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Neuroenhancement of the Aging Brain: Restoring Skill Acquisition in Old Subjects

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Abstract

Objective—Decline in cognitive functions, including impaired acquisition of novel skills, is a feature of older age that impacts activities of daily living, independence, and integration in modern societies.

Methods—We tested whether the acquisition of a complex motor skill can be enhanced in old subjects by the application of transcranial direct current stimulation (tDCS) to the motor cortex.

Results—The main finding was that old participants experienced substantial improvements when training was applied concurrent with tDCS, with effects lasting for at least 24 hours.

Interpretation—These results suggest noninvasive brain stimulation as a promising and safe tool to potentially assist functional independence of aged individuals in daily life.

In the past years, human life expectation has increased significantly. Current trends in the demographics of developed countries show a rapid growth of the older segment of the workforce. Workers >50 years old represent the largest growing labor force segment in the next decade. The integration of subjects into modern societies relies increasingly on their ability to acquire constantly new skills to master current technologies. Advancing age is paralleled by a reduction of the ability to acquire new skills,[1] impacting social and professional life. Potential underlying mechanisms are altered neuronal plasticity due to age-related changes in synaptic function and neurotransmission.[2] Recent work demonstrated that application of transcranial direct current stimulation (tDCS) over the motor cortex (MC) can

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Additional supporting information can be found in the online version of this article.

Potential Conflicts of Interest

P.G.: paid educational presentations, Pfizer; travel expenses, Merz Pharmaceuticals. C.G.: consultancy, Boehringer Ingelheim, Lundbeck, Glaxo Smith Kline, Bayer Vital, UCB, EBS Technologies, Silk Road Medical, Sanofi Aventis; speaking fees, Boehringer Ingelheim, Sanofi Aventis, Bayer Vital, Pfizer. F.C.H.: consultancy, UCB, Lundbeck.

modulate neuroplasticity and facilitate motor learning in young humans.[3–5] In old subjects, first evidence was provided that tDCS might improve skilled motor performance.[6] However, the crucial question remains open whether this intervention can also enhance the acquisition and retention of complex motor tasks, yielding longer-lasting behavioral improvements.

To address this question, anodal tDCS (atDCS) was used as a noninvasive and well-tolerated technique to stimulate the cortex.[7] atDCS results in long-term potentiation (LTP)-like synaptic changes that accompany facilitatory effects on cortical excitability, neuroplasticity, and learning.[8]

Subjects and Methods

Subjects

Twenty-nine old (12 men; range, 55–88 years old) and 24 young right-handed subjects (10 men; range, 22–31 years old), naive to the task, participated in a series of experiments. The study was approved by the local ethics committee, and a written informed consent was obtained.

Motor Skill-Task

The task is a well-established finger-tapping task that engages activity in a distributed motor network including the contralateral MC.[9] It consists of sequential pressing of a 5-element sequence on a 4-button electronic keyboard with the right hand as quickly and accurately as possible. Participants attended a training session composed of 5 blocks of 3 minutes each with 2-minute breaks in between. The effects were re-evaluated up to 24 hours after training (retention session). No feedback was given by the investigators during the task. The primary outcome measure was the number of correct sequences achieved per block in the retention session (Fig 1). Notably, the present design allowed assessment of the temporal components of motor skill acquisition within and between each session. (For further details please see Supplementary Information.)

Experimental Setup

First, to corroborate an age-related deficit in the acquisition of novel motor skills, a pilot experiment was run in 14 old (67.9 ± 2.3 years) and 14 young (24.5 ± 0.5 years) participants without any intervention. The main experiment was conducted with a different set of old subjects (n = 10, mean 68.5 ± 3.2 years); atDCS was applied to the contralateral MC in a double-blind, sham-controlled, cross-over design concurrent with training. As a control group, 10 young subjects (mean 25.2 ± 2.9 years) were studied within the same design. tDCS was delivered through 2 sponge electrodes embedded in a saline-soaked solution (Eldith, DC-stimulator; neuroConn, Ilmenau, Germany). The anode was positioned on the projection of the hand knob area of the contralateral MC on the subject's scalp, whereas the cathode was placed on the contralateral supraorbital region.[10] In a control experiment in 5 old subjects (71.2 ± 1.9 years), the electrode montage was reversed (cathodal tDCS) to evaluate polarity specificity. The hand knob area of the MC was identified by single-pulse transcranial magnetic stimulation (70 mm figure-eight coil; Magstim, Dyfed, UK) by standardized procedures.[11] tDCS was applied for 20 minutes; current was initially increased in a ramplike fashion over 8 seconds until it reached 1mA (current density of 0.04mA/cm^2).[10] During sham, just as during real tDCS, stimulation was started in a ramplike fashion, but it faded out slowly after 30 seconds.[12] The participants and the examiner were blinded to the type of stimulation.

