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Prefrontal Cortex Neuromodulation Improves Motor-Cognitive Components in Latinx Hispanic People Living with HIV

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ABSTRACT

Background: HIV is an immunodeficiency virus that currently has no cure but is managed with antiretroviral medication (ART). ART has increased the life expectancy of those living with HIV. Evidence shows a correlation between the increase in life expectancy and increases in neurological motor-cognitive impairments, thus leading to a decline in functional mobility and overall quality of life. The current study aimed to address neurological motor cognitive impairments in Latinx HIV+ individuals using transcranial direct current stimulation (tDCS).

Methods: Female and male participants, ages 18-65, with an HIV diagnosis by a medical doctor and a CD4 count of >300 were obtained from an HIV clinic in La Perla de Gran Precio in Puerto Rico. Spatiotemporal data were collected; each subject participated in a dual cognitive ambulation task and completed the HIV dementia scale.

Results: Dual cognitive tasks were calculated for cadence, gait cycle, gait speed, single limb, double limb, stance, stride, swing, and sway were analyzed. After the application of tDCS, the only statistically significant difference found among the subjects was an improvement in gait speed ($p \leq .05$). In addition, the cognitive component showed an improvement in the HIV dementia scale total ($p \leq .05$), including an increase in motor speed and memory recall ($p \leq .05$).

Conclusion: tDCS may be a feasible and effective treatment option for this population to alleviate motor-cognitive alterations in those living with HIV. Future research should consider the benefits of tDCS combined with diverse training, such as gait or balance activities.

Keywords: Motor-cognitive Alterations, Supraorbital neuromodulation, Gait Deviations, HIV- Complications, Motor control Deficits, HIV dementia.

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INTRODUCTION

Currently, 38 million individuals live with the human immunodeficiency virus (HIV) worldwide [1]. HIV attacks CD-4 T lymphocytes, which results in a weakened immune system [2]. Furthermore, as HIV reproduces within the brain, it causes chronic inflammation, leading to disturbances of the frontostriatal systems and white matter abnormalities [3-6]. As a result, people with HIV present with progressive cognitive and motor changes known as HIV-associated neurocognitive disorders (HAND). HAND can present various neurological motor-cognitive impairments, such as memory loss, reasoning difficulty, judgment, problem-solving skills, and personality changes [1, 7]. In addition, the motor impairments that result from HAND can affect balance, gait, and muscle function in this population [1, 8]. For instance, in people living with HIV, postural control strategies utilized by healthy adults are negatively impacted by the aforementioned neuromotor deficits [9]. Ultimately, these motor-cognitive impairments can interfere with everyday activities and are linked to a decrease in quality of life. Furthermore, neurological motor-cognitive impairments have been attributed to an increased rate of morbidity, mortality, and accelerated aging [1].

Over the years, antiretroviral treatment has reduced morbidity and mortality rates among individuals living with HIV, increasing their lifespans and evolving treatment to improve the quality of life of this population [10]. In addition, antiretroviral medication decreases viral replication, thus reducing the risk of opportunistic infections [1]. However, according to Rosario et al. (2020), antiretroviral medications can also lead to undesirable side effects such as abnormal heart rate, muscle pain, weakness, and lactic acid build-up [11]. In addition, while antiretroviral therapy can slow the disruption of the disease on the motor-cognitive system, HIV is still detrimental to normal cognitive function, gait, and balance stability, increasing the risk of falls and early death in these individuals [10, 12, 13].

In addition to the side effects of ART and the clinical manifestations of HIV infection, the Hispanic population, particularly Puerto Ricans living with HIV, have presented with additional comorbidities such as hypertension, depression, peripheral neuropathy, and hyperlipidemia [11]. Peripheral neuropathy is one of the top three comorbidities in this population; however, its origin is unknown because there is no correlation between peripheral neuropathy and diabetes in people living with HIV. Nonetheless, diabetes is more commonly observed in HIV-infected patients than healthy controls. Furthermore, HIV and diabetes further affect locomotor, neurocognitive, kidney, and cardiovascular functions [14].

