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Aim and Scope

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RESEARCH PAPERS

CLINICAL CORNER

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Central Autonomic Network Disturbance in Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: A Pilot Study

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Abstract

Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) is a debilitating disease of the central nervous system known to be associated with multiple behavioral symptoms (fatigue, low stamina, dizziness, etc.) combined with autonomic nervous system (ANS) dysfunction, thus implicating the central autonomic network (CAN). Postexertional malaise (PEM) is a core feature of ME/CFS, characterized by a pathological reduction in stamina in response to performing minor physical or mental tasks, often lasting at least 24 hours. Exact low-resolution electromagnetic tomography (eLORETA) allows noninvasive investigation of cortical regions of interest that may contribute to better understanding of the role of the brain disturbances in behavioral manifestations of PEM. This pilot study therefore aimed to use eLORETA to characterize changes in current density in cortical structures related to the CAN following submaximal isometric handgrip exercise in seven patients with ME/CFS and six neurotypical healthy controls (HCs). Resting EEG was recorded at pre- and posthandgrip, and 24 hours later. Findings showed that significant differences occurred immediately posttest, which were most pronounced after 24 hours, particularly in the low alpha (8–10 Hz) and low beta (13–18 Hz) frequency subbands. Together, the present findings offer support for EEG source localization techniques to investigate PEM. If confirmed, this study could provide a useful instrument for aiding functional diagnosis and evaluation of treatment outcomes.

Keywords: chronic fatigue syndrome; myalgic encephalomyelitis; central autonomic network; handgrip; postexertional malaise; eLORETA; central fatigue

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Introduction

Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) is a complex disease of the central nervous system (Bansal et al., 2012; Loebel et al., 2014; Underhill, 2015) associated with neuroinflammation (Barah et al., 2014; Maes et al., 2012; Nakatomi et al., 2014, 2014; VanElzakker et al., 2018), autonomic dysfunction (Barnden et al., 2016), cellular hypometabolic problems (Naviaux et al., 2016), and progressive brain deterioration (Chen et al., 2008; Shan et al., 2016). Most cases of ME/CFS are precipitated by an acute viral infection (Rasa et al., 2018; Roos & Miravalle, 2014) or less commonly from traumatic brain injury (accident or other head trauma), endogenous brain injury (i.e., stroke, tumor, etc.), or chemical/toxin exposure (Cho et al., 2006). Signs and symptoms suggest a brain infection involving flu-like symptoms such as acute fever, headache, tender lymph nodes, sore throat, neurologic deficits, and altered mental status (i.e., impaired consciousness; Scheld et al., 2014). Recent studies have demonstrated a need for understanding the effects of physical activity on neurological processes in ME/CFS, specifically the central autonomic network (CAN) that controls the

peripheral autonomic nervous system (ANS) (Barnden et al., 2016; Beaumont et al., 2012; Bozzini et al., 2018; Cambras et al., 2018; Cvejic et al., 2017; Orjatsalo et al., 2018; Roerink et al., 2018; Van Cauwenbergh et al., 2014).

The cause of ME/CFS is unknown, as is the case with many known neurological diseases (Holgate et al., 2011), and patients with neurological disorders typically have a clinical presentation with complaints of severe, unrelenting central fatigue (Chaudhuri & Behan, 2004), depending on the nature and extent of central involvement. Central fatigue in neurological disorders is linked to cognitive impairments such as reduced perceptual awareness, attention problems, memory impairments, reduced reasoning ability (Gunzelmann et al., 2019), and sleep inversion (Pajediene et al., 2018). Accordingly, the infection–fatigue causal relationships for ME/CFS have been reported as a primary source of central fatigue (Cook et al., 2012; Togo & Natelson, 2013), which is known to be pervasive and multifactorial (Berelowitz et al., 1995; Zinn et al., 2018).

