Brain Stimulation 7 (2014) 773–783

Contents lists available at ScienceDirect

Brain Stimulation

journal homepage: www.brainstimjrnl.com

Original Articles

The Uncertain Outcome of Prefrontal tDCS

Sara Tremblay [a,b], Jean-François Lepage [c], Alex Latulipe-Loiselle [a,b], Felipe Fregni [c], Alvaro Pascual-Leone [d], Hugo Théoret [a,b,*]

[a] Department of Psychology, University de Montreal, Canada
[b] Research Center, Centre Hospitalier Universitaire Sainte-Justine, Montreal, Canada
[c] Neuromodulation Laboratory, Spaulding Rehabilitation Hospital, Harvard Medical School, USA
[d] Berenson Allen Center for Non-Invasive Brain Stimulation, Beth Israel Deaconess Medical Center, Harvard Medical School, USA

ARTICLE INFO

Article history:
Received 15 August 2014
Accepted 7 October 2014
Available online 28 October 2014

Keywords:
Transcranial direct current stimulation
Neurostimulation
Cognition
Executive functions
Dorsolateral prefrontal cortex

ABSTRACT

Background: Transcranial direct current stimulation (tDCS) is increasingly used in research and clinical settings, and the dorsolateral prefrontal cortex (DLPFC) is often chosen as a target for stimulation. While numerous studies report modulation of cognitive abilities following DLPFC stimulation, the wide array of cognitive functions that can be modulated makes it difficult to predict its precise outcome.
Objective: The present review aims at identifying and characterizing the various cognitive domains affected by tDCS over DLPFC.
Methods: Articles using tDCS over DLPFC indexed in PubMed and published between January 2000 and January 2014 were included in the present review.
Results: tDCS over DLPFC affects a wide array of cognitive functions, with sometimes apparent conflicting results.
Conclusion: Prefrontal tDCS has the potential to modulate numerous cognitive functions simultaneously, but to properly interpret the results, a clear a priori hypothesis is necessary, careful technical consideration are mandatory, further insights into the neurobiological impact of tDCS are needed, and consideration should be given to the possibility that some behavioral effects may be partly explained by parallel modulation of related functions.

© 2014 Elsevier Inc. All rights reserved.

Introduction

In 1865, Broca introduced the idea of studying the neural basis of cognitive processes by the anatomical-correlative method [1]. While studying the effect of a brain lesion in his famous patient "Monsieur Tan", who had a neurosyphilic lesion to the left hemisphere that impaired his language production, Broca concluded that it was possible to infer a causal relationship between a specific brain region and a cognitive function [2]. This discovery ultimately sparked the emergence of neuropsychology, which aims to better understand the link between brain and behavior, and led to a wide interest in the study of patients with various brain lesions. Subsequently, remarkable progress was made using this approach, for example during World War II, where researchers were able to study the effects of focal brain lesions induced by weapons in conjunction with cognitive testing [3].

Despite the numerous and significant insights derived from the "lesion method", researchers were – and still are – confronted with methodological limitations when trying to ascertain brain–behavior relationships in patient populations. Firstly, lesions are

This study was supported by grants from the Canadian Institutes of Health Research, the Natural Sciences and Engineering Research Council of Canada and the Fonds de Recherche du Québec - Santé. ST is supported by a Vanier Canada Graduate Scholarship from the Canadian Institutes of Health Research. JFL is supported by a postdoctoral fellowship from the Canadian Institutes of Health Research. APL is supported in part by grants from the Sidney R. Baer, Jr. Foundation, the National Institutes of Health (R01HD069776, R01NS073601, R21 MH099196, R21 NS082870, R21 NS085491, R21 HD07616), Harvard Catalyst | The Harvard Clinical and Translational Science Center (NCRR and the NCATS NIH, UL1 RR025758), and an investigator-initiated grant from Neuronix Ltd. The content is solely the responsibility of the authors and does not necessarily represent the official views of Harvard Catalyst, Harvard University and its affiliated academic health care centers, the National Institutes of Health or the Sidney R. Baer Jr. Foundation.

Conflict of interest disclosure: APL serves on the scientific advisory boards for Nexstim, Neuronix, Starlab Neuroscience, Neuroelectrics, Axilum Robotics, Magstim Inc., and Neosync; and is listed as an inventor on several issued and pending patents on the real-time integration of transcranial magnetic stimulation (TMS) with electroencephalography (EEG) and magnetic resonance imaging (MRI).

* Corresponding author. Département de Psychologie, Université de Montréal, CP 6128, Succ. Centre-Ville, Montréal, QC, Canada H3C 3J7. Tel.: +1 514 343 6362; fax: +1 514 343 5787.

E-mail address: hugo.theoret@umontreal.ca (H. Théoret).

http://dx.doi.org/10.1016/j.brs.2014.10.003
1935-861X/© 2014 Elsevier Inc. All rights reserved.

Table 1
tDCS studies of prefrontal cortex.

Authors	Target region(s)	Montage	Timing of tDCS	Duration	Intensity	Electrode size	Cognitive domain	Cognitive effect[a,b]
Fregni et al. (2005) [36]	Left DLPFC	Anodal F3/Cathodal contra SO Cathodal F3/Anodal contra SO Sham (F3/SO)	Online	10 min	1 mA	35 cm^2	Working memory	1) Left anodal: increased performance (sequential letter task)
Marshall et al. (2005) [62]	Left/Right DLPFC	Anodal F3/ Cathodal F4 Reference: mastoids Sham (F3/F4/mastoid)	Online	15 min (15 s on and 15 s off, intermittent)	260 uA	Diameter: 8 mm	Working memory	1) Bilateral (left anodal/right cathodal): decreased performance (slower RTs)
Fecteau et al. (2007) [61]	Left/Right DLPFC	Anodal F3/Cathodal F4 Anodal F4/Cathodal F3 Sham (F3/F4) Anodal F3/Cathodal contra SO Anodal F4/Cathodal contra SO Sham (F3 or F4/ contra. SO)	Online	20 min	2 mA	35 cm^2	Risk taking	1) Bilateral (left cathodal/right anodal): decreased risk taking (Baloon Analogue Risk Task) 2) Right anodal: no sign. effect on risk taking
Fecteau et al. (2007) [19]	Left/Right DLPFC	Anodal F3/ Cathodal F4 Anodal F4/ Cathodal F3 Sham (F3/F4)	Online	15 min	2 mA	35 cm^2	Risk taking	1) Bilateral (left cathodal/right anodal): reduced risk taking (Risk Task)
Beeli et al. (2008) [37]	Left DLPFC Right DLPFC	Anodal F3 or F4/ Cathodal ipsi. mastoid Cathodal F3 or F4/ Anodal ipsi. mastoid	Offline	15 min	1 mA	35 cm^2	Risk taking	1) Left anodal: reduced risk taking behaviors (driving stimulator) 2) Right anodal: reduced risk taking behaviors (driving stimulator)
Beeli et al. (2008) [14]	Right DLPFC	Anodal FC3/Cathodal ipsi. mastoid Cathodal FC3/Anodal ipsi. Mastoid Sham	Online	5.5 min	1.5 mA	35 cm^2	Executive function (impulsivity) Feeling of "presence"	1) Right cathodal: increases impulsiveness (Go-Nogo task)
Boggio et al. (2008) [52]	Left DLPFC	Anodal F3/Cathodal right SO Sham (F3/SO)	Online	5 min	2 mA	35 cm^2	Pain perception	1) Left anodal: decreased pain perception (higher pain threshold)
Fregni et al. (2008) [20]	Left/right DLPFC	Anodal F3/Cathodal F4 Anodal F4/Cathodal F3 Sham (F3/F4)	Offline	20 min	2 mA	35 cm^2	Food craving	1) Bilateral (left anodal/right cathodal): reduced food consumption but not craving 2) Bilateral (left cathodal/right anodal): reduced food craving and consumption
Knoch et al. (2008) [33]	Right DLPFC	Cathodal F4/Anodal contra. SO	Online	14 min	1.5 mA	35 cm^2 Reference: 100 cm^2	Emotions Social behaviors	1) Right cathodal: reduced propensity to punish unfair behavior
Ohn et al. (2008) [41]	Left DLPFC	Anodal F3/Cathodal right SO Sham (F3/SO)	Online	30 min	1 mA	25 cm^2	Verbal working memory	1) Left anodal: enhanced performance (3-back)
Priori et al. (2008) [71]	Left/Right DLPFC	Anodal F3 and F4/Cathodal deltoid Cathodal F3 and F4/Anodal deltoid Sham (F3–F4/Deltoid)	Offline	10 min	1.5 mA	Active: 32 cm^2 Reference: 64 cm^2	Decision making	1) Bilateral (left anodal/right anodal): increased lie responses
Boggio et al. (2009) [38]	Left DLPFC	Anodal F3/Cathodal contra SO Sham (F3/SO)	Online	5 min	2 mA	35 cm^2	Emotion processing Pain	1) Left anodal: decreased negative emotions perception (unpleasantness and emotional discomfort)
Cerruti et al. (2009) [55]	Left DLPFC Right DLPFC	Anodal F3 or F4/ Cathodal contra SO Cathodal F3 or F4/ Anodal contra SO Sham F3/F4	Online	20 min	1 mA	16.3 cm^2 on F3/F4 30 cm^2 on SO	Verbal problem solving	1) Left anodal: improvement (RAT task) 2) Cathodal: no sign. effect