To our knowledge, no treatment has addressed both neuromotor and neurocognitive impairments in this population. However, a commonly used treatment for other diagnoses has risen in current research, which may benefit the HIV population. The treatment involves transcranial direct current stimulation (tDCS), a low-level electrical stimulation applied to a specific location on the head concerning the desired location of the brain. tDCS is used to modulate neural activity and acts by altering the membrane potential of the axons, increasing or decreasing the polarity. Parameters that decrease the membrane polarity will make it easier to elicit an excitation response upon stimulation from neighboring neurons. An increase in the neuronal firing rate increases neuroplasticity [7]. Usually, the tDCS current is set between 1 and 2mA [15]. Research on the effects of tDCS has been ongoing for nearly half a century; however, there has been scarce research on the effects of tDCS in HIV-positive patients [16]. In 2019, Falezi et al. (2019) conducted a pilot study focusing on the effects of tDCS combined with cognitive training on cognitive function in older adults with HIV. Researchers have found the oral reading recognition measure to be statistically significant [7]. Currently, no known publication has focused on the effects of tDCS on motor-cognitive components in HIV patients.

Therefore, the question this study proposed to answer was, could a frontal lobe (forehead-supraorbital) neuromodulation therapy promote motor-cognitive execution in people living with HIV? The key objective of this study was to examine the effects of tDCS with cognitive frontal electrode placement on gait parameters and cognitive performance in those living with HIV. The ultimate goal is to expand on the current research on HIV and established tDCS as a potential treatment for motor-cognitive alterations.

METHODS

Participants

Participants were recruited via convenience sampling from an accessible population of HIV patients at the HIV clinic La Perla de Gran Precio in Puerto Rico. This study was approved by the Institutional Review Board (#FY2020-32). Informed consent for participation was provided and signed by all participants. Demographic information was collected before the initiation of the experimental protocol. The demographic characteristics included age, sex, years of diagnosis, timed 5x sit-to-stand (to assess lower limb strength), and Fukuda test (rule out vestibular disorders). These characteristics are presented in Table 1. Additional characteristics, such as weight, height, BMI, heart rate, oxygen saturation, leg dominance, and visual aids, can be found in the Results section.

Inclusion criteria were that the participant must have reasonable health without a diagnosis of metabolic syndrome, and the participant must be between the ages of 18-65 years. Additional inclusion criteria included an HIV diagnosis by a medical doctor and a CD4 count >300. Exclusion criteria included severe balance impairment, lower limb or back surgery within the last six months, non-ambulatory status, and pregnancy.

Motor-cognitive components were assessed before five tDCS treatments and at the end of the last day of the treatment session. Therefore, each data collection day took

an additional 20-25 minutes.

Motor Component Protocol

Measures for spatiotemporal parameters were taken (see below). In addition, kinematic parameters were collected using the APDM Mobility Lab (APDM Inc., http://apdm.com), a portable, easy-to-use system designed to measure upper extremity kinematics and lower extremities and trunk (sensors placed on the lumbar and chest).

The protocol included single and dual-task assessments, beginning with two trials of 7-meter-ambulation at the participant's preferred speed and ending with two trials of ambulating 7 meters with a cognitive task of counting down from 100 in increments of 3.

Cognitive Component Protocol

HIV dementia scale. This validated tool consists of four items: memory registration (repeating four items), motor speed (timed quick finger tapping over 5 seconds), psychomotor speed (timed alternating hand sequence test over 10 seconds), and memory recall (recall of four items 2 min after the first item). The total score on the HIV dementia scale was 12. According to Sacktor et al. (2005), a score below 10 indicates early signs of dementia in participants [17].

tDCS

tDCS was provided via two battery-powered electrical stimulators attached to a pair of saline-soaked 35-cm^2 synthetic sponge electrodes placed on the forehead. The black/negative electrode (cathode) was located over the right side of the frontal bone over the supraorbital margin. In contrast, the red/positive electrode (anode) was placed over the left side of the frontal bone over the supraorbital margin. This study used tDCS for 20 minutes, three times a week for two weeks, for five interventions. This timing and electrode placement has proven to be beneficial during neurocognitive interventions with *stroke* [18-22], *Parkinson*'s disease [23], and *Alzheimer's disease* [24] patients. The current was slowly ramped up manually from 0.5-mA to 2.0 mA in increments for safety. The participants were instructed to report uncomfortable sensations from the electrodes. At the end of the session, the current automatically decreased to 0.0 mA.