Numerous clinical conditions include fatigue as part of their etiology (Ropper & Samuels, 2009) and the symptom sequelae of postexertional malaise (PEM) are widely recognized as the most debilitating and unrelenting feature of ME/CFS (Carruthers et al., 2011). PEM refers to debilitating loss of stamina accompanied by symptom flareups following minor physical or mental activity, lasting 24 hours or more (Carruthers et al., 2003; Stevens et al., 2018). All patients suffer in some manner from PEM which interferes with their baseline level of function (Carruthers et al., 2003) and at least 25% of patients with ME/CFS are housebound or bedbound (Institute of Medicine, 2015; Pendergrast et al., 2016). PEM impacts the quality of life of sufferers and makes the disease particularly difficult to manage due to unpredictable variation in symptom frequency and severity (LaManca et al., 1998). Although mental activity is known to trigger PEM, it has been found to have close concordance with physical activity (Light et al., 2009, 2012). Studies using maximal cardiopulmonary exercise tests have found lower peak oxygen uptake (VO_2 max) in patients (Nijs et al., 2010; Ohashi et al., 2002; Snell et al., 2013; Stevens et al., 2018; Vanness et al., 2007; Vermeulen & Vermeulen van Eck, 2014; Yoshiuchi et al., 2007), showing lower aerobic capacity possibly due to insufficient metabolic adaptation to incremental exercise (Shungu et al., 2012). However, it has been reported that severe cases are unable to endure maximal exercise tests (Stevens et al., 2018). Submaximal exercise tests have been utilized, but their results are not necessarily comparable to maximal tests (Meeus et al., 2007; Nijs et al., 2010). Consequently, there is a need to investigate PEM using an alternative approach with a lower response cost.

Fatigue is one of the primary covariates of autonomic disorders (Oosterwijck et al., 2017), making the ANS a principal target of research and clinical applications (Tanaka et al., 2015). The ANS largely depends on the integrity of global CNS states for regulating behavioral states and the rapid allocation of neuronal resources (Pfaff et al., 2008). The ANS, in coordination with the neuroendocrine system, regulates the cascading physiological events which serve as primary mediators of stress and arousal (McEwen et al., 2015). Operating synergistically with the CNS, the ANS promotes physiological stability through adaptive response to ever-changing internal and external demands (Benarroch, 2012; McEwen et al., 2015; Porges, 1992, 2009). However, a compromised ANS may disrupt CNS function altogether (Cleare, 2004; Sclocco et al., 2016), resulting in negative effects on cognitive function due to orthostatic intolerance, dyspnea, paresthesia, nausea, ataxia, cardiopulmonary irregularities, and thermal dysregulation (Mathias & Bannister, 2013; Sandroni, 2012; Shan et al., 2016).

The CAN is a set of interconnected regions involved in top-down homeostatic control (Benarroch, 2012; Mo et al., 2019) of the peripheral ANS in coordination with intricate neuroimmune responses (Benarroch, 2019; Morrison & Nakamura, 2019) and arousal responses (Saper, 2002), emphasizing its potential importance in ANS-related disease. The structures of the CAN were recently confirmed in a comprehensive meta-analysis of 43 task-based studies using the activation likelihood estimation (Turkeltaub et al., 2002), a widely used technique for showing the convergence of activated brain areas across different experiments. Many cortical regions were reportedly involved in cognitive, affective, and sensorimotor tasks for initiating autonomic outflow with neuroendocrine responses of the hypothalamus and 1) upper brainstem nuclei which regulate pain modulation and stress responses, 2) lower brainstem nuclei which control circulation, respiration, and GI function, and 3) spinal level reflex centers (Benarroch, 1993, 2012).

The present study examined the cortical regions of the CAN using exact low-resolution electromagnetic tomography (eLORETA), an inverse solution that

estimates cortical current density from EEG signals recorded at the scalp (Grech et al., 2008; Pascual-Marqui et al., 2011). Previous iterations of LORETA and eLORETA have been extensively used for source localization of brain activity in clinical populations (Babiloni et al., 2010; Canuet et al., 2012; Cao & Slobounov, 2010; Caso et al., 2012; Clemens et al., 2008, 2010; Gianotti et al., 2007; Lantz et al., 1997; Lubar et al., 2003; Nishida et al., 2011; Toth et al., 2009). In a previous study, we used eLORETA to evaluate 50 patients with ME/CFS and 50 healthy controls (Zinn et al., 2018); patients were found to have generalized delta band (1–3 Hz) current density in 50% of the frontal lobe, bilaterally, including the anterior cingulate, insula, superior/inferior frontal gyrus, and ventromedial frontal gyrus. Focal delta activity in the left inferior frontal gyrus was associated with self-reported levels of reduced motivation from fatigue. The patients also demonstrated a reduction in beta-2 (19–21 Hz) current density in the somatomotor cortex, precuneus, and posterior cingulate. Together, these brain regions that were associated with central fatigue are also involved in central autonomic processing, thus implicating the CAN as a prime target for further investigation.

