline" and "online" stimulation administration (Fregni et al., 2005; Nitsche and Paulus, 2001; Ohn et al., 2008). It has been reported that "online" effects are related to membrane depolarization (Stagg and Nitsche, 2011), whereas "offline" effects additionally involve N-methyl-D-aspartic (NMDA) receptors, and long-term potentiation-like (LTP-like) mechanisms (Liebetanz et al., 2002). The results of the subgroup analyses implied that healthy older adults may benefit more by an LTP-like mechanism. However, the results must be interpreted with caution as this subgroup analysis compared the timing of the stimulation across studies with different subjects and various cognitive tasks, which limits the interpretation as to why online and offline effects may differ. Also, it is difficult to draw more broad conclusions regarding neural mechanisms as both TMS and tDCS studies were included in the meta-analysis, which are thought to affect neural activity through different mechanisms.

The subgroup analysis of session numbers of stimulation showed a relatively larger effect size for multiple sessions (mean effect size, 0.89) compared to a single session (mean effect size, 0.44), suggesting that multiple sessions of stimulation lead to more cognitive enhancement. Interestingly, it was generally thought that repeated sessions of stimulation would induce longer or stronger lasting effects in clinical populations (Baker et al., 2010; Fridriksson et al., 2011). Nevertheless, studies investigating rTMS or tDCS effects on cognitive function with multiple sessions of stimulation in healthy participants have been explored in only a few studies. Since there were only two studies (Kim et al., 2012; Park et al., 2014) that applied multiple sessions of stimulation in this meta-analysis, the present results must be viewed conservatively.

The results of the meta-analysis demonstrated that non-invasive brain stimulation has a positive influence on various cognitive functions in patients with AD. Among the 200 patients with AD from the studies included in the meta-analysis, a significant mean effect size of 1.35 was found. As a publication bias may exist, a Trim and Fill (Duval and Tweedie, 2000) procedure was applied, and an adjusted mean effect size of 0.78 was discovered. The adjusted mean effect size remained clinically meaningful and large (Sloan et al., 2005).

Subgroup analyses were conducted to determine factors that contribute to better cognitive outcomes in AD. In contrast to the results of healthy older adults, the mean effect size of an "online" design (mean effect size, 1.79) was larger than that of an "offline" design (mean effect size, 1.04), which indicated that the cognitive enhancement was more prominent in studies that applied stimulation while AD patients were engaged in cognitive tasks. It is noteworthy that the neural networks and the responses to non-invasive brain stimulation may be different between healthy older adults and patients with AD. Studies have demonstrated structural, metabolic, and functional alterations in brains with AD (Pearlson et al., 1992; Smith et al., 1999; Supekar et al., 2008). Amyloid-beta (Aβ) oligomers, a form of Aβ peptide, have been found to be related to the disruption of synaptic plasticity and inhibition of LTP (Lauren et al., 2009; Shankar et al., 2008). As the "offline" effects are related to LTP-like mechanisms (Liebetanz et al., 2002), changes in the synaptic plasticity

and disruption of LTP in AD may account for the more pronounced beneficial effects of "online" stimulation.

The analysis of session numbers showed comparable effects generated by multiple (mean effect size, 1.20) and single (mean effect size, 1.49) session stimulation. Previous studies have revealed that the effects of non-invasive brain stimulation critically depend on the prevailing brain-states (Neuling et al., 2013; Zaehle et al., 2010). As patients with AD have altered brain function and impaired cognitive function, it is possible that patients with AD would benefit from brain stimulation regardless of the number of stimulation sessions. The subgroup analysis of rTMS stimulus frequency showed a larger effect size generated by high frequency rTMS (mean effect size, 1.64) compared to that of low frequency rTMS (mean effect size, 0.23) when applied to AD patients. This result supports the concept that high frequency rTMS facilitates cortical excitability (Pascual-Leone et al., 2005; Peinemann et al., 2004) and enhances various cognitive functions (Grafman and Wassermann, 1999; Guse et al., 2010). However, since there were only two trials (Ahmed et al., 2012) that employed low frequency rTMS in this meta-analysis, this result must be taken with caution.

Other than immediate effects, how long rTMS/tDCS effects are sustained is another important issue. Most of the selected studies examined cognitive measurements immediately after the end of the stimulation period. Only two studies with healthy older adults assessed cognitive outcomes 1 month after the intervention (Park et al., 2014; Sandrini et al., 2014), and only five studies with AD patients reassessed cognitive outcomes with a follow-up duration ranging from 1 month to 6 months post stimulation (Ahmed et al., 2012; Boggio et al., 2012; Cotelli et al., 2011, 2014; Khedr et al., 2014). Since the data for the follow up assessments are limited and the results are varied, it is difficult to reach a definitive conclusion at this time regarding the sustainability of the stimulation effects.