Results

Pilot Experiment

During training, skill acquisition was reduced in the old compared to young ($slope_{old}$ = 0.07 ± 1.05; $slope_{young}$ = 6.39 ± 0.89; $T_{[13]}$ = 4.59, $p < 0.01$), further substantiated by the differences in the retention performance (for details, please see Supplementary Results and Supplementary Fig 1). Thus, these results were consistent with the suggestion of an age-related decline in skill acquisition.[1,13]

Main Experiment

Baseline performance in old subjects was comparable across the experimental arms ($Baseline_{tDCS}$ = 7.5 ± 1.3 vs $Baseline_{sham}$ = 9.2 ± 1.6; $T_{[9]}$ = 2.05, $p > 0.05$). Additionally, the order of the sequence (Seq-A vs Seq-B) did not have any impact on the baseline performance ($Baseline_{Seq\text{-}A}$ = 8.7 ± 1.8 vs $Baseline_{Seq\text{-}B}$ = 8 ± 1.4; $T_{[9]}$ = 0.7, $p > 0.05$), consistent with the absence of relevant carryover effects.

The analysis of the follow-up sessions revealed a significant effect of $INTERVENTION_{tDCS,sham}$ ($F_{[1,9]}$ = 9.2, $p = 0.01$) and $RETENTION_{Test\text{-}90,Test\text{-}24}$ ($F_{[1,9]}$ =.2, $p = 0.01$) for the number of correct sequences related to the respective baseline without a significant interaction of these factors ($F_{[1,9]}$ = 2.3, $p = 0.15$). Thus, Test-90 and Test-24 were clearly different between atDCS and sham ($atDCS_{Test\text{-}90}$ = 12.1 ± 1.4 and $sham_{Test\text{-}90}$ = 8.1 ± 0.9; $atDCS_{Test\text{-}24}$ = 14.4 ± 2, $sham_{Test\text{-}24}$ = 9.4 ± 1.1; Fig 2A).

Training with atDCS led to a significant performance improvement; repeated measures analysis of variance revealed a significant $INTERVENTION_{tDCS}$,-sham by $BLOCKS_{B1–B5}$ ($F_{[4,36]}$ = 3.2, $p = 0.03$; see Fig 2B) interaction, with a significant $INTERVENTION_{tDCS,sham}$ ($F_{[1,9]}$ = 5.4, $p < 0.04$) and $BLOCKS_{B1–B5}$ ($F_{[4,36]}$ = 4.2, $p < 0.02$) effect. The slope of improvement during training was steeper with atDCS than with sham ($slope_{tDCS}$ = 4.1 ± 1.1 vs $slope_{sham}$ = 0.2 ± 0.7, $T_{[9]}$ = 4.2, $p < 0.01$), consistent with an enhanced online effect (within-training improvement). Comparing the slope of improvement during training between old and young revealed a significant effect of $AGE_{old,young}$ ($F_{[1,9]}$ = 8, $p = 0.02$), with no effect on $INTERVENTION_{atDCS,sham}$ ($F_{[1,9]}$ = 3,2, $p = 0.1$) and a significant $AGE_{old,young}$ by $INTERVENTION_{atDCS,sham}$ interaction ($F_{[1,9]}$ = 5,4, $p = 0.045$). Remarkably, post hoc testing revealed that with atDCS, steepness of improvement during training in older subjects was no longer statistically different from that in younger subjects ($T_{[9]}$ = 1.6, $p = 0.12$; see Fig 2C). Furthermore, the slope of atDCS-induced improvement correlated positively with the age of the older subjects ($R = 0.65$, $p < 0.05$; Supplementary Fig 2), indicating that the older the subjects were, the more pronounced the improvement during training concurrent with atDCS.

The analysis performed in the young control group revealed no differences for the factor $\text{INTERVENTION}_{\text{tDCS,sham}}$ during training with atDCS compared to sham ($\text{slope}_{\text{tDCS}}$ 7.1 ± 1.0; $\text{slope}_{\text{sham}}$ 6.3 ± 1.3; $T_{[9]} = 0.6$, $p = 0.5$; see Supplementary Fig 1B) or in the follow-up sessions ($F_{[1,9]} = 0.6$, $p = 0.8$) for the number of correct sequences related to the respective baseline (for details and discussion of these findings please see also Supplementary Information.)

