Direct current stimulation boosts associative Hebbian synaptic plasticity and maintains its pathway specificity

Greg Kronberg*, Asif Rahman*, Belen Lafon, Lucas C. Parra, Marom Bikson
Department of Biomedical Engineering, The City College of New York, CUNY
*equal contribution

Abstract

There is evidence that transcranial direct current stimulation can boost learning performance. Arguably, this boost is related to synaptic plasticity. However, the precise effects on synaptic plasticity and its underlying mechanisms are not known. We hypothesized that direct current stimulation modulates endogenous Hebbian plasticity mechanisms due to its ability to polarize cellular membrane. To test this we induced long term plasticity (LTP) using theta-burst stimulation (TBS) in rat hippocampus, and measured the effects of concurrent direct current stimulation (DCS). Soma-depolarizing DCS increased TBS-induced LTP. Oscillating current stimulation is equally effective provided the soma-depolarizing phase is time-aligned with the theta-bursts, suggesting that only instantaneous depolarization is relevant. Importantly, the effect is pathway-specific and associative. These findings are consistent with classic theory on the role of post-synaptic membrane potential in Hebbian plasticity. These data suggest that the effects of direct current stimulation are specific because they modulate endogenous Hebbian plasticity, thus inheriting its exquisite functional specificity.

Keywords: synaptic plasticity, transcranial electrical stimulation, transcranial direct current stimulation, theta-burst stimulation, long term potentiation.

Introduction

Human tDCS studies have recently exploded in number and scope (1–4). While these studies have seen varying degrees of success (1), in aggregate they suggest that stimulation with weak constant current can have long term effects on cognitive function (5). One of the predominant theories to explain these long term effects is that stimulation affects synaptic plasticity (6), although a variety of alternative mechanisms have also been proposed (7,8) and are being explored (9). The synaptic plasticity theory is consistent with an array of findings in pharmacological studies in human (10) as well as animal electrophysiology studies conducted in-vivo (9,11,12) and in-vitro (13–15). We note that effects on cognition in many human behavioral studies appear to be task-specific (16,17). Stimulation during a given cognitive task can selectively modulate performance on that task without transferring gains to other tasks. Mechanistically, this observation implies that stimulation preferentially affects brain networks that are specific to the learned task. Our goal is to uncover the mechanisms that give rise to this functional specificity.

We previously demonstrated that direct current stimulation (DCS) preferentially affects synapses already undergoing plasticity (14). Here we explore the hypothesis that the effects of DCS follow the specific rules of endogenous synaptic plasticity, such as pathway specificity and associativity (18,19). To

test for this we apply weak DCS during the induction of long-term potentiation (LTP) using theta rhythms. Theta burst stimulation (TBS) in hippocampal brain slices is considered to be a physiologically relevant paradigm for inducing LTP (20–22). We show that DCS can enhance this form of LTP. A computational model of synaptic plasticity based on postsynaptic membrane voltage (23) reproduced this result when we account for the known effects of DCS on membrane polarization (24–26). Importantly, the endogenous LTP exhibited canonical Hebbian properties of pathway specificity and associativity (18). We show that the effects of DCS also exhibit this specificity and associativity, in good agreement with predictions of the voltage-based plasticity model. Based on these results we postulate that tDCS in human is specific to the trained task by inheriting the functional specificity of Hebbian synaptic plasticity. Importantly, we make the testable predictions that the most effective tDCS interventions are those that pair stimulation with a behavioral learning task and that performance gains are specific to the learned task.

Results

Anodal DCS boosts LTP

To mimic learning during a training task we applied theta-burst stimulation (TBS, 4 pulses at 100 Hz repeated for 15 bursts at 5 Hz) in the hippocampal Schaffer collateral pathway to induce long-term potentiation (LTP). This form of LTP is driven by somatic spikes (21,27,28), particularly for synapses close to soma, which is where we record field excitatory postsynaptic potentials (fEPSP)(within 200 μm from the somatic layer). We therefore expected anodal DCS, which depolarizes the somatic compartment (25) to boost TBS-induced plasticity. We applied acute anodal or cathodal direct current stimulation (DCS) for the duration of the LTP induction protocol (3 sec; 20 V/m; Fig. 1a, see methods for anodal/cathodal nomenclature). As predicted, when paired with anodal DCS, the resulting LTP was increased compared to TBS alone (control: 1.287+-0.025, N=52; anodal: 1.397+-0.047, N=32, p=0.027). However, cathodal stimulation had no significant effect (cathodal: 1.243+-0.031, N=12, p=0.424)(Figure 1b).