An important consideration for this systematic review and meta-analysis is the methodological quality of the selected studies. Most of the included studies used a randomized design and control groups, and the procedures of the blinding were reported in most of the studies. Nevertheless, some studies did not report point estimates and measures of variability, and the data were estimated from the figures. The impact of these non-precise data on the overall mean effect size should be taken into consideration. Publication bias is another noticeable concern. Possible publication bias was detected in studies with AD patients. Although a Trim and Fill procedure (Duval and Tweedie, 2000) was applied to adjust the mean effect size, the results obtained in the present meta-analysis must be viewed conservatively. The basis of the Trim and Fill procedure is to trim off the asymmetric outlying part of the funnel and to impute the potential missing studies, and then re-evaluate the mean effect size. As the procedure does not include detailed information of imputed studies, it limits us to clarify how the publication bias affects the subgroup analyses.

Interestingly, Tremblay et al. (2014) suggested that the effect of tDCS on cognitive performance in healthy participants is uncertain (Tremblay et al., 2014). As most of the studies included in their systematic review article measured tDCS effects in healthy young adults, the conflicting results may be due to ceiling effects. This is consistent with recent findings showing that the effects of non-invasive brain stimulation on neural activity and

task performance are highly interactive with individual capacity (Feurra et al., 2013; Kirov et al., 2009). Furthermore, our current results showed a more pronounced effect of non-invasive brain stimulation on cognitive function in patients with AD (adjusted effect size: 0.78) compared to that of healthy older adults (effect size: 0.42). Taken together, this suggests that the effects of non-invasive brain stimulation on cognitive function may be graded across different populations from healthy young adults to physiological aging, and then to pathological aging. Thus, non-invasive stimulation may only benefit those who need it most. It is also possible that the stimulation may lead to qualitatively different outcomes in intact versus dysfunctional neural circuits as studies have demonstrated diversity of structural, metabolic, and functional alterations in brains with AD (Pearlson et al., 1992; Smith et al., 1999; Supekar et al., 2008). Future studies with subgroups of AD patients based on disease severity may help differentiate these effects and to guide more appropriate targeting of populations. It may be hypothesized that a low cognitive performance subgroup in each population (healthy young adults, healthy older adults, AD patients) may benefit more from stimulation than a high cognitive performance subgroup. Furthermore, while the high performance subgroup may benefit the least from stimulation, the effects of stimulation may be minimal or null in AD patients, but deleterious in healthy young adults who do not necessarily exhibit a need for stimulation.

The current findings suggest that non-invasive brain stimulation techniques offer a promising method to ameliorate cognitive decline in healthy older adults and patients with AD. As no severe adverse effects were reported, investigators should continue to follow safety guidelines (Rossi et al., 2009; Wassermann, 1998) and conduct follow-up assessments to take longer-term risks and benefits into consideration. In addition to safety concerns, several open questions should be addressed in future studies or preclinical animal studies with proper experimental design. First, as previous studies have reported that combining non-invasive brain stimulation with cognitive training leads to a pronounced enhancement of training effects (Ditye et al., 2012; Martin et al., 2013; Park et al., 2014; Rabey et al., 2013), evaluation of effects of concurrent non-invasive brain stimulation with cognitive training or other behavioral interventions on the aging brain is needed. Second, it is important to assess structural and functional alterations in the physiological and pathological aging brain that may result in qualitatively different responses to brain stimulation compared to healthy young brains. Third, the most effective parameters and dosing of stimulation (i.e., stimulation tool, frequency of rTMS, intensity, number of rTMS pulses, duration of tDCS, target brain region stimulated, method of sham stimulation) in this population needs further investigation. Studies with different subgroups that vary by clinical severity and long-term follow ups are necessary to identify the target populations that benefit most from stimulation and determine the sustainability of beneficial effects. Lastly, it is essential that we better clarify the underlying neural mechanisms of positive effects induced by the stimulation.

There are some other concerns that need to be taken into account in the present study. First, methodological variations exist between the selected studies. The parameters of outcome measures, stimulation protocol, participant inclusion criteria, and the experimental design are varied across the studies. Second, it is possible that we may have missed relevant literatures published in non-English languages.

In conclusion, the present meta-analysis study suggests a favorable effect of non-invasive brain stimulation on cognitive function in physiological and pathological aging. In healthy older adults, “offline” and multiple sessions of stimulation are more effective than “online” design and single session stimulation, respectively. In patients with AD, applying stimulation during the execution of the cognitive task (i.e., online) leads to a more pronounced beneficial effect. Further well-designed studies are warranted to determine the sustainability of the stimulation effects and the neural plasticity changes induced by non-invasive brain stimulation.

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Highlights

1. We evaluated the effects of non-invasive brain stimulation on cognitive function in healthy older adults and patients with Alzheimer's disease.
2. Non-invasive brain stimulation has a positive effect on cognitive function in physiological and pathological aging.
3. In healthy older adults, "offline" design and multiple sessions of stimulation are most beneficial.
4. In patients with Alzheimer's disease, applying stimulation during the execution of the cognitive task leads to a more pronounced beneficial effect.

