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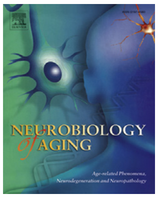

Brief communication

Cerebellar direct current stimulation enhances motor learning in older adults

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ABSTRACT

Developing novel approaches to combat age related declines in motor function is key to maintaining health and function in older adults, a subgroup of the population that is rapidly growing. Motor adaptation, a form of motor learning, has been shown to be impaired in healthy older subjects compared with their younger counterparts. Here, we tested whether excitatory anodal transcranial direct current stimulation (tDCS) over the cerebellum could enhance adaptation in older subjects. Participants performed a "center-out" reaching task, adapting to the sudden introduction of a visual cursor rotation. Older participants receiving sham tDCS (mean age 56.3 ± 6.8 years) were slower to adapt than younger participants (mean age 20.7 ± 2.1 years). In contrast, older participants who received anodal tDCS (mean age 59.6 ± 8.1 years) adapted faster, with a rate that was similar to younger subjects. We conclude that cerebellar anodal tDCS enhances motor adaptation in older individuals. Our results highlight the efficacy of the novel approach of using cerebellar tDCS to combat age related deficits in motor learning.

1. Introduction

Aging is associated with declines in motor function including slowing of self-paced movements, reduced coordination, and more variable kinematics (Bennett and Castiello, 1994; Heuninckx et al., 2008; Sarlegna, 2006). This decline is accompanied by changes in brain structure and function, such as decreased white matter integrity, reorganization of neural networks, and compensatory brain activity (Heuninckx et al., 2008; Stadlbauer et al., 2008). Considering average life expectancy in developed countries has increased by 30 years in the last century, and that the portion of older adults in society continues to expand, developing novel approaches to combat age related declines in motor function is an important scientific challenge (Zimerman and Hummel, 2010).

Motor adaptation, a form of motor learning that involves reducing systematic errors related to new environmental demands, plays a crucial role in everyday activities such as modifying walking patterns to account for surface traction, acclimatizing to wearing glasses, or adjusting to the gain of a computer mouse. Motor adaptation differs from skill learning, requiring modification of existing movement abilities rather than learning new ones (Krakauer, 2009). Importantly, it has been argued that adaptive motor learning is cerebellum dependent (Tseng et al., 2007), while skill learning is more closely associated with cerebral and basal ganglia structures (Krakauer and Mazzoni, 2011).

Evidence indicates both motor adaptation and skill learning are impaired in older adults (Bock, 2005; Zimerman et al., 2013). Recent studies have enhanced skill learning in healthy older individuals by applying transcranial direct current stimulation (tDCS), a form of noninvasive brain stimulation, over the motor cortex (Hummel et al., 2010; Zimerman et al., 2013). Delivered via small sponge electrodes placed on the head, anodal tDCS increases neural excitability via TrkB and NMDA receptor activation (Fritsch et al., 2010), and modulation of GABA activity (Stagg et al., 2009). Anodal tDCS delivered over the cerebellum in young individuals produces excitability changes and improvements in adaptive motor learning (Galea et al., 2009, 2011). However, to date it is not known whether anodal cerebellar tDCS can combat age-related declines in motor adaptation. Here, we hypothesized that older adults would show age-related declines in motor adaptation, and that these declines could be reduced using anodal cerebellar tDCS. We compared motor adaptation in groups of older and younger subjects receiving sham stimulation, replicating the result that older adults show a declined rate of adaptation (Bock, 2005; Seidler, 2006). Data from a further group of older adults demonstrate that anodal cerebellar tDCS decreases age-related deficits in adaptation.

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2. Methods

2.1. Subjects

Thirty-three individuals participated in the study, split across 3 groups; an older sham group (n = 11, mean age 56.3 ± 6.8 years, 4 female, 9 right handed), a younger sham group (n = 11, mean age 20.7 ± 2.1 years, 6 female, 9 right handed), and an older anodal group (n = 11, mean age 59.6 ± 8.1 years, 7 female, 9 right handed). All participants completed a screening questionnaire before their participation. Eligible participants had no history of neurologic conditions or motor impairments, were not taking neurologic medications, lived independently, and were able to complete their routine daily activities without assistance. Procedures were conducted in accordance to the declaration of Helsinki, and all subjects gave written informed consent approved by the Johns Hopkins Institutional Review Board.