Interestingly, the effects of atDCS appear to be polarity specific: (1) applying cathodal tDCS to the left MC in 5 old subjects did not elicit any behavioral effects ($\text{slope}_{\text{tDCS}} = 0.9 \pm 0.4$; $\text{slope}_{\text{sham}} = 0.6 \pm 0.5$, $Z = -1.2$, $p = 0.26$; Supplementary Fig 3A) and (2) comparing the results of the control experiment with an age-and sex-matched subset of 5 old subjects (70 ± 1.8 years) from the main experiment revealed a trend for a difference for the slope of improvement for atDCS ($\text{slope}_{\text{ctDCS}} = 0.9 \pm 0.4$; $\text{slope}_{\text{atDCS}}$ 3.7 ± 0.9; $Z = -1.85$, $p = 0.06$; see Supplementary Fig 3B).

Please note that there were no differences in features that might potentially influence skill acquisition, such as attention level, perception of fatigue, or hand tiredness, between groups in all experiments (Table; Supplementary Tables 1 and 2). Furthermore, in line with previous findings,[12] subjects were reliably blinded for the experimental condition. When probed, none of them was able to distinguish between tDCS and sham.

Discussion

The ability to acquire new motor skills is required for almost every daily life activity, such as the use of modern communication tools like cell phones or computers, necessary for individual independence and social integration. Here, we demonstrated that healthy old subjects experience significant declines in skill acquisition during training of a motor task relative to young subjects, adding substantially to a progressive disintegration in modern society. Strikingly, noninvasive brain stimulation, by means of atDCS applied to MC, can to a relevant extent restore the response to motor training in old subjects, translating behaviorally into an improved retention of the acquired skills.

Recent advances in the understanding of the mechanisms of motor learning have elucidated that the MC is clearly more than a simple executor of motor commands and is likely involved in the encoding and consolidation of motor skills,[14] making it a promising target for interventional strategies to enhance learning. Animal studies have provided evidence that age-related declines in memory and learning are associated with a decrease in neuronal excitability and an altered induction of synaptic plasticity.[15] In humans, an age-related decline in MC plasticity has been recently probed by different techniques.[16] Moreover, as a function of age, a reduction of LTP-like mechanisms involved in use-dependent motor memory formation was consistently described.[17] Age-related behavioral impairments are known to result in part from biomechanical changes but also, and more conspicuously, from region-specific changes in dendritic morphology, cellular connectivity, Ca^{2+} dysregulation, and gene expression, among others, altering neuroplasticity and network dynamics of neural ensembles that support cognition, memory, and learning.[2,15]

Training-induced plasticity is based on processes analogous to LTP, resulting in the modification of motor cortical networks following skill acquisition. These processes are most likely based on unmasking of excitatory connections within the cortex, allowing rapid changes in sensory–motor representations, leading to synaptic strengthening of cortical horizontal connections.[18,19] Consequently, it was proposed that noninvasive brain stimulation with tDCS affects the activity of intrinsic cortical circuits by modulating N-methyl-D-aspartate (NMDA) and γ-aminobutyric acid (GABA) dependent neurotransmission.[12,20] Within the present setting, atDCS-induced facilitation of motor skill acquisition could potentially be explained by a modulation of GABA-ergic neurotransmission, promoting the unmasking of excitatory connections, as well as an indirect enhancement of NMDA-dependent processes supporting LTP.[21] Thus, it can be speculated that atDCS in old subjects influences the ability of the aged cortex to undergo plastic modifications by preparing the cortical ground for successful plastic changes due to motor training, a view supported by recent human and animal data.[5,8] Dissecting the skill acquisition process in its temporal components (online, offline) revealed that the main part of the atDCS-induced behavioral improvement determined at follow-up (retention), was mediated through a selective enhancement of online effects in the old.

Although the results reported here demonstrated an additive effect of atDCS combined with training, some limitation of the study must be taken into account. Motor skill acquisition represents a complex cognitive process with a number of areas involved in the task, such as primary and secondary motor areas, and prefrontal and subcortical structures.[22] In the current study, atDCS was applied to MC. However, given that the size of the electrodes delivering atDCS was 25cm^2, the focality is rather low. With this limited spatial resolution, it cannot be ruled out that the effect of atDCS was not exclusively attributed to the primary motor cortex. It might also be possible that the atDCS-related effects were in part driven by modulation of the premotor cortex, a possibility that has to be addressed in upcoming studies.