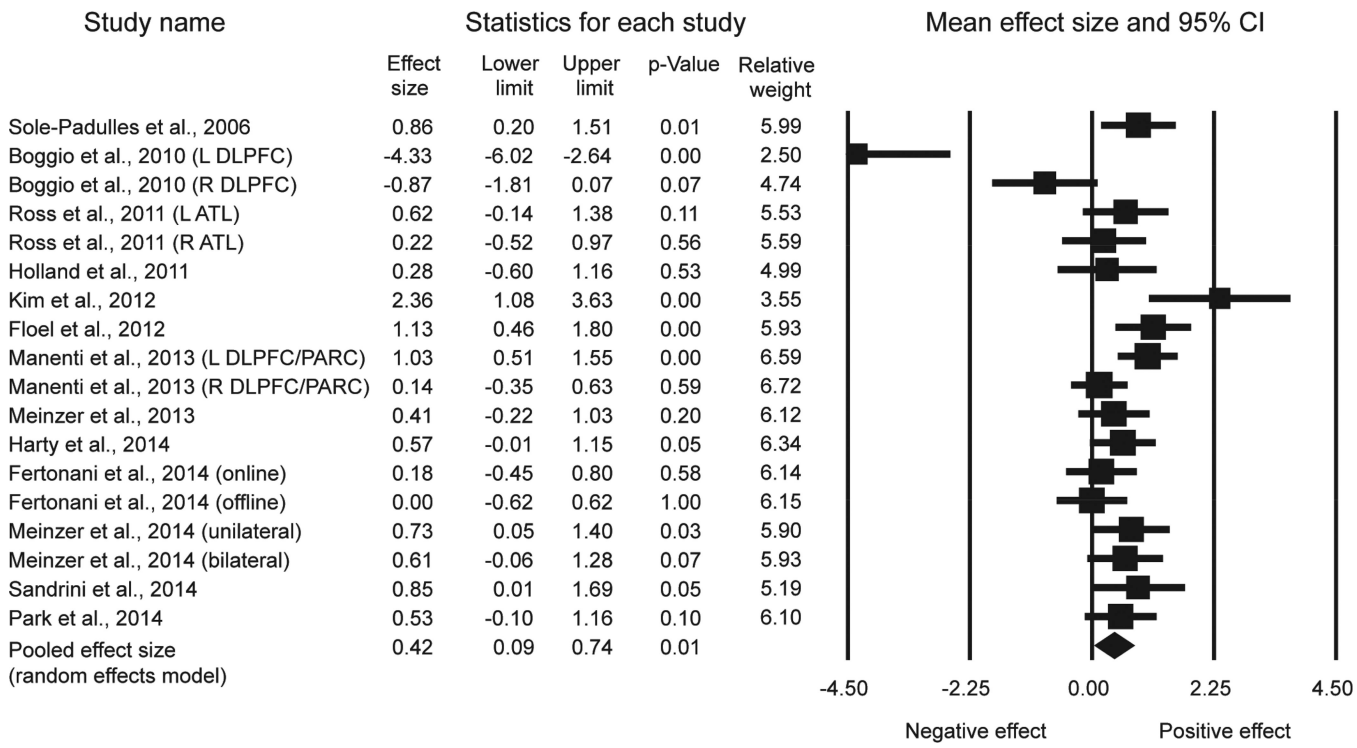

Figure 1.

Statistical summary and forest plot of effect sizes for cognitive outcome measures in healthy older adults. Five articles contributed more than one effect size.

CI, confidence interval; L, left; R, right; ATL, anterior temporal lobe; DLPFC, dorsolateral prefrontal cortex; PARC, parietal cortex.