Electric field interacts with plasticity induction on subsecond timescale

We previously argued that the effect of DCS on tetanus-induced LTP are due to membrane polarization (14). If this is the case for TBS-induced LTP as well, then there is no need for the DCS to be constant over long periods of time. It would suffice for the DCS field to coincide with TBS on the time scale of the neuronal membrane time constant (30ms (25)). To test for this, we applied theta-frequency alternating current stimulation (ACS, 5 Hz at 20 V/m) during TBS induction. The peak phase of this ACS corresponds to the same electric field as anodal DCS, while trough corresponds to cathodal DCS. When TBS bursts were timed to coincide with the peak of the ACS, LTP was enhanced, as with anodal DCS (Figure 1C; (control: 1.287+-0.025, N=52; peak: 1.467+-0.093, N=9, p=0.014). TBS timed to the trough of the ACS had no significant effect on LTP, as with cathodal DCS (Figure 1C; trough: 1.184+-0.035, N=6, p=0.173). These data suggest that the electric field need only coincide with strong synaptic input on the millisecond timescale, and does not require any prolonged buildup of DCS effects in order to affect LTP. This is consistent with the notion that instantaneous membrane polarization due to DCS is what interacts with synaptic activity to modulate the resulting plasticity (14).

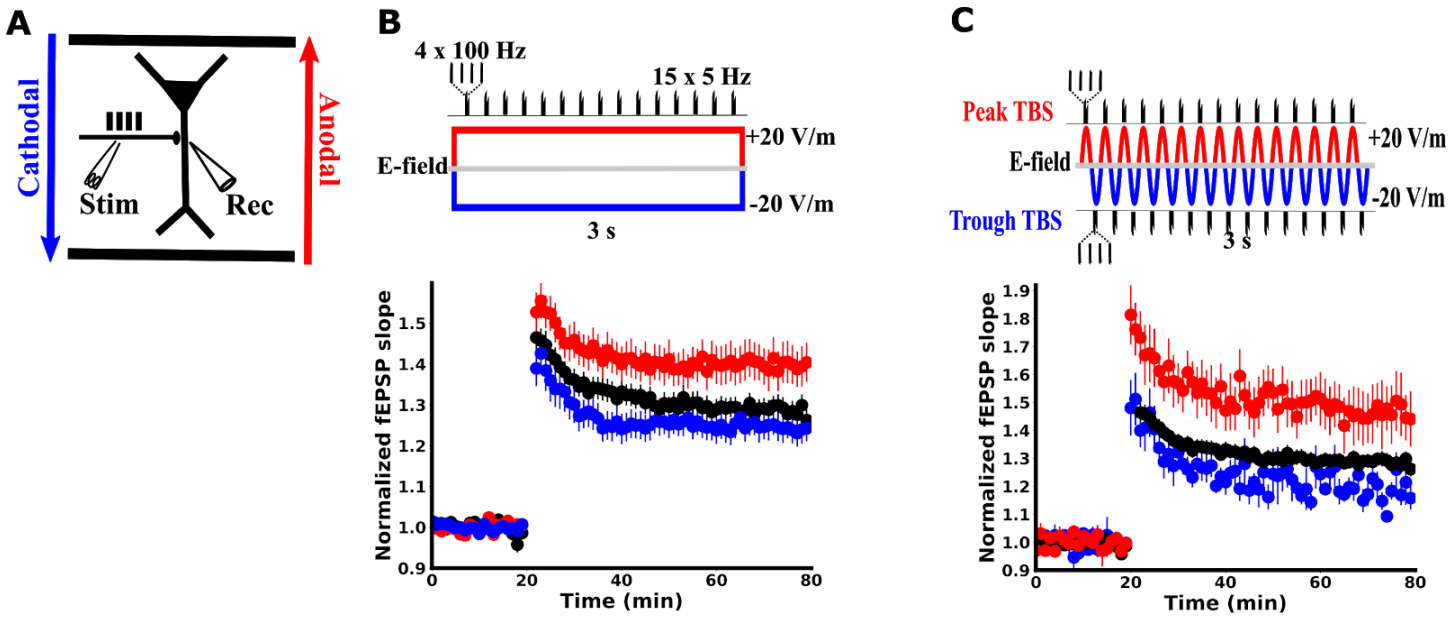

Figure 1. Soma depolarizing DCS modulates LTP in hippocampal Schaffer Collateral pathway during theta burst stimulation. A) Schematic of the experimental setup. Direct current is passed across the CA1 region of a hippocampal slice using two Ag-AgCl wires to induce a uniform electric field over CA1. B) Direct current stimulation (DCS) applied concurrently with theta-burst stimulation (TBS) modulates long-term potentiation (LTP) along the hippocampal Schaffer collateral pathway. B) Soma-depolarizing DCS (anodal, red) increased synaptic strength for at-least 60 min after stimulation compared to control (no DCS, black). Soma-hyperpolarizing DCS (cathodal, blue), had no significant effect on LTP. Plasticity modulation is consistent with modulation of membrane potential on milisecond timescale. When TBS bursts were timed to the peak of 5 Hz alternating current stimulation (ACS, red, soma-depolarizing, same electric field direction as anodal DCS), LTP was enhanced as with anodal DCS. When TBS bursts were timed to the trough of 5 Hz ACS (blue, soma-hyperpolarizing, same electric field direction as cathodal DCS), LTP was not significantly altered as with cathodal DCS.

