Clinical Neurology and Neurosurgery 220 (2022) 107345

Contents lists available at ScienceDirect

Clinical Neurology and Neurosurgery

journal homepage: www.elsevier.com/locate/clineuro

Middle cerebral artery blood flow stability in response to high-definition transcranial electrical stimulation: A randomized sham-controlled clinical trial

Luiz H.S. Stefano [a], Diandra B. Favoretto [a], Diego C. Nascimento [b,c], Luan R.A. Santos [a], Francisco Louzada [c], Marom Bikson [d], Joao P. Leite [a], Octavio M. Pontes-Neto [a], Dylan J. Edwards [e,f], Taiza G.S. Edwards [a,*]

[a] Department of Neurosciences and Behavioral Sciences, Ribeirao Preto Medical School, University of Sao Paulo, Ribeirao Preto, SP, Brazil
[b] Departamento de Matemática, Faculdad de Ingeniería, Universidad de Atacama, Copiapó, Chile
[c] Institute of Mathematical Science and Computing, University of Sao Paulo, Sao Carlos, Brazil
[d] Neural Engineering Laboratory, Department of Biomedical Engineering, The City College, City University of New York, New York, NY, USA
[e] Moss Rehabilitation Research Institute, Thomas Jefferson University, PA, USA
[f] Exercise Medicine Research Institute, School of Medical and Health Sciences, Edith Cowan University, Joondalup, Australia

ARTICLE INFO

Keywords:
High-definition transcranial electric stimulation
Transcranial doppler
Hemodynamic response
Safety

ABSTRACT

Since neuronal activity is coupled with neurovascular activity, we aimed to analyze the cerebral blood flow hemodynamics during and following high-definition transcranial direct current stimulation (HD-tDCS). We assessed the mean middle cerebral artery blood flow velocity (MCA-BFv) bilaterally using transcranial doppler ultrasound, during and after HD-tDCS, in eleven right-handed healthy adult participants (6 women, 5 men; mean age 31 ± 5.6 years old), with no evidence of brain or cardiovascular dysfunction. The HD-tDCS electrode montage was centered over the right temporo-parietal junction. The stimulation protocol comprised 3 blocks of 2 min at each current intensity (1, 2, and 3 mA) and an inter-stimulus interval of 5 min between blocks. Participants received three electrical stimulation conditions (anode center, cathode center, and sham) on three different days, with an interval of at least 24 h. Stimulation was well tolerated across HD-tDCS conditions tested, and the volunteers reported no significant discomfort related to stimulation. There was no significant difference in the right or the left MCA-BFv during or after the stimulation protocol across all stimulation conditions. We conclude that at a range of intensities, vascular reaction assessed using middle cerebral artery blood flow is not significantly altered during or after HD-tDCS both locally and remotely, which provides further evidence for the safety of HD-tDCS.

1. Introduction

High-definition transcranial direct current stimulation (HD-tDCS) is an emergent experimental treatment option in psychiatry and neurology [1,2]. There has been a focus on HD-tDCS behavioral, imaging, and electrophysiological effects, yet there is a dearth of literature on hemodynamic effects of the main cerebral arteries, which may be particularly important in applications of cerebrovascular disease [3,4].

More than half of patients after stroke experience visual vertical (VV) disorder, for which there is no present established treatment [5–7]. Typically, patients with VV disorder do not complain about their abnormal sense being undetected unless appropriately assessed [5]. While still overlooked in some neurological settings, VV disorder is known to strongly impact functional recovery after stroke [5,7,8]. The most severe expression of VV disorder is termed “pusher syndrome’ or ”lateropulsion”. It is a severe body tilt associated with pushing behavior and resistance to any external attempt to correct the patient’s body to the true vertical position [7,9–11]. The resolution of VV disorder is

Abbreviations: HD-tDCS, High-definition transcranial direct current stimulation; TPJ, temporo-parietal junction; MCA-BFv, middle cerebral artery blood flow velocity; TCD, transcranial doppler ultrasound.

* Correspondence to: Department of Neurosciences and Behavioral Sciences, Ribeirao Preto Medical School, University of Sao Paulo, Ribeirão Preto, CEP 14049-900 SP, Brazil.

E-mail address: taiza@fmrp.usp.br (T.G.S. Edwards).

https://doi.org/10.1016/j.clineuro.2022.107345
Received 13 May 2022; Received in revised form 11 June 2022; Accepted 16 June 2022
Available online 20 June 2022