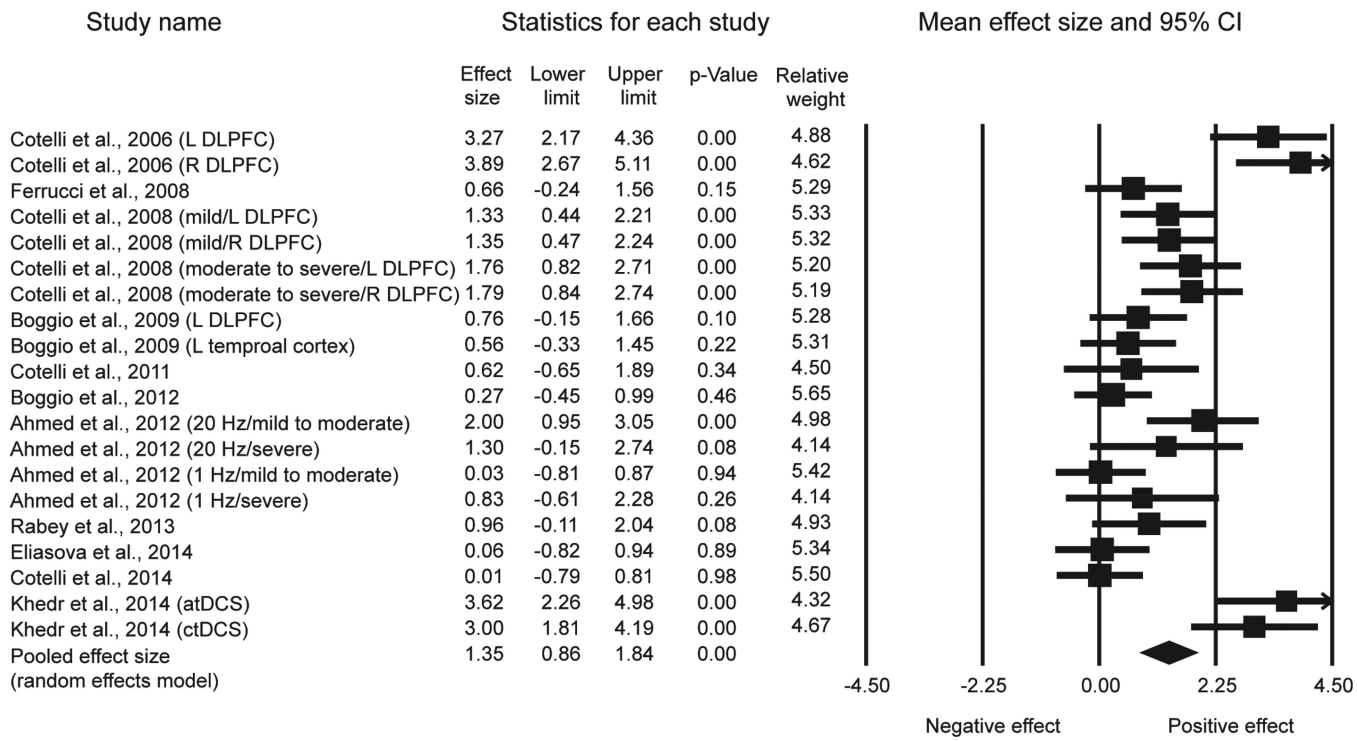

Figure 2.

Statistical summary and forest plot of effect sizes for cognitive outcome measures in patients with Alzheimer's disease. Five articles contributed more than one effect size.

CI, confidence interval; L, left; R, right; DLPFC, dorsolateral prefrontal cortex; atDCS, anodal transcranial direct current stimulation; ctDCS, cathodal transcranial direct current stimulation.