Data Analysis

Motor Components: Kinematic data were collected pre- and post-five tDCS treatments. Gait measurements were obtained for cadence, gait cycle, gait speed, support time (single/double), stance time, stride time, swing phase, and posture. All the data were organized in an Excel sheet. The percentage of dual-task costs for each variable of interest was calculated using the following formula previously employed by [(dual-task performance – single-task performance) / single-task performance] × 100 [25-27]. Finally, a MANOVA was performed between the calculated cognitive cost percentages before and after tDCS intervention. A P value of ≤ 0.05 was considered significant in the current study.

Cognitive components: The HIV dementia scale score was compiled pre-and post-five tDCS treatments. All data were gathered and arranged in an Excel sheet. The MANOVA procedure was performed between the total score of each subsection (motor speed, psychomotor speed, and memory recall). A P value of ≤ 0.05 was considered significant in the current study.

RESULTS

Table 1 presents the characteristics of the sample population. The sample consisted of 29 participants with a mean age of 60.31 ± 7.82. The sample consisted of 11 women and 18 men. The average CD4 count was 899.9 ± 155.6. Additionally, the average weight of participants was 177 ± 50.2 pounds, with an average height of 65.58 ± 3.25. Participants' average BMI was 29.03 ± 8.03 kg/m^2. Other demographic averages included: HR 79 ± 15.07 beats per minute (bpm) and SaO2 97.5% ± 1.02%. Of the included individuals, 24 were right-leg dominant, and five were left-leg dominant. Nineteen participants used visual aids, either glasses or contact lenses, during the testing administration.

Table 1: Demographic characteristics and measurements data of all participants

	pre tDCS	post tDCS
Age (years)	M = 60.31±7.82	
Gender	Male= 18 Female = 11	
Year of Dx (years)	M= 1997 (23.6 years)	
Cd4	M= 899.9 ± 155.6	
5-time sit to stand	13.45+/-5.8 seconds	10.9+/-2.5 seconds
Fukuda Average	32.0+/-37.6	13.8+/-28.9

Table 2 demonstrates the motor component results from the MANOVA analysis of cognitive cost before and after the intervention, revealing gait speed as the only statistically significant change among subjects. The mean gait speed before tDCS was -21.13, while following tDCS treatment, the mean gait speed was 12.81%, revealing a p-value of .05. All other variables were not significant pre-to post-intervention (Table 2).

Table 2: Comparison of Motor Components of Walking Parameters Dual-tasks cost percentage between pre and post TDCS treatment. Results of MANOVA performed comparing tasks. Significance level set at p≤0.05

Motor Component Variables	Pre-TDCS COG Cost %	Post TDCS COG Cost %	P-Value
Cadence	10.10 (13.03)	8.95 (12.62)	.648
Gait Cycle	10.31 (13.22)	12.33 (16.91)	.506
Gait Speed	24.13 (30.83)	12.81 (24.88)	0.05**
Single Limb	2.44 (8.27)	2.21 (7.74)	.883
Double Limb	12.27 (18.70)	10.95 (17.88)	.715
Stance	2.26 (3.52)	2.05 (3.34)	.757
Stride	5.53 (14.93)	5.54 (13.91)	.998
Swing	2.99 (8.17)	2.73 (7.63)	.864
Sway	5.69 (36.36)	7.58 (34.19)	.785

Percentage of dual-task costs: [(dual-task performance –

single-task performance) / single-task performance] × 100 [25-27]

Table 3 shows the cognitive component outcomes from the MANOVA analysis after the tDCS treatment. Results revealed a significant (P= 0.001) increase from 8.78+/-1.4 points to 10.5+/-1.5 points in the HIV DS total score after TDCS treatment. Further, the specific component of the HIV Dementia related to Motor speed increased significantly (0.001) from 2.85+/-0.98 pre to 3.84+/-0.5 post after TDCS treatment. The other section related to Memory Recall improved significantly in score from 3.0+/-1.1 pre to 3.8+/-0.30 post after TDCS treatment. The psychomotor speed did not differ from the tDCS treatment.