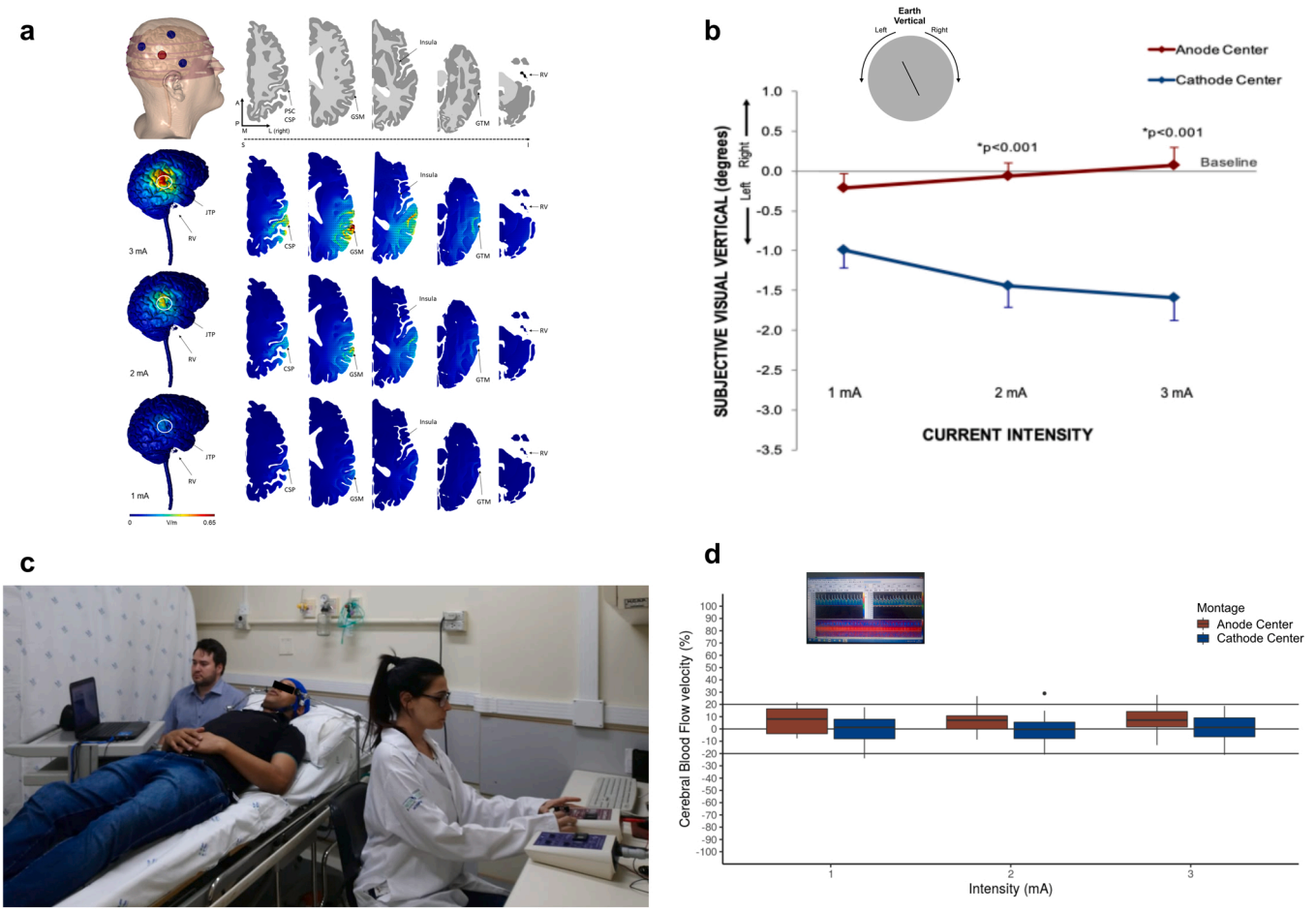

Fig. 1. : High-definition transcranial electrical stimulation (HD-tDCS) protocol that induced sustained behavioral effects did not induce a significant vascular response. a: Finite element models of tDCS using the 3 × 1 HD-tDCS electrode montage over TPJ predicted the induced electric field on the brain; previously published by Santos et al. [22]. b: Difference between the visual vertical perception assessed at baseline and 2 min after the end of HD-tDCS with current intensities of 1, 2, and 3 mA (mean; S.E.M.). There were intensity and polarity-specific effects only after the cathode center HD-tDCS condition. Inset represents the line inside the bucket used to assess visual vertical perception from the participant's perspective. The arrows illustrate the side of the bucket's rotation; previously published by Santos et al. [22]. c: Experimental setup of the cerebral hemodynamics trial. d: Difference between the middle cerebral artery blood flow velocity (MCA-BFv, expressed as a percentage) assessed at baseline and 2 min after the end of stimulation of HD-tDCS with current intensities of 1, 2, and 3 mA, showing no significant change. Inset represents a sample of transcranial doppler data (picture of the monitor) during the HD-tDCS at 3 mA. (a and b: Images under Open Access and Creative Commons Attribution License). Written informed consent was obtained from the participants to publish this image.

associated with better functional outcomes [7,8,12,13]. Neuroanatomical studies indicate several cortical areas associated with verticality disorder, including insula [9,14–16], postcentral gyrus [14,16], inferior frontal gyrus [9,16,17], parietal cortex [9,14,17,18], superior and middle temporal gyrus [9,16,17,19], and the temporo-parietal junction (TPJ) [20,21].

Targeting the TPJ, we have developed a non-invasive neuromodulation method that can exert a powerful, sustained direction-specific manipulation on visual vertical perception and postural control using HD-tDCS in neurotypical and post-stroke subjects [22,23]. However, to establish an effective and safe therapeutic strategy for stroke patients using HD-tDCS, it is critical to determine hemodynamic effects on main cerebral arteries.