Table 1 (*continued*)

Authors	Target region(s)	Montage	Timing of tDCS	Duration	Intensity	Electrode size	Cognitive domain	Cognitive effect[a,b]
Dockery et al. (2009) [15]	Left DLPFC	Anodal F3/Cathodal contra. SO Cathodal F3/Anodal contra. SO Sham (F3/SO)	Online	15 min	1 mA	35 cm^2	Executive functioning (planning)	1) Left cathodal and left anodal: enhanced performance (Tower of London)
Elmer et al. (2009) [24]	Left DLPFC Right DLPFC	Anodal F3 or F4/ Cathodal mastoid Cathodal F3 or F4/ Anodal mastoid Sham (F3 or F4/ Mastoid)	Online	5 min	1.5 mA	28 cm^2 on F3/F4 100 cm^2 on SO	Verbal learning	1) Left cathodal: impaired short-term verbal learning
Fertonani et al. (2010) [53]	Left DLPFC	Anodal F3/Cathodal shoulder Cathodal F3/Cathodal shoulder Sham (F3/Shoulder)	Offline	8–10 min	2 mA	35 cm^2	Language (picture naming)	1) Left anodal: facilitation (faster RTs) 2) Left cathodal: no sign. effect
Hecht et al. (2010) [69]	Left/Right DLPFC	Anodal F3/Cathodal F4 Anodal F4/Cathodal F3 Control (no stimulation)	Online	22 min	2 mA	9 cm^2	Decision making	1) Bilateral (left anodal/right cathodal): modified strategies (Probabilistic Guessing Task)
Mameli et al. (2010) [68]	Left/Right DLPFC	Anodal F3/Anodal F4/Reference right deltoid muscle Sham (F3/F4/Deltoid)	Offline	15 min	2 mA	Target: 32 cm^2 Reference: 64 cm^2	Decision making (lies)	1) Bilateral (left anodal/right anodal): modulated responses to lies (decreased RTs)
Ambrus et al. (2011) [28]	Left DLPFC Right DLPFC	Anodal F3 or F4/ Cathodal Cz Cathodal F4/Anodal Cz Sham (F4/Cz)	Online	10 min	1 mA	35 cm^2	Categorization learning	1) Left anodal and right anodal: decreased performance (accuracy of identification of prototype)
Andrews et al. (2011) [44]	Left DLPFC	Anodal F3/Cathodal SO	Online	10 min	1 mA	35 cm^2	Working memory	1) Left anodal: enhanced performance (digit span forward)
Hammer et al. (2011) [26]	Left DLPFC	Anodal F3/Cathodal contra. SO Cathodal F3/Cathodal contra. SO Sham (F3/SO)	Online	30 min	1 mA	35 cm^2	Memory	1) Left cathodal: hampered memory performance after errorful learning
Leite et al. (2011) [22]	Left DLPFC	Anodal F3/Cathodal contra. SO Cathodal F3/Cathodal contra. SO Sham (F3/SO)	Online	15 min	1 mA	35 cm^2	Executive functions (mental/ motor flexibility)	1) Left anodal: increased performance (set switching task) 2) Left cathodal: decreased performance (set switching task)
Mulquiney et al. (2011) [42]	Left DLPFC	Anodal F3/Cathodal contra. SO Sham (F3/SO)	Online	10 min	1 mA	35 cm^2	Working memory	1) Left anodal: improved speed of performance (2-back task).
Peña-Gómez et al. (2011) [56]	Left DLPFC	Anodal F3/Cathodal C4 Sham (F3/C4)	Online	20 min	1 mA	35 cm^2	Emotion processing	1) Left anodal: enhanced down-regulation of negative emotions
Teo et al. (2011) [43]	Left DLPFC	Anodal F3/Cathodal right SO Sham (F3/SO)	Online	20 min	1 mA and 2 mA	35 cm^2	Working memory	1) Left anodal: enhanced performance at 2 mA (faster RTs, no effect on accuracy)
Zaehle et al. (2011) [21]	Left DLPFC	Anodal F3/Ipsi. mastoid Cathodal F3/Ipsi. mastoid Sham (F3/mastoid)	Offline	15 min	1 mA	35 cm^2	Working memory	1) Left anodal: increased performance 2) Left cathodal: reduced performance

(*continued on next page*)

Table 1 (*continued*)

Authors	Target region(s)	Montage	Timing of tDCS	Duration	Intensity	Electrode size	Cognitive domain	Cognitive effect[a,b]
Balconi and Vitaloni (2012) [31]	Left DLPFC	Cathodal F3/Anodal right SO Sham (F3/Right SO)	Offline	15 min	2 mA	35 cm^2	Semantic congruence processing	1) Left cathodal: improved performance (reduced RTs for incorrect object)
Gladwin et al. (2012) [45]	Left DLPFC	Anodal F3/Cathodal right SO Sham (F3/Right SO)	Offline	10 min	1 mA	35 cm^2	Working memory	1) Left anodal: improved performance (congruent blocks of the IAT task)
Hortensius et al. (2012) [64]	Left/Right DLPFC	Anodal F3/Cathodal F4 Anodal F4/Cathodal F3 Sham (F3/F4)	Offline	15 min	2 mA	35 cm^2	Emotion regulation	1) Bilateral (left anodal/right cathodal): increased aggressive behaviors and anger
Javadi and Walsh (2012) [57]	Left DLPFC	Anodal F3/Cathodal contra. SO Cathodal F3/Cathodal contra. SO Sham (F3/SO)	Online	20 min	1 mA	Target: 12.2 cm^2 Reference: 30.2 cm^2	Declarative memory	1) Left anodal: enhanced memory performance (applied during encoding and recognition (trend)) 2) Left cathodal: impaired memory performance (applied during encoding and recognition)
Javadi et al. (2012) [25]	Left DLPFC	Anodal F3/Cathodal contra. SO Cathodal F3/Cathodal contra. SO Sham (no stimulation)	Online	3 min	1.5 mA	Target: 12.2 cm^2 Reference: 30.2 cm^2	Verbal memory	1) Left anodal: enhanced memory performance (accuracy) 1) Left cathodal: impaired memory performance (accuracy)
Jeon and Han (2012) [46]	Left DLPFC Right DLPFC	Anodal F3/Cathodal right SO Anodal F4/Cathodal left SO Sham (F3 or F4/SO)	Offline	20 min	1 mA	35 cm^2	Working memory Attention Executive functions (inhibition, mental flexibility)	1) Left anodal: enhanced performance (stroop, digit span backwards, K-BNT) 2) Right anodal: enhanced performance (stroop, visuospatial memory/ attention task)
Leite et al. (2012) [16]	Left/Right DLPFC	Anodal F3/Cathodal F4 Anodal F4/Cathodal F3 Sham (F3/F4)	Online	<30 min	2 mA	35 cm^2	Executive functions (mental flexibility)	1) Bilateral (left anodal/right cathodal): increased switching performance (letter-digit task), improved accuracy and decreased switching performance (vowel-consonant parity task) 2) Bilateral (left cathodal): increased accuracy (letter-digit task)
Maeoka et al. (2012) [39]	Left DLPFC	Anodal F3/Cathodal contra. SO Sham (F3/SO)	Offline	20 min	1 mA	35 cm^2	Emotion processing	1) Left anodal: decreased negative emotion (decreased unpleasantness subjective report)

