Modulation of synaptic plasticity in single neurons with transcranial direct current stimulation

Introduction

Transcranial direct current stimulation (tDCS) involves low-intensity electrical current applied to the brain via electrodes placed over the scalp [1]. Lasting therapeutic effects of tDCS are thought to be mediated by synaptic plasticity [2]. Direct current stimulation (DCS) is known to affect synaptic long-term potentiation (LTP) in vitro [3].

We hypothesized that this is the result of a modulation of somatic spiking with DCS in the postsynaptic neuron, as opposed to indirect network effects. Previous studies with population activity provided only indirect evidence for this hypothesis. Here we aim to directly record somatic spiking in a postsynaptic neuron during LTP induction with concurrent DCS.

Method

We recorded single-neuron activity by patching the soma of individual CA1 pyramidal neurons in a rodent in-vitro slice preparation. LTP was induced with theta-burst stimulation (TBS) applied concurrently with DCS. To test the causal role of somatic polarization during DCS, we manipulated this polarization via patch pipette current injections. To explain the observed effects, we used a computational multicompartment neuron model that captures the effect of electric fields on membrane polarization and activity-dependent synaptic plasticity.

Results

Anodal DCS boosts LTP and somatic spiking



Fig 1 A: Experimental configuration with somatic patch-clamp recording and stimulation of Schaffer-Collateral fibers in the presence of an electric field (red) caused by anodal DCS. B: Top: TBS pulse pattern. TBS: 5 pulses at the frequency of 100 Hz were repeated 5 times at the frequency of 5 Hz. TBS was repeated three times with the time interval of 30 seconds. C: Normalized EPSP amplitude. D: Number of spikes during TBS. E. Normalized EPSP amplitude vs. spike count. Significant differences indicated as * p<0.05, **p<0.01, *** p<0.001, n.s. p>0.05.

Effects of DCS can be emulated or abolished with somatic current injection



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Fig 2. A: Experimental setup. B: Illustration of induction protocol. C: Membrane polarization with somatic current injection in a multicompartment neuronal model. Left: Somatic hyperpolarizing current injection with anodal DCS, Middle: anodal DCS, Right: Somatic depolarizing current injection. D: Normalized EPSP amplitude in different conditions: anodal (N=26) cells), control (N=48 cells), anodal with hyperpolarizing somatic current injection (N=24 cells), and depolarizing somatic current injection (N=25 cells). E: The number of spikes. F: Positive correlation of LTP with somatic spiking across all cells and experimental conditions.



Fig 3. Example traces of whole-cell recording during induction. A: Number of cells exhibiting action potentials before TBS onset. Fisher exact test with FDR. *p<0.05 (20V/m vs. 20 V/m with GABA blocker) and *p<0.05 (10V/m with GABAblocker vs. 20 V/m with GABA blocker). B: firing was evoked by a stimulator while GABAergic inputs were intact under 20 V/m electric field (N=20 cells). The gray area shows the period prior to TBS and after DCS onset. C: firing was evoked by a stimulator under 10 V/m when GABA antagonists were added. D: neuronal firing was evoked by a stimulator electrode under 20 V/m electrode when GABA antagonists were added.

r=0.38, p=0.006

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Computational modeling explains results as single neuron

We used a biologically realistic model of a CA1 pyramidal neuron. We postulate that this excess spiking is the result of elevated network activity induced by DCS. To emulate this effect of DCS in the model we added synapses located at the basal and apical dendrites and activated them at random with independent Poisson spike trains. However, this increase in spiking further enhances LTP for DCS in disagreement with experiments. Thus, we considered the effect of this same network activity on LTP. There is prior evidence for a homeostatic mechanism, whereby elevated network

Fig. 4. A: Simulated biophysically realistic CA1 pyramidal neuron with synapses stimulated by applied TBS (pink) and synapses stimulated by spontaneous network activity due to DCS (green). B: For experiments this shows the normalized EPSP amplitude relative to control condition. For models this shows the normalized synaptic efficacy relative to control condition. C: Normalized spike count relative to

Conclusion

TBS-induced LTP was enhanced when paired with anodal DCS as well as depolarizing current injections. In both cases, somatic spiking during the TBS was increased, suggesting that evoked somatic activity is indeed the primary factor affecting LTP modulation. However, the boost of LTP with DCS was less than expected given the increase in spiking activity alone. In some cells, we also observed spontaneous somatic spiking during DCS, suggesting that DCS also modulates LTP via spontaneous network activity. The computational model reproduces the observed effects of DCS on LTP and suggests that these effects are driven by both direct changes in postsynaptic spiking and indirect changes due to network activity.

References

- [1] Nitsche MA, Cohen LG, Wassermann EM, Priori A, Lang N, Antal A, et al. Transcranial direct current stimulation: State of the art 2008. Brain Stimulat 2008;1:206-23. https://doi.org/10.1016/j.brs.2008.06.004.
- [2] Stagg CJ, Nitsche MA. Physiological Basis of Transcranial Direct Current Stimulation. The Neuroscientist 2011;17:37–53. https://doi.org/10.1177/1073858410386614.
- [3] Kronberg G, Rahman A, Sharma M, Bikson M, Parra LC. Direct current stimulation boosts 2020;13:287–301. https://-Stimulat plasticity Brain doi.org/10.1016/j.brs.2019.10.014.
- [4] Delattre V, Keller D, Perich M, Markram H, Muller EB. Network-timing-dependent plasticity. Front Cell Neurosci 2015;9. https://doi.org/10.3389/fncel.2015.00220.







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