Reply to Hoy and Fitzgerald: Considering homeostatic mechanisms in long-term treatments

We welcome the intent of the letter by Hoy and Fitzgerald (1) in response to our paper (2), linking basic research to clinical findings, but we also recommend caution when doing this. Hoy and Fitzgerald (1) wish to explain the discrepancy they see when using transcranial direct current stimulation (tDCS) in the healthy population versus patients with schizophrenia and, in addition, highlight the perils of using tDCS in healthy individuals. The authors use our study (2) as an example from the basic research literature to help them provide a potential mechanism for their observations.

Because we are not experts in the field of tDCS, we will refrain from commenting on the technique itself. However, we do wish to highlight the importance of considering homeostatic or adaptive forms of plasticity in general, and especially in the context of long-term treatments, that cause alterations in network activity or function. Our paper (2) is one of many that have shown the remarkable ability that neurons possess to adapt to chronic alterations in activity by opposing changes that could destabilize the network (3). As a result, any treatment that causes long-term changes in the activity of neurons or networks could, in principle, elicit one of the many adaptive forms of plasticity that will counteract the treatment. Hoy and Fitzgerald (1) suggest that the lack of a dose-dependent effect of tDCS on cognitive function in healthy individuals, where higher currents show no improvement in cognitive function, may be down to the induction of adaptive mechanisms with larger currents. However, it is worth noting that homeostatic forms of plasticity generally operate over the long-term (hours to days), whereas the tDCS experiments reported by the authors are much faster in comparison, occurring within minutes (up to 40 min) of stimulation. Although homeostatic mechanisms of the type shown in our paper (2) are unlikely to operate within this temporal domain, long-term repetitive treatment could, in principle, elicit adaptive responses. However, because it is still unclear what type of brain activity tDCS elicits, we should remain cautious about the conclusion we reach.

Our recent paper in PNAS (2), which is an extension of a previous report from our laboratory (4), places the single-cell plasticity of the axon initial segment into a network-wide context by studying the GABAergic axo-axonic synapses that form onto it. Because these synapses have been implicated in schizophrenia (5), Hoy and Fitzgerald (1) suggest that, perhaps, this particular form of homeostatic plasticity can explain the disparity they observe in response to tDCS treatment between healthy individuals and those with schizophrenia. Again, although it is tempting to speculate on these issues, our basic data are too far removed to shed any light on these findings. As we learn more about the effects of tDCS in the human brain and better understand the mechanisms behind homeostatic forms of plasticity, we may gradually be able to bring the two together. Right now this seems like too large an undertaking.

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2 Wefelmeyer W, Cattaert D, Burrone J (2015) Activity-dependent mismatch between axo-axonic synapses and the axon initial segment controls neuronal output. *Proc Natl Acad Sci USA* 112(31): 9757–9762.
3 Turrigiano G (2011) Too many cooks? Intrinsic and synaptic homeostatic mechanisms in cortical circuit refinement. *Annu Rev Neurosci* 34:89–103.
4 Grubb MS, Burrone J (2010) Activity-dependent relocation of the axon initial segment fine-tunes neuronal excitability. *Nature* 465(7301):1070–1074.
5 Lewis DA (2011) The chandelier neuron in schizophrenia. *Dev Neurobiol* 71(1):118–127.

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The authors declare no conflict of interest.

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