Table 1 (*continued*)

Authors	Target region(s)	Montage	Timing of tDCS	Duration	Intensity	Electrode size	Cognitive domain	Cognitive effect[a,b]
Metuki et al. (2012) [54]	Left DLPFC	Anodal F3/Cathodal Fp2 Sham (F3/Fp2)	Online	11 min	1 mA	35 cm^2	Executive functions: Problem solving	1) Left anodal: increased performance (verbal insight task)
Minati et al. (2012) [70]	Left/Right DLPFC	Anodal F3/Cathodal F4 Anodal F4/Cathodal F3 Sham (F3/F4)	Online	20.5 ± 4.1 min	2 mA	N.S.	Decision making	1) Bilateral (left cathodal/ right anodal): no sign. effect on risk taking (Gambling Task) but enhanced response confidence
Mylius et al. (2012) [29]	Left DLPFC Right DLPFC	Anodal F3 or F4/ Cathodal contra SO Cathodal F3 or F4/ Anodal contra SO Sham (F3 or F4/ contra SO)	Online	20 min	2 mA	35 cm^2	Working memory Pain perception	1) Right anodal: increased tolerance to pain 2) Left cathodal: decreased number of outliers in 2-back task
Nitsche et al. (2012) [50]	Left DLPFC	Anodal F3/Cathodal contra. SO Cathodal F4/Anodal contra. SO Sham (F3/contra. SO)	Offline Online	10 min or 20 min	1 mA	35 cm^2	Emotion processing	1) Left anodal: enhanced positive emotion (positive emotion detection)
Sela et al. (2012) [65]	Left/Right DLPFC	Anodal F3/Cathodal F4 Cathodal F3/Anodal F4 Sham (F3/F4)	Offline	15 min	1.5 mA	35 cm^2	Language comprehension (semantic processing)	1) Bilateral (left anodal/ right cathodal): enhancement of performance (predictable idioms) 2) Bilateral (left cathodal/ right anodal): enhancement of performance (unpredictable idioms)
Vannorsdall et al. (2012) [18]	Left DLPFC	Anodal F3/Cathodal Cz Cathodal F3/Cathodal Cz Sham (F3 or F4/Cz)	Online	30 min	1 mA	27 cm^2	Verbal fluency	1) Left anodal: increased performance (category-cued) 2) Left cathodal: decreased performance (clustered words)
Asthana et al. (2013) [17]	Left DLPFC	Anodal F3/Ipsi. mastoid Cathodal F3/Ipsi. mastoid Sham (F3/mastoid)	Offline	12 min	1 mA	35 cm^2	Fear memory	1) Left cathodal: disrupted fear memory consolidation
Cattaneo et al. (2013) [51]	Left DLPFC	Anodal (between F3 and F5)/Cathodal contra. SO Sham (F3–F5/SO)	Offline	20 min	2 mA	35 cm^2	Emotion processing	1) Left anodal: enhancement of beauty experience
Fecteau et al. (2013) [66]	Left/Right DLPFC	Anodal F3/Cathodal F4 Anodal F4/Cathodal F3 Sham (F3/F4)	Offline	20 min	2 mA	35 cm^2	Decision making	1) Bilateral (left cathodal/ right anodal): enhanced the generation of untruthful answers 2) Bilateral (left anodal/ right cathodal): enhanced the generation of untruthful answers
Feeser et al. (2013) [35]	Right DLPFC	Anodal F4/Cathodal contra. SO Sham (F4/SO)	Online	20 min	1.5 mA	Anode: 35 cm^2 Cathode: 100 cm^2	Emotion regulation	1) Right anodal: enhancement of performance (down-regulation or upregulation of emotions)

(*continued on next page*)

Table 1 (*continued*)

Authors	Target region(s)	Montage	Timing of tDCS	Duration	Intensity	Electrode size	Cognitive domain	Cognitive effect[a,b]
Foerster et al. (2013) [59]	Left DLPFC	Anodal F3/Cathodal contra. SO Sham (F3/SO)	Online	13 min	2 mA	20 cm^2	Motor learning	1) Left anodal: enhanced motor learning (motor-imagery-induced learning)
Hoy et al. (2013) [47]	Left DLPFC	Anodal F3/Cathodal right SO Sham (F3/SO)	Offline	20 min	1 mA and 2 mA	35 cm^2	Working memory	1) Left anodal: enhanced performance (both 1 mA and 2 mA)
Iuculano and Cohen Kadosh (2013) [63]	Left/Right DLPFC	Anodal F3/Cathodal F4 Sham (F3/F4)	Online	20 min × 6 sessions	1 mA	3 cm^2	Learning and automaticity	1) Bilateral: impaired numerical learning but enhanced automaticity for learned materials
Javadi and Cheng (2013) [27]	Left DLPFC	Anodal F3/Cathodal contra. SO Cathodal F3/Cathodal contra. SO Sham (F3/SO)	Online	20 min	1.5 mA	Target: 12.2 cm^2 Reference: 30.2 cm^2	Long term memory	1) Left anodal: enhanced memory performance (recognition)
Kongthong et al. (2013) [23]	Left DLPFC	Cathodal F3/Anodal T6 Sham (F3/T6)	Offline	20 min	1 mA	25 cm^2	Visual semantic processes	1) Left cathodal: decreased performance (elimination of priming effect)
Manenti et al. (2013) [58]	Left/Right DLPFC	Anodal F3 or F4/Cathodal contra. SO Sham (F3 or F4/SO)	Online	6 min	1.5 mA	35 cm^2	Verbal episodic memory	1) Left and right anodal: increased memory performance in young subjects 2) Left anodal: increased memory performance in older subjects
Meiron and Lavidor (2013) [48]	Left DLPFC Right DLPFC	Anodal F3 or F4/Cathodal Cz Sham (F3/Cz)	Online	15 min	2 mA	Anode: 16 cm^2 Cathode: 35 cm^2	Working memory	1) Left anodal: improved performance (highest memory load males only) 2) Right anodal: improved performance (highest memory load females only)
Mengarelli et al. (2013) [32]	Left DLPFC Right DLPFC	Cathodal F3/Anodal contra SO Cathoal F4/Anodal contra SO Sham (F3 or F4/SO)	Online	15 min	1 mA	35 cm^2	Decision making	1) Left cathodal: reduced behavior-induced preference change
Motohashi et al. (2013) [60]	Left DLPFC	Anodal F3/Cathodal contra SO Sham (F3/SO)	Offline	20 min	1 mA	35 cm^2	Mood	1) Left anodal: no sign. effect on mood
Nozari et al. (2013) [67]	Left/Right DLPFC	Anodal F3/Cathodal F4 Sham (F3/F4)	Online	20 min	1.5 mA	25 cm^2	Attention Language	1) Bilateral (left anodal/right cathodal): increased performance (verbal task)
Plewnia et al. (2013) [40]	Left DLPFC	Anodal F3/Cathodal contra SO Sham (F3/SO)	Online	20 min	1 mA	35 cm^2	Executive functions	1) Left anodal: no sign. effect for whole group but decreased performance for COMT Met–Met
Tanoue et al. (2013) [34]	Right DLPFC	Cathodal F4/Anodal contra. cheek Sham (F4/contra. cheek)	Offline	10 min	1.5 mA	35 cm^2	Attention	1) Right cathodal: impairs internal attention
Vanderhasse et al. (2013) [49]	Left DLPFC	Anodal F3/Cathodal contra SO Sham (F3/SO)	Online	20 min	2 mA	35 cm^2	Working memory Emotion processing	1) Left anodal: enhanced performance (working memory of angry faces)