The main objective of this pilot study was to quantify the effects of physical exertion on CAN function in ME/CFS using an isometric handgrip task. Handgrip tasks are commonly used in stress literature to perturb the ANS (Nielsen & Mather, 2015) and for the assessment of physiological function in clinical populations, such as mitochondrial disorders (Meulemans et al., 2007) and functional status of cancer patients (Norman et al., 2010). In patients with ME/CFS, handgrip studies have found increased heart rate and blood pressure, higher levels of norepinephrine (Wyller et al., 2009) as well as slowed motor speed (Ickmans et al., 2014), and associations with fatigue (Neu et al., 2014; Siemionow et al., 2004; Staud et al., 2015), maximal oxygen uptake (Jammes et al., 2020), and disease severity (Nacul et al., 2018).

Resting-state qEEG data were collected from all participants during 3 separate time points: 1) before handgrip, 2) immediately after handgrip, and 3) 24 hours later. Thus, the discrepancy between CAN function at pre vs. posthandgrip exercise was used to quantify PEM. It was hypothesized that patients with ME/CFS would differ significantly from the neurological healthy control (HC) group at Time 1 (baseline). Next, due to the effects of PEM, it was predicted that differences between groups would increase at time 2 (immediately after the handgrip task) compared to baseline. Finally, differences between groups were predicted to be greater at time 3 (24 hours) due to the adverse effects of PEM in patients and return to baseline in HCs.

Method

Participants

This study was approved by the DePaul University Institutional Review Board in Chicago, Illinois (protocol #MA119118PSY) and informed consent was obtained from all study participants after reading a written explanation of the experiment. There was no compensation for their involvement. Seven patients diagnosed with ME/CFS (4 female and 3 male, mean age: 54.29 years, ±17.52) and six healthy individuals (2 female and 4 male, mean age: 30.51, ±5.65) were enrolled in this study. Participants in this study were recruited from the Chicago, IL, metropolitan area from waitlists of past research studies and email communications. All patients met inclusion criteria specified by Fukuda et al. (1994) and Carruthers et al. (2003) with a physician diagnosis of ME/CFS. Exclusion criteria ruled out those with a history of a neurological disorder such as epilepsy or traumatic brain injury, presence of psychiatric disorders such as anxiety or depression, and other comorbidities. None of the participants were taking medications known to affect the EEG.

Design

This study utilized a mixed-model quasi-experimental design with repeated measures. The EEG data were collected at the Center for Community Research at DePaul University. For the period between the second recording on day 1 (posthandgrip) and the third recording on day 2 (24 hours later), all participants were instructed to avoid performing any laborious tasks such as lifting, housecleaning, grocery shopping, or any other strenuous physical tasks.

Prior to study visit, all participants completed an online version of the DePaul Symptom Questionnaire (DSQ; Jason et al., 2010) and the Short Form Medical Outcomes Survey (SF-36; Ware & Sherbourne, 1992). Data for both questionnaires were collected and managed using the Research Electronic Data Capture (REDCap) hosted at DePaul University (Harris et al., 2009). The DSQ has good test–retest reliability above 0.70 and test–retest correlations for symptom categories (Jason et al., 2015). The total score was calculated using the DSQ items regarding PEM.

The SF-36 has been widely used in studies for the assessment of health status (Ware et al., 1993). It has shown high internal consistency and test–retest reliability estimates and discriminant validity among subscales (Ware et al., 1995). Questions are scored from 0 to 100 with lower scores indicating greater disability. Items 23, 27, 29, and 31 from the vitality subscale were used to calculate the energy/fatigue scores.

