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High definition-transcranial direct current stimulation changes older adults' subjective sleep and corresponding resting-state functional connectivity

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ABSTRACT

With advanced age, older adults show functional deterioration in sleep. Transcranial direct current stimulation (tDCS), a noninvasive brain stimulation, modulates individuals' behavioral performance in various cognitive domains. However, the modulation effect and neural mechanisms of tDCS on sleep, especially for the elderly population are not clear. Here, we aimed to investigate whether high-definition transcranial direct current stimulation (HD-tDCS) could modulate community-dwelling older adults' subjective sleep and whether these potential improvements are associated with the large-scale brain activity alterations recorded by functional magnetic resonance imaging. Thirty-one older adults were randomly allocated to the HD-tDCS group and the control group. HD-tDCS was applied for 25 min at 1.5 mA per day for two weeks. The anode electrode was placed over the left dorsolateral prefrontal cortex, surrounded by 4 cathodes at 7 cm radius. All participants completed sleep neuropsychological assessments and fMRI scans individually before and after intervention. Behaviorally, we observed a HD-tDCS-induced enhancement of older adults' sleep duration. On the aspect of the corresponding neural alterations, we observed that HD-tDCS decreased the functional connectivity between the default mode network (DMN) and subcortical network. More importantly, the decoupling connectivity of the DMN-subcortical network was correlated with the improvements of subjective sleep in the HD-tDCS group. Our findings add novel behavioral and neural evidences about tDCS-induced sleep improvement in community-dwelling older adults. With further development, tDCS may be used as an alternative treatment for sleep disorders and alleviate the dysfunction of brain networks induced by aging.

1. Introduction

Sleep is essential for human biological and cognitive functions, such as body recovery, cell detoxification, memory consolidation, and emotion regulation (Stickgold and Walker, 2005; Tononi and Cirelli, 2006; Walker, 2009). However, with advanced age, older adults show functional deterioration in sleep (Phillips and Ancoliisrael, 2001; Ohayon et al., 2004; Hornung et al., 2005). Epidemiological studies reported a high prevalence rate of sleep disorders in the population of older adults (Foley et al., 1995; Ford and Kamerow, 1989; Foley et al., 2004; Ohayon, 2002), and over half of community-dwelling older adults reported at least one sleep complaints as occurring most of the time (Foley et al., 1995). Most of these older adults choose to endure the sleep complaints (e.g. trouble falling asleep, waking up, awaking too early) other than treat or reduce the symptoms on purpose.

Transcranial direct current stimulation (tDCS) is a noninvasive brain stimulation technique by means of a weak direct current applied to the scalp over sponge electrodes. It has been demonstrated that this approach modulates individuals' behavioral performance in various cognitive domains (Nitsche et al., 2003; Marshall et al., 2004; Fregni et al., 2005; Boggio et al., 2006; Monti et al., 2008; Nitsche et al., 2008), and these behavioral alterations were found to be associated with corresponding neuronal changes in brain activations, functional connectivity, and metabolite concentrations (Fertonani and Miniussi, 2017). However, the modulation effect of tDCS on sleep characteristics, especially for the elderly population are not well understood. Since the alterations of excitability and activity in cortex play a fundamental role in the onset of sleep and the transition of sleep stages (Riemann et al., 2015; Ding et al., 2016), the modulation of cortical activity by tDCS could be a potential approach in the treatment of sleep disorders. Previous studies reported that tDCS has a sleep-stabilizing or improvement effect on sleep, manifested as increased sleep efficiency and

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improved scores of the Pittsburgh Sleep Quality Index (PSQI) after tDCS treatment (Roizenblatt et al., 2007; Acler et al., 2013; Minichino et al., 2014; Saebipour et al., 2015). These studies discussed the mechanisms of tDCS on sleep from the perspective of behavior and neuropsychology, whereas the underlying neural basis is unclear. Gaining a better understanding of the neural mechanism underlying tDCS-induced sleep modulation would contribute to the development of alternative treatment for older adults' disturbed arousal and sleep by aging. In the present study, HD-tDCS stimulation was used instead of traditional tDCS. Traditional tDCS techniques are relatively spatial crude (Borckardt et al., 2012). Usually sponge electrodes (5–7 cm) are used to stimulate the brain cortex and it is difficult to locate smaller cortical regions. The high-definition transcranial direct current stimulation is a new modified version of traditional tDCS and uses plenty of specialized compact scalp electrodes to supply current without skin irritation and minimal discomfort (Lang et al., 2005), which facilitates the applicability of this noninvasive intervention on community-dwelling older adults.