Table 1 (*continued*)

Authors	Target region(s)	Montage	Timing of tDCS	Duration	Intensity	Electrode size	Cognitive domain	Cognitive effect[a,b]
Vanderhasse et al. (2013) [49]	Left DLPFC	Anodal F3/Cathodal contra SO Sham (F3/SO)	Offline	20 min	2 mA	35 cm^2	Emotion processing	1) Left anodal: enhanced cognitive control for positive stimuli
Balconi et al. (2014) [30]	Left DLPFC	Cathodal F3/Anodal right SO Sham (F3/Right SO)	Offline	15 min	2 mA	35 cm^2	Semantic processing of actions	1) Left cathodal: modulated performance (reduced RTs to incorrect object use but increased errors rates)
Nelson et al. (2014) [72]	Right/Left DLPFC	Anodal F3/Cathodal F4 Cathodal F3/Anodal F4 Sham (F3/F4)	Online	10 min	1 mA	35 cm^2	Attention/ Vigilance	1) Bilateral (anodal left/ cathodal right and anodal right/ cathodal left): enhanced performance (detection task)

[a] Only main results were included in the present table.
[b] Presented results are restricted to the DLPFC. Results from an additional method of investigation (such as EEG) or an alternative region were not included.

usually large and often encompass multiple brain areas or networks, as they are most frequently acquired through stroke, ischemia, or traumatic brain injury. Secondly, and consequently, multiple functions are often altered simultaneously, inducing substantial variability in the nature and amplitude of the deficits observed in patients with relatively similar and overlapping lesions. Thirdly, patients often suffer from other medical conditions, either pre-existent or consequent to injury, further contributing to the heterogeneity of the studied population. Lastly, it is difficult to conduct a study with a large sample of patients with overlapping lesions, which has led to numerous case studies and findings that have been difficult to replicate [4].

The development of non-invasive neuromodulation methods in the early 1980's offered the promise to circumvent many of the methodological caveats associated with the "lesion method", allowing causal inference in the study of brain–behavior relationship in healthy populations. While repetitive transcranial magnetic stimulation (rTMS) was increasingly used in the mid 1990's to study the influence of so-called "virtual lesions" in different regions of the brain, interest in transcranial direct current stimulation (tDCS) emerged more recently. tDCS involves the induction of a constant low-amperage electric current (usually 1–2 mA) applied to the cortex via surface electrodes positioned on the scalp of the subject that can be used to probe and modulate cortical plasticity in the human cortex [5]. In standard protocols, the "active" electrode is positioned over the region of interest while the "reference" electrode is placed contralaterally over the homologous region or supraorbital area. The current flows from the positively charged anode toward the negatively charged cathode. The effect of tDCS on a specific region is partly determined by the polarity of the stimulation: cortical excitability is thought to be enhanced under the anode, and decreased under the cathode [6].

As with TMS protocols, initial studies using tDCS [6,7] investigated its effects on motor cortex, mainly because of the possibility to directly measure the increase or reduction of cortical excitability through TMS-induced motor evoked potentials (MEPs). Since tDCS was shown to be efficient in this regard, many studies began to report the impact of tDCS on other brain functions in healthy subjects, such as vision [8], language [9], and learning [10]. The investigation of the method's potential for the treatment of different neurological and psychiatric disorders, such as depression [11], stroke [12], and schizophrenia [13] has also recently arisen. In fact, over the past 16 years, over one thousand papers have been published on the use of tDCS on different brain functions. However, studies investigating the effect of tDCS on cognition have shown a lack of specificity and a relative inconsistency in both the modulatory effects and the choice of tDCS parameters, which has led to a large number of heterogenous results. For example, modulation of the dorsolateral prefrontal cortex (DLPFC), which is often chosen as target for tDCS because of its role in numerous high-order cognitive processes, has been associated with both an increase and a decrease in executive functions [14–16] and has been suggested to influence – among others – spatial memory [17], verbal fluency [18], risk taking [19] and craving [20].

Therefore, it remains to be determined to which extent tDCS can compensate for obvious limitations to the lesion method. For example, it is debatable whether tDCS can target specific behaviors associated with a given area when the physiologic impact of tDCS itself can vary considerably between subjects. Indeed, the effect of tDCS on a specific brain area will depend on a variety of factors including electrode montage and size, but also according to size and shape of the participant head and fat tissue amount, among others. As a result, the amount of current induced in a given brain area may vary considerably across individuals. Furthermore, the brain region and neuronal populations that underlie a specific cognitive function may also be subject to important variations. Finally, the effects of tDCS for a given brain region are state-dependent and the state of brain activity will differ for different cognitive functions (even if the same brain area is engaged in different functions).

Another, often overlooked issue arises from the fact that stimulation of a given area produces widespread modulation of brain activity, which in turn can affect multiple cognitive functions simultaneously. This can lead to an important problem of interpretation since the observed effect of stimulation could be due to the interaction of several parallel cognitive effects, which are sometimes in opposite directions. To better understand the challenges of interpretation of results of studies using tDCS to modulate dorsolateral prefrontal cortical functions, we undertook a systematic review of the literature. Care was taken to select and compare studies that target the same area and use similar electrode montages. The international 10-20 electrode system areas F3 and F4 were chosen, as they are the most commonly used in tDCS studies of the DLPFC.

Material and methods

A systematic review of the literature was performed using the following database: PubMed (2000 to Jan 2014) and Medline (2000 to Jan 2014). We used the following search keywords: "tDCS", "transcranial direct current stimulation", "prefrontal", "DLPFC", "cognition". We initially identified 202 articles corresponding to our search criteria. After carefully reviewing the abstract of the different papers, we identified 67 articles investigating only healthy subjects. Of these 67 publications, we selected the 63 articles using F3 and/or F4 as stimulation targets. Subsequently, we read through the full texts of the final sample of articles in order to gather the following information: location of stimulation; electrode montage; duration of stimulation; timing of stimulation and task; intensity; electrode size; cognitive domain; and results. We also looked through the references of the selected papers for additional relevant papers, which led to the inclusion of one additional paper. Studies were only included if they were published in English and described thoroughly their methodology. Studies that did not directly assess the impact of prefrontal tDCS on a cognitive task were also excluded, leading to the exclusion of two additional studies and a final sample of 61 publications.