Handgrip Protocol

Each participant performed an isometric handgrip task based on a protocol taken from (Jeppesen et al., 2007) using an adjustable handgrip strengthener (Kootek, Inc.). Before performing this task, grip strength was calibrated to 50% of the average maximal voluntary contraction force taken from three synchronized maximal voluntary contractions using the dominant hand. While performing the protocol, the participants were seated upright in a padded office chair while resting their elbow flexed at a 90° angle on the armrest of the chair. After a 2-min break, the protocol was initiated whereby participants made repetitive submaximal grip force contractions in this manner for 3 min (18 total contractions). They were instructed to squeeze the handgrip for 5 s, then relax for 5 s while watching a PowerPoint presentation (Microsoft, version 2010) with timed slides serving as cues for when to squeeze/relax. For each contraction, participants were instructed to fully squeeze the handgrip to achieve equal intensity levels throughout the task. They were encouraged to complete the task or continue until they could go no further. However, each participant was able to complete the task, and afterward, intensity ratings on a 1–10 visual analog scale were reported to be in the moderate range.

EEG Recording

Each EEG recording lasted for 5 min, during which participants were instructed to sit quietly while keeping their eyelids closed gently. The eyes-closed condition was chosen to minimize ocular artifact and maintain internal consistency with previous resting EEG studies. Participants were seated in a padded office chair and the examination room was well-lit. International 10/20 system electrode placement was achieved using an electrode cap system (Electro-Cap International, Eaton, OH) with a linked-ears reference. Impedances were checked and adjusted until all electrodes were below 5 kΩ. EEG signals were acquired at 256 Hz sample frequency using a BrainMaster Discovery amplifier (BrainMaster Technologies, Bedford, OH) to record 19 channels simultaneously from the following electrode locations: Fp1, Fp2, F3, F4, F7, F8, Fz, C3, C4, Cz, P3, P4, Pz, T3, T4, T5, T6, O1, and O2. Before their first EEG recording, participants were briefly trained to minimize ocular and muscle artifacts. During training, they were asked to observe changes in the raw signal while blinking their eyes frequently and after tensing their facial muscles. After training, participants were subsequently asked to refrain from blinking as much as possible, and to relax their jaw and forehead muscles to the best of their ability. NeuroGuide software version 3.0.4 (Applied Neuroscience, Inc., Largo, FL) was used for recording and off-line processing. Eye-blink, muscle, and drowsiness artifacts were identified and eliminated using NeuroGuide's automated *z*-score artifact rejection algorithm set to high sensitivity, followed by visual inspection and manual editing by the technician. The remaining EEG epochs maintained greater than 95% split-half and greater than 90% test–retest reliability coefficients as computed by NeuroGuide with at least 1.5 total minutes of artifact-free data remaining for analysis. Each participant record was then filtered offline between 1 and 30 Hz and exported into separate text files containing 2-s segments using a 75% overlapping taper window (Kaiser & Sterman, 2000).

Source Localization

LORETA-KEY software was used to estimate eLORETA for the intracortical distribution of electrical sources generated from scalp-recorded activity in a solution space of 6,239 voxels at 5mm^3 resolution and restricted to unambiguous cortical gray matter (Lancaster et al., 2000). Using a realistic head model (Fuchs et al., 2002), computations are mapped onto orthogonal brain slices of the MNI 152 standard template (Mazziotta et al., 2001) using standardized Montreal Neurological Institute (MNI) voxel coordinates in millimeters with neuroanatomical labels established by von Brodmann in 1909 referred to as Brodmann areas, which are based on corrected Talairach space (Brett et al., 2002). The latest iteration in a series of well-established tomography methods, including sLORETA (Pascual-Marqui, 2002) and LORETA (Pascual-Marqui et al., 1994), eLORETA has been validated in studies using combined magnetic resonance imaging (Mulert et al., 2004; Vitacco et al., 2002), and Positron Emission Tomography (Dierks et al., 2000; Pizzagalli et al., 2004; Zumsteg et al., 2005) and source findings obtained from implanted depth electrodes (Zumsteg et al., 2006a, 2006b). Furthermore, eLORETA has been validated for resting-state investigations based on 19 channels (Miraglia et al., 2021), a montage configuration found in many clinical studies (Aoki et al., 2019; Hata et al., 2016; Pascarelli et al., 2020; Vanneste &

