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Extended Abstract

High definition tDCS effect on postural control in healthy individuals: entropy analysis of a crossover clinical trial

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Abstract: Objective: The identification of dose-response effects of transcranial direct current stimulation (tDCS) on postural control after stroke has highlighted this strategy as promising for post-stroke rehabilitation. Nonetheless, spatial-temporal dependence data have not been investigated using entropy analysis. Thus, we performed a nonlinear time series analysis of ground reaction force during and after the application of the high-definition transcranial direct current stimulation (HD-tDCS), over the right temporo-parietal junction (TPJ). Materials and Methods: We conducted a randomized, double-blind, placebo-controlled, crossover clinical trial. Twenty-one healthy young adults received the HD-tDCS and sham protocols. We evaluated the exchanging information (causal direction) between both force plates, using the summarized time series of transfer entropy, and compared the dose-response across the healthy subjects by a generalized linear mixed model (GLMM). Results: We found significant variation during the dynamic information flow ($p<0.001$) among the dominant bodyside. Specifically, all participants were right-handed, and a greater force transfer was observed from the right- to the left-side during the experiment. We observed a causal relationship in the information flow (equilibrium force transfer) from right to left and a decrease in entropy over time. Conclusions: HD-tDCS intervention induced a dynamic influence over time on postural control. Right-TPJ stimulation using HD-tDCS can induce an asymmetry of body weight distribution, leaning to the contralateral side of the stimulation, and thus a plausible post-stroke treatment.

Keywords: high-definition transcranial direct current stimulation; postural control; entropy; nonlinear time series.

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1. Introduction

Stroke is a cerebrovascular disease being of the second leading cause of death and disability worldwide [1]. About 30-50% of patients become dependent in activities of daily living (ADL) [2]. The postural imbalance leads to functional deficits in this population. It may occur due to changes in mechanical components such as muscle weakness, limitation of joint movement, changes in muscle tone as well as sensory damage [3]. The visual verticality perception (VV) disorder, the incapacity to judge the orientation of the body or environment in relation to Earth vertical within normal limits,

is commonly observed after stroke and associated with poor balance [4] due to a weight asymmetry towards the same side of the VV tilt [5–8].

Lesions of the temporoparietal juction (TPJ), a hub area for multisensory integration, can cause VV disorder and postural imbalance [9]. NIBS techniques, such as conventional and high-definition transcranial direct current stimulation (HD-tDCS) are current therapeutic resources with potential modulation on the pathophysiology and behavior of brain mechanisms [10]. Recently we verified the effects of conventional noninvasive transcranial stimulation (tDCS) [11] and HD-tDCS [12] applied over the TPJ in both healthy subjects and patients after stroke.

Clinical findings observed in patients after stroke in VV and weight-bearing asymmetry (WBA) [4,12,13] were reproduced in healthy individuals after using our stimulation protocol. We found action dependent on the cathode center condition with induction of asymmetry in the discharge of body weight towards the side of brain stimulation [12]. However, we did not demonstrate to be dependent on the intensity of the electrical current. Other studies evaluated electroencephalography (EEG) after our HD-tDCS protocol in healthy subjects and suggested entropy (nonlinear analysis) as a robust alternative for data analysis complementing linear [14,15].

We hypothesized that the HD-tDCS would induce a sequence of events on postural control demonstrated by an influence in the discharge of weight. Thus, we analyzed the ground reaction force in each platform through the flow of information using transfer entropy.

2. The Data

This study was conducted according to the Helsinki Declaration requirements for human investigation, and was approved by the local ethics committee. All participants provided written informed consent. This article followed the guidelines of the Checklist of Information to include when reporting a randomized trial followed the Consolidated Standards of Reporting Trials (CONSORT) for randomized trials.

2.1. Participants

The study included a distinct sample population blinded to the HD-tDCS approach for assessing ground reaction force. The study candidates were healthy subjects aged 20 to 28 years, male and female, right-handed, non-smokers, with no evidence of brain, vestibular or orthopedic dysfunction, with normal or corrected vision. To ensure the absence of vestibular deficits, was accomplished oculomotor tests, the head shake and head thrust test. Inclusion and evaluation period of study participants was 10 months.

2.2. Intervention

We used the HD-tDCS protocol organized in the 3 x 1 standard. The assembly was composed of a central electrode on the right cerebral hemisphere TPJ and 3 peripheral electrodes located at EEG coordinates P4, C4 and T8. We used a Soterix HD-tDCS device (Soterix Medical®, NY-USA). During and after the application of the electric current we assessed the body movement kinetics measured by two force plates (Bertec 4060-NC, Columbus, OH, USA) in the static orthostatic posture of each individual.

