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Review

Effects of noninvasive 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 noninvasive brain stimulation on cognitive function in healthy older adults and patients with Alzheimer's disease. A comprehensive literature search was performed on noninvasive 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 the effects of stimulation on Alzheimer's disease patients, 11 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 with studies delivering the stimulation before the execution of the task. Noninvasive brain stimulation has a positive effect on cognitive function in physiological and pathological aging.

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 noninvasive brain stimulation techniques have been applied to healthy older adults and patients with AD 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 noninvasive brain stimulation techniques are repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS). rTMS is a painless, noninvasive 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

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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 toward 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 (Cotelli et al., 2006, 2008, 2011; Ahmed et al., 2012; Boggio et al., 2009, 2012; 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 Examination (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) used 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 noninvasive 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 most 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 AD because 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

To collect pertinent studies, computerized searches were performed in Pubmed and Web of Science. The search terms were aging and/or elder and/or older adult, AD, rTMS, and 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 $\geq$10 participants receiving noninvasive brain stimulation; (3) outcome measures were quantitatively reported; and (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.