De Ridder, 2013). A detailed description of this inverse method and its exact zero-error localization property are described in Pascual-Marqui et al. (2011). The LORETA-KEY software package for eLORETA/sLORETA is freely provided by the Key Institute for Brain-Mind Research, University Hospital of Psychiatry, Zurich at http://www.uzh.ch/keyinst/loreta.

Software utilities for eLORETA were used to define each cortical region of interest of the CAN a priori, using MNI coordinates reported in Beissner et al. (2013), and the single nearest voxel method was chosen to assign each region of interest to a single voxel with closest proximity to the coordinate entered. The voxel coordinates and regions of interest of the CAN used in this study included the anterior, middle, and posterior cingulate, ventromedial prefrontal gyri, anterior and posterior insula, supramarginal gyri, inferior parietal lobe, and other structures located within the parahippocampal gyri (e.g., amygdalae and hippocampi). The thalamus, red nucleus, and cerebellum regions were not included, given the subcortical limitations of eLORETA. Current density estimates within each CAN region of interest were then extracted for each of the following frequency bands: Delta (1–3 Hz), Theta (4–7 Hz), Alpha–1 (8–10 Hz), Alpha-2 (10–12 Hz), Beta-1 (13–18 Hz), Beta-2 (19–21 Hz), and Beta-3 (22–30 Hz). To eliminate variability in spectral power and lower error variance, subject-wise normalization was performed, where the total activity over all voxels and frequencies was computed, giving a single number, used as divisor for scaling the data. Statistical analyses of the eLORETA data were performed using SPSS version 25 (IBM, Armonk, NY). To create text output according to each frequency band, eLORETA utilities were used and the data were then imported into SPSS, log-transformed to achieve normality, and *z*-transformed for better interpretability.

Results

Table 1 shows clinical and demographic data collected from the patients with ME/CFS and the HC group. A significant difference between groups was found in the DSQ PEM symptom scores and SF-36 energy/fatigue scores. A lower score on the SF-36 indicates greater disability.

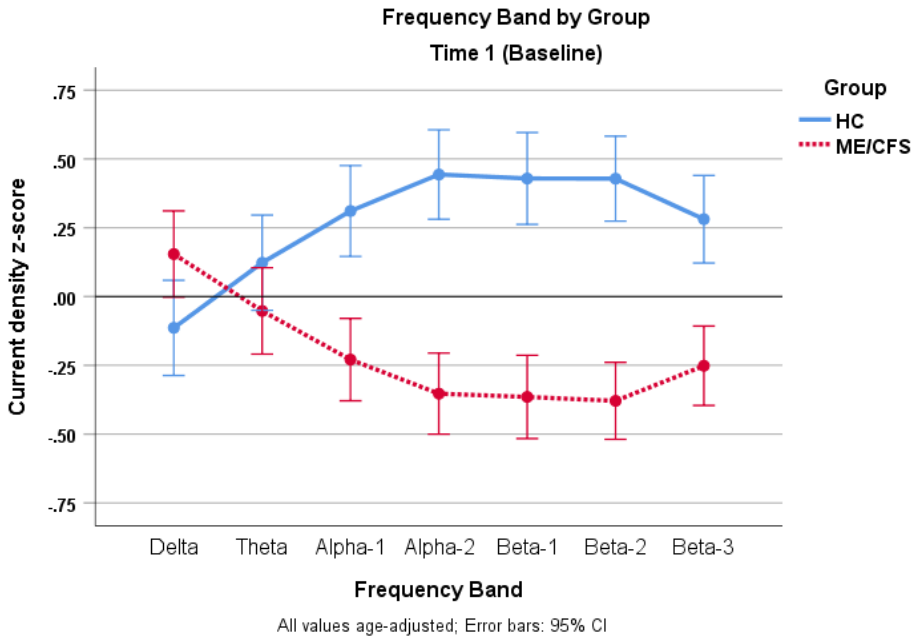
To evaluate group differences in current density for each frequency band at pretest, posttest, and 24 hours (see Figures 1, 2, 3), a mixed multivariate analysis of variance was conducted (age was entered as a covariate). Hotelling's τ^2 was employed to describe multivariate tests due to its inherent