Most recently, the need to investigate the hemodynamic effects of non-invasive transcranial electric neuromodulation on the main cerebral arteries using transcranial doppler ultrasound (TCD) was highlighted [3,4]. Changes in middle cerebral artery blood flow velocity were described after different transcranial electric and magnetic neuromodulation protocols [23–28] (for review, see [3,4]). However, no study described the hemodynamic effects of HD-tDCS on the main cerebral arteries.

Therefore, we sought to evaluate for the first time if cerebral blood flow might change in the middle cerebral artery using an HD-tDCS montage involving a central cathode and surrounding anode electrodes where we previously demonstrated behavior effects. We reasoned that understanding potential main cerebral artery blood flow changes would be relevant to implementing our stimulation protocol in cerebrovascular disorders. We conducted a clinical trial using the range of our stimulation parameters typically applied and systematically evaluated during and after stimulation effects. We hypothesized that middle cerebral artery cerebral blood flow would increase associated with stimulation, either due to a direct effect on the blood vessel or secondary to the increase in neuronal activity, and that protocol would be well tolerated.

2. Methods

In a randomized, sham-controlled, double-blind, crossover design, we studied eleven right-handed healthy adult participants (6 women; mean 31 ± 5.6 years old) with no brain or cardiovascular dysfunction evidence.

This study was conducted according to the Helsinki Declaration requirements for human investigation and approved by the local ethics committee. All participants provided written informed consent.

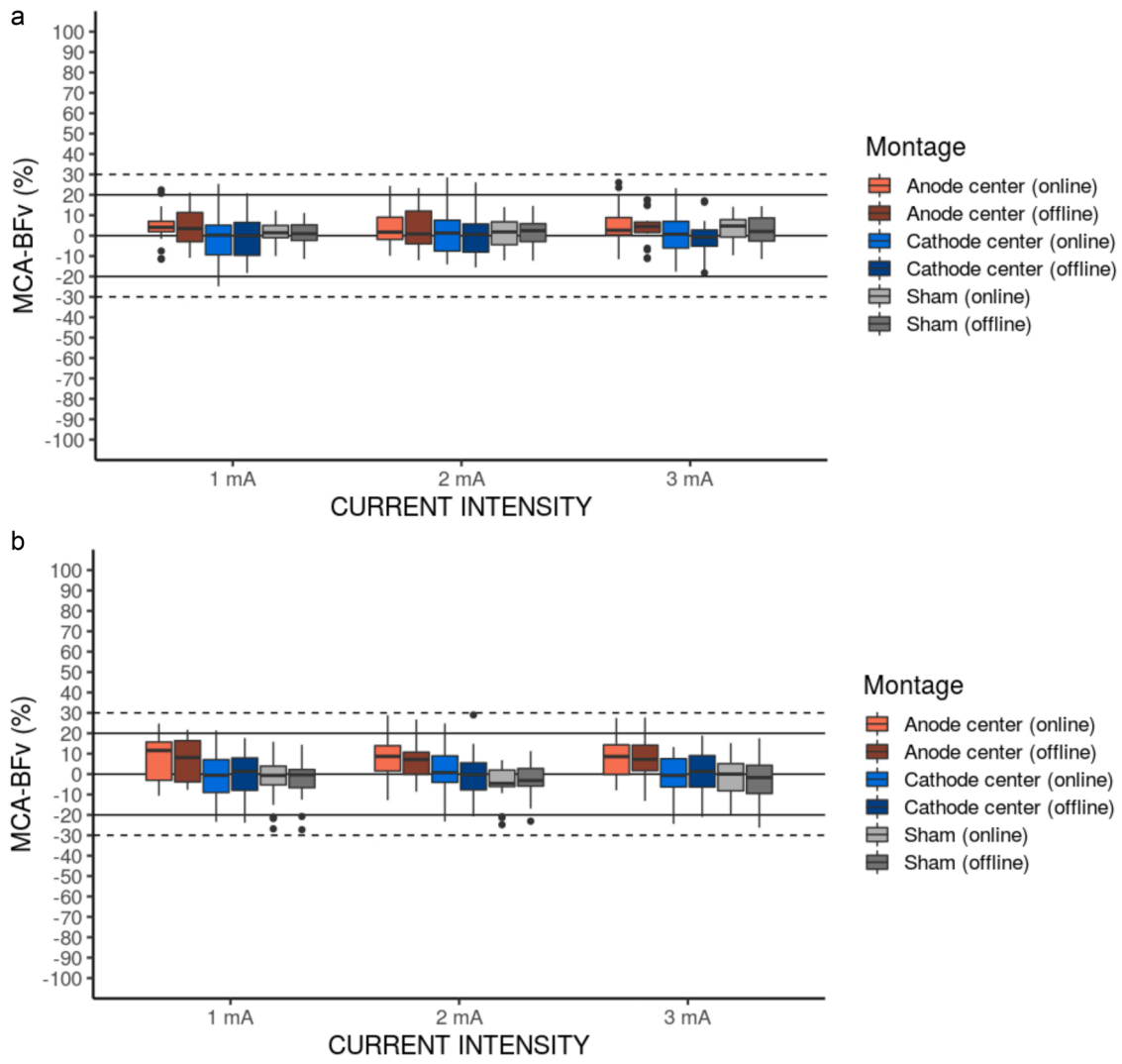

Fig. 2. : Right (upper graph) and left (lower graph) middle cerebral artery blood flow velocity (MCA-BFv); expressed by the difference from baseline as percentage) showing no significant changes during (2 min of stimulation) and after (5 min following stimulation) 1, 2, and 3 mA HD-tDCS over the right temporo-parietal junction.