2.2. Experimental procedures

Participants made movements in a KINARM robot exoskeleton (BKIN Technologies, Kingston, Ontario, Canada). The robot allowed 2-dimensional movements in the horizontal plane. A projector and mirror allowed presentation of visual targets in the same plane as the arm (Fig. 1B). Vision of the hand and arm was occluded. Participants controlled a circular cursor (1 cm diameter blue circle) projected over the position of their index fingertip. Participants moved the cursor from a start circle (2 cm diameter, purple) through a target circle (2 cm diameter, white) appearing in 1 of 8 positions, all 10 cm from the start circle. We instructed participants to perform rapid "shooting" movements through the center of the target. Target presentation was pseudorandom, with a target appearing in each of the 8 locations once every 8 trials. Once the hand reached a distance of 10 cm from the start circle, the cursor froze in place, the target turned green, and the robot applied forces to slow and cushion the movement, as well as move the hand back toward the start position. The cursor reappeared when the fingertip returned within 2 cm of the start position. The next trial started once the cursor was held in the start position for at least 2 seconds.

Following 96 practice trials, participants completed 3 phases of experimental trials (Fig. 1A). The first phase established baseline-reaching accuracy (blocks pre 1 and 2, 48 trials each). Block pre 1 was completed without tDCS, while block pre 2 was completed with cerebellar anodal or sham tDCS, controlling for potential effects of tDCS on simple reaching performance. The second phase examined adaptation (blocks adapt 1 and 2, 64 trials each). Cursor feedback was rotated by 30° during this phase, requiring participants to correct the direction of their reaches to hit the target. The final phase assessed post-adaptation aftereffects (blocks post 1, 2, and 3, each 48 trials). In this phase, the cursor was initially present in each trial to allow the participant to center on the start