Table 1
Demographic Data and Clinical Scores

	ME/CFS (*n* = 7)	HCs (*n* = 6)	*p*-value
Age Mean (*SD*)	54.29 (±17.52)	30.51 (±5.65)	.008[a]
Sex	4 Female 3 Male	2 Female 4 Male	.782[b]
Education	1 Partial college 2 College degree 4 Graduate degree	1 Partial college 3 College degree 2 Graduate degree	.146[b]
Ethnicity	6 White 1 Asian	3 White 3 Asian	.166[b]
DSQ PEM Total Mean (*SD*)	31.29 (±13.03)	8.67 (±6.28)	.005[a]
SF-36 Energy/Fatigue Mean (*SD*)	13.57 (±5.42)	55 (±25.5)	.008[a]
Illness duration Mean years (*SD*)	11.43 (±10.39)		

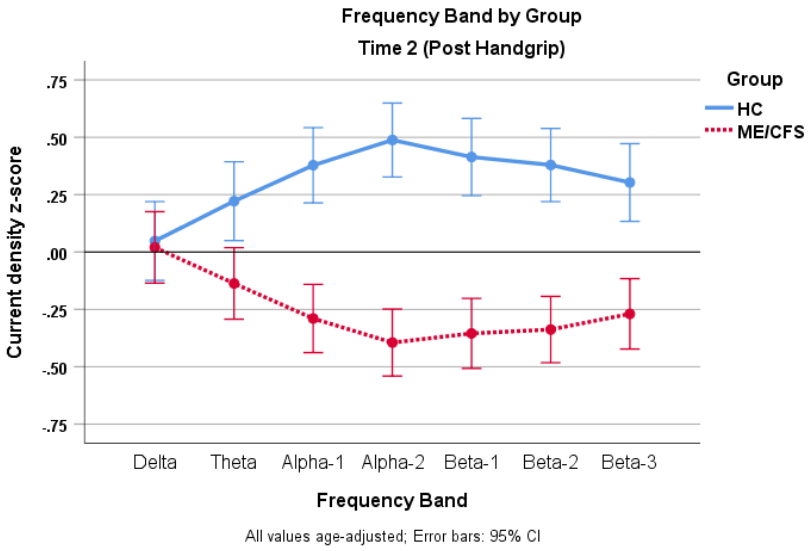
[a] Unpaired Mann-Whitney U test
[b] χ^2 test

Figure 1. *Significant Group Differences at Time 1 (Prehandgrip) for Each Frequency Band Measured During the Eyes-closed Condition*.



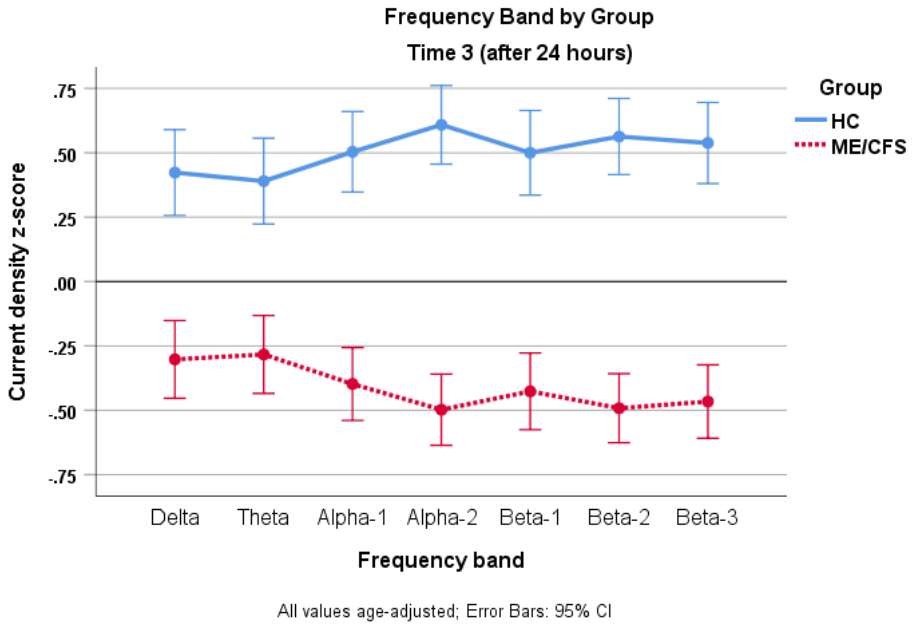
Note. Comparisons for each frequency band were evaluated as follows: Delta, p = .052; Theta, p = .171; Alpha-1, p < .001; Alpha-2, p < .001; Beta-1, p < .001; Beta-2, p < .001; Beta-3, p < .001.