2.1. Stimulation Protocol

The HD-tDCS (Soterix Medical, New York, USA) was placed over the right TPJ region and composed of four electrical stimulation electrodes; the single-center electrode was placed on the right hemisphere in the circumcenter of a triangle with vertices on the 10–20 electroencephalogram (EEG) system [27] coordinates C4, T4, P4. The three surrounding electrodes were placed over C4, T4, and P4. The same position of the electrodes was used during the sham condition. The stimulation protocol comprised 3 blocks of 2 min at each current intensity (1, 2, and 3 mA), and an inter-stimulus interval of 5 min between blocks. The approximate total duration of each session was 120 min. Participants received three electrical stimulation conditions (anode center, cathode center, and sham) on three different days, with an interval of at least 24 h.

Block randomization was used for HD-tDCS conditions (anode center, cathode center, and sham) and current intensity (1, 2, and 3 mA). Simple balanced randomization was used to determine the sham condition (anode or cathode center). A detailed description of the protocol can be found elsewhere [22].

The participants, assessor, and statistician were blind to the intervention.

2.2. Outcome measures

We assessed the middle cerebral artery blood flow velocity (MCA-BFv) using a portable transcranial doppler ultrasound (Compumedics, Germany). Two 2 MHz ultrasound transducers were placed over the right and the left temporal bone windows and fixed with a headpiece (Multidop®X; Compumedics, Germany), assessing the MCA-BFv at an average depth of 55 mm (± 3 mm) [29–31]. The primary outcome was the mean MCA-BFv since it is a central parameter in TCD with good reproducibility and less interindividual variability than the systolic or diastolic peak velocities [31–33]. The time-points of MCA-BFv assessment collected in relation to each block of stimulation were: T0: baseline; T1/online: 30 s after stimulation (immediately after ramp-up); T2/online: 2 min (before ramp-down); T3/offline: immediately after the end of stimulation (after ramp-down); T4/offline: 5 min after stimulation.

Tolerability was assessed using the visual analog scale for discomfort degree after each application of HD-tDCS, graded from zero to 10 [22, 34]. After each session, the participants were also instructed to report any study-related adverse effects.

Table 1
Descriptive data of the right and left Middle Cerebral Artery Blood Flow velocity (MCA-BFv) for each HD-tDCS condition and current intensity.