Effect of DCS on LTP is pathway specific

Hebbian synaptic plasticity is classically characterized as a pathway specific process. Our proposal that DCS enhances LTP through membrane potential implies that the effects of DCS should follow this pathway specificity. We tested this by monitoring two independent synaptic pathways in CA1 (Figure 2A). During induction, the strong pathway received a TBS protocol while the other pathway was inactive. LTP was observed in the strong pathway (Figure 2B black; 1.377+-0.052, N=16 p=2.8E-6), but not the inactive pathway (Figure 2B gray; 0.986+-0.031, N=14 p=0.657), demonstrating canonical pathway specificity. When this induction protocol was paired with anodal DCS, LTP was enhanced only in the strong pathway (Figure 2B red; 1.613+-0.071, N=14, p=0.011 vs control), while the inactive pathway was unaffected (Figure 2B light red; 0.971+-0.028, N=14, p=0.724 vs. control), showing that the effects of DCS respect the endogenous pathway specificity.

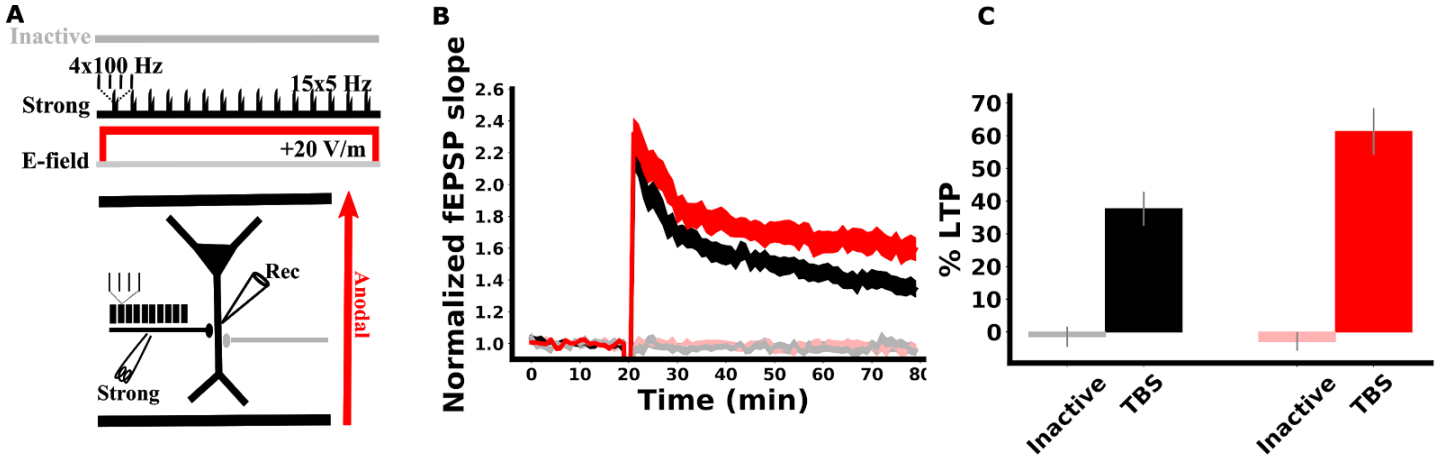

Figure 2. DCS upholds pathway specificity. A) Schematic of the experimental setup. Two synaptic pathways are monitored before and after plasticity induction. During induction, one pathway is activated with TBS (black, strong), while the other pathway is inactive (grey), and anodal DCS is applied across the slice throughout the duration of induction (3 s, red). B) Plasticity is pathway specific and so is the DCS effects. LTP was observed only in the pathway that received TBS (black trace), demonstrating pathway specificity, in line with canonical Hebbian plasticity. Anodal DCS enhanced LTP only in the strong pathway (red) and had no effect on the inactive pathway (light red), upholding Hebbian specificity. C) Summary of pathway specific effects of DCS. fEPSP slopes are normalized to the mean of the 20 of baseline responses prior to induction. %LTP in panel C is the mean of the last 10 normalized slopes (51-60 min after induction).

