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Probing the mechanisms underlying the mitigation of cognitive aging with anodal transcranial direct current stimulation

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Kar K, Wright J. Probing the mechanisms underlying the mitigation of cognitive aging with anodal transcranial direct current stimulation. *J Neurophysiol* 111: 1397–1399, 2014. First published December 11, 2013; doi:10.1152/jn.00736.2013.—Meinzer et al. (*J Neurosci* 33: 12470–12478, 2013) have recently reported that anodal transcranial direct current stimulation (atDCS) mitigates age-related cognitive changes. Simultaneous measurement of BOLD signal during atDCS also showed "youth-like" processing in an elderly population. Although the effects are very promising, the underlying mechanisms of atDCS are still not clear. In this article, we provide a critical review of the results, emphasizing the article's significance and providing additional insight that will help elucidate the results and atDCS mechanisms.

anodal transcranial direct current stimulation; BOLD; brain-derived neurotrophic factor; cognitive aging; regional cerebral blood flow

NORMAL AGING HAS BEEN ASSOCIATED with deficits in cognitive function even in the absence of neurodegenerative diseases. Studies have suggested that these impairments are linked to changes in synaptic connectivity that in turn make the neurons vulnerable to degeneration (Morrison and Baxter 2012). Therefore, as human longevity increases, it necessitates therapies and treatments to prevent and delay age-related cognitive decline.

Previous studies have shown the efficacy of repetitive transcranial magnetic stimulation in improving memory in individuals with mild cognitive impairment (Sole-Padulles et al. 2006). Transcranial direct current stimulation (tDCS) is another potential technique (cheaper and more portable compared with TMS) that has been shown to improve cognitive performance in elderly subjects. For instance, Flöel and colleagues (2012) reported that older subjects treated with tDCS during an associative learning task showed an improved recall administered after a week from the initial learning phase. Despite overwhelming evidence supporting tDCS-induced modulations of behavior across subjects of varying age, a parsimonious explanation of tDCS mechanisms is still lacking. The commonly hypothesized neuromodulatory effect of tDCS is subthreshold membrane polarization, with long-lasting aftereffects mediated by NMDA receptor-dependent changes (Nitsche et al. 2003). Numerous behavioral results suggest that anodal tDCS (atDCS) upregulates cortical excitability while cathodal tDCS (ctDCS) downregulates it, with effects being most prominent near the stimulation electrodes (Utz et al. 2010). However, multiple recent reports (Medeiros et al. 2012) have suggested that the neurobiological mechanisms of action of these externally induced electric fields are rather complex. To elucidate the neural correlates of the behavioral changes induced by tDCS, recent studies have started examining BOLD signal changes while simultaneously applying tDCS (Antal et al. 2011; Meinzer et al. 2012).

In their recent article, Meinzer and colleagues (2013) were among the first to utilize tDCS to mitigate age-related alterations in behavioral performance and BOLD activity. Meinzer and colleagues tested the effects of atDCS on an older population during a semantic word generation task. Subjects viewed six different categories (one at a time) and responded verbally with an exemplar of the shown category. Repetitions, omissions, wrong exemplars, or synonyms of previous exemplars were scored as errors. It is important to note that the authors did not employ a learning task in this experiment. The authors demonstrated the ability of atDCS over the left inferior frontal gyrus (IFG) to induce a number of changes. First, it improved performance temporarily on the semantic word generation task in a healthy elderly population to a level comparable with younger controls. Second, atDCS reversed the increment of activity observed at both left and right ventral IFG and right medial frontal gyrus in older relative to younger participants. atDCS also reduced task-related activity in regions outside the a priori targeted areas, the anterior cingulate gyrus and precuneus (which have also been shown to be hyperactive in aging populations). Third, atDCS induced large-scale network changes as evident through alterations in functional connectivity during resting state. The hyperconnectivity in fronto-temporal regions and hypoconnectivity in posterior regions observed in older subjects was partially reversed by atDCS. These results support that atDCS in older adults not only mitigates age-related behavioral impairments, but also alters neural activity and connectivity resulting in more "youth-like" processing.

The authors suggest that atDCS-induced cognitive improvements in older adults may be linked to an increase in neural efficiency upon application of atDCS. Haier and colleagues (1988) introduced the neural efficiency hypothesis to explain the reduction in cortical metabolic rates in individuals with increased cognitive ability. They suggested that individuals with less cognitive ability, or in this context, older individuals with poor performance in the task, utilized more neural resources, which led to an increase in energy consumption. Given the positive correlation between glucose consumption (oxygen demand) and regional cerebral blood flow (rCBF), one may predict that lower efficiency (higher glucose consumption) will be manifested as increased BOLD signal (higher rCBF). Therefore, in regard to the neural efficiency hypothesis, if

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atDCS improves efficiency, then it is expected to produce decrements in the BOLD signal at regions known to be hyperactive in the elderly.