Label		Mean ± SD Median [IQR]	Mean ± SD Median [IQR]	Mean ± SD Median [IQR]	Mean ± SD Median [IQR]	Mean ± SD Median [IQR]	Mean ± SD Median [IQR]
Time-points of assessment	Current Intensity (mA)	Sham	Cathode Center	Anode Center	Sham	Cathode Center	Anode Center
		RIGHT MCA-BFv (cm/s)			LEFT MCA-BFv (cm/s)		
Baseline (raw data)	0	68.73 ± 7.04 67.50 [64; 70.83]	66.66 ± 9.18 63.17 [60.42; 69.58]	67.23 ± 7.68 64.83 [62.83; 74.58]	72.03 ± 6.93 72 [66.75; 76.75]	68.43 ± 7.52 67.50 [61.42; 75.42]	65.23 ± 7.34 62.67 [60.67; 67.83]
Online (30 s) - baseline	1	1.86 ± 5.3 1.91 [− 0.19; 5.83]	-0.95 ± 12.44 -1.14 [− 7.83; 3.12]	4.04 ± 8.64 3.29 [0.96; 5.73]	-1.68 ± 8.59 -0.18 [− 4.22; 3.44]	-0.34 ± 12.54 -0.59 [− 7.47; 7.17	7.08 ± 10.89 13.45 [− 2.83; 15.46]
	2	2.00 ± 7.87 3.31 [− 3.67; 6.11]	2.51 ± 12.37 4.2 [− 5.88; 6]	4.06 ± 10.24 1.71 [− 0.65; 8.39]	-3.5 ± 7.83 -4.92 [− 5.8; 1.78]	2.05 ± 13.26 1.67 [− 3.49; 8.78]	7.11 ± 10.05 6.3 [0.57; 16.08]
	3	4.49 ± 6.15 7.01 [0.35; 8]	-0.11 ± 11.3 1.1 [− 4.63; 2.25]	5.38 ± 10.29 3.55 [− 0.68; 8.87]	0.26 ± 8.84 1.01 [− 7.46; 5.74]	0.86 ± 10.64 1.98 [− 6.32; 10.1]	7.76 ± 10.51 11.18 [− 0.49; 13.07]
Online (2 min) - baseline	1	0.87 ± 6.86 0.47 [− 1.52; 2.72]	-0.07 ± 12.47 -1.84 [− 7.85; 8.51]	5.45 ± 6.26 5.12 [3; 9.76]	-2.53 ± 10.09 -2.03 [− 5.49; 3.28]	-0.18 ± 13.19 0.51 [− 8.42; 6.58]	7.92 ± 12.68 9.16 [− 2.84; 18.78]
	2	0.32 ± 7.47 -0.27 [− 4.42; 7.01]	1.62 ± 11.62 -0.46 [− 7.87; 8.62]	4.4 ± 9.43 2.79 [− 1.91; 9.92]	-4.05 ± 7.57 -4.04 [− 6.93; 1.07	1.67 ± 12.05 1.63 [− 4.09; 7.95]	7.66 ± 11.94 8.7 [2.02; 12.23]
	3	1.94 ± 7.22 3.68 [− 3.39; 7.84]	0.28 ± 11 -0.65 [− 5.51; 5.83]	5.1 ± 8.85 2.62 [1.8; 6.23]	-3.14 ± 9.61 -2.1 [− 9.37; 1.08]	-2.46 ± 11.17 -2.6 [− 6.62; 4.85]	6.8 ± 10.23 5.75 [1.06; 15.58]
Offline (30 s) - baseline	1	2.5 ± 4.92 1.5 [− 0.58; 5.34]	0.18 ± 11.82 1.35 [− 7.73; 7.84]	6.1 ± 10.41 6.55 [− 0.47; 13.48]	-1.88 ± 10.77 0.04 [− 3.64; 2.52]	0.46 ± 11.96 0.79 [− 6.35; 8.28]	6.96 ± 11.02 9.8 [− 4.16; 16.02]
	2	3.11 ± 8.3 2.42 [− 2.33; 10.25]	0.1 ± 12.31 0.47 [− 9.78; 4.85]	5.78 ± 11.01 0.81 [0.39; 15.52]	-3.49 ± 6.8 -4.35 [− 5.83; 2.26]	0.31 ± 13.06 -0.3 [− 6.85; 5.79]	8.04 ± 10.07 8.77 [1.4; 12.79]
	3	3.32 ± 8.21 3.69 [− 1.28; 8.51]	0.25 ± 11.07 -0.74 [− 6.34; 6.05]	5.58 ± 8.16 5.15 [2.83; 7.06]	-1.95 ± 12.2 -0.26 [− 8.65; 5.66]	1.09 ± 10.82 2.47 [− 5.39; 9.32]	7.64 ± 10.22 11.09 [1.67; 14.38]
Offline (5 min) - baseline	1	0.43 ± 6.17 0.95 [− 2.98; 4.23]	-1 ± 11.92 -1.56 [− 8.99; 4.94]	2.26 ± 9.94 2.81 [− 5.26; 9.37]	-3.93 ± 8.48 -2.51 [− 7.78; 1.59]	-1.7 ± 12.34 1.36 [− 9.74; 7.02]	6.75 ± 11.27 7.85 [− 3.15-; 5.74]
	2	-0.22 ± 6.55 1.99 [− 2.68; 4.75]	-0.41 ± 8.74 2 [− 7.01; 5.5]	2.53 ± 9.97 0.42 [− 4.45; 10.2]	-3.04 ± 9.22 -3.08 [− 5.96; 2.43]	-0.68 ± 10.2 1.49 [− 7.12; 5.08]	5.57 ± 7.45 4.8 [0.2; 10.15]
	3	1.8 ± 5.74 1.59 [− 3.26; 7.38]	-2.89 ± 7.84 -0.8 [− 4.23; 1.96]	2.4 ± 8.68 2.94 [− 4.38; 5.87]	-3.75 ± 10.89 -1.69 [− 9.73; 2.23]	-0.89 ± 11.07 -2.38 [− 6.53;; 5.91]	5.72 ± 11.47 3.61 [2.01; 11.58]

mA: milliampere; SD: standard deviation; IQR: interquartile interval range; MCA-BFv: middle cerebral artery blood flow velocity; cm: centimeter; s: second; min: minutes.

2.3. Statistical analysis

The statistical guidelines for the analysis of crossover studies were followed with its longitudinal/temporal structure [35]. We used the Kruskal–Wallis test to assess the effect of current intensity for each HD-tDCS condition (anode center, cathode center, or sham) and the effect of HD-tDCS condition for each current intensity (1, 2, or 3 mA). Since the hypotheses were defined a priori, and we used a global test across comparison treatments, no adjustments for multiple comparisons were performed [36]. A 5% level of significance was used (two-sided). Statistical analyses were performed using R Project for Statistical Computing. The descriptive results of the figures are presented as the difference from the baseline. A 20–30% difference from baseline in MCA-BFv is considered a clinically significant change for inducing neurological symptoms [30,31].

3. Results

Stimulation was well tolerated across stimulation conditions tested (see the companion dataset paper), consistent with prior results [22]. There were no serious adverse effects reported in this study.

The present study revealed no statistically significant difference in MCA-BFv during the stimulation protocol across all conditions, on either the ipsilateral or the contralateral stimulation side (Figs. 1 and 2; Table 1). The change in MCA-BFv, observed both during and following stimulation, was below the range of change (20–30%) that is described to have a potential threshold for clinical significance [30,31] (Fig. 1).