Computational model of plasticity based on membrane voltage replicates LTP modulation and predicts pathway specificity and associativity

To explain the above results we implement in a computational model two well-studied phenomena. First, weak electric fields modulate neuronal membrane potential. Second, postsynaptic membrane potential is a critical determinant of Hebbian plasticity. The second phenomenon is well captured by a phenomenological model of synaptic plasticity based on postsynaptic voltage (23). This model is easily adapted to incorporate the effects of DCS as an additional depolarizing current injection (see methods for details). We simulate the pathway specific TBS experiments of Figure 2, and find that the effect of DCS on plasticity in a given cell depends on the strength of baseline synaptic inputs. For sufficiently subthreshold synaptic input, DCS does not lead to any spiking (Figure 3Ai) or any change in synaptic strength (Figure 3Aii). If however, a cell is near threshold, changes in membrane potential due to DCS can cause the cell to fire (Figure 3Bi) leading to a jump in plasticity (Figure 3Bii). Similarly, if a cell is above threshold, DCS will shift the timing of spikes (Figure 3Ci), leading to increased plasticity (Figure 3Cii). Our field recordings in brain slice likely reflects the average of a population of cells with a random mixture of these three scenarios. In the model, if we generate a population of cells with input strengths drawn from a normal distribution (see methods for exact distribution), the average response of this model population qualitatively reproduces the pathway specific DCS modulation of LTP (Figure 3Ei, Eii).

Another important property of Hebbian plasticity is pathway associativity, which is a cellular mechanism thought to underlie the formation of cell assemblies and associative learning (18,29,30). Pathway associativity refers to the potentiation of separate synaptic pathways arriving onto the same postsynaptic neuron when they cooperate to drive the postsynaptic cell. For example, a synaptic input that is too weak on its own to induce plasticity can be brought to undergo plasticity by a coactive strong input that helps to drive the postsynaptic cell. We simulated this scenario in the voltage-based computational model as separate excitatory inputs arriving onto a postsynaptic cell. A weak input was activated at 5 Hz for 15 pulses, while a strong pathway was activated with the TBS protocol described for

the experiments above. Associativity can be measured in the weak pathway by comparing its plasticity when it is paired with a strong input against when it is activated alone. The model predicts that weak stimulation is unable to induce plasticity on its own, but does induce plasticity when paired with the strong input (Figure 4Ci left). When DCS is applied during induction, no effect is seen on the weak pathway alone, but when paired with the strong input, the resulting plasticity is boosted (Figure 4Cii right). The model therefore predicts that Hebbian associativity is boosted by DCS.

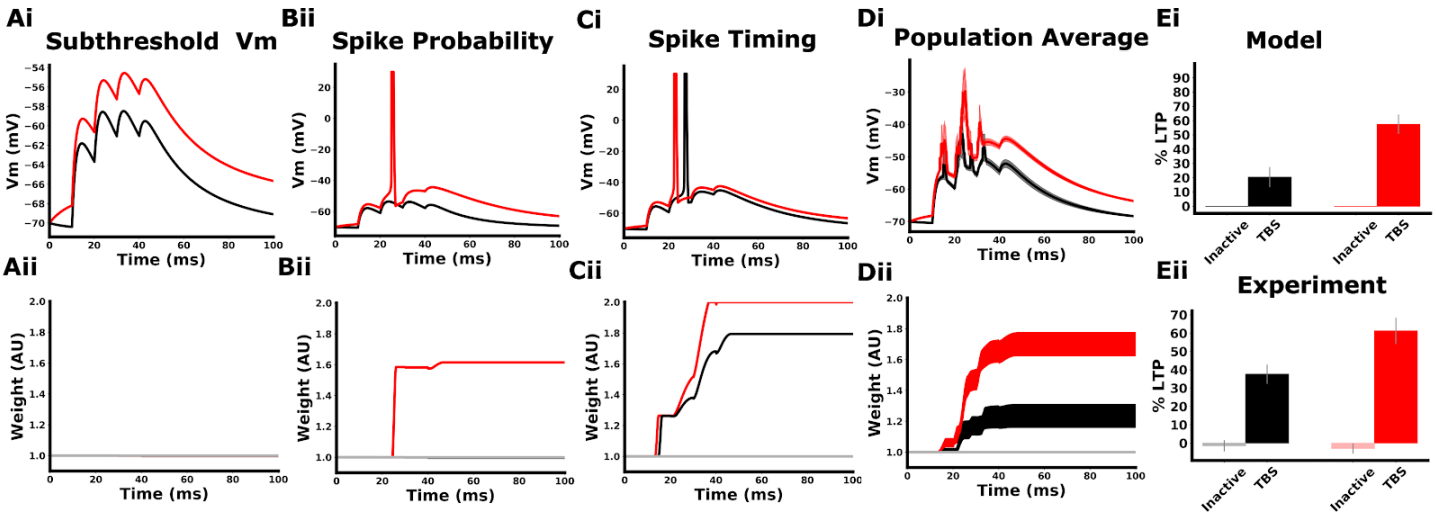

Figure 3. Voltage based plasticity model predicts LTP modulation and pathway specificity. A population of cells were modeled as point neurons, with parameters fit to multiple experimental plasticity results as in (23). A-C) Representative cases of membrane potential regimes during plasticity induction with TBS (top panel) and the resulting weight changes in the model (bottom panel). A) In the subthreshold regime, DCS causes a shift in membrane potential but the cell does not fire and no plasticity results. B) If a cell is close to threshold, DCS can lead to spiking and plasticity. C) If a cell spikes in response to TBS, DCS can shift the spike timing, leading to increased plasticity. D) Average membrane response and plasticity across the population of cells. E) Model (top) predicts experimental observation (bottom) that anodal DCS increases LTP, which is specific to the active pathway.

