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Multisession anodal transcranial direct current stimulation induces motor cortex plasticity enhancement and motor learning generalization in an aging population

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HIGHLIGHTS

- Multisession anodal transcranial direct current stimulation (a-tDCS) of primary motor cortex (M1) induces motor learning generalization in aging.
- Multisession a-tDCS-M1 induces M1 cortical disinhibition in aging.
- Persistent M1 disinhibition induced by tDCS predicts motor learning generalization.

ABSTRACT

Objectives: The present aging study investigated the impact of a multisession anodal-tDCS protocol applied over the primary motor cortex (M1) during motor sequence learning on generalization of motor learning and plasticity-dependent measures of cortical excitability.
Methods: A total of 32 cognitively-intact aging participants performed five consecutive daily 20-min sessions of the serial-reaction time task (SRTT) concomitant with either anodal ($n = 16$) or sham ($n = 16$) tDCS over M1. Before and after the intervention, all participants performed the Purdue Pegboard Test (PPT) and Transcranial Magnetic Stimulation (TMS) measures of cortical excitability were collected.
Results: Relative to sham, participants assigned to the anodal-tDCS intervention revealed significantly greater performance gains on both the trained SRTT and the untrained PPT as well as a greater disinhibition of long-interval cortical inhibition (LICI). Generalization effects of anodal-tDCS significantly correlated with LICI disinhibition.
Conclusion: Anodal-tDCS facilitates motor learning generalisation in an aging population through intracortical disinhibition effects.
Significance: The current findings demonstrate the potential clinical utility of a multisession anodal-tDCS over M1 protocol as an adjuvant to motor training in alleviating age-associated motor function decline. This study also reveals the pertinence of implementing brain stimulation techniques to modulate age-associated intracortical inhibition changes in order to facilitate motor function gains.

1. Introduction

Transcranial direct-current stimulation (tDCS) is a non-invasive technique of cortical brain neuromodulation with potential therapeutic effects. Using a constant and low intensity direct current

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that flows between two electrodes over the scalp (Webster et al., 2006; Fregni and Pascual-Leone, 2007), this technique influences trans-membrane neuronal potentials and modifies the level of cortical excitability in the targeted brain region (Priori et al., 1998; Fregni and Pascual-Leone, 2007; Nitsche et al., 2008; Bastani and Jaberzadeh, 2012). The application of anodal tDCS (a-tDCS) increases cortical excitability by strengthening synaptic connections through long-term potentiation (LTP)-like mechanisms of brain plasticity (Bindman et al., 1964). By soliciting this brain plasticity mechanism, which is known to be critically involved in learning and memory (Rioult-Pedotti et al., 2000), a-tDCS has been shown to enhance cognitive and behavioral functions such as language processing (Metuki et al., 2012), working memory (Fregni et al., 2005), inhibitory control (Hsu et al., 2011) and motor learning (Nitsche et al., 2003). While it is generally agreed that brain plasticity and cognitive function decline with advancing age (Raz, 2000; Burke and Barnes, 2006), hence purporting serious consequences on the quality of life and safety of the elderly, limited information is available on the potential benefits of a-tDCS to either maintain or restore brain function via the stimulation of brain plasticity mechanisms in the latter population.

To date, the clinical utility of tDCS is best supported by studies showing enhanced primary motor cortex (M1) excitability and associated motor functions such as motor execution and learning, procedural memory formation and consolidation of motor skills (Muellbacher et al., 2000; Sanes and Donoghue, 2000; Fregni and Pascual-Leone, 2007; Galea and Celnik, 2009; Reis et al., 2009; Fritsch et al., 2010; Stagg et al., 2011; Ditye et al., 2012). Indeed, tDCS studies conducted over other brain areas such as the dorsolateral prefrontal cortex and aiming to modulate cognition show conflicting results in young as well as in aging adults (Tremblay et al., 2014; Nilsson et al., 2017). Moreover, M1 represents a particularly appealing site for a-tDCS intervention given that it is possible to overtly quantify a-tDCS-associated changes of cortical excitability over M1 using transcranial magnetic stimulation (TMS). The latter constitutes another brain stimulation technique that uses electromagnetic pulses to trigger a rapid magnetic field (Fregni and Pascual-Leone, 2007). One main difference between tDCS and TMS is that tDCS has a modulatory subthreshold impact on resting membrane potentials, whereas TMS induces cortical action potentials, which result in muscle twitches (motor evoked potentials, MEP) when the motor cortex is stimulated. Thereby, while tDCS acts on cortical excitability by inducing sustained changes in neural cell membrane potential, TMS applied over M1 induces muscle contractions that are easily recorded using surface electromyography. Plasticity-dependent cortical excitability changes due to tDCS can therefore easily be measured via peak-to-peak MEP amplitude calculation (Wassermann et al., 2008).