An important issue that needs to be taken into consideration when comparing tDCS studies is the electrode montage and the use of terms such as 'cathodal stimulation' and 'anodal stimulation'. It is not possible to apply anodal or cathodal stimulation, as a second electrode is always needed to deliver current to the brain. It is therefore important to emphasize that the 'site of stimulation' is not simply the location of one electrode, but rather the combination of the anode and cathode. In the present review, a distinction was made between stimulation paradigms that place one electrode (cathode or anode) over the specific target area (F3 or F4) and the other over a 'reference' site (usually the supraorbital area) and those that place both electrodes over the target area bilaterally.

Results

Using the same site of stimulation (F3 and F4, or F3/F4 and reference site), results from the 61 publications suggest that tDCS applied over the prefrontal cortex can influence the performance of a wide range of cognitive functions. The results and description of the studies are shown in Table 1. Note that these results are restricted to the effects of DLPFC stimulation on cognitive tasks, even if a study investigated other regions or if other methods were used to quantify the effects of tDCS (i.e. EEG). In order to be succinct, only the main results of the different studies are reported. Non-significant results in supplementary tasks included in the paradigms are not reported. For a clearer understanding of the effects of different types of stimulation (target regions and polarity) on cognitive function, the results are divided into the seven different types of electrode montages that were used in the included articles.

1. **Cathode over left DLPFC, anode over reference site**. Was shown to *decrease*: a) working memory performance [21]; b) executive function performance (mental flexibility: [22]); c) verbal and semantic performance (visual priming effect: [23]; word fluency task: [18]); d) fear memory consolidation [17]; e) verbal memory performance [17,25–28]). Was shown to *increase*: a) working memory performance [29]; b) semantic processing performance [30,31]; c) executive functioning performance (planning: [15]). Was shown to *modulate*: a) decision making [32].
2. **Cathode over right DLPFC, anode over reference site**. Was shown to *decrease*: a) propensity to punish unfair behavior [33], b) executive function performance (impulsivity: [14]); c) attention control [34]. Was shown to *increase*: a) cognitive control during emotion regulation [35]; b) tolerance to heat pain [29]; c) executive functioning performance (planning: [15]).
3. **Anode over left DLPFC, cathode over reference site**. Was shown to *decrease*: a) working memory performance [36]; b) risk taking behaviors [37]; c) negative emotions perception [38,39]; d) categorization learning [28]); e) executive functioning performance only in a COMT Met–Met group (cognitive flexibility [40]). Was shown to *increase*: a) working memory performance [21,41–49]; b) positive emotion processing [49–51]; c) pain thresholds [52]; d) performance on verbal tasks (verbal; word retrieval: [53]; word fluency: [18]); e) executive function performance (mental flexibility: [22]; inhibition: [46]; problem solving: [24,54,55]; planning [15]); f) control of negative emotions [39,56]; g) memory performance and learning [25,27,57–59]. Showed *no significant effect* on: a) mood [60].
4. **Anode over right DLPFC, cathode over reference site**. Was shown to *decrease*: a) risk taking [37]; b) propensity to punish unfair behaviors [33]. Was shown to *increase*: a) working memory performance [48]; b) visuospatial memory [46]; c) executive functioning performance (inhibition: [46]); d) pain thresholds [29]; e) emotion regulation [35]; f) memory performance [58]. Showed *no significant effect* on: risk taking [61].
5. **Anode over left DLPFC, cathode over right DLPFC**. Was shown to *decrease*: a) working memory performance [62]; b) food consumption but not craving [20]; c) executive function performance (mental flexibility: [16]). Was shown to *increase*: a) aggressive behaviors and anger [64]; b) executive function performance (mental flexibility: [16]); c) language comprehension [65]; d) generation of untruthful answer [66]; e) attention and language performance [67]; f) automaticity for learned materials [65]. Was shown to *modulate*: a) responses to lies [68]; b) decision making [69].
6. **Cathode over left DLPFC, anode over right DLPFC**. Was shown to *increase*: a) executive function performance (mental flexibility: [16]); b) response confidence in a gambling task [70]; c) working memory performance [29]; d) generation of untruthful answers [66]; e) language comprehension [65]. Was shown to *decrease*: a) risk-taking behaviors [19,61]; b) food craving and consumption [20].
7. **Anode over left DLPFC, anode over right DLPFC**. Was shown to *increase*: a) lie responses [71]; b) attention and vigilance [72].

To summarize, tDCS intending to modulate activity of the same target region (DLPFC) can interfere with a wide range of cognitive functions, from relatively simple and low-level attentional processes, to complex, higher-order functions such as decision-making and working memory. The results also show that the effects of tDCS are highly variable and may be dependent upon the task and stimulation parameters, as illustrated in studies probing working memory function. For instance, working memory was shown to be enhanced by cathodal tDCS over the left DLPFC [29], anodal tDCS over the left DLPFC [21,41–49]; and anodal tDCS over the right DLPFC [48]. Working memory performance was also shown to be decreased by cathodal tDCS over the left DLPFC [21], anodal tDCS over the left DLPFC [36]; and tDCS over bilateral DLPFC (left anodal/right cathodal: [62]). In general, the present review shows that 1) studies probing the same cognitive function using similar tDCS protocols can lead to opposite results; 2) a specific tDCS protocol can induce cognitive effects over a wide variety of functions.

Discussion

The present review highlights the fact that tDCS over the prefrontal cortex can modify a wide range of behaviors from various domains. Due to the presence of many important variations in experimental protocols that have a similar aim (for example reducing excitability of the DLPFC to inhibit a specific cognitive function), it is difficult at this point in time to confidently point to a general pattern describing the effects of "prefrontal tDCS". This is further compounded by the fact that the physiological effects of tDCS themselves are highly variable and dependent upon a variety of individual characteristics.

Polarity

The highly variable effects of tDCS on cognition highlight the fact that the idea of a polarity-specific effect of tDCS, as described originally for the primary motor cortex, cannot be easily transposed to non-motor areas [73]. Theoretically, tDCS increases excitability in the area under the anode, thus facilitating performance on a specific task whereas the opposite effect would occur in the area under the cathode, inhibiting behavior by decreasing cortical excitability. However, the reality of tDCS effects on cognition is much more complex [74]. For example, many studies report a facilitatory effect associated with stimulation of areas under the cathode [74]. It has been suggested that this effect may be due to the reduction of noise in a specific network that enables facilitation of behavior [74]. Alternatively, it is possible that 'cathodal tDCS' inhibits a specific function, which would consequently enhance a specific behavior (e.g. faster reaction times).

In a recent study by Batsikadze and collaborators [75], 20 min of cathodal tDCS over the primary motor cortex (reference electrode over supraorbital area) was shown to produce an enhancement of corticospinal excitability instead of the expected inhibition when the intensity of the stimulation was doubled from 1 mA to 2 mA. This suggests that different stimulation parameters can directly affect the direction of tDCS-induced changes in cortical excitability. In the studies that were included in the present review, the intensity of stimulation ranged from 260 uA to 2 mA, stimulation duration varied from 3 min to 30 min and electrode size ranged from 8 mm diameter to 100 cm^2. This inconsistency in the choice of the parameters may contribute to the variable direction of the cognitive changes induced by prefrontal tDCS.

State-dependency

Out of the 61 articles presented in this review, 38 used a so-called "online" paradigm where the prefrontal cortex is modulated by tDCS during a specific task. Conversely, 23 studies applied tDCS before a specific task ("offline" paradigm). Both methods are thought to rely on partially distinct mechanisms, which could contribute to the apparent discrepancies among results [76]. Indeed, "offline" stimulation has been suggested to rely on modification of neuronal activity that lasts beyond the period of stimulation, whereas "online" stimulation is believed to modulate a specific network that is involved in the task [76].