DCS boosts Hebbian associativity

We tested the above model predictions by again monitoring two synaptic pathways. First, only a weak input (15 pulses at 5 Hz) was used during induction (Figure 4Ai). In the absence of DCS, no lasting plasticity was observed in this weakly activated pathway (Figure 4Aii gray; 0.998+-0.041, N=13 p=0.966) or the other inactive pathway (Figure 4Aii black; 0.958+-0.037, N=13, N=13 p=0.275). DCS also had no effect on the weak (Figure 4Aii light red; 1.041+-0.038, N=13, p=0.445) or inactive pathway (Figure 4Aii red; 0.963+-0.011, N=13, p=0.908). This result further confirms the specificity of DCS effects, in that pathways that are not undergoing plasticity are unaffected by DCS.

In a second experiment, the weak input is now paired with a strong input (TBS) during induction (Figure 4Bi). During induction, weak pathway inputs are timed to arrive at precisely the same time as the the second pulse of each theta burst. This induces LTP in the strong pathway as before (Figure 4Bii black; 1.435+-0.067, N=13 p=3.1E-5), but now the weak pathway is also potentiated (Figure 4Bii gray; 1.115+-0.031, N=13 p=0.003), replicating classic associativity between the two pathways (18). If this protocol is paired with DCS during induction, LTP is now boosted in both the strong (Figure 4Bii red; 1.705+-0.094, N=13, p=0.029) and the weak pathway (Figure 4Bii light red; 1.242+-0.029, N=13,

p=0.006). DCS therefore enhances the Hebbian associativity between the strong and weak pathways, as predicted by the voltage-based plasticity model (Figure 4C).