4. Discussion

This is the first report of cerebral hemodynamic effects of HD-tDCS assessed using TCD. The effects of conventional tDCS were previously investigated by Vernieri et al. (2010), who did not observe any significant change in MCA-CBFv [3,4,25]. Under the same stimulation protocol, Giorli et al. (2015) found an increase in MCA-BFv during and after anodal condition and a decrease after cathodal condition [24]. Different results might occur due to methodology discrepancies or individual variability.

Changes in microvasculature cerebral blood flow and blood oxygenation during and after HD-tDCS were described in healthy subjects [37–40] and patients after traumatic brain injury [41]. Indeed, different methods such as functional magnetic resonance imaging, functional near-infrared spectroscopy, and computerized tomography can also investigate cerebral hemodynamic features [3,4]. However, TCD is advantageous since it is a non-invasive, low-cost, and radiation-free tool that allows measurement at the bedside, with

continuous and real-time evaluation of main cerebral artery hemodynamics. It is widely used in clinical practice as a reliable and high sensitivity tool in experienced hands for assessing the cerebral blood flow of main cerebral arteries [30,32]. Furthermore, TCD is recommended by the American Heart Association for monitoring cerebral vascular clinical situations such as stenosis, vasospasm, shunt, and emboli [30]. Thus, TCD can be considered an optimal tool to assess safety relating to middle cerebral artery hemodynamic effects from transcranial brain stimulation protocols.

The experimental use of tDCS for the prevention of infarct growth in hyperacute stroke requires cerebrovascular safety analyses [42,43]. A recent pilot study in humans showed a promising application of conventional tDCS applied before completing the recanalization procedure in hyperacute middle cerebral artery stroke patients [44]. The focal HD-tDCS method as used in the present study, might be applied for the same purpose in the future and our findings could contribute to a positive risk-benefit assessment for developing new protocols.

Here we provide evidence that vascular reaction assessed by blood flow was unaltered during and after HD-tDCS at a range of intensities, both locally and remotely. Together with the tolerability data, these findings are essential considerations in safety and mechanism for neurologic and psychiatric patients associated with cerebrovascular disease etiology. Yet, further exploration is warranted given that the potential middle cerebral artery vascular response to brain electric fields (either directly or indirectly) might increase with more prolonged stimulation or with brain lesions. Future studies should analyze the characteristics of continuous data.

CRediT authorship contribution statement

Luiz H Stefano: Conceptualization, Methodology, Project administration, Data curation, Formal analysis, Investigation, Writing – original draft. **Diandra B Favoretto:** Methodology, Data curation, Data curation, Investigation, Writing – original draft. **Francisco Louzada**: Data curation, Formal analysis, Visualization, Writing – review & editing. **Marom Bikson**: Conceptualization, Methodology, Writing – review & editing. **Joao P Leite:** Conceptualization, Methodology, Writing – review & editing. **Octavio M Pontes-Neto:** Conceptualization, Methodology, Resources, Writing – review & editing. **Dylan J Edwards:** Conceptualization, Methodology, Formal analysis, Visualization, Writing – review & editing. **Taiza GS Edwards:** Conceptualization, Methodology, Project administration, Data curation, Formal analysis, Resources, Supervision, Visualization, Writing – review & editing.

Declaration of interest

The City University of New York has inventions on tES with MB as inventor. MB has equity in Soterix Medical and serves on the scientific advisory boards or has grants from Mecta, Halo Neuroscience, Boston Scientific and GlaxoSmithKline. The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Acknowledgements

This work was supported by the Coordenaçao de Aperfeiçoamento de Pessoal de Nível Superior (CAPES; funding code 001), Brazil. We acknowledge Dr. Mersedeh Bahr Hosseini for the helpful suggestions on the manuscript development, and Thiago Bronhara for the helpful development of the figures.

References

[1] D. Edwards, M. Cortes, A. Datta, P. Minhas, E.M. Wassermann, M. Bikson, Physiological and modeling evidence for focal transcranial electrical brain stimulation in humans: a basis for high-definition tDCS, Neuroimage 74 (2013) 266–275.

[2] J. Reckow, A. Rahman-Filipiak, S. Garcia, S. Schlaefflin, O. Calhoun, A.F. DaSilva, et al., Tolerability and blinding of 4x1 high-definition transcranial direct current stimulation (HD-tDCS) at two and three milliamps, Brain Stimul. 11 (5) (2018) 991–997.

[3] P.C. Iyer, S. Madhavan, Non-invasive brain stimulation in the modulation of cerebral blood flow after stroke: a systematic review of transcranial doppler studies, Clin. Neurophysiol. 129 (12) (2018) 2544–2551.

[4] M. Barh-Hosseini, M. Bikson, Neurovascular-modulation: a review of primary vascular responses to transcranial electrical stimulation as a mechanism of action, Brain Stimul. 14 (4) (2021) 837–847.

[5] J.A. Sharpe, What's up, doc? Altered perception of the haptic, postural, and visual vertical, Neurology 61 (9) (2003) 1172–1173.

[6] A.P. Yelnik, F.O. Lebreton, I.V. Bonan, F.M. Colle, F.A. Meurin, J.P. Guichard, et al., Perception of verticality after recent cerebral hemispheric stroke, Stroke 33 (9) (2002) 2247–2253.