2.3. Outcome Measure

Each volunteer underwent 3 different randomized HD-tDCS conditions (cathode-central, anode-central and sham) on 3 different days. Each HD-tDCS condition was applied in a sequence of 3 stimulation intensities (1, 2 and 3 mA) repeated 3 times. Each stimulation intensity was conducted for 2 minutes with rest interval of 5 minutes. The intervention of this study followed the stimulation protocol previously validated and published by our group [12]. Detailed analysis of the stimulation protocol as well as dose calculation for each stimulation session, HD-tDCS computational modeling, induced

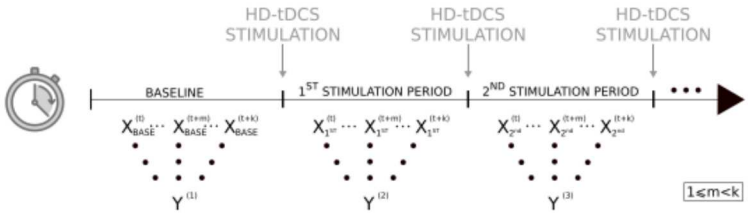

Figure 1. Visual data transformation whereas a time series (X) data is summarized into a entropy index (Y). For each experiment period, before or after the electrical stimulation, and during the clinical trial, the transfer entropy calculation segmentation into a complexity measure value (entropy index) the exchanging information (causal direction) between both force plates.

current flow, safety and tolerability criteria, randomization protocol and allocation concealment of this study was published elsewhere [12].

2.4. Statistical Analyses

In the statistical context, entropy is a measure of complexity between signal data or time series (TS) that links the amount of information to a probability distribution [16,17]. One option for analyzing and modeling the entire TS is to apply as summary statistics. This can be, for example, the processor average.

We have previously outlined a dose-response model testing the intensity and polarity-dependent effect of HD-tDCS in which we compared the effect of anodal and cathodal stimulation polarity at different intensities (1 mA, 2 mA and 3 mA) in VV, electroencephalogram (EEG) and WBA [12]. Moreover, an entropy study was performed and discussed on the same protocol using only the EEG results [14].

We adopted the usage of entropy in our data analysis. The time series process was initially performed using entropy index for all data acquired towards the complexity of the vertical force component (Fz) of the force plates before, during and after the stimulation protocol application, as shown in the data pre-processing procedure in Figure 1.

We evaluated the effect of HD-tDCS applied in TPJ on postural control, observing the intensity for each condition and the condition for each intensity. Thus, using as an entropy measure the transfer entropy [18,19], enabled to encompass if past state of one Fz signal could improves the prediction of the other Fz signal on each force plate (right- and left-side), addressing the causal inference among the Fz components.

Therefore, we sought to compare the summarizations across the different TS moments, using a Mixed-Effect Models, as a Longitudinal study, to distinguish between stimulus types versus intensity, and quantify the differences in regularity between the force plates.

As the hypotheses were defined a priori we used a global test between comparison treatments complexity. In all tests, a significance level of 5% (front and back) was used. Statistical analyzes were performed using R software for Statistical Computing and Analysis. The descriptive results of the figures are presented as the difference from baseline. We describe Transfer Entropy (TE) and Generalized Linear Mixed Effect Models (GLMM).

3. Results

A total of 21 consecutive healthy subjects were included in the study, a mean age 24.2 $\pm$ 4.1 years. There were 13 women and 8 men all right-handed. All volunteers finalized the three days of HD-tDCS stimulation protocol with posturography evaluations.

In the literature, it is often common to find only discussion towards functional connectivity. This limits on inferences related only with the statistical covariation of signals, typically revealed by cross-correlograms or coherence measures. Therefore,