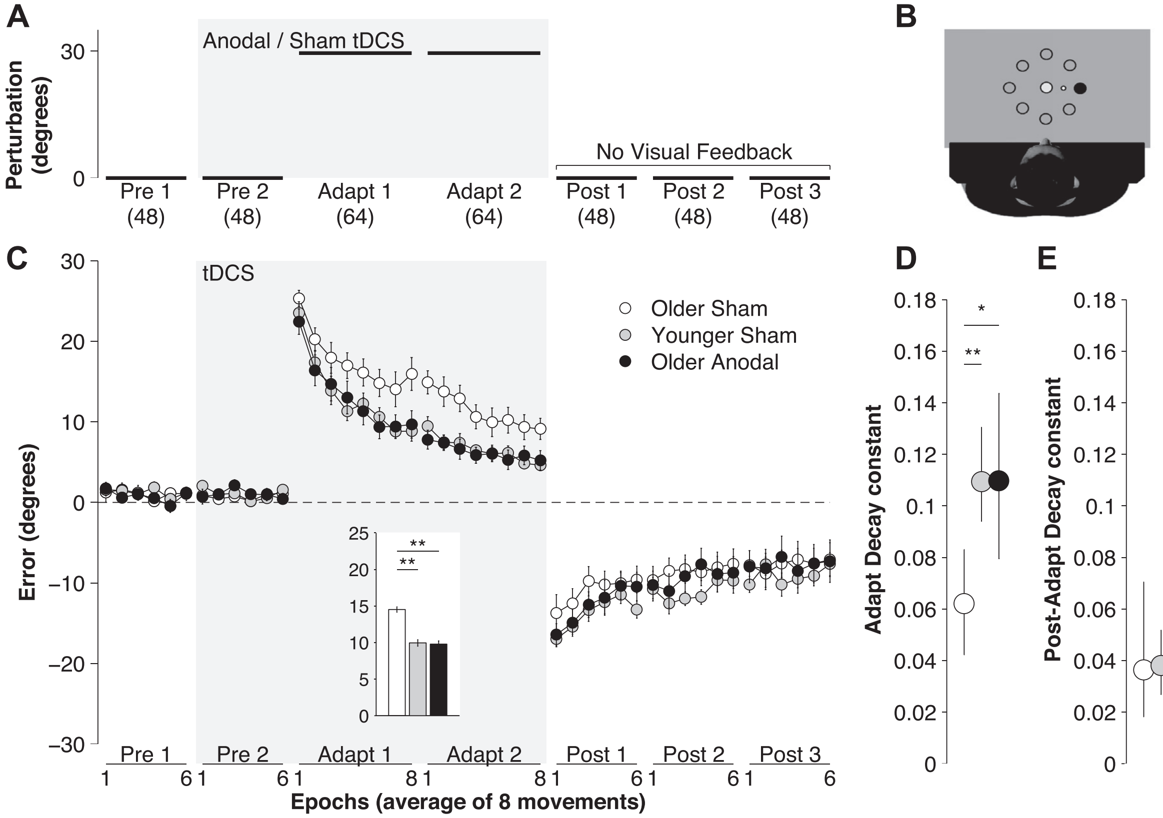

Fig. 1. (A) Design of the experiment. The experiment was composed of 3 phases. In the baseline phase participants completed 2 blocks of pre perturbation trials. Pre 1 was completed with no stimulation, while pre 2 was completed with anodal/sham tDCS. In the second phase, a 30° cursor rotation was applied (blocks adapt 1 and 2). In the third phase participants completed 3 post adaptation blocks; both the rotation and visual cursor feedback were removed. The numbers within parenthesis represent the number of trials in each block. (B) A schematic representation of the experimental setup. Participants sat in a robotic exoskeleton device with a monitor and bib blocking vision of their body. They moved their arm to shoot a cursor from a start position through a circular target in 1 of 8 potential positions (other target locations shown by open circles). (C) Mean error across epochs for the older sham (white), younger sham (gray), and older anodal (black) groups. Error bars represent SEM. Shaded region presents the period during which the older anodal group received tDCS. Inset presents significant differences between mean group error during the adaptation phase. (D) Parameter estimates for the error decay constant λ during the adaptation phase for the 3 groups (error bars represent 95% confidence intervals). (E) Estimates of parameter λ during the post adaptation phase for the 3 groups. * and ** indicate $p < 0.05$ and $p < 0.01$, respectively. Abbreviations: SEM, standard error of the mean; tDCS, transcranial direct current stimulation.

position, but disappeared upon target presentation. Participants reached for the target without accuracy feedback, allowing assessment of the retention of the recently learned movement directions (after effects of adaptation).

2.3. Transcranial DC stimulation

A Chattanooga Ionto iontophoresis unit (DJO International, Surrey, UK) delivered tDCS via 5 × 5cm sponge electrodes, soaked in a saline solution. We delivered cerebellar stimulation at 2 mA (Galea et al., 2009), with an anodal electrode positioned 3 cm lateral to the inion and a cathodal electrode on the ipsilateral buccinator muscle. This protocol has previously been shown to modulate cerebellar activity without affecting the excitability of the brainstem, the corticospinal tract, or the occipital cortex (Galea et al., 2009, 2011). In addition, in a number of behavioral controls this protocol did not affect vestibular function (Jayaram et al., 2012). Both electrodes were positioned on the side of the head ipsilateral to the dominant hand. We started the stimulation at the beginning of block “pre 2” for all subjects. We gradually increased the current over 30 seconds until it reached 2 mA. For participants in the anodal group, this 2 mA current was maintained until the end of the block “adapt 2” (approximately 15 minutes). Stimulation was applied during (rather than before) performance of the task as previous studies have demonstrated that combining tDCS and motor tasks is the most effective in enhancing motor behavior (Kuo et al., 2008; Nitsche et al., 2003; Stagg et al., 2004). For participants in the sham stimulation groups, we ramped down the current over the 30 seconds after it reached full intensity. This method effectively blinds participants as to whether they are receiving real or sham tDCS (Galea et al., 2009, 2011). Following the experiment participants rated their sensations of pain and/or discomfort during tDCS on a 10-point scale, with 1 indicating small discomfort and/or pain and 10 indicating large discomfort and/or pain.