[7] S. Dai, C. Piscicelli, E. Clarac, M. Baciu, M. Hommel, D. Pérennou, Balance, lateropulsion, and gait disorders in subacute stroke, Neurology 96 (17) (2021 27) e2147–e2159.

[8] S.R. Babyar, M.G. Peterson, M. Reding, Case-control study of impairments associated with recovery from "pusher syndrome" after stroke: logistic regression analyses, J. Stroke Cereb. Dis. 26 (1) (2017) 25–33.

[9] D.A. Pérennou, G. Mazibrada, V. Chauvineau, R. Greenwood, J. Rothwell, M. A. Gresty, et al., Lateropulsion, pushing and verticality perception in hemisphere stroke: a causal relationship? Brain 131 (Pt 9) (2008) 2401–2413.

[10] T.E. Santos-Pontelli, O.M. Pontes-Neto, J.F. Colafêmina, D.B. de Araujo, A. C. Santos, J.P. Leite, Contraversive pushing in non-stroke patients, J. Neurol. 251 (11) (2004) 1324–1328.

[11] P.M. Pedersen, A. Wandel, H.S. Jørgensen, H. Nakayama, H.O. Raaschou, T. S. Olsen, Ipsilateral pushing in stroke: incidence, relation to neuropsychological symptoms, and impact on rehabilitation. The Copenhagen Stroke Study, Arch. Phys. Med Rehabil. 77 (1) (1996) 25–28.

[12] I.V. Bonan, K. Hubeaux, M.C. Gellez-Leman, J.P. Guichard, E. Vicaut, A.P. Yelnik, Influence of subjective visual vertical misperception on balance recovery after stroke, J. Neurol. Neurosurg. Psychiatry 78 (1) (2007) 49–55.

[13] T. Brandt, M. Dieterich, Perceived vertical and lateropulsion: clinical syndromes, localization, and prognosis, Neurorehabil. Neural Repair 14 (1) (2000) 1–12.

[14] L. Johannsen, D. Broetz, T. Naegele, H.O. Karnath, "Pusher syndrome" following cortical lesions that spare the thalamus, J. Neurol. 253 (4) (2006) 455–463.

[15] T.E. Santos-Pontelli, O.M. Pontes-Neto, D.B. Araujo, A.C. Santos, J.P. Leite, Neuroimaging in stroke and non-stroke pusher patients, Arq. Neuropsiquiatr. 69 (6) (2011) 914–919.

[16] B. Baier, J. Suchan, H.O. Karnath, M. Dieterich, Neural correlates of disturbed perception of verticality, Neurology 78 (10) (2012) 728–735.

[17] L.F. Ticini, U. Klose, T. Nägele, H.O. Karnath, Perfusion imaging in Pusher syndrome to investigate the neural substrates involved in controlling upright body position, PLoS One 4 (5) (2009), e5737.

[18] T.E. Santos-Pontelli, O.M. Pontes-Neto, D.B. Araujo, A.C. Santos, J.P. Leite, Neuroimaging in stroke and non-stroke pusher patients 69 (6) (2011) 914–919.

[19] B. Baier, F. Thömke, J. Wilting, C. Heinze, C. Geber, M. Dieterich, A pathway in the brainstem for roll-tilt of the subjective visual vertical: evidence from a lesion-behavior mapping study, J. Neurosci. 32 (43) (2012) 14854–14858.

[20] A. Kheradmand, A. Winnick, Perception of upright: multisensory convergence and the role of temporo-parietal cortex, Front. Neurol. 8 (2017) 552.

[21] F. Fiori, M. Candidi, A. Acciarino, N. David, S.M. Aglioti, The right temporoparietal junction plays a causal role in maintaining the internal representation of verticality, J. Neurophysiol. 114 (5) (2015) 2983–2990.

[22] T.E.G. Santos, D.B. Favoretto, I.G. Toostani, D.C. Nascimento, B.P. Rimoli, E. Bergonzoni, et al., Manipulation of human verticality using high-definition transcranial direct current stimulation, Front Neurol. 9 (2018) 825.

[23] S. Babyar, T. Santos, T. Will-Lemos, S. Mazin, D. Edwards, M. Reding, Sinusoidal transcranial direct current versus galvanic vestibular stimulation for treatment of lateropulsion poststroke, J. Stroke Cereb. Dis. 27 (12) (2018) 3621–3625.

[24] E. Giorli, S. Tognazzi, L. Briscese, T. Bocci, A. Mazzatenta, A. Priori, et al., Transcranial direct current stimulation and cerebral vasomotor reserve: a study in healthy subjects, J. Neuroimaging 25 (4) (2015) 571–574.

[25] F. Vernieri, P. Maggio, F. Tibuzzi, M.M. Filippi, P. Pasqualetti, J.M. Melgari, et al., High frequency repetitive transcranial magnetic stimulation decreases cerebral vasomotor reactivity, Clin. Neurophysiol. 120 (6) (2009) 1188–1194.

