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Review article

Using tDCS priming to improve brain function: Can metaplasticity provide the key to boosting outcomes?

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ABSTRACT

Transcranial direct current stimulation (tDCS) has been trialled by many researchers attempting to improve brain function. Outcomes have been quite variable with seemingly similar protocols yielding either inconsistent or insufficiently robust improvements for clinical translation. A potentially fruitful avenue for increasing benefits conferred by tDCS stems from findings from motor and visual cortex studies that indicate tDCS priming prior to a subsequent period of stimulation (tDCS or transcranial magnetic stimulation) can in some cases boost outcomes compared to protocols without priming. The heightened effects from tDCS priming protocols are thought to be underpinned by metaplastic interactions, in which the state induced by the priming influences the effects of the second stimulation period. The purpose of the current review is to evaluate the potential of tDCS priming protocols to boost outcomes. After dissecting the literature, we conclude that although outcomes have varied, tDCS priming protocols have demonstrated sufficient promise to warrant attention from researchers trying to enhance the efficacy of tDCS.

1. Introduction

Despite numerous studies demonstrating that transcranial direct current stimulation (tDCS) applied over cortical regions can enhance brain function, tDCS therapies have yet to translate to the clinic (Yavari et al., 2017a). A key factor prohibiting clinical translation has been the inability to consistently yield robust tDCS effects (Li et al., 2015). Thus, researchers need to look to new strategies to enhance outcomes. One strategy that has shown promise in studies investigating motor and visual cortex excitability entails the application of a prior period of tDCS (i.e., priming) before a subsequent period of non-invasive brain stimulation (NIBS), which has involved either tDCS or repetitive transcranial magnetic stimulation (rTMS). Using this strategy, researchers have shown that tDCS priming can alter the effects of subsequent NIBS in a manner that shows potential with respect to generating more robust outcomes. The altered effects have been attributed to the initial priming stimulation setting in motion regulatory metaplastic mechanisms that protect against subsequent under- or over-activity.

In considering the potential of tDCS priming protocols to boost effects through metaplastic interactions, in this review we first provide a brief introduction to metaplasticity (Section 2), and then report on studies investigating effects of tDCS priming protocols on motor cortex excitability (Section 3) and visual cortex excitability (Section 4). To ensure that readers can easily interpret each study's design and outcomes, Table 1 displays the methodology and results of the reviewed studies in a visual format, with results symbols colour coded to indicate whether the outcomes were consistent with standard expected effects (black/grey) or with effects expected based on principles of metaplasticity (red). In cases where the outcomes could be consistent with metaplasticity but a lack of critical control conditions prevented confirmation of this, the results symbol is coloured with black and red stripes. The right column of Table 1 summarises all outcomes that could be consistent with metaplasticity.

2. Brief background on metaplasticity in relation to tDCS priming

Neurons can modify their structure and function in response to activity and, depending on the activity, undergo persistent forms of synaptic plasticity involving long-term-potentiation (an increase in synaptic strength, otherwise known as LTP) or long-term-depression (a decrease in synaptic strength, otherwise known as LTD) (Takeuchi et al., 2014; Thompson, 2000). In the Bienenstock et al. (1982) model of synaptic modification (referred to as BCM), in order to preserve network stability and allow for ongoing LTP or LTD, a bidirectional sliding threshold dynamically adjusts depending on prior synaptic activity. The model was later extended to incorporate homeostatic regulatory

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Table 1
Summary of motor and visual studies using tDCS priming protocols.