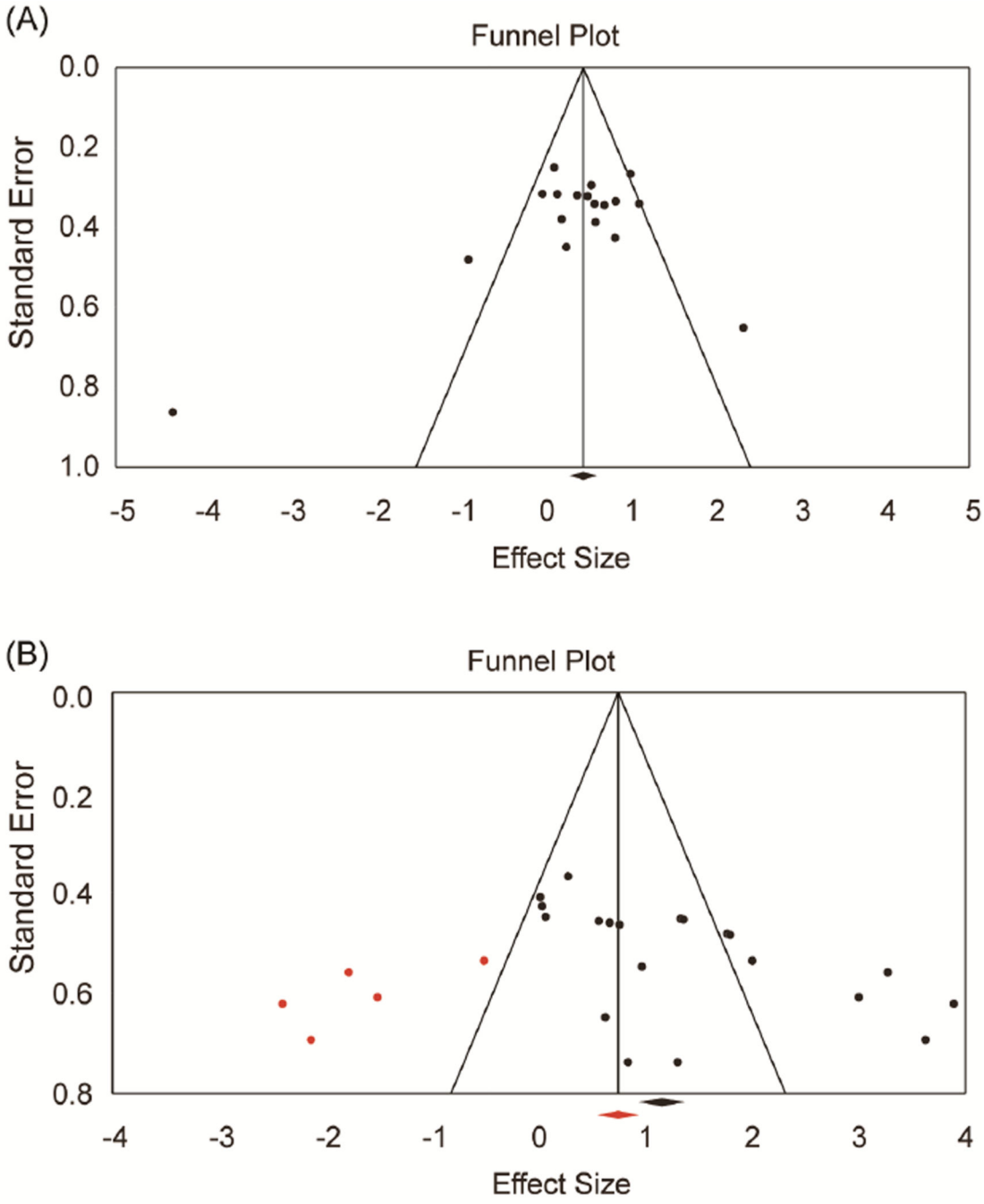

Figure 3.

(A) Funnel plot of standard errors and effect sizes of the studies with healthy older adults included in the meta-analysis. (B) Funnel plot for studies with Alzheimer's disease included in the meta-analysis. Red circles represent the imputed missing studies. Red rhombus shows the adjusted mean effect size.

Table 1

Characteristics of Each Study Included in the Meta-Analysis (studies with healthy older adults)

Study	Number of participants (stim/sham)	Mean age (years) (stim/sham)	Mean MMSE (stim/sham)	Mean education (years) (stim/sham)	Stimulation tool and protocol	Stimulation position	Method of sham stimulation	Main outcome measures for cognitive function
Sole-Padulles et al., (2006)	40 (20/19)	67.0/68.7	26.5/26.2	N/R	rTMS 5 Hz, 80% RMT, 50 pulses × 10 trains	Prefrontal area	Coil perpendicular to scalp	Associative memory
Boggio et al., (2010)	28 (9/9)[a] (10/9)[b]	68.9/67.0 69.4/67.0	26.7/26.2 27.4/26.2	7.0/5.2 9.2/5.2	ITI=20 s atDCS 2 mA (0.06 mA/cm^2) 15 min	(1) L DLPFC Ref: R DLPFC (2) R DLPFC Ref: L DLPFC	Stimulation was applied for 30 s	Gambling risk task
Ross et al., (2011)*	14 (14/14)	64.4/64.4	28.6/28.6	N/R	atDCS 1.5 mA (0.04 mA/cm^2) 15 min	(1) L ATL Ref: R cheek (2) R ATL Ref: L cheek	Stimulation was applied for 30 s	Face naming task
Holland et al., (2011)*	10 (10/10)	69.0/69.0	N/R	N/R	atDCS 2 mA (0.06 mA/cm^2)	L IFC Ref: R fronto-polar cortex	Stimulation was applied for 31 s	Picture naming task
Kim et al., (2012)	16 (8/8)	63.5/62.7	27.6/28.0	12.3/11.5	rTMS 10 Hz, 30% MO(0.6T) 20 pulses × 13 trains per session, ITI=15 s ISI=2 min 3 sessions/day for 5 d	L DLPFC	Coil perpendicular to scalp	Stroop test
Berryhill et al., (2012)*	25 (25/25)	63.7/63.7	N/R	N/R	atDCS 1.5 mA (0.04 mA/cm^2) 10 min	(1) L DLPFC Ref: R cheek (2) R DLPFC Ref: L cheek	Stimulation was applied for 40 s	2-back WM
Floel et al., (2012)*	20 (20/20)	62.1/62.1	28.6/28.6	13.2/13.2	atDCS 1 mA (0.03 mA/cm^2) 20 min	R temproprietal cortex Ref:L supra-orbital area	Stimulation was applied for 30 s	Object-location memory task
Manenti et al., (2013)*	32 (32/32)	67.9/67.9	28.6/28.6	10.8/10.8	atDCS 1.5 mA (0.04 mA/cm^2) 6 min	(1) L and R DLPFC (2) L and R PARC	Stimulation was applied for 20 s	Verbal episodic memory
Meinzer et al., (2013)*	20 (20/20)	68.0/68.0	28.9/28.9	15.9/15.9	atDCS 1 mA (0.03 mA/cm^2) 20 min	L vIFG Ref: R orbital-frontal cortex	Stimulation was applied for 30 s	Semantic word retrieval
Harty et al., (2014)*	24 (24/24)	72.1/72.1	28.5/28.5	14.9/14.9	atDCS 1 mA	R DLPFC Ref: vertex	Stimulation was applied for 20 s	Error awareness task