Although these findings augment our current understanding of the applicability of tDCS, some of the observed changes in the BOLD signal from tDCS are open to multiple interpretations. One of the notable findings by Meinzer et al. (2012, 2013) was a decrease in the BOLD activity at the site of atDCS, the left ventral IFG. This is intriguing because atDCS is thought to increase excitability of a neuronal population, and, therefore, should increase rCBF and BOLD signal at the site of tDCS (Zheng et al. 2011). Therefore, the question remains, how does atDCS lead to a decrease in the BOLD signal? Since changes in neural excitability are not sufficient to explain this decrease, we propose a qualitative model that incorporates changes in rCBF, neural metabolism, and brain-derived neurotrophic factor (BDNF) secretion that can parsimoniously explain the atDCS-induced reduction of the BOLD signal.

The amplitude of the BOLD signal at any voxel is proportional to the ratio between oxygenated and deoxygenated hemoglobin in that voxel. The amount of deoxygenated and oxygenated hemoglobin depends on the cerebral metabolic rate of oxygen consumption ($CMRO_2$) and rCBF, respectively (see Fig. 1). Age-related impairment in neural metabolism (Δb, Fig. 1) might trigger an increase in oxygen demand that would predict an increase in rCBF and hence an elevated BOLD signal. However, rCBF has been shown to be reduced in elderly individuals (Δa, Fig. 1) due to age-related changes in the vasculature (D'Esposito et al. 2003). Since reductions in rCBF also correlate with reductions of oxygenated hemoglobin, this predicts an age-related decrease in the BOLD signal. These effects will not cancel each other if, for instance, $CMRO_2$ deteriorates as a function of age to a greater extent than the reduction of rCBF. In this case, the BOLD signal will be higher in older individuals. Furthermore, if atDCS improves the oxygen metabolism of the cells (Δd, Fig. 1) in the elderly population (or in general) more than the increase in rCBF (Δc, Fig. 1), then atDCS could reduce the BOLD signal. Recent experiments have shown that $CMRO_2$-induced BOLD signal changes can be estimated by hypercapnia- or hypoxia-based calibration methods (for review, see Hoge 2012). Future experiments can utilize these methods in an aging population to test the above-mentioned hypothesis.

The hypothesized age-related impairment in cerebral oxidative metabolism may be the result of decreases in BDNF secretion in the elderly human brain (Li et al. 2009). This neurotrophic factor has been shown to regulate brain metabolism and neural efficiency via oxygen utilization (Markham et al. 2012). Therefore, changes in BDNF secretion may manifest as changes in the BOLD signal. Given that atDCS has been shown to enhance BDNF secretion in mouse M1 slices (Fritsch et al. 2010), we speculate that similar mechanisms may be responsible for an improvement in neural oxygen metabolism and thereby cognition in the aging adults. We acknowledge that BDNF may also have a direct effect on neuronal plasticity and thereby, in part, influences performance of the human subjects.

Besides changes in BOLD amplitude at the site of atDCS, Meinzer and colleagues (2013) also reported network effects: atDCS-induced task-related BOLD activity changes away from