Unlike TMS, tDCS does not induce a direct depolarization of neurons but rather is thought to modulate the membrane permeability of neurons leading to a change in the neuronal firing rate [77]. Therefore, theoretically, tDCS should induce a depolarization of the neurons that are the closest to firing, but that would not have necessarily fired otherwise. In an "online" paradigm, the targeted neuronal populations are already prone to discharge, given that they are presumably part of a neural network thought to be involved in the cognitive task under study [78]. Hence, the effects of prefrontal tDCS are highly dependent on the state of the underlying targeted network, a principle known as "state-dependency" [76,79,80]. In other words, any tDCS-induced activity occurs in the context of a baseline neural activity or a specific state [81]. This state-dependent effect of neuromodulation on the motor region has been taken into consideration from the very first motor studies because the level of cortical excitability is measured before and after the stimulation via MEPs. However, this is more challenging to achieve when studying cognitive functions because many factors can influence the initial state of a neuronal network, such as the level of fatigue, knowledge of the task, pre-existent network connectivity, etc. [80]. For example, a recent meta-analysis showed that "cathodal tDCS" has a very minor effect on language function, which could be explained by the strongly connected brain networks [74]. In other words, because of the high intensity of the firing rate of these strongly interconnected neurons, the current induced by tDCS might not be strong enough to significantly modulate network activity and induce behavioral changes. A further example can be drawn from a tDCS study on motor cortex where the induction of motor imagery during the application of stimulation abolished the excitatory effect of anodal tDCS [82]. In this case, the neurons are already depolarized, which constrains the excitatory effects of the stimulation, possibly by engaging metaplasticity mechanisms.

If the effect of tDCS is dependent on the state of the networks, it must thus also be dependent on the specific task the subjects are engaged in. As a result, the targeted cognitive function has a higher probability of being modulated, and online and offline tDCS protocol would be expected to lead to different results. Similarly, the instructions given to study participants prior to the tDCS would be predicted to exert significant effects onto the results, and thus need to be scripted and controlled with care. Further investigation and leveraging of the "state-dependent" effect could benefit tDCS prefrontal studies in order to better specify the effects of stimulation of a targeted network or function. To date, very few studies have taken this important factor into consideration: within the articles included in the present review, only five mentioned the impact of state-dependency.

Inter-subject variations

Two recent large-scale prospective studies evaluated the inter-subject variation of tDCS effects on primary motor cortex excitability and showed high variability in the participants' response to stimulation [5,83]. Results from Lopez-Alonso and colleagues [5] showed that only 45% of participants respond to "anodal tDCS" over the target area. Similarly, Wiethoff and colleagues [83] showed a response ratio of 74:26 (facilitation: inhibition) after anodal stimulation of the target area and a ratio of 60:40 (facilitation: inhibition) after cathodal stimulation of the target area. As mentioned previously, there exists a large number of *stimulation* parameters that can modulate the physiologic response to tDCS. Chief among them are electrode size, stimulation duration and stimulation intensity. As can be seen from Table 1, these parameters vary widely between studies and considerably limit the generalizability and comparison of results between studies. Similarly, *participant* characteristics are also important factors that contribute to the variability observed in tDCS studies of prefrontal cortex. Participant head size and shape, as well as amount of fat tissue and fiber orientation all contribute to the physiologic effects of tDCS. When taken together, the presence of these confounding factors strongly suggest that the level of induced current in a specific brain area can vary quite extensively. It is therefore not surprising that the behavioral response to prefrontal tDCS is also subject to large hetererogeneity. All of these factors are compounded by the fact that sample sizes are often relatively small in tDCS studies of prefrontal cortex. A study of cathodal and anodal effects on motor cortex excitability suggested that based on acquired data in healthy individuals, a minimum of 87 participants per group would be needed to achieve a sufficient level of power and confidence to detect a significant difference between patients and healthy subjects [83]. Although this seems to be an extreme case, it should be noted that the mean sample size for the studies included in the present review was only 21 participants.

Conclusion

When using tDCS over the DLPFC with a specific set of parameters, it is possible to modulate a specific cognitive function. However, as highlighted in this review, a given stimulation protocol may simultaneously modulate various other cognitive functions in similar or opposite directions (i.e. facilitation or inhibition). This implies that any effect of prefrontal tDCS on a given task is probably associated with the extensive modulation of a wide range of *multiple* cognitive functions. This, in turn, makes it hard to attribute an observed effect on a specific task to a single mechanism, at least with traditional stimulation protocols. When differing participant characteristics, stimulation parameters and state-dependency effects are also taken into consideration, it becomes clear that more neurobiologic insights of the effects of tDCS are needed to properly interpret the results of studies and appropriately conclude brain-behavior relations.

In conclusion, refined protocols that take into account the numerous caveats associated with tDCS and a better standardization of stimulation protocols are needed to improve study quality. One possible way to reduce uncertainty is to monitor the brain impact of tDCS separately and independently of behavioral and cognitive effects. Techniques such as EEG (e.g. Ref. [84]), TMS-EEG (e.g. Ref. [85]), magnetic resonance spectroscopy (e.g. Ref. [86]), functional magnetic resonance imaging (e.g. Ref. [87]) and modeling of induced currents (e.g. Ref. [88]) have all been shown to be effective in characterizing the physiologic effects of tDCS. Relating behavioral and cognitive effects to the measured brain impact (induced current, physiologic effect) would offer a significant advance for the interpretation of tDCS data.