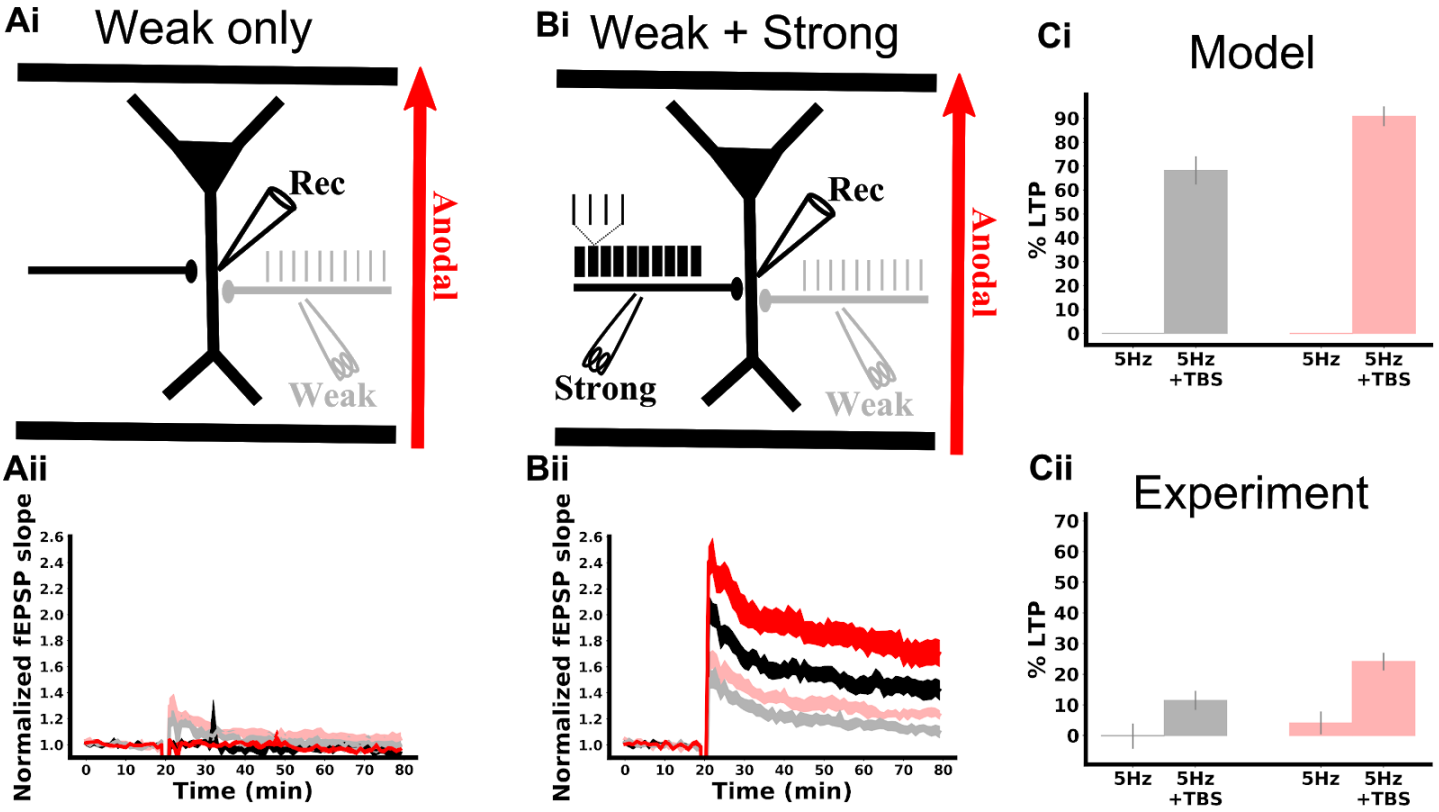

Figure 4. DCS enhances associativity between synaptic pathways. Ai) Schematic of experimental design. Two synaptic pathways were monitored. During induction, one pathway was activated at 5 Hz with 15 pulses (grey, weak), while the other pathway was inactive. Anodal DCS was applied throughout induction (3 s, red). Aii) Weak synaptic activation had no lasting effect on synaptic strength in either pathway with DCS (red, light red) or without DCS (grey, black). Bi) Schematic of experimental design. Again, two synaptic pathways were monitored. Now during induction, one pathway was activated with a TBS protocol (strong, black). The other pathway was activated with 15 pulses at 5 Hz (weak, grey), with pulses temporally aligned to the second pulse in each TBS burst. Bii) Without DCS, the strong pathway was potentiated (black) and the weak pathway was now also potentiated (grey), demonstrating associative plasticity between these pathways. With DCS, LTP was enhanced in the strong pathway (red) and the weak pathway (light red), demonstrating that the associativity between pathways was enhanced. C) Voltage-based plasticity model with a population of cells were modeled as point neurons, with parameters fit to multiple experimental plasticity results as in (23). The model (Ci) predicts associativity between pathways, which is observed in experiments (Cii)

Discussion

Synaptic plasticity is critical for many forms of learning and tDCS has been thought to alter synaptic plasticity. How stimulation may interact with ongoing synaptic activity to alter plasticity remains poorly understood. Here we found that weak electrical stimulation with constant direct currents can enhance multiple properties of synaptic plasticity. We propose a parsimonious model in which DCS boosts endogenous Hebbian synaptic plasticity through modulation of pyramidal neuron membrane potential. As the model predicts, the effects of DCS also reflect the input specificity and input associativity of the endogenous Hebbian plasticity. This framework produces a number of testable predictions for clinical experimentation. First, the efficacy of clinical protocols should improve when tDCS is paired with a learning task which induces plasticity, instead of the common practice of pairing tDCS with rest. Second, when tDCS is paired with a learning task, we postulate that the effects should be highly specific to

the trained task. Finally, the pairing of tDCS with Hebbian plasticity and learning can be thought of as a method for functional targeting, since tDCS should only affect synaptic pathways that are already undergoing plasticity due to the paired task. This may alleviate some of the requirement for precise anatomical targeting of the stimulation.

Hebbian plasticity

Hebb originally proposed that it was coincident pre and postsynaptic firing required for enhanced synaptic efficacy (31). Over time the concept of Hebbian plasticity has come to incorporate forms of plasticity that depend on correlated pre and postsynaptic activity variables, regardless of the exact biophysical implementation (32). While we do not directly measure or manipulate postsynaptic firing here, TBS-induced LTP at CA1 Schaffer collaterals has been shown to be Hebbian in that it depends on pre- and post-synaptic activity and exhibits classic Hebbian properties of input specificity and associativity (27).

Input specificity

Input specificity is a property of Hebbian plasticity whereby only synaptic connections that are relevant (active) for a given task are strengthened (18). The computational significance of this specificity has been recognized for some time, as it allows a network to learn sparse, non-overlapping neural representations (33). In practice, this is implemented in the brain by molecular machinery which responds to elevated activity specifically at task-relevant synapses (34). Here we show that DCS enhances LTP in a manner that respects this input specificity. DCS only boosts the strength of synapses that are highly active and already undergoing endogenous plasticity. Based on this observation, we make two predictions for the optimization of tDCS effects in humans.

First, tDCS effects in humans should similarly exhibit synaptic input specificity, which would be reflected as task specificity in the cognitive domain. Indeed there is good evidence for task-specific effects of tDCS, despite its lack spatial focality in the brain (16,17). This property may be central to the useful application of tDCS, as it implies that the technique can be deployed flexibly in combination with many different tasks and with limited side effects, despite stimulation reaching large regions of the brain. Second, tDCS effects may be most pronounced when paired concurrently with training that induces plasticity. Again, there is evidence for this in the human literature (35). It may be possible to leverage these properties further by pairing stimulation with forms of learning that rely heavily on Hebbian mechanisms (36–38).