[26] J.D. Rollnik, A. Düsterhöft, J. Däuper, A. Kossev, K. Weissenborn, R. Dengler, Decrease of middle cerebral artery blood flow velocity after low-frequency repetitive transcranial magnetic stimulation of the dorsolateral prefrontal cortex, Clin. Neurophysiol. 113 (6) (2002) 951–955.

[27] M.B. Connolly, F.W. Sharbrough, P.K.H. Wong, Electrical Fields and Recording Techniques, in: J.S. Ebersole, T.A. Pedley (Eds.), Current Practice of Clinical Electroencephalography. 3rd ed., Lippincott Williams & Wilkins, Philadelphia, 2003, pp. 72–99.

[28] D. Sander, B.U. Meyer, S. Röricht, J. Klingelhöfer, Effect of hemisphere-selective repetitive magnetic brain stimulation on middle cerebral artery blood flow velocity, Electro Clin. Neurophysiol. 97 (1) (1995) 43–48.

[29] A. D'Andrea, M. Conte, M. Cavallaro, R. Scarafile, L. Riegler, R. Cocchia, et al., Transcranial doppler ultrasonography: from methodology to major clinical applications, World J. Cardiol. 8 (7) (2016) 383–400.

[30] C.K. Willie, F.L. Colino, D.M. Bailey, Y.C. Tzeng, G. Binsted, L.W. Jones, et al., Utility of transcranial Doppler ultrasound for the integrative assessment of cerebrovascular function, J. Neurosci. Methods 196 (2) (2011) 221–237.

[31] W. Sorteberg, I.A. Langmoen, K.F. Lindegaard, H. Nornes, Side-to-side differences and day-to-day variations of transcranial Doppler parameters in normal subjects, J. Ultrasound Med. 9 (7) (1990) 403–409.
[32] M. Hennerici, W. Rautenberg, G. Sitzer, A. Schwartz, Transcranial Doppler ultrasound for the assessment of intracranial arterial flow velocity–Part 1. examination technique and normal values, Surg. Neurol. 27 (5) (1987) 439–448.
[33] Jawad Naqvi, Kok Hooi Yap, Gulraiz Ahmad, Jonathan Ghosh, Transcranial doppler ultrasound: a review of the physical principles and major applications in critical care, Int. J. Vasc. Med. (2013).
[34] R. Russo, D. Wallace, P.B. Fitzgerald, N.R. Cooper, Perception of comfort during active and sham transcranial direct current stimulation: a double blind study, Brain Stimul. 6 (6) (2013) 946–951.
[35] B. Jones, M. Kenward, in: D.C. Washington (Ed.), Design and Analysis of Cross-over Trials. Second Edition, Chapman & Hall/CRC, 2003.
[36] K.F. Schulz, D.A. Grimes, Multiplicity in randomised trials I: endpoints and treatments, Lancet 365 (9470) (2005) 1591–1595.
[37] W. Sorteberg, I.A. Langmoen, K.F. Lindegaard, H. Nornes, Side-to-side differences and day-to-day variations of transcranial Doppler parameters in normal subjects, J. Ultrasound Med. 9 (7) (1990) 403–409.
[38] M. Muthalib, P. Besson, J. Rothwell, S. Perrey, Focal hemodynamic responses in the stimulated hemisphere during high-definition transcranial direct current stimulation, Neuromodulation 21 (4) (2018) 348–354.
[39] M. Muthalib, P. Besson, J. Rothwell, T. Ward, S. Perrey, Effects of anodal high-definition transcranial direct current stimulation on bilateral sensorimotor cortex activation during sequential finger movements: an fNIRS study, Adv. Exp. Med. Biol. 876 (2016) 351–359.
[40] M. Sood, P. Besson, M. Muthalib, U. Jindal, S. Perrey, A. Dutta, et al., NIRS-EEG joint imaging during transcranial direct current stimulation: online parameter estimation with an autoregressive model, J. Neurosci. Methods 274 (2016) 71–80.
[41] A.O. Trofimov, G. Kalentiev, M. Karelsky, C. Ksenofontova, A. Ruzavina, M. Yuriev, et al., Cerebral hemodynamics after transcranial direct current stimulation (tDCS) in patients with consequences of traumatic brain injury, Adv. Exp. Med. Biol. 1072 (2018) 59–62.
[42] F. Notturno, M. Pace, F. Zappasodi, E. Cam, C.L. Bassetti, A. Uncini, Neuroprotective effect of cathodal transcranial direct current stimulation in a rat stroke model, J. Neurol. Sci. 342 (2014) 146–151.
[43] L. Peruzzotti-Jametti, M. Cambiaghi, M. Bacigaluppi, M. Gallizioli, E. Gaude, S. Mari, S. Sandrone, M. Cursi, L. Teneud, G. Comi, et al., Safety and efficacy of transcranial direct current stimulation in acute experimental ischemic stroke, Stroke 44 (2013) 3166–3174.
[44] E. Pruvost-Robieux, J. Benzakoun, G. Turc, A. Marchi, R.L. Mancusi, C. Lamy, V. Domigo, C. Oppenheim, D. Calvet, J.C. Baron, J.L. Mas, M. Gavaret, Cathodal transcranial direct current stimulation in acute ischemic stroke: pilot randomized controlled trial, Stroke 52 (6) (2021) 1951–1960 (Jun).