Study	Number of participants (stim/sham)	Mean age (years) (stim/sham)	Mean MMSE (stim/sham)	Mean education (years) (stim/sham)	Stimulation tool and protocol	Stimulation position	Method of sham stimulation	Main outcome measures for cognitive function
					(0.03 mA/cm^2) 7.5 min × 5 sessions ISI=1 min			
Fertonani et al., (2014)*	20 (20/20)	66.5/66.5	29.0/29.0	10.5/10.5	atDCS 2 mA (0.06 mA/cm^2) (1) Online: 5 min (2) Offline: 10 min	L DLPFC Ref: R shoulder	Stimulation was applied for 40 s	Picture naming task
Meinzer et al., (2014)*	18 (18/18)	68.4/68.4	29.4/29.4	15.9/15.9	atDCS 1 mA (0.03 mA/cm^2) 30 min	(1) L M1 Ref: R supra-orbital area (2) L M1 Ref: R M1	Stimulation was applied for 30 s	Semantic word retrieval
Sandrini et al., (2014)	24 (12/12)	67.6/66.4	29.0/28.9	11.3/13.2	atDCS 1.5 mA (0.04 mA/cm^2) 15 min	L DLPFC Ref: R supra-orbital area	Stimulation was applied for 40 s	Verbal episodic memory
Park et al., (2014)	40 (20/20)	70.1/69.4	29.3/28.8	10.9/10.9	atDCS 2 mA (0.08 mA/cm^2) 30 min/session 5 sessions/week for 2 weeks	Bilateral prefrontal cortex Ref: non-dominant arm	Stimulation was applied for 30 s	2-back WM

stim, stimulation group; sham, sham group; MMSE, Mini-Mental State Examination; rTMS, repetitive transcranial magnetic stimulation; RMT, resting motor threshold; R, right; L, left; DLPFC, dorsolateral prefrontal cortex; atDCS, anodal transcranial direct current stimulation; ITI, inter-train interval; N/R, not reported; Ref, reference electrode; MO, maximal stimulator output; WM, working memory; ATL, anterior temporal lobe; PARC, parietal cortex; vIFG, ventral inferior frontal gyrus; IFC, inferior frontal cortex; ISI=inter-session interval; M1, primary motor area.

*Crossover design.

*a*participants in the left anodal/right cathodal stimulation group.

*b*participants in the right anodal/left cathodal stimulation group.

Table 2

Characteristics of Each Study Included in the Meta-Analysis (studies with Alzheimer's disease)

Study	Number of participants (stim/sham)	Mean age (years) (stim/sham)	Mean MMSE (stim/sham)	Mean education (years) (stim/sham)	Stimulation tool and protocol	Stimulation position	Method of sham stimulation	Main outcome measures for cognitive function
Cotelli et al., (2006)*	15 (15/15)	76.6/76.6	17.8/17.8	6.0/6.0	rTMS 20 Hz, 90% RMT, 10 pulses × 20 trains	(1) L DLPFC (2) R DLPFC	Coil perpendicular to vertex	Picture naming
Ferrucci et al., (2008)*	10 (10/10)	75.2/75.2	22.7/22.7	10.9/10.9	atDCS 1.5 mA (0.06 mA/cm^2)	Bilateral temporopariatel areas	Stimulation was applied for 10 s	Word recognition
Cotelli et al., (2008)*	24 (12/12)[a] (12/12)[b]	75.0/75.0 77.6/77.6	19.7/19.7 14.3/14.3	6.8/6.8 5.7/5.7	15 min rTMS 20 Hz, 90% RMT, 10 pulses × 20 trains	Ref: R deltoid (1) L DLPFC (2) R DLPFC	Coil perpendicular to vertex	Picture naming
Boggio et al., (2009)*	10 (10/10)	79.1/79.1	17.0/17.0	8.7/8.7	atDCS 2 mA (0.06 mA/cm^2) 30 min	(1) L DLPFC (2) L TC Ref: R supra-orbital area	Stimulation was applied for 30 s	Visual recognition memory
Cotelli et al., (2011)	10(5/5)	71.2/74.4	16.2/16.0	6.4/4.8	rTMS 20 Hz, 100% RMT 40 pulses × 50 trains, ITI=28 s for 2 weeks	L DLPFC	N/R	Auditory sentence comprehension
Boggio et al. (2012)*	15(15/15)	78.9/78.9	20.0/20.0	14.4/14.4	atDCS 2 mA (0.06 mA/cm^2) 30 min for 5 days	Bilateral temporal regions Ref: R deltoid	Stimulation was applied for 30 s	Visual recognition memory
Ahmed et al., (2012)	45 (10/11)[c] (5/4)[d] (11/11)[e] (4/4)[f]	65.9/68.3 68.6/68.3	14.7/13.9 12.7/13.9	N/R	rTMS (1) 20 Hz, 90% RMT, 100 pulses × 20 trains ITI=25 s for 5 d (2) 1 Hz, 100% RMT, 2000 pulses in 2 train ITI=30 s for 5 d	Bilateral DLPFC s	Coil angled away from the head	MMSE
Rabey et al., (2013)	18 (7/8)	72.6/75.4	22.0/22.0	N/R	rTMS 10 Hz, 90% RMT for Broca's area. L and R DLPFC 110% RMT for Wernicke's area, L and R PSAC 20 pulses × 20 trains for 2 brain sites and	Broca's area L DLPFC R DLPFC Wernicke's area L PSAC R PSAC	Sham coil	ADAS-Cog