Table 3: Comparison of Cognitive Components of HIV Dementia Scale between pre and post TDCS treatment. Results of MANOVA performed comparing tasks. Significance level set at p≤0.05

Cognitive Components	Pre tDCS	Post tDCS	P-values
HIV Dementia: Motor speed	2.85+/-0.98	3.84+/-0.5	0.001**
HIV Dementia: Psychomotor speed	2.93+/-0.8	2.68+/-1.2	0.41
HIV Dementia: Memory Recall	3.0+/-1.1	3.8+/-0.30	0.001**
HIV dementia scale total score	8.78+/-1.4	10.5+/-1.5	0.001**

DISCUSSION

This study investigated the effects of tDCS with frontal electrode placement on gait parameters and cognitive performance in patients living with HIV. The study's question was, could a tDCS frontal lobe (forehead-supraorbital) neuromodulation therapy promote motor-cognitive execution in people living with HIV? Yes, PFC tDCS neurostimulation can improve motor cognitive alterations in patients with HIV. This remark was proven by an increased gait speed and better HIV dementia scale scores after tDCS treatment.

Motor component: Based on the results mentioned above, the supraorbital and prefrontal cortex (PFC) approach for tDCS enhances cognitive function and improves gait. According to our results, the PFC approach for tDCS is feasible for those living with HIV. The effectiveness of PFC neurostimulation has been previously studied. Similar to our findings, a systematic review by Pol et al. (2021) stated that tDCS improved gait speed [28]. However, Pol and Colleagues, in their report, also identified additional improvements in stride length, step length, and step width in patients with Parkinson's disease (PD) [28]. In this review, eight studies reported tDCS placement over the PFC at an intensity of 1 mA or 2 mA on five consecutive days or in a single session. The current research used 2mA for five days of treatment as a protocol. Mishra and Thrasher (2021) assessed tDCS at the PFC in combination with dual tasks during gait to improve dual tasking in patients with PD [29]. Comparable to the current inquiry, Mishra & Thrasher (2021) applied the anodal electrode on the left PFC and the cathodal electrode on the contralateral PFC, which positively improved gait and cognitive task performance 15 min after tDCS application [29].

This study acknowledged that the only parameter that improved was the gait speed. Nevertheless, gait speed is one of the most crucial gait parameters, commonly referred to as the sixth vital sign [30]. According to Takayanagi et al. (2019), there is a correlation between gait speed and functional abilities [31]. For example, a decline in gait speed may indicate deterioration in functional mobility [31]. In addition, slow gait speed is correlated with the inability to maintain instrumental activities of daily living, mild cognitive decline, and risk of cardiovascular death [31].

Furthermore, Fritz et al. (2009) suggested that gait speed is predictive of future health status and disease occurrences that could provide information regarding hospitalization, discharge location, and mortality [30]. Finally, gait speed decline is often seen with a decrease in age, as in the HIV population compared to non-infected HIV individuals [32]. Thus, it is an important parameter that should be considered when examining interventions for the HIV population.

It is well established that gait speed is a function of stride length and stride frequency [33, 34]. However, our results showed a significant change in gait speed without a concomitant change in stride length or cadence (stride frequency or rate). One explanation may be the diverse clinical backgrounds and comorbidities of the participants in this study. Several of our participants had comorbidities or impairments that could have confounded our results. The enrollment of participants at assorted phases of HIV infection was intended for adequate identification of the motor cognitive profile of this population. However, we are mindful of the influence of other comorbidities on gait. Future investigations could identify distinct motor-cognitive profiles in those with HIV; however, separating the different groups among comorbidities to adequately associate the impact of tDCS on each stage of the disease. Our study aligns with other investigations regarding improved motor components, gait speed, and tDCS effect [28, 29].