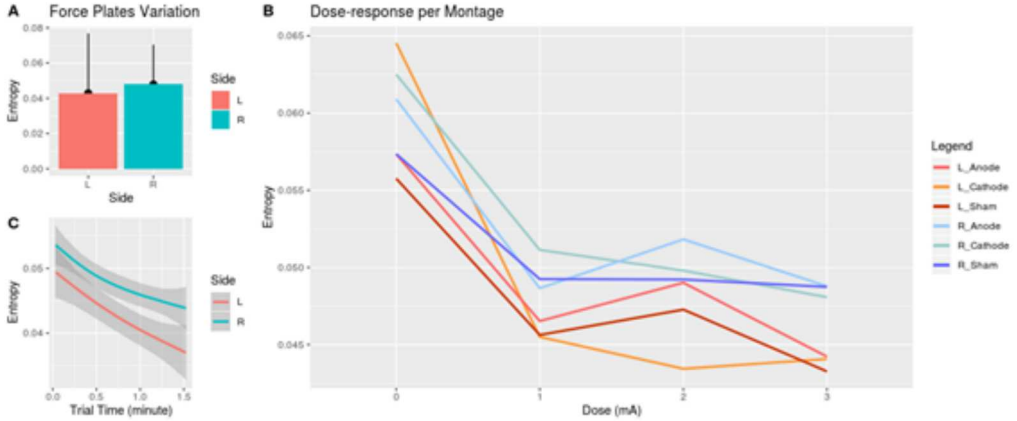

Figure 2. Comparison across the Fz measurements from the force plates and dose-response on each montage. Panel A represents the mean causal entropy from the left side to the right side (L) and from right-side to left- (R). The black lines represent one standard error. Panel B shows the evolution across the dose-response, regarding its transfer entropy of each force plate per montage. Visual results indicate a decay in the causal entropy highlighting the greatest variation on the left-side across cathodal baseline - 2mA. Panel C displays the complexity dynamic of each force plate across time, smoothing the entropy trials evolution through a generalized additive model (GAM) and considering a confidence interval of 95%.

effective connectivity is more suitable to be used in explaining causal relationships, that is, the time dependence across the Force plates signals.

Analyzing the HD-tDCS dose-response effects on the weight bearing asymmetry we found a decrease of the entropy on each force plate (suggesting an addition of determinism in the system, that is, creating a pattern among the post-stimulation period), as shown in Figure 2-C. Moreover, visually an increase in the variability (across the montages) on 2mA (Figure 2-B). As well, a causal effect from the right-side on the left- (Figure 2-A).

The robustness in the dominant side (causal effect from the right-side to the left-), where the right-hand panel presents smaller transfer entropy variation on the dose-response. Moreover, the baseline seems to have higher entropy (associated with the randomness), than reduction as an electrical stimulation is applied (1, 2 and 3mA) or after that (as offline dose).

The transfer entropy analysis presented here contributes to the findings reported by our group that described the effects of HD-tDCS protocol on postural control, now looking for the predictive information between the right and left sides of the weight bearing discharge on the force plates showing a causal relationship from the right side to the left side. Therefore, empirical evidence related with the HD-tDCS on postural control over right-hemisphere TPJ is statistically noticeable, as a modulator, in healthy subjects.

4. Conclusions

This work supported our previous research that showed the transfer entropy as a strategy to explore the dynamic time-variable parameter through stimulus (intensity) versus condition (polarity). Here we addressed the causal inference between weight support asymmetry in two separate forces plates in healthy subjects. We complemented the evidence of the effects elucidated by our stimulation protocol [12] with a nonlinear time-series analysis. Thus, we showed that past states of the right Fz component can improve the prediction of the left Fz component. The effects induced an asymmetry in body weight distribution with a decrease in entropy over time. That is, the process is becoming more deterministic was influenced by the electrical stimulation. The visually observed greater variability of the entropy on the left side can suggest that our HD-tDCS

montage with the cathodal polarity and intensity of 2mA promoted a greater effect on the postural control. Here, the intensity and the polarity-dependent effects did not show a statistical difference that can be related to the short time of stimulation.

Future studies are necessary to explore random effects related to personal characteristics to promote a broader knowledge involving causality on dynamic entropy data.

Author Contributions: D.B.F: study concept and design of the clinical trial, data acquisition, analysis and interpretation of the clinical trial, and manuscript writing. EB: data acquisition, analysis and interpretation of the clinical trial, and manuscript writing. D.C.N: statistical analysis and interpretation of data of the clinical trial, and manuscript writing. FL: supervision of the statistical analysis and interpretation of data of the clinical trial, and critical revision of the manuscript for intellectual content. T.W.L: data supervision, analysis and interpretation of the clinical trial, and critical revision of the manuscript for intellectual content. R.A.B: data acquisition, analysis and interpretation of the clinical trial, and critical revision of the manuscript for intellectual content. R.M: data supervision and interpretation of the clinical trial, and critical revision of the manuscript for intellectual content. J.P.L: study concept and design of the clinical trial, data supervision and interpretation, and critical revision of the manuscript for intellectual content. D.J.E: study concept and design of the clinical trial, interpretation of computational modeling, data analysis and interpretation of the clinical trial and critical revision of the manuscript for intellectual content. T.S: study concept and design of the clinical trial, interpretation of computational modeling, data acquisition, analysis and interpretation of the clinical trial, and manuscript writing.