Study	Number of participants (stim/sham)	Mean age (years) (stim/sham)	Mean MMSE (stim/sham)	Mean education (years) (stim/sham)	Stimulation tool and protocol	Stimulation position	Method of sham stimulation	Main outcome measures for cognitive function
					20 pulses × 25 trains for 1 brain site 5 sessions/week for 6 weeks and 2 sessions/week over 3 months			
Eliasova et al., (2014)*	10 (10/10)	75.0/75.0	23.0/23.0	N/R	rTMS 10 Hz, 90% RMT, 50 pulses × 45 trains ITI=25 s	R IFG	Vertex stimulation	Trail making test
Cotelli et al., (2014)	24 (12/12)	76.6/74.4	20.1/20.8	5.5/8.9	atDCS 2 mA (0.08 mA/cm^2) 25 min/day 5 days/week for 2 weeks	L DLPFC Ref: R deltoid	Stimulation was applied for 40 s	Face-name association task
Khedr et al., (2014)	34 (11/11)[g] (12/11)[h]	68.5/67.3 70.7/67.3	18.4/16.9 18.8/16.9	N/R N/R	(1) atDCS (2) ctDCS 2 mA (0.08 mA/cm^2) 25 min/day for 10 d	L DLPFC Ref: R supra-orbital area	Stimulation was applied for 30 s	MMSE

stim, stimulation group; sham, sham group; MMSE, Mini-Mental State Examination; rTMS, repetitive transcranial magnetic stimulation; RMT, resting motor threshold; R, right; L, left; DLPFC, dorsolateral prefrontal cortex; atDCS, anodal transcranial direct current stimulation; TC, temporal cortex; ITI, inter-train interval; N/R, not reported; PSAC, parietal somatosensory association cortex; IFG, inferior frontal gyrus; ADAS-Cog, Alzhermer Disease Assessment Scale-cognitive subsection; ctDCS, cathodal transcranial direct current stimulation; Ref, reference electrode.

*Crossover design.

[a]patients in the mild group.

[b]patients in the moderate to severe group.

[c]patients with mild to moderate dementia in 20 Hz group.

[d]patients with severe dementia in 20 Hz group.

[e]patients with mild to moderate dementia in 1 Hz group.

[f]patients with severe dementia in 1 Hz group.

[g]patients in the atDCS group.

[h]patients in the ctDCS group.

Table 3

Quality Assessment for Studies Included in the Meta-Analysis

Study	Random allocation	Blind procedure	Drop-outs	Between conditions statistical comparison	Point estimates and variability	Adverse effects
Studies with healthy older adults						
Sole-Padulles et al., 2006	1	2	1	1	1	None
Boggio et al., 2010	1	2	0	1	0	None
Ross et al., 2011	1	0	0	1	1	N/R
Holland et al., 2011	0	0	0	1	0	None
Kim et al., 2012	1	1	0	0	0	N/R
Berryhill et al., 2012	0	0	0	1	1	N/R
Floel et al., 2012	1	1	0	1	1	N/R
Manenti et al., 2013	1	1	0	1	1	itching and irritation
Meinzer et al., 2013	0	2	0	1	0	None
Harty et al., 2014	1	1	0	1	1	itching
Fertonani et al., 2014	0	1	0	1	1	14 pitching and 6 burning sensation
Meinzer et al., 2014	1	1	0	1	0	None
Sandrini et al., 2014	1	1	0	1	1	itching and irritation
Park et al., 2014	1	2	0	0	1	None
Studies with Alzheimer's disease						
Cotelli et al, 2006	1	0	0	1	0	None
Ferrucci et al., 2008	1	2	0	1	1	N/R
Cotelli et al., 2008	1	0	0	1	0	None
Boggio et al., 2009	1	0	0	1	0	None
Cotelli et al., 2011	1	1	0	1	1	None
Boggio et al., 2012	1	2	0	1	0	None
Ahmed et al., 2012	1	2	0	1	1	None
Rabey et al., 2013	1	2	3	1	1	None
Eliasova et al., 2014	1	0	0	0	1	3 painful scalp sensation

Study	Random allocation	Blind procedure	Drop-outs	Between conditions statistical comparison	Point estimates and variability	Adverse effects
Cotelli et al., 2014	1	2	0	1	0	N/R
Khedr et al., 2014	1	2	0	1	0	2 itching, headache and dizziness

N/R, not reported.