Previous results obtained from sleep researches revealed that identified alterations of the default network (DMN) as a neural correlate of sleep activity (Horovitz et al., 2009; Samann et al., 2011; Chow et al., 2013; Regen et al., 2016). The DMN consists of the bilateral posterior cingulate cortex (PCC), retrosplenial cortex (RspC), inferior parietal lobule (IPL), medial prefrontal cortex (mPFC), temporal lobe and parts of the hippocampal formation (Buckner et al., 2008). Recent study used resting-state functional MRI to investigate the difference of functional connectivity of DMN between patients with primary insomnia and good sleeper control (Regen et al., 2016). The results exhibited that participants with greater connectivity between the retrosplenial cortex/hippocampus and various nodes of the DMN was associated with lower sleep efficiency, lower amounts of rapid eye movement sleep and longer sleep-onset latency. These findings indicated that relatively lower connectivity within the DMN is more beneficial for good sleep. In addition to the DMN, the subcortical network, including the amygdala, hippocampus, striatum, globus pallidus, and thalamus, is also thought to be involved in the mediating of sleep (Miyamoto et al., 2012; Abbott et al., 2013). The median preoptic nucleus and ventrolateral preoptic area of the hypothalamus in subcortical network is currently pointed out as the crucial sleep-promoting brain regions (Gvilia et al., 2006; Luppi and Fort, 2011). Neurons in these areas function to promote sleep via reducing inhibitory modulation of arousal systems and regulating sleep depth (Gvilia et al., 2006). These findings suggest one intriguing possibility that tDCS-induced sleep improvement might be associated with the corresponding alterations of functional connectivity within or between these large-scale brain networks.

In the present study, we aimed to study whether high-definition transcranial direct current stimulation (HD-tDCS) could modulate community-dwelling older adults' subjective sleep and whether these potential improvements are associated with alterations in the large-scale brain network at rest. As aforementioned the critical role of the DMN and subcortical network in sleep, we are particularly interested in identifying whether there are functional connectivity alterations within or between these two brain networks, and whether individuals' resting-state functional connectivity alterations of certain networks could predict their HD-tDCS-induced sleep changes.

2. Experimental procedures

2.1. Participants

Thirty-three community-dwelling older adults were recruited for the study. Patients had to fulfill the following criteria: (1) aged 60 or above community dwelling elderly people; (2) the vision and hearing function were normal; (3) the score of Mini-Mental State Examination (MMSE) in illiterate older adult ≥24, the score of MMSE in educated older adult ≥26 (Folstein et al., 1975); (4) without any oral complain about sleep disorders; (5) without any nervous system disease or neuropsychiatric disorders; (6) the metal in body should be retrievable; (7) without taking any sleep medications or other drugs. Participants were randomly assigned to the HD-tDCS group and the control group. Two participants in the HD-tDCS group were excluded due to excessive head movement during fMRI scanning (see below for exclusion procedure). Thus, thirty-one participants were included in the final analyses: 16 in the HD-tDCS group and 15 in the control group. These two groups were matched on demographic and neuropsychological data, and the details were presented in Table 1.

Table 1
Demographic and neuropsychological data.

	HD-tDCS group (n = 16)	Control group (n = 15)	p
Age (years)	67.56 ± 4.69	65.80 ± 5.23	0.33
Education (years)	8.84 ± 3.62	7.93 ± 4.59	0.54
Sex (male/female)	7/9	5/10	0.21[a]
Daytime nap (yes/no)	11/5	9/6	0.11[a]
MMSE	27.63 ± 1.96	27.40 ± 2.20	0.77
MoCA	24.25 ± 3.53	23.73 ± 3.77	0.70
CES-D	9.19 ± 7.96	14.20 ± 12.56	0.20

Note. MMSE, Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment; CES-D, Center for Epidemiologic Studies Depression Scale.
[a] The p value was obtained using chi-square test.

This study is approved by the Ethics Committee of Southwest University (No. H15001), and all procedures involved were in accordance with the sixth revision of the Declaration of Helsinki. Informed consent is obtained from each participant. The protocol for this study has been registered in Chinese Clinical Trial Registry (ChiCTR, Registration number: ChiCTR-IOR-15007371).

2.2. Sleep assessment

For the assessment of sleep alterations, all participants completed a battery of standardized sleep neuropsychological tests individually before and after sessions. The battery of standardized sleep neuropsychological tests included the Pittsburgh Sleep Quality Index (PSQI; Buysse et al., 1989), Self-Rating Scale of Sleep (SRSS; Li, 2000), Global Sleep Assessment Questionnaire (GSAQ; Roth et al., 2002), REM Sleep Behavior Disorder Screening Questionnaire (RBDSQ; Karin et al., 2007). Due to the intervention is across two weeks, the instructions of standardized sleep scales were modified accordingly. Participants were required to report retrospective sleep quality over the past week. For the HD-tDCS group, participants received a two-week HD-tDCS intervention. For the control group, participants were assigned to the waiting-list. All participants underwent MRI scan before and after the corresponding sessions (Fig. 1A).

2.3. High definition-transcranial direct current stimulation (HD-tDCS)

Participants in the HD-tDCS group received high definition transcranial direct current stimulation at left dorsolateral prefrontal cortex (DLPFC). Soterix medical 4 × 1 ring configuration HD-tDCS adapter is carried out by an experienced researcher. To stimulate left DLPFC, the anode electrode will be placed over F3 according to the 10–20 international system for EEG electrode placement, surrounded by 4 cathodes at 7 cm radius (Fig. 1A)—all the electrodes are high-definition mini electrodes (Borckardt et al., 2012), with a constant current of 1.5 mA intensity lasts for 25 min (Ferrucci et al., 2008). Interventions were performed 5 times a week for 2 weeks in daytime (9:00–11:00, 14:00–17:00).