Study	Sample	Stimulation	tDCS Priming Protocol and Outcomes							Metaplastic Results
First author (year)	N ppts	tDCS electrode positions and rTMS protocol	Duration and details of the two stimulation periods: tDCS polarity (A = anodal, C = cathodal, S = sham) and strength (mA), delay interval duration, rTMS active or sham (SrTMS). Outcomes: increase (up arrow), decrease (down arrow), or no change (x).							This column details only outcomes consistent with tDCS priming yielding subsequent metaplastic changes.
Motor studies applying tDCS priming prior to rTMS										
First author (year)	N ppts	active/reference rTMS dose	Baseline MEPs	tDCS priming		Delay	rTMS	MEPs (direction of change)		Significant differences compared to (cf) baseline, unless stated in bold.
Siebner		LM1/RSO		10 min			15 min	0-10 min	10-20 min	*Mean MEPs post rTMS*
(2004)	8 ppts	1 Hz rTMS@85%		S 1	x	10-min	rTMS	x	x	
		RMT		A 1	↑	10-min	rTMS	↓	↓	Decrease post rTMS.
		(subthreshold)		C 1	↓	10-min	rTMS	↑	↑	Increase post rTMS.
	5 ppts*			A 1	↑	10-min	SrTMS	↑	↑	
				C 1	↓	10-min	SrTMS	↓	↓	
Lang		LM1/RSO		10 min			20 sec	0-8 min	10-18 min	*Mean MEPs post rTMS*
(2004)	10 ppts	5 Hz rTMS@100%		S 1	x	10-min	rTMS	x	x	
		AMT		A 1	↑	10-min	rTMS	x	↓	**Expected increases post rTMS counteracted at 0-8 and reversed at 10-18 min cf AtDCS-SrTMS.**
		(subthreshold)		C 1	↓	10-min	rTMS	x	↑	**Expected decreases post rTMS counteracted at 0-8 and reversed at 10-18 min cf CtDCS-SrTMS.**
	5 ppts*			A 1	↑	10-min	SrTMS	↑	↑	
				C 1	↓	10-min	SrTMS	↓	↓	
Cosentino		LM1/RSO	12 min	15 min			12 min			*MEPs during rTMS (6 rTMS trains of 10 pulses every 2 min)*
(2012)	12 ppts	5 Hz rTMS@120%	rTMS	↑ (2 x baseline sessions)						
		RMT		A 1.5		0-min	rTMS	↓		Expected increases during rTMS reversed.
		(suprathreshold)		C 1.5		0-min	rTMS	↑		Increases during rTMS not counteracted by CtDCS priming.
	7 ppts*			S 1.5		0-min	rTMS	↑		
	7 ppts*			A 1.5		30-min	rTMS	x		Expected increases during rTMS counteracted.
Cambieri		LM1/R Shoulder	10 min	10 min		0-min	0-10 min	10-20 min		*MEPs during rTMS (5 rTMS trains of 10 pulses every 2 min)*
(2012)	11 ppts	5 Hz rTMS@120% RMT	rTMS ↑	A 1		0-min	rTMS x	rTMS x		Expected increases during rTMS counteracted at 0-10 and 10-20 min.
		(suprathreshold)	rTMS ↑	C 1		0-min	rTMS ↑	rTMS ↑		Increases during rTMS not counteracted by CtDCS priming at 0-10 or 10-20 min.
Motor studies applying tDCS priming prior to tDCS										
First author (year)	N ppts	active/reference	Baseline MEPs	tDCS priming		Delay	tDCS	Post tDCS MEPs change direction	change duration	Significant differences cf baseline, unless stated in bold.
Monte-Silva		LM1/RSO		9 min			9 min			*Mean MEPs post tDCS at 0, 5, 10, 15, 20, 25, 30, 60, 90 and 120 min, same evening and next day (ND)*
(2010)	12 ppts			C 1				↓	0-60	
	12 ppts			C 1		0-min	C 1	↓	0-90	
	12 ppts			C 1		3-min	C 1	↓	0-120	Decrease prolonged for extra 30 min.
	12 ppts			C 1		20-min	C 1	↓	0-120 **20-30**	Decrease prolonged for extra 30 min. **Greater decrease at 20-30 min cf 0-min delay protocol.**
	12 ppts			C 1		3-hr	C 1	↓	60	Decrease disrupted (significant only at 60 min post).
	12 ppts			C 1		24-hr	C 1	↓	25, 60-120	Decrease disrupted (significant only at 25 and 60-120 min).
Fricke		LM1/RSO								*Mean MEPs post tDCS at 0, 1, 2, 3, 4, 10, 15, 20, 25, 30, 60 and 90 min*
(2011)	9 ppts			5 min			5 min			
				C 1				↓	0-5	
				C 1		0-min	C 1	↓	0-30	
				C 1		3-min	C 1	↑	15-30 **0-60**	Increase at 15-30 min. **Increase at 0-60 min cf 0-min delay CtDCS protocol.**
				C 1		30-min	C 1	↓	0-5	
	8 ppts			5 min			5 min			