2.4. Data collection and analysis

Using the robot we continuously recorded the 2D position of the fingertip at 1 kHz. We calculated the movement error as the angular difference between a straight line from the start position to the target and the position of the fingertip at peak velocity (Bock, 2005; Seidler, 2006). We then averaged sets of 8 consecutive trials (containing one attempt to each target) to create epochs, and calculated the mean error within epoch for each subject. Using separate 1-way analyses of variance (ANOVAs) we examined error for each phase of the experiment (baseline, adaptation, and post-adaptation). We conducted a repeated measures ANOVA to control for effects of tDCS on baseline pointing accuracy, comparing mean error in blocks pre 1 (without tDCS) and pre 2 (with tDCS). We controlled for differences in movement speed using a separate ANOVA. Finally, when appropriate we conducted post hoc analysis. Following model selection (Supplementary Materials) we applied an exponential model to mean data for each group:

$$Error_n = Error_i \times e^{(n \times -\lambda)}$$

Where n is the epoch number, i is the initial error, and λ is a decay constant. Pairwise permutation tests examined differences between groups. In each case we took 2 groups and fit the model to their mean data. We calculated the observed difference in λ between groups. We generated a null distribution by randomly shuffling participants between the 2 groups, fitting the model to the mean for each resample, and computing the difference in λ between groups. Repeating this 10,000 times, we used the proportion of values exceeding the observed difference to determine statistical significance (Holm–Bonferroni corrected for multiple comparisons). We generated confidence intervals on best-fit parameters by bootstrapping model fits (Smith et al., 2006). We calculated 10,000 estimates of the mean group data, averaging data from 11 random selections from the 11 subjects within each group, with replacement. We fit the model to each estimate, with the 2.5 and 97.5 percentiles being used as 95% confidence intervals.

3. Results

Performance in the baseline phase did not differ between groups ($F_{2,32} = 0.02$, $p = 0.99$). Importantly, tDCS did not change baseline performance (repeated measures ANOVA on block pre1 vs. pre2, no significant main effect: $F = 0.61$, $p = 0.44$, and no significant block by group interaction: $F_{2,32} = 0.03$, $p = 0.97$). The cursor rotation led to a significant difference in error between groups during the adaptation phase ($F_{2,32} = 5.27$, $p = 0.011$). Error was greater for the older sham group than the younger sham group ($p = 0.01$), a result consistent with previous studies (Bock, 2005; Seidler, 2006). Remarkably, the older anodal group experienced a significant decrease in error relative to the older sham group ($p = 0.008$), reaching a level of performance similar to the younger sham group ($p = 0.92$). Error did not differ between groups in the post adaptation phase ($F_{2,32} = 0.50$, $p = 0.61$).

We found no group differences in peak velocity (mean ± SE: older sham = 36.5±5.1 cm/s, younger sham = 34.3 ± 1.8 cm/s, older anodal 31.4 ± 4.4 cm/s; $F_{2,32} = 0.39$, $p = 0.68$), or perceptions of tDCS (discomfort: older sham = 1.9 ± 0.1, younger sham = 2.5 ± 0.1, older anodal = 1.5 ± 0.1; $F_{2,32} = 1.75$, $p = 0.191$, pain: older sham = 1.3 ± 0.04, younger sham = 1.7 ± 0.1, older anodal = 1.6 ± 0.2; $F_{2,32} = 0.34$, $p = 0.72$).

Bootstrap comparisons (Holm–Bonferroni corrected) found the error reduction rate during adaptation was slower for the older sham group than the younger sham group ($p < 0.01$). Adaptation was faster in the older anodal group than the older sham group ($p < 0.025$) and did not differ from the younger sham group (Fig. 1D). Decay of post adaptation after effects did not differ between groups (all $p > 0.50$; Fig. 1E).