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Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: The datasets generated for this study are available on request to the corresponding author.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Campbell, B.C.; De Silva, D.A.; Macleod, M.R.; Coutts, S.B.; Schwamm, L.H.; Davis, S.M.; Donnan, G.A. Ischaemic stroke. *Nature Reviews Disease Primers* **2019**, *5*, 1–22.
2. Capistrant, B.D.; Wang, Q.; Liu, S.Y.; Glymour, M.M. Stroke-associated differences in rates of activity of daily living loss emerge years before stroke onset. *Journal of the American Geriatrics Society* **2013**, *61*, 931–938.
3. Mizuta, N.; Hasui, N.; Nakatani, T.; Takamura, Y.; Fujii, S.; Tsutsumi, M.; Taguchi, J.; Morioka, S. Walking characteristics including mild motor paralysis and slow walking speed in post-stroke patients. *Scientific Reports* **2020**, *10*, 1–10.
4. Barra, J.; Oujamaa, L.; Chauvineau, V.; Rougier, P.; Pérennou, D. Asymmetric standing posture after stroke is related to a biased egocentric coordinate system. *Neurology* **2009**, *72*, 1582–1587.
5. Bonan, I.; Leman, M.; Legargasson, J.; Guichard, J.; Yelnik, A. Evolution of subjective visual vertical perturbation after stroke. *Neurorehabilitation and neural repair* **2006**, *20*, 484–491.
6. Piscicelli, C.; Perennou, D. Visual verticality perception after stroke: A systematic review of methodological approaches and suggestions for standardization. *Annals of physical and rehabilitation medicine* **2017**, *60*, 208–216.
7. Pérennou, D. Postural disorders and spatial neglect in stroke patients: a strong association. *Restorative neurology and neuroscience* **2006**, *24*, 319–334.

8. Baggio, J.A.; Mazin, S.S.; Alessio-Alves, F.F.; Barros, C.G.; Carneiro, A.A.; Leite, J.P.; Pontes-Neto, O.M.; Santos-Pontelli, T.E. Verticality perceptions associate with postural control and functionality in stroke patients. *PLoS One* **2016**, *11*, e0150754.
9. Kheradmand, A.; Winnick, A. Perception of upright: multisensory convergence and the role of temporo-parietal cortex. *Frontiers in neurology* **2017**, *8*, 552.
10. Rossi, S.; Hallett, M.; Rossini, P.M.; Pascual-Leone, A.; of TMS Consensus Group, S.; others. Safety, ethical considerations, and application guidelines for the use of transcranial magnetic stimulation in clinical practice and research. *Clinical neurophysiology* **2009**, *120*, 2008–2039.
11. Santos-Pontelli, T.E.; Rimoli, B.P.; Favoretto, D.B.; Mazin, S.C.; Truong, D.Q.; Leite, J.P.; Pontes-Neto, O.M.; Babyar, S.R.; Reding, M.; Bikson, M.; others. Polarity-dependent misperception of subjective visual vertical during and after transcranial direct current stimulation (tDCS). *PLoS One* **2016**, *11*, e0152331.
12. Santos, T.E.; Favoretto, D.B.; Toostani, I.G.; Nascimento, D.C.; Rimoli, B.P.; Bergonzoni, E.; Lemos, T.W.; Truong, D.Q.; Delbem, A.C.; Makkiabadi, B.; others. Manipulation of human verticality using high-definition transcranial direct current stimulation. *Frontiers in neurology* **2018**, *9*, 825.
13. Baier, B.; Suchan, J.; Karnath, H.O.; Dieterich, M. Neural correlates of disturbed perception of verticality. *Neurology* **2012**, *78*, 728–735.
14. Nascimento, D.C.; Depetri, G.; Stefano, L.H.; Anacleto, O.; Leite, J.P.; Edwards, D.J.; Santos, T.E.; Louzada Neto, F. Entropy analysis of high-definition transcranial electric stimulation effects on eeg dynamics. *Brain sciences* **2019**, *9*, 208.
15. Nascimento, D.C.; Pinto-Orellana, M.A.; Leite, J.P.; Edwards, D.J.; Louzada, F.; Santos, T.E. BrainWave Nets: Are sparse dynamic models susceptible to brain manipulation experimentation? *Frontiers in systems neuroscience* **2020**, *14*.
16. Pincus, S.M. Approximate entropy as a measure of system complexity. *Proceedings of the National Academy of Sciences* **1991**, *88*, 2297–2301.
17. Richman, J.S.; Moorman, J.R. Physiological time-series analysis using approximate entropy and sample entropy. *American Journal of Physiology-Heart and Circulatory Physiology* **2000**.
18. Vicente, R.; Wibral, M.; Lindner, M.; Pipa, G. Transfer entropy—a model-free measure of effective connectivity for the neurosciences. *Journal of computational neuroscience* **2011**, *30*, 45–67.
19. Aziz, N.A. Transfer entropy as a tool for inferring causality from observational studies in epidemiology. *bioRxiv* **2017**, p. 149625.