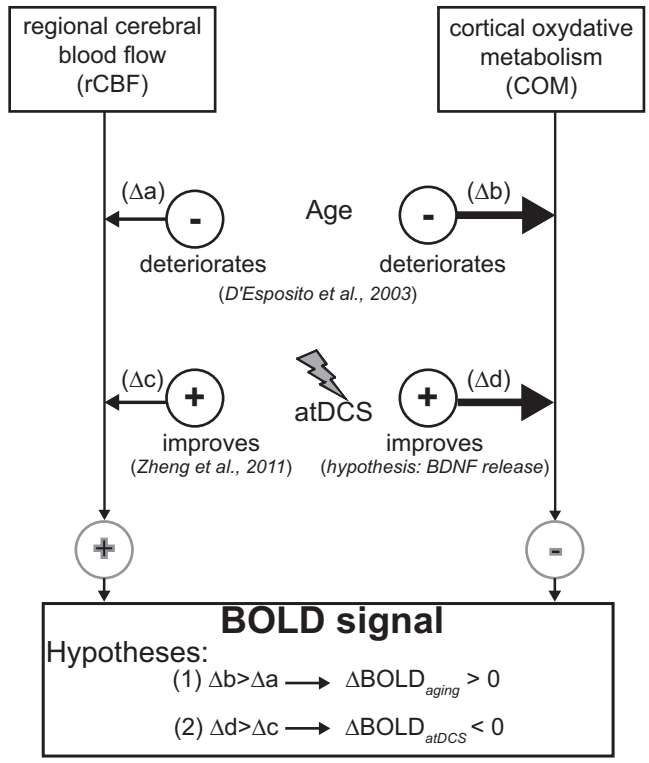

Fig. 1. Interaction between age-related and anodal transcranial direct current stimulation (atDCS)-induced changes in BOLD signal. Increases in regional cerebral blood flow (rCBF) increase the BOLD signal, whereas increases in cortical oxidative metabolism (COM) decrease the BOLD signal (gray circles). Aging deteriorates rCBF (Δa) and COM (Δb), whereas tDCS improves them (Δc and Δd), respectively. The extent of these effects determines the effective change in BOLD signal. Our hypotheses are as follows: *1*) an increase in the BOLD signal (ΔBOLD >0) due to age is expected if the reduction of COM (Δb) exceeds the reduction of rCBF (Δa); and *2*) a decrease in the BOLD signal due to atDCS is expected if the increase in COM (Δd) exceeds the increase in rCBF (Δc). Thicker arrows indicate higher magnitudes.

the lateral prefrontal area and resting state connectivity changes. During the task, they found that the anterior cingulate gyrus and left precuneus in older subjects showed increased activity during sham compared with younger adults. This increment in activity was significantly attenuated on the application of atDCS. During resting state, connectivity patterns in anterior and posterior brain regions were reversed after the application of atDCS. Neurovascular coupling, especially in the posterior cortical regions, in the healthy elderly population can be affected by normal aging (D'Esposito et al. 2003). Factors like age-related atherosclerosis contribute to a decreased rCBF in the posterior parietal cortex. The extent of the current spread and its local and distant effects on the neurovascular coupling are not well understood. Hence, it remains unclear whether the tDCS-driven reversal of functional hypoconnectivity in the posterior regions of the older subjects during resting state is due to vascular factors, neural activity, or a combination of both.

Our proposed underlying tDCS mechanisms, changes in rCBF and neural metabolism (including BDNF), both operate at different timescales. Therefore, a reanalysis of the behavioral data over time may disentangle the effects of rCBF and neural metabolism and provide novel insight into the underlying tDCS mechanisms. Meinzer et al. (2013) compare the average error between young controls, old controls, and old

atDCS groups combined across all six categories and trials (refer to Fig. 2, Meinzer et al. 2013). We suggest estimating the average time course of error rates across subjects under different stimulation conditions. If the change in error rate is constant across time it may suggest that tDCS effects are mediated by changes in rCBF, which are almost instantaneous (Zheng et al. 2011). On the other hand, if the error rate drops as a function of time (indicative of a behavioral change due to tDCS), it may link changes in neural metabolism to the effects of atDCS. In vitro data from Fritsch et al. (2010) suggest that BDNF-dependent effects had an onset delay of a few minutes. However, the experimental task starts 6 min after the onset of atDCS. Hence, one might argue that BDNF mechanisms are likely to be recruited before the beginning of the word generation task. BDNF secretion has been shown specifically to increase during simultaneous synaptic activity (low frequency stimulation in vitro) and direct current stimulation. Therefore, we speculate that task-related activation of the brain areas is necessary to induce BDNF level increments and thereby produce BDNF-dependent behavioral changes. Fritsch et al. (2010) also reported that these BDNF-dependent effects remained active even after the stimulation offset. This provides motivation for a future study whereby the long-lasting effects of atDCS on cognitive performance of older adults can be tested. In conjunction with this, it might be interesting to test if repeated learning and simultaneous atDCS would induce some form of plasticity, which might lead to sustained gains in performance. Such a longitudinal study might help elucidate the long-term potential of atDCS-induced cognitive benefits in older adults.

In conclusion, Meinzer et al. (2013) have provided strong evidence supporting the efficacy of atDCS to mitigate age-related changes in cognitive performance. They support the behavioral findings with simultaneously recorded BOLD signal changes. Their valuable work demonstrates the strength in combining tDCS and fMRI to assess behavioral changes induced by tDCS. However, it remains important to address how the current results and their interpretation help probe the specific mechanisms by which atDCS can lead to cognitive improvements in normal and aging adults.

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

AUTHOR CONTRIBUTIONS

K.K. conception and design of research; K.K. and J.W. prepared figures; K.K. drafted manuscript; K.K. and J.W. edited and revised manuscript; K.K. and J.W. approved final version of manuscript.

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