References

[1] Cubelli R, De Bastiani P. 150 years after Leborgne: why is Paul Broca so important in the history of neuropsychology? Cortex 2011;47:146–7.
[2] Broca P. Sur le siège de la faculté du langage articulé. Bull De La Societe D'Anthropologie De Paris 1865;6:377–93.
[3] Newcombe F. Missile wounds of the brain: a study of psychological deficits. Oxford University Press; 1969.
[4] Koenigs M, Tranel D, Damasio AR. The lesion method in cognitive neuroscience. In: Handbook of Psychophysiology. Cambridge University Press; 2007.
[5] López-Alonso V, Cheeran B, Río-Rodríguez D, Fernández-del-Olmo M. Inter-individual variability in response to non-invasive brain stimulation paradigms. Brain Stimul 2014;7:372–80.
[6] Nitsche MA, Paulus W. Excitability changes induced in the human motor cortex by weak transcranial direct current stimulation. J Physiol 2000;527:633–9.
[7] Priori A, Berardelli A, Rona S, Accornero N, Manfredi M. Polarization of the human motor cortex through the scalp. Neuroreport 1998;9:2257–60.
[8] Antal A, Kincses TZ, Nitsche MA, Paulus W. Modulation of moving phosphene thresholds by transcranial direct current stimulation of V1 in human. Neuropsychologia 2003;41:1802–7.
[9] Floel A, Rösser N, Michka O, Knecht S, Breitenstein C. Noninvasive brain stimulation improves language learning. J Cogn Neurosci 2008;20:1415–22.
[10] Kincses TZ, Antal A, Nitsche MA, Bártfai O, Paulus W. Facilitation of probabilistic classification learning by transcranial direct current stimulation of the prefrontal cortex in the human. Neuropsychologia 2004;42:113–7.
[11] Nitsche MA. Transcranial direct current stimulation: a new treatment for depression? Bipolar Disord 2002;4(Suppl. 1):98–9.
[12] Fregni F, Boggio PS, Mansur CG, et al. Transcranial direct current stimulation of the unaffected hemisphere in stroke patients. Neuroreport 2005;16:1551–5.
[13] Tranulis C, Sepehry AA, Galinowski A, Stip E. Should we treat auditory hallucinations with repetitive transcranial magnetic stimulation? A metaanalysis. Can J Psychiatry 2008;53:577–86.
[14] Beeli G, Casutt G, Baumgartner T, Jäncke L. Modulating presence and impulsiveness by external stimulation of the brain. Behav Brain Funct 2008;4:33.
[15] Dockery CA, Hueckel-Weng R, Birbaumer N, Plewnia C. Enhancement of planning ability by transcranial direct current stimulation. J Neurosci 2009;29:7271–7.
[16] Leite J, Carvalho S, Fregni F, Boggio PS, Gonçalves OF. The effects of cross-hemispheric dorsolateral prefrontal cortex transcranial direct current stimulation (tDCS) on task switching. Brain Stimul 2012;5:231–4.
[17] Asthana M, Nueckel K, Mühlberger A, et al. Effects of transcranial direct current stimulation on consolidation of fear memory. Front Psychiatry 2013;4:1–7.
[18] Vannorsdall TD, Schretlen DJ, Andrejczuk M, et al. Altering automatic verbal processes with transcranial direct current stimulation. Front Psychiatry 2012;3:73.
[19] Fecteau S, Knoch D, Fregni F, Sultani N, Boggio P, Pascual-Leone A. Diminishing risk-taking behavior by modulating activity in the prefrontal cortex: a direct current stimulation study. J Neurosci 2007;27:12500–5.
[20] Fregni F, Orsati F, Pedrosa W, et al. Transcranial direct current stimulation of the prefrontal cortex modulates the desire for specific foods. Appetite 2008;51:34–41.
[21] Zaehle T, Sandmann P, Thorne JD, Jäncke L, Herrmann CS. Transcranial direct current stimulation of the prefrontal cortex modulates working memory performance: combined behavioural and electrophysiological evidence. BMC Neurosci 2011;12:2.
[22] Leite J, Carvalho S, Fregni F, Gonçalves OF. Task-specific effects of tDCS-induced cortical excitability changes on cognitive and motor sequence set shifting performance. PLoS One 2011;6:e24140.
[23] Kongthong N, Minami T, Nakauchi S. Semantic processing in subliminal face stimuli: an EEG and tDCS study. Neurosci Lett 2013;544:141–6.
[24] Elmer S, Burkard M, Renz B, Meyer M, Jäncke L. Direct current induced short-term modulation of the left dorsolateral prefrontal cortex while learning auditory presented nouns. Behav Brain Funct 2009;5:29.
[25] Javadi AH, Cheng P, Walsh V. Short duration transcranial direct current stimulation (tDCS) modulates verbal memory. Brain Stimul 2012;5:468–74.
[26] Hammer A, Mohammadi B, Schmicker M, Saliger S, Münte TF. Errorless and errorful learning modulated by transcranial direct current stimulation. BMC Neurosci 2011;12:72.
[27] Javadi AH, Cheng P. Transcranial direct current stimulation (tDCS) enhances reconsolidation of long-term memory. Brain Stimul 2013;6:668–74.
[28] Ambrus GZG, Zimmer M, Kincses ZT, et al. Neuropsychologia 2011;49:1974–80.
[29] Mylius V, Jung M, Menzler K, et al. Effects of transcranial direct current stimulation on pain perception and working memory. Eur J Pain 2012;16:974–82.
[30] Balconi M, Vitaloni S. Dorsolateral pFC and the representation of the incorrect use of an object: the transcranial direct current stimulation effect on N400 for visual and linguistic stimuli. J Cogn Neurosci 2014;26:305–18.
[31] Balconi M, Vitaloni S. The tDCS effect on alpha brain oscillation of correct vs. incorrect object use: the contribution of the left DLPFC. Neurosci Lett 2012;517:25–9.
[32] Mengarelli F, Spoglianti S, Avenanti A, di Pellegrino G. Cathodal tDCS over the left prefrontal cortex diminishes choice-induced preference change. Cereb Cortex 2013. http://dx.doi.org/10.1093/cercor/bht314.
[33] Knoch D, Nitsche MA, Fischbacher U, Eisenegger C, Pascual-Leone A, Fehr E. Studying the neurobiology of social interaction with transcranial direct current stimulation-the example of punishing unfairness. Cereb Cortex 2008;18:1987–90.
[34] Tanoue RT, Jones KT, Peterson DJ, Berryhill ME. Differential frontal incolvement in shifts of internal and perceptual attention. Brain Stimul 2013;6:675–82.
[35] Feeser M, Prehn K, Kazzer P, Mungee A, Bajbouj M. Transcranial direct current stimulation enhances cognitive control during emotion regulation. Brain Stimul 2013;7:105–12.
[36] Fregni F, Boggio PS, Nitsche M, et al. Anodal transcranial direct current stimulation of prefrontal cortex enhances working memory. Exp Brain Res 2005;166:23–30.
[37] Beeli G, Koeneke S, Gasser K, Jäncke L. Brain stimulation modulates driving behavior. Behav Brain Funct 2008;4:34.
[38] Boggio PS, Zaghi S, Fregni F. Modulation of emotions associated with images of human pain using anodal transcranial direct current stimulation (tDCS). Neuropsychologia 2009;47:212–7.
[39] Maeoka H, Matsuo A, Hiyamizu M, Morioka S, Ando H. Influence of transcranial direct current stimulation of the dorsolateral prefrontal cortex on pain related emotions: a study using electroencephalographic power spectrum analysis. Neurosci Lett 2012;512:12–6.
[40] Plewnia C, Zwissler B, Längst I, Maurer B, Giel K, Krüger R. Effects of transcranial direct current stimulation (tDCS) on executive functions: influence of COMT Val/Met polymorphism. Cortex 2013;49:1801–7.
[41] Ohn SH, Park CI, Yoo WK, et al. Time-dependent effect of transcranial direct current stimulation on the enhancement of working memory. Neuroreport 2008;19:43–7.
[42] Mulquiney PG, Hoy KE, Daskalakis ZJ, Fitzgerald PB. Improving working memory: exploring the effect of transcranial random noise stimulation and transcranial direct current stimulation on the dorsolateral prefrontal cortex. Clin Neurophysiol 2011;122:2384–9.
[43] Teo F, Hoy KE, Daskalakis ZJ, Fitzgerald PB. Investigating the role of current strength in tDCS modulation of working memory performance in healthy controls. Front Psychiatry 2011;2:45.

