Clinical/Scientific Notes

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IMPACT OF tDCS ON CEREBRAL AUTOREGULATION IN AGING AND IN PATIENTS WITH CEREBROVASCULAR DISEASES

Following seminal articles on the technique and underlying mechanisms of transcranial direct current stimulation (tDCS) at the turn of this century,[1] tDCS has gained special attention in neurorehabilitative research, given its ability to modulate brain function in a polarity-specific manner in stroke patients together with an excellent safety profile.[2] However, an important safety concern emerged recently with regard to its impact on cerebral autoregulation, given a report on decreased autoregulation after 15 minutes anodal tDCS (atDCS) over primary motor cortex (M1) in young healthy subjects.[3] Cerebral autoregulation, assessed by vasomotor reactivity (VMR), reflects the autonomic ability of cerebral arterioles to dilate following a vasodilatory stimulus. It is consistently decreased in patients with cerebrovascular diseases,[4] and has been linked to stroke risk.[5] Thus, a decrease of VMR after atDCS may be harmful to patients with already impaired VMR, such as stroke patients.[4] Importantly, >40 ongoing trials with stroke patients and atDCS are registered on www.clinicaltrials.gov as of May 2014. Thus, the concerns raised by Vernieri et al.[3] may carry important clinical implications.

We investigated effects of 20 minutes atDCS over M1 on cerebral autoregulation, as assessed by VMR (primary) and autonomic function using the cephalic electrode montage most commonly employed in ongoing stroke studies.

Classification of evidence. This study provides Class II evidence that in patients with cerebrovascular diseases, tDCS using the cephalic electrode montage does not decrease cerebral autoregulation.

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Methods. In a double-blind crossover within-subject design, we investigated effects of 20 minutes atDCS over M1 on cerebral autoregulation, as assessed by VMR (primary) and autonomic function using the cephalic electrode montage most commonly employed in ongoing stroke studies, in young (25.3 ± 2.8 years, n = 15) and older healthy individuals (67.9 ± 5.7 years, n = 10), patients with severe white matter disease (white matter hyperintensities [WMH] group, 68.1 ± 10.2 years, n = 10), and patients with unilateral carotid occlusive disease (internal carotid artery [ICA] group, 61.6 ± 14.4 years, n = 15). For control, participants were also assessed after cathodal tDCS (ctDCS) and sham stimulation in separate sessions (randomized order). In all participants, VMR was measured before and immediately after tDCS by transcranial Doppler sonography (supplementary material on the *Neurology*® Web site at Neurology.org).

For VMR, analysis of variance $(ANOVA)_{RM}$ with time (before vs after tDCS), stimulation (atDCS vs ctDCS vs sham), and hemisphere (left vs right) as within-subject factors was employed for each group separately. In addition, for the ICA group, the same $ANOVA_{RM}$ was conducted with within-subject factor hemisphere (affected hemisphere [AH] vs unaffected hemisphere [UH]). To test for changes in autonomic activity during tDCS, we further evaluated low-frequency oscillations (LFO) of cerebral blood flow reflecting autoregulatory fluctuations in vessel diameter. The influence of tDCS on LFO was determined by a stimulation (atDCS vs ctDCS vs sham) × hemisphere (left vs right) $ANOVA_{RM}$ along with post hoc *t* test if indicated.

Results. All subjects tolerated the experimental procedures well. None reported neurologic deficits during or after tDCS. One subject showed transient skin reddening without itching under the return electrode, which was not noted in subsequent assessments. Analysis of stimulation condition on VMR yielded no significant effects in the young, old, and WMH group (table e-3). In the ICA group, $ANOVA_{RM}$ revealed a significant time × stimulation × hemisphere interaction. Post hoc paired *t* tests revealed no effect of tDCS on VMR, when comparing VMR_{pre} and VMR_{post} for each hemisphere and stimulation condition, while differences emerged regarding VMR_{post} between atDCS and ctDCS on the left hemisphere ($p = 0.02$; $t = 2.82$), and atDCS and sham on the left hemisphere ($p = 0.04$, $t = -2.30$), not significant after correcting for multiple comparisons (Bonferroni correction, number of comparisons = 12, critical $p < 0.0042$). Within the ICA group, $ANOVA_{RM}$ revealed a significant main

Table 1 Changes in VMR due to stimulation condition

	Young (n = 15)	Old (n = 10)	ICA (n = 15)	WMH (n = 10)
Anodal left	0.001 (−0.068; 0.071)	0.050 (−0.032; 0.131)	0.032 (−0.006; 0.070)	0.004 (−0.006; 0.106)
Anodal right	−0.004 (−0.072; 0.065)	0.058 (−0.024; 0.141)	0.003 (−0.042; 0.047)	0.063 (−0.042; 0.169)
Cathodal left	−0.022 (−0.064; 0.020)	0.020 (−0.029; 0.070)	−0.033 (−0.079; 0.013)	0.004 (−0.098; 0.106)
Cathodal right	−0.021 (−0.063; 0.021)	0.019 (−0.060; 0.097)	0.024 (−0.018; 0.067)	0.026 (−0.096; 0.145)
Sham left	0.012 (−0.046; 0.070)	0.051 (−0.043; 0.146)	0.008 (−0.039; 0.054)	−0.033 (−0.094; 0.029)
Sham right	0.011 (−0.054; 0.075)	0.016 (−0.086; 0.118)	0.005 (−0.052; 0.063)	−0.060 (−0.121; 0.001)
Anodal AH	—	—	0.006 (−0.028; 0.040)	—
Anodal UH	—	—	0.020 (−0.030; 0.071)	—
Cathodal AH	—	—	−0.0021 (−0.065; 0.023)	—
Cathodal UH	—	—	0.014 (−0.042; 0.069)	—
Sham AH	—	—	0.012 (−0.034; 0.058)	—
Sham UH	—	—	−0.001 (−0.062; 0.061)	—

Abbreviations: AH = affected hemisphere; CI = confidence interval; ICA = internal carotid artery; tDCS = transcranial direct current stimulation; UH = unaffected hemisphere; VMR = vasomotor reactivity; WMH = white matter hyperintensities.
Values are ΔVMR ($VMR_{post\text{-}tDCS}$ − $VMR_{pre\text{-}tDCS}$) (95% CI).

effect of hemisphere (AH vs UH), indicating lower VMR on the AH, as compared to UH, but no effects of stimulation. Changes in VMR ($VMR_{post\text{-}tDCS}$ − $VMR_{pre\text{-}tDCS}$) are listed in table 1. No changes of LFO due to stimulation condition were noted (table e-3).

Discussion. atDCS and ctDCS may be safely applied in older adults and in patients with cerebrovascular diseases, using a cephalic electrode montage. Based on head and body models, a setup with a cephalic (e.g., M1) placement of the target electrode and an extracephalic placement of the return electrode (e.g., deltoid muscle[3]) leads to a twofold to threefold higher electric field in the brainstem as compared to the more commonly used cephalic setup with the target electrode over left M1, and the return electrode over the right eyebrow.[6] The effects reported by Vernieri[3] may have been mediated via stimulation of brainstem autonomic centers[7] induced by the extracephalic return electrode montage. We would thus strongly recommend the use of a cephalic return electrode montage in any population with potential vulnerability to changes in cerebral autoregulation. In addition, strict monitoring for possible adverse effects of tDCS in patients with cerebrovascular diseases, particularly those with carotid occlusive disease, should be conducted even with this montage.

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