Table 4

Summary of the Effect Sizes (studies with healthy older adults)

Study	Outcome Measures	Nstim/Nsham	Mstim/Msham	SDstim/SDsham	Effect Size
Sole-Padulles et al., 2006	Associative Memory	20/19	1.6/−0.63	3.08/1.98	0.86
Boggio et al., 2010					
(1) L DLPFC	Gambling Risk Task	9/9	54.5/74.0	4.5/4.5	−4.33
(2) R FLPFC	Gambling Risk Task	10/9	70.0/74.0	4.7/4.5	−0.87
Ross et al., 2011					
(1) L ATL	Face Naming Task	14/14	40/29	19.1/16.1	0.62
(2) R ATL	Face Naming Task	14/14	34/29	27.3/16.1	0.22
Holland et al., 2011	Picture Naming Task	10/10	785/805	63.2/79.0	0.28
Kim et al., 2012	Stroop Test	8/8	860/1000	62.2/56.5	2.36
Floel et al., 2012	Object-location Memory	20/20	24.0/8.5	17.4/8.5	1.13
Manenti et al., 2013					
(1) L DLPFC/PARC	Verbal Episodic Memory	32/32	942/1027	72/92	1.03
(2) R DLPFC/PARC	Verbal Episodic Memory	32/32	1016/1027	68/92	0.14
Meinzer et al., 2013	Semantic Word Retrieval	20/20	5.75/7.20	4.0/3.1	0.41
Harty et al., 2014	Error Awareness Task	24/24	56.9/44.6	22.7/20.4	0.57
Fertonani et al., 2014					
(1) Online stimulation	Picture Naming Task	20/20	95.7/94.6	5.6/6.9	0.18
(2) Offline stimulation	Picture Naming Task	20/20	94.6/94.6	8.5/6.9	0.00
Meinzer et al., 2014					
(1) Unilateral stimulation	Semantic Word Retrieval	18/18	5.2/8.1	3.18/4.66	0.73
(2) Bilateral stimulation	Semantic Word Retrieval	18/18	5.5/8.1	3.81/4.66	0.61
Sandrini et al., 2014	Verbal Episodic Memory	12/12	49.9/31.9	24.6/17.1	0.85
Park et al., 2014	2-back Working Memory	20/20	57.96/51.48	11.35/13.04	0.53

stim, stimulation group; sham, sham group; N, number of participants; M, mean; SD, standard deviation; L, left; R, right; DLPFC, dorsolateral prefrontal cortex; ATL, anterior temporal lobe; PARC, parietal cortex

Table 5

Summary of the Effect Sizes (studies with Alzheimer's disease)

Study	Outcome Measures	Nstim/Nsham	Mstim/Msham	SDstim/SDsham	Effect Size
Cotelli et al., 2006					
(1) L DLPFC	Picture Naming Task	15/15	46.0/30.3	5.0/4.6	3.27
(2) R DLPFC	Picture Naming Task	15/15	48.0/30.3	4.5/4.6	3.89
Ferrucci et al., 2008	Word Recognition Task	10/10	17.9/16.0	2.5/3.2	0.66
Cotelli et al., 2008					
(1) Mild/L DLPFC	Picture Naming Task	12/12	56.0/35.0	10.0/20.0	1.33
(2) Mild/R DLPFC	Picture Naming Task	12/12	56.0/35.0	9.0/20.0	1.35
(3) Moderate to severe/ L DLPFC	Picture Naming Task	12/12	43.5/32.0	6.0/7.0	1.76
(4) Moderate to severe/ R FLPFC	Picture Naming Task	12/12	45.0/32.0	7.5/7.0	1.79
Boggio et al., 2009					
(1) L DLPFC	Visual Recognition Memory Task	10/10	35.9/32.0	6.1/4.0	0.76
(2) L temporal cortex	Visual Recognition Memory Task	10/10	37.0/32.0	12.0/4.0	0.56
Coteilli et al., 2011	Auditory Sentence Comprehension	5/5	77.3/65.9	14.5/21.5	0.62
Boggio et al., 2012	Visual Recognition Memory Task	15/15	5.08/4.84	0.85/0.92	0.27
Ahmed et al., 2012					
(1) 20 Hz/ Mild to moderate	MMSE	10/11	21.4/15.6	3.2/2.6	2.00
(2) 20 Hz/Severe	MMSE	5/4	11.0/8.3	1.9/2.3	1.30
(3) 1 Hz/ Mild to moderate	MMSE	11/11	15.7/15.6	4.0/2.6	0.03
(4) 1Hz/Severe	MMSE	4/4	10.2/8.3	1.9/2.6	0.83
Rabey et al., 2013	ADAS-Cog	7/8	3.76/0.47	3.49/3.34	0.96
Eliasova et al., 2014	Trail Making Test	10/10	90.8/95	68.4/72.9	0.06
Cotelli et al., 2014	Face-Name Association Task	12/12	41.1/41.0	10.4/6.9	0.01
Khedr et al., 2014					

Study	Outcome Measures	Nstim/Nsham	Mstim/Msham	SDstim/SDsham	Effect Size
(1) atDCS	MMSE	11/11	20.0/18.0	0.5/0.6	3.62
(2) ctDCS	MMSE	12/11	20.5/18.0	1.0/0.6	3.00

stim, stimulation group; sham, sham group; N, number of participants; M, mean; SD, standard deviation; L, left; R, right; DLPFC, dorsolateral prefrontal cortex; MMSE, Mini-Mental State Examination; ADAS-Cog, Alzhermer Disease Assessment Scale-cognitive subsection; atDCS, anodal transcranial direct current stimulation; ctDCS, cathodal transcranial direct current stimulation

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