4. Discussion

The present study shows that anodal tDCS over the cerebellum improves adaptive motor learning in healthy older subjects. Older adults are typically slower to adapt than younger healthy individuals (Bock, 2005; Seidler, 2006). However, we found that older subjects receiving anodal cerebellar stimulation reduced movement errors at a faster rate than older participants receiving sham stimulation. This improvement brought the older anodal group to a level of performance comparable to younger subjects.

The age of the older participants in the present study is slightly less than those in previous studies showing age-related declines in adaptation (Bock, 2005; Seidler, 2006). However, in line with this previous research, subjects in our older sham group showed a reduced rate of adaptation in comparison to the younger sham group. Cerebellar structure, function, and connectivity can be affected by age (Bernard et al., 2013; Bernard and Seidler, 2013a, 2013b; Luft et al., 1999; Raz et al., 2001, 2010). Cerebellar anodal tDCS may therefore improve adaptation by enhancing the spared function of the cerebellum. However, reversing cerebellar decline or dysfunction is not the only potential mechanism of action in the present study. For instance, enhancing cerebellar function in healthy younger adults also increases their rate of adaptation, and the effect is of a similar magnitude to the effect shown here (Galea et al., 2011). Thus, an alternative possibility is that enhancing cerebellar function may compensate for age-related declines in other distant connected brain areas. It has been proposed that 2 processes underlie adaptation (Redding and Wallace, 1996). The first process, spatial realignment, involves updating a forward model through the identification of errors by comparing predicted movement outcomes with sensory feedback. The second suggested process, strategic control, involves using cognitive schemes to overcome the perturbation. Declines in adaptation in older individuals have been attributed to reduced strategic control (Bock, 2005; Heuer et al., 2011).

Previously, we have shown cerebellar tDCS enhances adaptation in younger subjects (Block and Celnik, 2013; Galea et al., 2011). These results and others point to the role of the cerebellum in adaptive motor learning (Bernard and Seidler, 2013a, Hardwick et al., 2013; Taylor et al., 2010), supporting the view that it acts as a forward model (Hardwick et al., 2012; Schlerf et al., 2012; Wolpert et al., 1998). Increasing cerebellar excitability with anodal tDCS may have enhanced the spatial realignment process, compensating for deficits in strategic control and leading to faster reduction of movement errors. On the other hand, it could be argued that anodal cerebellar tDCS enhanced motor adaptation by improving cognitive processes involved in strategic control. Previous work has taken the finding that adaptive improvements are larger than the after effects present when the perturbation is removed as evidence of impaired strategic control in older adults (Bock, 2005). However, this is only an indirect inference, and further testing with paradigms specifically designed to address the contribution of explicit strategies during motor adaptation is required (Taylor et al., 2014). In addition, previous studies have shown anodal cerebellar tDCS has either no effect on cognitive tasks (Pope and Miall, 2012) or impairs working memory (Ferrucci et al., 2008). On the other hand, other research has shown that anodal cerebellar tDCS enhances adaptation in tasks where the role of strategic control is minimal (Jayaram et al., 2012; Malone and Bastian, 2010). Therefore, the anodal cerebellar tDCS effects in the present study appear to be more likely due to an enhancement of spatial realignment processes in older individuals, though further study is required to clarify the exact effects of anodal cerebellar tDCS on spatial realignment and strategic control.

Anodal tDCS increases neural excitability via TrkB and NMDA receptor activation as well as via modulation of GABA (Fritsch et al., 2010; Stagg et al., 2011). Empirical evidence shows that anodal motor cortex tDCS can revert skill acquisition declines in healthy older individuals (Hummel et al., 2010; Zimerman et al., 2013). Here we extend these results, showing that adaptation, another form of motor learning, can be enhanced in older individuals by stimulating the cerebellum. Further investigation will determine whether the within session effects of tDCS shown here also lead to a more rapid rate of relearning (i.e., enhanced "savings" Krakauer and Shadmehr, 2008).

In conclusion, we have shown for the first time that cerebellar anodal tDCS is an effective method of overcoming age related declines in adaptive motor learning. These results illustrate the efficacy of cerebellar tDCS as a technique to combat motor learning and performance decline in older adults.

Disclosure statement

The authors have no conflicts of interest to disclose.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.neurobiolaging.2014.03.030.

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