It is of note that in young controls, atDCS concurrent with training did not lead to behavioral changes, probably due to ceiling effects. This negative finding is in line with recent work using comparable tasks.[23] Nevertheless, there is also evidence provided by other recent studies that tDCS can enhance (implicit) motor learning.[3,4] The heterogeneous findings might be due to different tasks (eg, implicit vs explicit) responding differently to tDCS (this issue is discussed in more detail in the Supplementary Information).

In conclusion, atDCS led to a behavioral improvement in old subjects during training, still persistent in the retention period of 24 hours following the training. Driving neuroplasticity by atDCS might have re-engaged and strengthened the neuromodulatory systems that control learning, resulting in increased fidelity, reliability, and power of cortical representations of the trained skill. The exact underlying mechanisms (e.g., GABA-ergic, glutamatergic) cannot be determined from the present data and have to be addressed in upcoming studies. This information will be indispensable in providing a good basis for the application of this promising and safe intervention to assist functional independence and restore, at least in part, the ability to acquire novel skills in old healthy subjects, an ability crucial for optimal integration in daily life.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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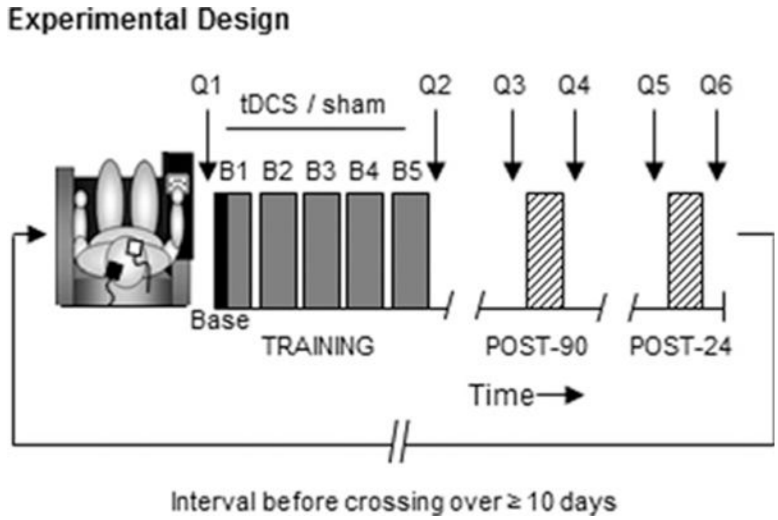

FIGURE 1.

Experimental design. Participants attended two experimental arms (crossover design). Anodal transcranial direct current stimulation (tDCS) or sham was applied concurrent with training. Training was separated in 5 blocks (B1–B5). Behavioral outcome was retested 90 minutes and 24 hours after training (retention period). Questionnaires in which subjects characterized (on visual analog scales, Q_{1-6}) level of attention and fatigue were given before and after each session.

