

Vascular safety of brain plasticity induction via transcranial direct currents

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Experience alters the strength of neuronal connections as a fundamental feature of brain physiology. This process, termed neuroplasticity, appears crucially involved in cognitive processes such as learning, memory formation, and adaptive behavior. Neuroplasticity is increasingly implicated in not only a number of neurologic diseases, but also in restitution after brain injury. Noninvasive brain stimulation can induce and modulate neuroplasticity in humans.¹ In accordance with the functional relevance of neuroplasticity, noninvasive brain stimulation not only modulates psychological processes and behavior in healthy humans, but also reduces symptoms, and improves rehabilitation, in patients with neurologic diseases, including stroke.^{2–4}

One of these techniques, transcranial direct current stimulation (tDCS), exerts its effects via sub-threshold membrane polarization. Depending on stimulation polarity and duration, tDCS alters the resting membrane potential, modulating the rate of spontaneous neuronal activity and synaptic strength. This process shares characteristics with neuroplasticity from animal experiments, such as long-term potentiation and depression.³ The physiologic background, relative ease of application, low costs, and favorable results of pilot studies² make it a potentially attractive therapeutic tool. The safety profile of tDCS, albeit from limited data, seems favorable, with only rare adverse effects such as itching and tingling under the stimulation electrode, and no documented serious adverse events.⁵

Beyond its effects on cerebral neurons, tDCS may directly influence cerebral vascular autoregulation and could compromise blood supply of brain tissue leading to ischemic damage. Indeed, DC stimulation directly affects skin vessels.⁶ A recent report showed that excitability-enhancing anodal tDCS decreases cerebral autoregulation in healthy young humans.⁷ Because of the potential of tDCS as a treatment in stroke, it is particularly important to acquire data about the safety of tDCS in patients with cerebrovascular disease who may have compromised cerebral autoregulation. Further disturbance of autoregulation induced by tDCS might enhance stroke risk, and

potentially limit application of tDCS as a therapeutic agent in this patient group.

In this issue of *Neurology*®, List et al.⁸ evaluated the effects of excitability-enhancing anodal tDCS on cerebral autoregulation in a double-blind crossover within-subject design study. Young and old healthy participants as well as older participants with cerebrovascular disease (severe white matter disease and unilateral carotid occlusive disease) were exposed to 20 minutes of anodal, cathodal, or sham tDCS with 1 mA intensity over the primary motor cortex. Their stimulation protocol corresponds to that applied in clinical treatment studies. They also used a longer stimulation duration than that applied previously. Moreover, the authors applied tDCS via a bicephalic montage, whereas in the previous study⁷ the return electrode was positioned at the arm. Vasomotor reactivity and low-frequency oscillations were monitored immediately before and after stimulation via transcranial Doppler sonography. The results show no significant effects of tDCS on cerebral autoregulation in healthy subjects or in the white matter disease group. However, for subjects with carotid occlusive disease, the affected hemisphere consistently showed lower cerebral autoregulation independent from stimulation. In this group, autoregulation of the left hemisphere appeared diminished after anodal tDCS, as compared to cathodal and sham stimulation, although this did not reach statistical significance. This effect was not specific for the treated hemisphere, and not supported by respective pre vs post tDCS differences. Compared to the work of Vernieri and coworkers,⁷ List and coworkers conclude that the present protocol is preferable in high-risk patient groups based on lack of effect of their tDCS protocol on cerebral autoregulation even in high-risk persons.

This study provides important new insights on the safety of tDCS. Since tDCS is increasingly considered as a therapeutic agent in neurologic and psychiatric diseases,^{2,9} such information is crucial. Important strengths of this study include that the experiments were conducted in the therapeutic target populations and with a stimulation protocol frequently used in clinical trials. Thus, the present results have

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immediate implications for the safety evaluation of tDCS with regard to the treatment of these patients. The differences between the present and previous studies may reflect stimulation protocol differences. It cannot be ruled out that the electrode arrangement used by Vernieri et al. with one cephalic and one arm electrode resulted in relevant current flow via the brainstem, which could potentially affect autonomic centers, thereby compromising cerebral autoregulation. However, lacking direct evidence, and in comparison with only one study, this reasoning is speculative at present. Moreover, stimulation of autonomic perivascular fibers may be differentially affected depending on current flow direction, determined by the position of the target, and return electrodes. Taking into account the limited number of participants in both studies, the results might also be prone to statistical errors, and the sensitivity, especially for small effects, and transferability to the population level might be limited. Larger studies would be needed for definite conclusions. However, given the increasing attractiveness of tDCS for treatment of neurologic patients, and limited systematic information about safety of application beyond monitoring of tolerability, this study represents an important step.

The study by List and coworkers thus adds evidence to the safety of bicephalic tDCS protocols for treatment of patients with cerebrovascular disease, but also points to the need to monitor for possible adverse effects of tDCS in this patient group.

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