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# Commentary: Transcranial direct current stimulation for depression in Alzheimer's disease: study protocol for a randomized controlled trial

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Dementia is a progressive neurodegenerative disorder that is characterized by a decline in cognition in one or more cognitive domains such as learning and memory, language, executive function, complex attention, perceptual-motor, social cognition[1]. World Alzheimer Report 2015 reported that 36 million people were living with dementia in 2010, nearly doubling every 20 years to 66 million by 2030 and to 115 million by 2050[2]. Alzheimer's disease (AD) is the most common form of dementia in the elderly that is increasingly prevalent with advancing age, and the overall burden of it is substantial worldwide[3-8]. Cognitive dysfunction in AD decreases the quality of life (QOL) of patients and caregivers[9]. The cholinergic drugs, introduced first in 1997, have been approved worldwide and considered to be the first line pharmacotherapy for mild to severe AD. The mechanism of these drugs is to inhibit the breakdown of acetylcholine, a neurotransmitter associated with memory or cognitive activity, by blocking the enzyme acetylcholinesterase[10]. Although these drugs can slow the progression of AD, a review study revealed the limited efficacy of these compounds[10]. Future disease-modifying treatments and therapeutic interventions augmenting current pharmacologic treatments are awaited.

Neuropsychiatric symptoms in patients with AD also compromise their QOL[11]. Depressive mood is one of the most frequent neuropsychiatric symptoms in AD as well as agitation and apathy[12]. The prevalence rate of depression in AD is estimated as from 36.7 %[13] to 47.8 %[12]. On the other hand, antidepressant drugs and electroconvulsive therapy (ECT) have not shown significant effect on depression in AD. A meta-analysis revealed that selective serotonin reuptake inhibitors and serotonin and norepinephrine reuptake inhibitors did not show significant effect on depression in AD[14]. A randomized controlled trial (RCT) with a large sample, also revealed that neither selective serotonin reuptake inhibitors nor noradrenergic and specific serotonergic antidepressants showed superiority to placebo, and concluded that antidepressants should not be used first for depression in AD considering adverse events induced by antidepressants[15]. Moreover, a recent thorough review, in neither older patients over 65 years nor patients with dementia, verified the effect of ECT[16].

Our recent study entitled "Transcranial direct current stimulation for depression in Alzheimer's disease: study protocol for a randomized controlled trial" was designed to evaluate the safety and effect of transcranial direct current stimulation (tDCS) on depression in patients with AD over 65 years[17]. tDCS is a simple, cheap, and safe technique of neuromodulation, based on the application of weak, direct electrical current to the brain through relatively large electrodes. Two

electrodes are typically placed over the scalp, in which anodal and cathodal stimulation increases and decreases cortical excitability, respectively[18]. As a novel therapeutic intervention for potentially affecting both cognition and depression, our study may bring a significant impact on these domains in patients with AD, and may be useful to enhance their quality of life. Other than our study, novel studies investigating the effect of tDCS in AD are being explored. For instance, Inagawa, et al. (2016) presented a protocol of the pilot study to assess the safety and efficacy of tDCS during cognitive rehabilitation on cognitive function for patients with major or minor cognitive disorders[19].

Seven double-blind RCTs have been so far conducted for AD[20–26]. Here we review five of them that evaluated multiple-session effects[20,22,23,25,26] since a meta-analysis suggests that a larger number of sessions may be more effective[27]. Two of five controlled trials revealed significant effect on some domains in AD. One study reported a significant improvement in cognitive function after 10 sessions of anodal or cathodal stimulations over left dorsolateral prefrontal cortex (DLPFC) in 34 patients with AD[25]. In this study, the P300 component of the event-related potential, which is known to be pathologically increased in AD, was also reduced[25].The other trial demonstrated significant improvement in visual recognition memory after five sessions of anodal stimulations over left DLPFC in 15 subjects with AD although it did not verify significant effect on neither general cognitive performance measures nor a visual attention measure[20].

In remaining three RCTs, tDCS did not show significant improvement in AD. Suemoto, et al. (2014), employing 40 apathetic patients with AD, assessed the effect of six sessions of tDCS in two weeks, and found the lack of a significant benefit on apathy and cognitive outcomes[26]. This study also reported adverse effects systematically to find that tingling and scalp burning were significantly more frequent in the active tDCS group[26]. Cotelli, et al. (2014) enrolled 36 subjects with AD, assigning them into three groups, active left DLPFC tDCS plus individualized computerized memory training (ICMT), sham left DLPFC tDCS plus ICMT, and active left DLPFC tDCS plus motor training, with 10 sessions in two weeks[23]. Active tDCS plus ICMT group did not significantly improve performance across time compared to sham tDCS plus ICMT group, although it revealed significant improvement in a face-name association task compared to active tDCS plus motor training[23]. Bystad, et al. (2016) included 25 participants with AD to assess the effect of left temporal cortex tDCS with six sessions in 10 days[22]. Compared with placebo stimulation, active tDCS stimulation did not significantly improve verbal memory function[22].

The controlled studies so far provided are largely heterogeneous in methodology and outcomes. Also, a small sample may raise caution in concluding that these results represent effects in the population, which might be an issue of external validity. Moreover, only one RCT has reported adverse effects systematically although they are of concern in trials enrolling elderly participants. Limitations in recruitments should be also noted. Since patients with AD have cognitive dysfunction, they might not be able to decide whether they should give consent. In addition, self report of patients with AD is simply not enough to make an objective assessment of their cognition or QOL. In this context, it is necessary to have caregivers with them; but this might decrease the opportunity of enrollments. Furthermore, as stated above, daily sessions would be preferred to acquire effect; but the long study period might have negative effect on patients' motivation and increase the dropout rate.

Despite all these potential pitfalls pointed out above, controlled studies investigating tDCS in patients with AD are still advantageous, considering their significant impacts. Further RCTs with larger sample and additional evaluations will be required. Although adverse effects mentioned above were so mild that participants could tolerate them, they must be systematically described to avoid reporting bias. Also, high quality of randomization, allocation concealment, and blinding will be necessary to make trials well-controlled. With more controlled trials, the effect of tDCS in AD should be fully investigated with a systematic review and meta-analysis.

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