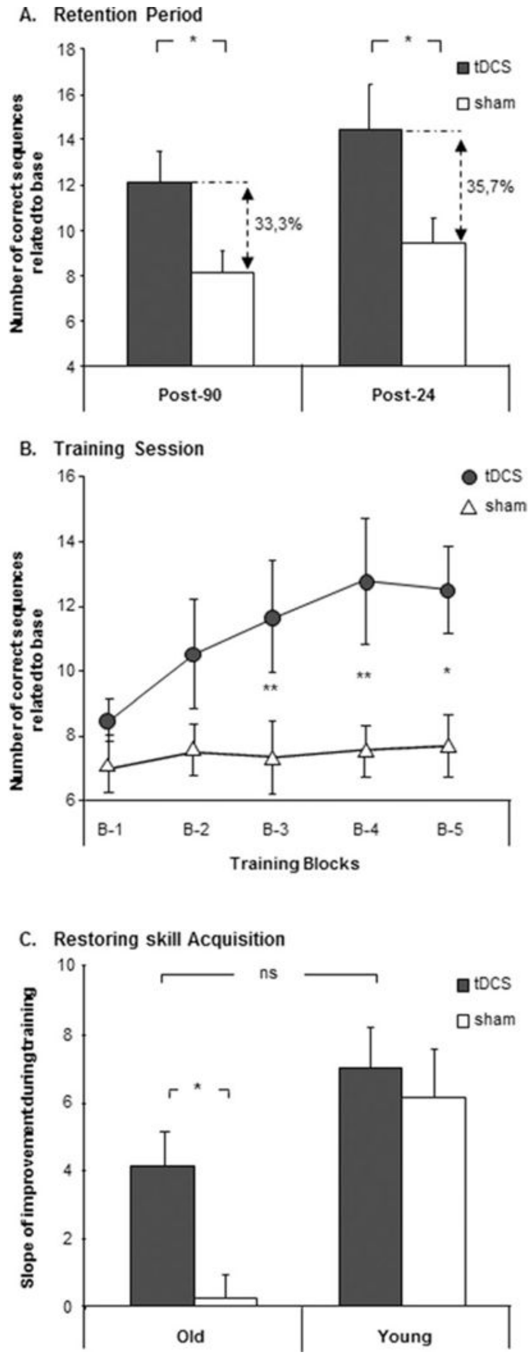

FIGURE 2.

(A) Behavioral results: retention. Anodal transcranial direct current stimulation (tDCS) concurrent with training led to an increased number of correct sequences at follow-up. Relative improvement in relation to baseline is displayed in the graph for anodal tDCS and sham. The y-axis displays the number of correct sequences related to baseline. (B) Behavioral results: training. During the training session, a significant improvement with atDCS compared to sham stimulation was observed. The y-axis displays the number of correct sequences related to baseline. (C) Effects of tDCS on training in old and young.

Slope analyses are displayed showing an increase of steepness of improvement with anodal tDCS compared to sham in old subjects, close to the levels of young subjects. The y-axis displays the slope of improvement during training. Data are expressed as mean values; error bars = standard error of the mean; *$p \le 0.01$, **$p < 0.05$.

TABLE

Attention and Fatigue (Main Experiment)

Scale	Sham Q1	Sham Q2	Sham Q3	Sham Q4	Sham Q5	Sham Q6	tDCS Q1	tDCS Q2	tDCS Q3	tDCS Q4	tDCS Q5	tDCS Q6	Statistics, $ANOVA_{RM}$
Old subjects													
Attention	7.0 ± 0.4	5.6 ± 0.4	7.2 ± 0.4	6.6 ± 0.9	7.4 ± 0.7	6.8 ± 0.3	7.3 ± 0.4	6.0 ± 0.4	7.6 ± 0.6	5.4 ± 0.9	7.9 ± 0.7	5.6 ± 0.3	ns
Fatigue	3.3 ± 0.6	3.8 ± 0.9	3.2 ± 0.3	4.0 ± 0.8	2.4 ± 0.6	2.4 ± 0.6	3.8 ± 0.4	4.0 ± 0.4	3.2 ± 0.8	4.9 ± 0.7	1.8 ± 0.6	2.7 ± 0.7	ns
Hand fatigue	1.6 ± 0.8	4.0 ± 0.7	1.6 ± 0.8	3.8 ± 0.9	1.6 ± 0.8	2.8 ± 0.7	1.0 ± 0.7	3.4 ± 1.1	1.2 ± 0.8	3.4 ± 0.7	1.6 ± 0.7	3.4 ± 1.2	ns
Young subjects													
Attention	7.8 ± 0.6	6.9 ± 0.6	8.3 ± 0.5	7.6 ± 0.5	7.2 ± 0.4	7.4 ± 0.8	7.7 ± 0.4	6.5 ± 0.5	7.4 ± 0.4	7.1 ± 0.5	7.6 ± 0.4	7.0 ± 0.6	ns
Fatigue	3.1 ± 0.8	3.2 ± 0.7	3.3 ± 0.8	3.5 ± 0.8	2.2 ± 0.5	2.1 ± 0.4	3.3 ± 0.6	2.8 ± 0.7	2.8 ± 0.7	2.9 ± 0.7	2.4 ± 0.7	1.9 ± 0.8	ns
Hand fatigue	0.2 ± 0.2	3.1 ± 0.8	0.8 ± 0.4	3.3 ± 0.9	0.7 ± 0.5	2.2 ± 0.7	0.2 ± 0.1	2.9 ± 0.8	0.3 ± 0.2	2.6 ± 0.8	0.9 ± 0.6	2.7 ± 0.8	ns

Attention and fatigue were assessed with visual analog scale questionnaires (Q; see timing of questionnaires in Fig 1, $Q_{1–6}$). Scales included: attention (0–10; 0 = no attention, 10 = highest level of attention), fatigue (0–10; 0 = no fatigue, 10 = highest level of fatigue), and hand fatigue (0–10; 0 = no hand fatigue, 10 = highest level of hand fatigue). All values were expressed at mean ± standard error.

$ANOVA_{RM}$ = repeated measures analysis of variance; ns = not significant.