[44] Andrews SC, Hoy KE, Enticott PG, Daskalakis ZJ, Fitzgerald PB. Improving working memory: the effect of combining cognitive activity and anodal transcranial direct current stimulation to the left dorsolateral prefrontal cortex. Brain Stimul 2011;4:84–9.
[45] Gladwin TE, den Uyl TE, Wiers RW. Anodal tDCS of dorsolateral prefrontal cortex during an implicit association test. Neurosci Lett 2012;517:82–6.
[46] Jeon SY, Han SJ. Improvement of the working memory and naming by transcranial direct current stimulation. Ann Rehabil Med 2012;36:585.
[47] Hoy KE, Emonson MRL, Arnold SL, Thomson RH, Daskalakis ZJ, Fitzgerald PB. Testing the limits: Investigating the effect of tDCS dose on working memory enhancement in healthy controls. Neuropsychologia 2013;51:1777–84.
[48] Meiron O, Lavidor M. Unilateral prefrontal direct current stimulation effects are modulated by working memory load and gender. Brain Stimul 2013;6:440–7.
[49] Vanderhasselt M-A, De Raedt R, Brunoni AR, et al. tDCS over the left prefrontal cortex enhances cognitive control for positive affective stimuli. PLoS One 2013;8:e62219.
[50] Nitsche MA, Koschack J, Pohlers H, Hullemann S, Paulus W, Happe S. Effects of frontal transcranial direct current stimulation on emotional state and processing in healthy humans. Front Psychiatry 2012;3(58):1–10.
[51] Cattaneo Z, Lega C, Flexas A, Nadal M, Munar E, Cela-Conde CJ. The world can look better: enhancing beauty experience with brain stimulation. Soc Cogn Affect Neurosci 2013:1–10.
[52] Boggio PS, Zaghi S, Lopes M, Fregni F. Modulatory effects of anodal transcranial direct current stimulation on perception and pain thresholds in healthy volunteers. Eur J Neurol 2008;15:1124–30.
[53] Fertonani A, Rosini S, Cotelli M, Rossini PM, Miniussi C. Naming facilitation induced by transcranial direct current stimulation. Behav Brain Res 2010;208:311–8.
[54] Metuki N, Sela T, Lavidor M. Enhancing cognitive control components of insight problems solving by anodal tDCS of the left dorsolateral prefrontal cortex. Brain Stimul 2012;5:110–5.
[55] Cerruti C, Schlaug G. Anodal transcranial direct current stimulation of the prefrontal cortex enhances complex verbal associative thought. J Cogn Neurosci 2009;21:1980–7.
[56] Peña-Gómez C, Vidal-Piñeiro D, Clemente IC, Pascual-Leone A, Bartrés-Faz D. Down-regulation of negative emotional processing by transcranial direct current stimulation: effects of personality characteristics. PLoS One 2011;6:e22812.
[57] Javadi AH, Walsh V. Transcranial direct current stimulation (tDCS) of the left dorsolateral prefrontal cortex modulates declarative memory. Brain Stimul 2012;5:231–41.
[58] Manenti R, Brambilla M, Petesi M, Ferrari C, Cotelli M. Enhancing verbal episodic memory in older and young subjects after non-invasive brain stimulation. Front Aging Neurosci 2013;5:49.
[59] Foerster A, Rocha S, Wiesiolek C, et al. Site-specific effects of mental practice combined with transcranial direct current stimulation on motor learning. Eur J Neurosci 2013;37:786–94.
[60] Motohashi N, Yamaguchi M, Fujii T, Kitahara Y. Mood and cognitive function following repeated transcranial direct current stimulation in healthy volunteers: a preliminary report. Neurosci Res 2013;77:64–9.
[61] Fecteau S, Pascual-Leone A, Zald DH, et al. Activation of prefrontal cortex by transcranial direct current stimulation reduces appetite for risk during ambiguous decision making. J Neurosci 2007;27:6212–8.
[62] Marshall L, Mölle M, Siebner HR, Born J. Bifrontal transcranial direct current stimulation slows reaction time in a working memory task. BMC Neurosci 2005;6:23.
[63] Iuculano T, Cohen Kadosh R. The mental cost of cognitive enhancement. J Neurosci 2013;33:4482–6.
[64] Hortensius R, Schutter DJ, Harmon-Jones E. When anger leads to aggression: induction of relative left frontal cortical activity with transcranial direct current stimulation increases the anger-aggression relationship. Soc Cogn Affect Neurosci 2012;7:342–7.
[65] Sela T, Ivry RB, Lavidor M. Prefrontal control during semantic decision task that involves idiom comprehension: a transcranial direct current stimulation study. Neuropsychologia 2012;50:2271–80.
[66] Fecteau S, Boggio P, Fregni F, Pascual-Leone A. Modulation of untruthful responses with non-invasive brain stimulation. Front Psychiatry 2013;3:1–9.
[67] Nozari N, Thompson-Schill SL. More attention when speaking: does it help or does it hurt? Neuropsychologia 2013;51:2770–80.
[68] Mameli F, Mrakic-Sposta S, Vergari M, et al. Dorsolateral prefrontal cortex specifically processes general – but not personal – knowledge deception: multiple brain networks for lying. Behav Brain Res 2010;211:164–8.
[69] Hecht D, Walsh V, Lavidor M. Transcranial direct current stimulation facilitates decision making in a probabilistic guessing task. J Neurosci 2010;30:4241–5.
[70] Minati L, Campanhã C, Critchley HD, Boggio PS. Effects of transcranial direct-current stimulation (tDCS) of the dorsolateral prefrontal cortex (DLPFC) during a mixed-gambling risky decision-making task. Cogn Neurosci 2012;3:80–8.
[71] Priori A, Mameli F, Cogiamanian F, et al. Lie-specific involvement of dorsolateral prefrontal cortex in deception. Cereb Cortex 2008;18:451–5.
[72] Nelson JT, McKinley RA, Golob EJ, Warm JS, Parasuraman R. Enhancing vigilance in operators with prefrontal cortex transcranial direct current stimulation (tDCS). Neuroimage 2014;85:909–17.
[73] Nitsche MA, Cohen LG, Wassermann EM, et al. Transcranial direct current stimulation: state of the art 2008. Brain Stimul 2008;1:206–23.
[74] Jacobson L, Koslowsky M, Lavidor M. tDCS polarity effects in motor and cognitive domains: a meta-analytical review. Exp Brain Res 2011;216:1–10.
[75] Batsikadze G, Moliadze V, Paulus W, Kuo MF, Nitsche MA. Partially non-linear stimulation intensity-dependent effects of direct current stimulation on motor cortex excitability in humans. J Physiol 2013;59:1987–2000.
[76] Miniussi C, Harris JA, Ruzzoli M. Modelling non-invasive brain stimulation in cognitive neuroscience. Neurosci Biobehav Rev 2013;37:1702–12.
[77] Liebetanz D, Nitsche MA, Tergau F, Paulus W. Pharmacological approach to the mechanisms of transcranial DC-stimulation-induced after-effects of human motor cortex excitability. Brain 2002;125:2238–47.
[78] Miniussi C, Ruzzoli M. Transcranial stimulation and cognition. 1st ed. Elsevier B.V.; 2013.
[79] Weigand A, Richtermeier A, Feeser M, et al. State-dependent effects of prefrontal repetitive transcranial magnetic stimulation on emotional working memory. Brain Stimul 2013;6:905–12.
[80] Silvanto J, Muggleton N, Walsh V. State-dependency in brain stimulation studies of perception and cognition. Trends Cogn Sci 2008;12:447–54.
[81] Silvanto J, Pascual-Leone A. State-dependency of transcranial magnetic stimulation. Brain Topogr 2008;21:1–10.
[82] Quartarone A, Morgante F, Bagnato S, et al. Long lasting effects of transcranial direct current stimulation on motor imagery. Neuroreport 2004;15:1287–91.
[83] Wiethoff S, Hamada M, Rothwell JC. Variability in response to transcranial direct current stimulation of the motor cortex. Brain Stimul 2014;7:468–75.
[84] Keeser D, Padberg F, Reisinger E, et al. Prefrontal direct current stimulation modulates resting EEG and event-related potentials in healthy subjects: a standardized low resolution tomography (sLORETA) study. Neuroimage 2011;55:644–57.
[85] Romero Lauro LJ, Rosanova M, Mattavelli G, et al. TDCS increases cortical excitability: direct evidence from TMS-EEG. Cortex 2014;58C:99–111.
[86] Stagg CJ, Best JG, Stephenson MC, et al. Polarity-sensitive modulation of cortical neurotransmitters by transcranial stimulation. J Neurosci 2009;29:5202–6.
[87] Weber MJ, Messing SB, Rao H, Detre JA, Thompson-Schill SL. Prefrontal transcranial direct current stimulation alters activation and connectivity in cortical and subcortical reward systems: a tDCS-fMRI study. Hum Brain Mapp 2014;35:3673–86.
[88] Truong DQ, Magerowski G, Blackburn GL, Bikson M, Alonso-Alonso M. Computational modeling of transcranial direct current stimulation (tDCS) in obesity: Impact of head fat and dose guidelines. Neuroimage Clin 2013;2:759–66.