				A 1				↑	0-5	
				A 1		0-min	A 1	↑	0-30	
				A 1		3-min	A 1	↑ ↓	1-3 **10-30**	**Decrease at 10-30 min cf 0-min delay AtDCS protocol.**
				A 1		30-min	A 1	↑	0-5	
	8 ppts			5 min			5 min			
				A 1				↑	0-2	
				A 1		1-min	A 1	x		No expected increase.
				A 1		10-min	A 1	↓	0-25	Decrease for 25 min.
				A 1		20-min	A 1	x		No expected increase.
	12 ppts			7 min			5 min			
				A 1				↑	0-20	
				A 1		1-min	A 1	x		No expected increase.
				A 1		3-min	A 1	↓	10-12 **0-60**	Decrease at 10-12 min. **Decrease at 0-60 min cf single dose 7 min AtDCS protocol.**
				A 1		10-min	A 1	x ↓	No expected increase. **0-20**	**Decrease at 0-20 min cf single dose 7 min AtDCS protocol.**
				A 1		20-min	A 1	↑	1	
				A 1		30-min	A 1	x		No expected increase.
Monte-Silva	15 ppts	LM1/RSO								*Mean MEPs post tDCS at 0, 5, 10, 15, 20, 25, 30, 60, 90 and 120 min, same evening and next day (ND)*
(2013)				13 min			13 min			
				A 1				↑	0-60	
				A 1		0-min	A 1	↓	0-120	Unexpected decrease at 0-120 min.
				A 1		3-min	A 1	↑	0, ND	Increase at 0 min and ND (i.e., largely delayed excitatory effects).
				A 1		20-min	A 1	↑	ND	Increase ND only (i.e., delayed excitatory effects).
				A 1		3-hr	A 1	↓	20	Decrease at 20 min.
				A 1		24-hr	A 1	↓	5	Decrease at 5 min.
Visual studies applying tDCS priming prior to rTMS										
First author (year)	N ppts	active/reference rTMS dose	Baseline PT/VEP	tDCS priming		Delay	rTMS	Post rTMS PT/VEPs direction of change		Significant difference as a percentage of baseline
Lang	9 ppts	Oz/Cz		10 min			15 min	0 min	5 min 15 min	*Mean PT post rTMS (decrease indicates excitatory change)*
(2007)		1 x 20 sec 5 Hz		S 1	x	none	rTMS	x	x x	
		rTMS@90%		A 1	↓	none	rTMS	x	x x	**Expected decrease post rTMS counteracted cf AtDCS-SrTMS.**
		phosphene		C 1	↑	none	rTMS	x	x x	
		threshold		A 1	↓	none	SrTMS	↓	x x	
		(subthreshold)		C 1	↑	none	SrTMS	x	x x	
Bocci	10 ppts	Oz/R Shoulder		20 min			20 min	0 min	30 min 60 min	*Mean VEPs post rTMS (increase indicates excitatory change)*
(2014)				A 1.5	↑	15-20 min	SrTMS	↑	↑ ↑	
				C 1.5	↓	15-20 min	SrTMS	↓	↓ ↓	
		1 Hz rTMS@85%		S 1.5	x	15-20 min	rTMS 1 Hz	↓		
		RMT								
		(suprathreshold)		A 1.5	↑	15-20 min	rTMS 1 Hz	↓*	↓ ↓	Decrease at 0-60 min post rTMS (i.e., prolonged inhibitory effects). ***Greater decrease cf CtDCS-SrTMS and StDCS-1Hz rTMS.**
				C 1.5	↓	15-20 min	rTMS 1 Hz	↑	↑ ↑	Increase at 0-60 min post rTMS (inhibitory protocol).
							60 sec			
		5 Hz rTMS@85%		S 1.5	x	15-20 min	rTMS 5 Hz	↑		
		RMT		A 1.5	↑	15-20 min	rTMS 5 Hz	↓	↓ ↓	Decrease at 0-60 min post rTMS (excitatory protocol).
		(suprathreshold)		C 1.5	↓	15-20 min	rTMS 5 Hz	↑	x x	Increase post rTMS. **Greater increase cf StDCS-5Hz rTMS.**

ppts* = participants from main pool retested.
tDCS electrode positions: Cz = central midpoint, L = left, M1 = primary motor cortex, Oz = central occipital cortex, R = right, SO = supraorbital area.
rTMS protocol: AMT = active motor threshold, Hz = Hertz (times per second), RMT = resting motor threshold.
Outcome measures: MEP = motor evoked potential, PT = phosphene threshold, VEP = visual evoked potential.
Protocol symbols and colours: ∿/V= single-pulse TMS, orange = rTMS, green = tDCS.
Result symbols and colours: upward arrow = increase, downward arrow = decrease, grey arrow = trend level change consistent with standard expected effect, x = no change, black = result consistent with standard expected effect, red = result consistent with metaplasticity, black/red striped = result could be consistent with metaplasticity (additional research needed to confirm).