Cognitive component: The main finding was improving the HIV dementia scale total score with a five-day treatment of PFC tDCS at 2mA for 20 minutes. The data showed an increase in motor speed and memory recall after tDCS treatment. In addition, this tDCS protocol has proven to be beneficial during neurocognitive interventions with *stroke* [18-20, 22], *Parkinson* [24] and *Alzheimer's* [23] and now with HIV participants.

The amount of TDCS research proceeds to thrive as the literature supports its use in people with mild cognitive impairment, Parkinson's disease, and individuals who have experienced a stroke. TDCS has demonstrated significant improvements in processing speed, planning of tasks, selective attention, and memory in older adults with mild motor-cognitive alterations [35]. However,

before the current investigation, limited research had been conducted using TDCS in the HIV population, and these investigations have focused on decreasing depressive symptoms. These studies have concluded that further research is needed to understand better how TDCS works within this population [36-38].

A new approach to improving motor-cognitive components for HIV is imperative because the virus damages the immune and nervous systems. This injury causes neurological disorders and atrophy of the brain structures related to motor and cognitive functions that directly affect activities of daily living [39-41]. One solution to the progression of motor cognitive alterations is antiretroviral therapy (ART). ART has increased lifespan and survival rates for over a decade in people living with HIV [42] and has reduced the motor-cognitive alterations associated with HIV [43]. However, in its mildest form, neurological modifications are still prevalent and negatively impact the quality of life of these individuals [44-45]. Poor therapy adherence, neurotoxicity, comorbidities, and drug resistance are among the components associated with motor cognitive alterations and can be attributed to why these impairments remain prominent within this population [46].

Motor-cognitive alterations that impact motor speed, information processing, executive functions, attention, new learning, memory, and new information retrieval are distinct and particularly prominent traits of HIV [47]. In the early stages of this disease, with normal CD4 immune cells, mild motor-cognitive alterations affecting the central nervous system can be identified in individuals with HIV; however, these motor-cognitive neurological modifications increase in severity as the condition progresses [48]. These motor cognitive alterations are related to frontal lobe involvement, specifically, the frontostriatal brain system [49], developing the current investigation with a PFC tDCS neurostimulation approach.

This study has several limitations. First, the study was conducted using convenience sampling. Second, a small sample size of participants was obtained from only one HIV clinic in Puerto Rico, which may not represent the entire Latinx population. Nevertheless, La Perla de Gran Precio represents a large part of the metropolitan area of Puerto Rico. Third, time constraints were also a limiting factor, as we do not know if the increase in gait speed would be sustainable over time or if this was only a short-term benefit.

Therefore, future directions should focus on increasing the amount of literature and research on the impact of tDCS protocols in the HIV population and the effects of tDCS on gait parameters to draw more concrete conclusions. In addition, since the average CD4 count was 899.9 ± 155.6, it would be beneficial to repeat this study with lower CD4 counts, including those with AIDS diagnosis, below a 200 cell count. Future directions should also focus on replicating this study in other regions with more significant populations of people living with HIV, such as Texas, to represent the HIV population. Altogether, research needs to include studies that focus on longitudinal time frames.

CONCLUSION

Our research aimed to investigate the effects of tDCS on motor cognitive components in male and female Latinx HIV+ patients. The results showed that gait speed and HIV dementia score improved significantly, suggesting the effectiveness of the treatment. This is the first study to address the impact of tDCS intervention on cognitive dual-task cost for ambulation in this patient population, which is the novelty of this work. HIV is currently affecting millions of individuals. Even remaining consistent with antiretroviral therapy, they are highly likely to develop some motor-cognitive alterations that will negatively alter their way of life. This study is timely, impactful, and proposes an innovative intervention strategy to reduce motor cognitive alterations and potentially prolong a productive quality of life in people with HIV. Future research could focus on utilizing tDCS in cognitive areas during active tasks. For instance, combining tDCS with gait training on a treadmill, balance protocols, and memory exercises improves cognition and, therefore, quality of life in those living with HIV. Since most current research is investigating the effects of tDCS in conjunction with other interventions on gait parameters in different conditions, the future direction of this study will provide more helpful information on the tDCS treatment of gait and cognition in HIV.

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