Just like a-tDCS, motor skill acquisition modulates brain plasticity (Scholz et al., 2009; Hofer and Bonhoeffer, 2010) as performance progression increases M1 excitability and suppresses M1 inhibitory mechanisms (Ljubisavljevic, 2006; van Beers, 2009; Smyth et al., 2010). Previous studies conducted with young healthy subjects revealed that the concurrent application of a-tDCS over M1 (a-tDCS-M1) during motor training can accentuate behavioral gains (Nitsche et al., 2003; Galea and Celnik, 2009; Reis et al., 2009; Stagg et al., 2011). For instance, the application of a-tDCS-M1 during an explicit sequence-learning task was associated with faster learning, compared with either online sham stimulation or offline a-tDCS-M1 stimulation (tDCS prior to task; Stagg et al., 2011). Moreover, a study by Nitsche and colleagues showed that a-tDCS-M1 stimulation significantly facilitated online implicit motor sequence learning (serial reaction time task, SRTT), whereas stimulation of the premotor and prefrontal cortices had no effect (Nitsche et al., 2003). Taken together, these findings suggest that implicit motor learning further benefit from a-tDCS facilitation effects when the latter is applied both online and over M1.

In keeping with findings from young adult cohort, motor function gains are observed in aging with the application a-tDCS-M1 (Zimerman et al., 2013; Parikh and Cole, 2014; Hoff et al., 2015; Panouillères et al., 2015; Dumel et al., 2016). Moreover, a recent literature review on tDCS effects in the aging population revealed a larger effect size for a-tDCS stimulation applied during, as opposed to prior to, the execution of a motor task (Summers et al., 2016). While it is generally agreed that M1 neuronal plasticity significantly declines with age (Nitsche et al., 2008; Fathi et al., 2010), a recent study conducted on older adults showed a significant association between online visuomotor skills improvements after a single a-tDCS-M1 session and plasticity-dependent enhancement of MEP size and a decrease of short-term intracortical inhibition (Goodwill et al., 2013). This study suggests that despite age-related decline of brain plasticity, functional improvements in aging could be enhanced by stimulating LTP mechanisms via the application of a-tDCS-M1.

From a clinical perspective, one crucial element in assessing cognitive rehabilitation efficacy is the capacity of the trained skills to improve performance on untrained tasks, a concept often referred to the generalizability of training gains. In a study conducted by Seidler (2007), in which older participants exhibited significantly more errors than young ones in a baseline joystick orientation task, both age groups showed equivalent adaptive learning transfer to others joystick rotations tested using a single training session. The author suggested that aging does not result in impaired motor learning transfer. Two other studies conducted in cognitively intact aging individuals showed improvements in manual dexterity, as measured with the Purdue Pegboard Task (PPT), after several weeks of training involving only fingers (skilled finger movement training for Ranganathan et al., 2001, steadiness finger training for Kornatz et al., 2005). Interestingly, Kornatz et al. (2005), showed a significantly greater improvement on the PPT for the trained hand compared to the untrained hand. More recently, Boraxbekk et al. (2016), showed that six weeks of training allowed the transfer of learning of a finger tapping sequence to another untrained sequence in an aging population. Although of crucial clinical significance, the generalization of motor skills after motor training remains largely understudied (King et al., 2013; Boraxbekk et al., 2016). However, emerging data tend to suggest that generalizability of training gains can only be achieved via extensive training involving numerous sessions. A significant benefit from the online application of a-tDCS-M1 during motor training could therefore be to facilitate generalizability of training gains through a limited number of training sessions.

In a recent study from our group, we sought to investigate the effects of five consecutive, daily 20-min sessions of a-tDCS-M1 during SRTT performance on motor learning in cognitively intact aging adults (Dumel et al., 2016). Results revealed a significantly greater implicit motor learning through the 5 days of intervention in aging individuals assigned to the a-tDCS-M1 group relative to a sham control group. Using the same protocol, the aim of the present aging study was to explore the impact of a multisession a-tDCS-M1 protocol on plasticity-dependent measures of cortical excitability as measured by TMS. We also tested whether a-tDCS-M1 applied during implicit motor sequence training was effective in facilitating generalizability of training gains to an untrained motor task. We hypothesized that cognitively-intact aging individuals assigned to the a-tDCS group would exhibit greater M1 intracortical facilitation as well as greater improvements on an untrained motor learning task when compared to a sham control group.