Associativity

Associativity refers to the potentiation of a weak synaptic input when it is paired with strong input at other synapses to the same neuron. This can serve as a cellular mechanism to bind previously unrelated information as in classical condition (19). Here we show that DCS can further enhance this associativity, which may manifest as an increased probability of forming associations between stimuli during learning that involves Hebbian plasticity.

Asymmetry

As in our previous work (14,39) and in many tDCS studies (40–42), we observe asymmetric results with respect to DCS polarity. Anodal DCS enhanced LTP, while cathodal DCS had no measurable

effect with the current sample sizes. This may reflect distributions of initial synaptic state, such that synapses are biased towards an increase in strength (43). An alternative explanation may be that during cathodal stimulation, dendritic membrane depolarization counterbalances somatic hyperpolarization so that there is no reduction in LTP (39).

Mirroring the asymmetric effect of DC polarity, the effects with respect to phase of AC stimulation was also asymmetric. This suggests that even in the absence of information about the precise timing of synaptic inputs, a net enhancement of LTP may be expected when tACS is paired with synaptic plasticity induction. Notably, the boost in LTP was also larger here for ACS than DCS, perhaps owing to the frequency response properties of pyramidal neuron membranes showing a peak at theta frequencies (44).

Mechanism

Perhaps the most well characterized effect of electrical stimulation is modulation of somatic membrane potential and firing probability. Here we propose a model which translates this acute change in firing probability and timing into long term changes in synaptic plasticity. Several other mechanisms for tDCS effects have been proposed elsewhere (7–9). Electric fields are known to alter cell motility and immune responses (45,46). However, these effects unfold over the course over many minutes to hours. During prolonged stimulation, it is likely that various effects on cellular physiology begin to take hold simultaneously, with interactions between them. However, robust effects were generated here with remarkably short stimulation duration (3 s), which depended on stimulation polarity with timing on the order of milliseconds (100 ms, Figure 1C). Polarization of neuronal membranes is the only known effect of stimulation that acts on these timescales, making it the most likely source of effects here. While prolonged stimulation necessarily includes effects operating on both short (membrane polarization, plasticity induction) and longer (cell motility and immune responses) timescales, shortening the stimulation and pairing it with quicker (sub-minute) bouts of training as we have done here, could be a useful strategy to isolate effects based on Hebbian plasticity. While a simple model based on polarization of pyramidal neuron somas is sufficient to explain these results, we cannot exclude a role for membrane polarization of inhibitory interneurons or glia as well based on these data.

In previous work we proposed that DCS may alter plasticity through modulation of dendritic membrane potential, whereas here we propose that somatic membrane potential is the key mechanism. An important difference between these studies is the pattern of synaptic activity used as well as the location where plasticity was induced. The extended train of synaptic activity at 20 Hz used in the previous study has been shown be more dependent on dendritically generated potentials, rather than action potentials back-propagating from the soma (47–50). This is consistent with the dendritic effects we observed previously. Theta burst stimulation however, which we used here, is more dependent on somatic bAP, consistent with the somatic model proposed here (21,28). Additionally, we induced plasticity in a pathway closer to the soma, as compared to our previous study. Together these studies point to a more nuanced interpretation, where membrane polarization induced by stimulation interacts with regenerative potentials induced by endogenous synaptic activity. The overall effect on synaptic plasticity is then determined by the DCS-induced polarization at the neural elements that dominate during a given synaptic activity pattern.

Limitations

In this study we made sacrifices in two main experimental design choices that should be noted and interpreted with caution. First, here we mostly used a 20 V/m electric field in order resolve effects within a reasonable number of slices. Electric fields in the brain during typical tDCS experiments are expected to be under 1 V/m (46). While we do not measure effects with this intensity, our computational model predicts a monotonic relationship between plasticity effects and electric field magnitude. To first order this implies effects of ~1% for fields of 1V/m in line with effect sizes observe for acute effects of DCS (51). We note recent efforts to increase stimulation intensity up to 6mA by distributing current across multiple electrodes (52). Our estimates suggest that this can achieve fields of 3 V/m in the brain (53) putting the effects observed here in the range of small but measurable effect sizes in clinical studies.

Second, while current does reach hippocampus and subcortical structures during stimulation (53), tDCS is thought to primarily act on cortex. Here we chose hippocampus as a model system for the wealth of studies on hippocampal synaptic plasticity and the much neater organization of input pathways. While not identical, many excitatory plasticity mechanisms are conserved in pyramidal neurons between cortex and hippocampus (54), making our observations here informative for cortex as well. Of course, further work is needed to validate this relationship. It is also worth noting that this work, in addition to other recent studies (12,15,55), motivates the hippocampus as a target for tDCS in future studies.

The degree to which the present results are observed in vivo would likely depend on the role that Hebbian plasticity plays in the task that stimulation is paired with. Moreover, it is important to note that an increase in LTP may not necessarily improve learning. At one extreme, synaptic plasticity may be perfectly tuned for a certain form of learning in the endogenous case, making any alteration in LTP detrimental. Thus the degree to which these effects would be beneficial may depend on the computational needs of the learner. For example, stimulation may be most beneficial when it is paired with suboptimal learning (56–58).

Methods

Electrophysiology

All animal experiments were carried out in accordance with guidelines and protocols approved by the Institutional Animal Care and Use Committee (IACUC) at The City College of New York, CUNY (Protocol No: 846.3).

Hippocampal brain slices were prepared from male Wistar rats aged 3–5 weeks old, which were deeply anaesthetized with ketamine (7.4 mg kg^{-1}) and xylazine (0.7 mg kg^{-1}) applied I.P., and killed by cervical dislocation. The brain was quickly removed and immersed in chilled (2–6 °C) artificial cerebrospinal fluid (ACSF) containing (in mm): NaCl, 125; KCl, 4.4; NaH_2PO_4, 1; $MgSO_4$, 1.5; CaCl, 2.5; $NaHCO_3$, 26; d-glucose, 10; bubbled with a mixture of 95% O_2–5% CO_2. Transverse slices (400 µm thick) were cut using a vibrating microtome (Campden Instruments) and transferred to a holding chamber for at least 1 h at ambient temperature. Slices were then transferred to a fluid–gas interface chamber (Harvard Apparatus) perfused with warmed ACSF (30.0 ± 0.1 °C) at 1.0 ml min^{-1}. The humidified atmosphere over the slices was saturated with a mixture of 95% O_2–5% CO_2. Recordings started 2–3 h after dissection.

Field excitatory postsynaptic potentials (fEPSPs) were evoked using a platinum–iridium bipolar stimulating electrode placed in stratum radiatum of CA1 within 200 μm of the somatic layer. Recording electrodes made from glass micropipettes pulled by a Sutter Instruments P-97 and filled with ACSF (resistance 1–8 MΩ) were placed in stratum radiatum approximately 500 μm from the stimulating electrode in CA1 to record fEPSPs. For two-pathway experiments (Figure 2,4), a second stimulating electrode was placed on the opposite side of the recording electrode. fEPSPs were quantified by the average initial slope, taken during the first 0.5 ms after the onset of the fEPSP. Stimulus intensity was set to evoke fEPSPs with 40% of the maximum slope, which was determined at the onset of recording. Stable baseline fEPSPs were recorded every minute for at least 20 minutes before any plasticity induction was applied. For two pathway experiments, stimulation of each pathway was offset by 30 s. fEPSPs were then recorded again every minute for 60 minutes after plasticity induction.

Uniform extracellular EFs (±20 V/m) were generated by passing constant current (D/A driven analog follower; A-M Systems, WA, USA) between two large Ag-AgCl wires (1 mm diameter, 12 mm length) positioned in the bath across the slice starting 0.5 s before the onset of theta burst stimulation. Slices were oriented such that the somato-dendritic axis of CA1 pyramidal neurons was parallel to the electric field between the DCS wires (Fig. 1A). We name each polarity of DCS based on the orientation of the field relative to CA1 pyramidal neurons, and how pyramidal neurons are expected to be polarized. Here, anodal DCS depolarizes CA1 pyramidal neuron somas as it is expected to do in cortical pyramidal neurons under an anode in tDCS. Cathodal stimulation of course refers to the opposite polarity. Before each recording, DCS current intensity was calibrated to produce a 20 V/m electric field across each slice (typically 100–200 μA) by adjusting the current so that two recording electrodes separated by 0.8 mm in the slice measured a voltage difference of 16 mV (16 mV/0.8 mm = 20 V/m).

Voltage-based plasticity model

Postsynaptic cells were modeled exponential integrate and fire neurons with a voltage-based plasticity rule (24). This model has already been fit to various hippocampal synaptic plasticity experiments, so parameters were taken directly from the original paper (24). Synaptic pathways were simulated as excitatory inputs as in Clopath et al. 2010. We assume that in our experiment, the baseline strength of synaptic input varies between individual cells in the population being recorded from. This is modeled as 40 independent postsynaptic cells, with the initial strength of synaptic input (as maximum ampa conductance) drawn from a normal distribution with mean 40 nS and standard deviation 10 nS. The 20 V/m DCS electric field was modeled as an intracellular current injection of 100 pA, yielding a ~2 mV shift in steady-state membrane potential. This is in accordance with the 0.1-0.2 mV depolarization per V/m electric field observed experimentally (25). Code for the simulations will be made available after publication.

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