Figure 2. *Significant Group Differences at Time 2 (Posthandgrip) for Each Frequency Band Measured During the Eyes-closed Condition*.



Note. Comparisons for each frequency band were evaluated as follows: Delta, p = .745; Theta, p = .005; Alpha-1, p < .001; Alpha-2, p < .001; Beta-1, p < .001; Beta-2, p < .001; Beta-3, p < .001.

Figure 3. *Significant Differences at Time 3 (After 24 Hours) for Each Frequency Band Measured During the Eyes-closed Condition*.



Note. Comparisons for each frequency band were evaluated as follows: Delta, $p < .001$; Theta, $p < .001$; Alpha-1, $p < .001$; Alpha-2, $p < .001$; Beta-1, $p < .001$; Beta-2, $p < .001$; Beta-3, $p < .001$.

adjustment for heterogeneity of variances and covariances (multivariate sphericity) when the underlying distributions are normal at each level of the independent variables (Tatsuoka & Lohnes, 1988). For every outcome, the null hypothesis was tested at the 0.05 level of significance. Bonferroni correction was applied to all comparisons, and adjusted *p* values are reported.

A statistically significant multivariate effect of current density was found, Hotelling's $\tau^2 = .459$, $F(6, 395) = 30.19$, $p < .001$, $\eta^2 = .31$. HC within-group differences between each time of testing at each frequency band were as follows: Delta, Time 1–2, $p < .001$; Time 1–3, $p < .001$; Time 2–3, $p < .001$. Theta, Time 1–2, $p = .001$; Time 1–3, $p < .001$; Time 2–3, $p < .001$. Alpha-1, Time 1–2, $p = .038$; Time 1–3, $p < .001$; Time 2–3, $p = .001$. Alpha-2, Time 1–2, $p = .161$; Time 1–3, $p < .001$; Time 2–3, $p < .001$. Beta-1, Time 1–2, $p = .99$; Time 1–3, $p = .002$; Time 2–3, $p < .001$. Beta-2, Time 1–2, $p = .399$; Time 1–3, $p < .001$; Time 2–3, $p < .001$. Beta-3, Time 1–2, $p = .99$; Time 1–3, $p < .001$; Time 2–3, $p < .001$.

ME/CFS within-group differences between each time of testing at each frequency band were as follows: Delta, Time 1–2, $p < .001$; Time 1–3, $p < .001$; Time 2–3, $p < .001$. Theta, Time 1–2, $p = .002$; Time 1–3, $p < .001$; Time 2–3, $p < .001$. Alpha-1, Time 1–2, $p = .055$; Time 1–3, $p < .001$; Time 2–3, $p = .001$. Alpha-2, Time 1–2, $p = .203$; Time 1–3, $p < .001$; Time 2–3, $p < .001$. Beta-1, Time 1–2, $p = .99$; Time 1–3, $p = .004$; Time 2–3, $p < .001$. Beta-2, Time 1–2, $p = .464$; Time 2–3, $p < .001$; Time 1–3, $p < .001$. Beta-3, Time 1–2, $p = .99$; Time 1–3, $p < .001$; Time 2–3, $p < .001$. Between Time 1 and Time 2, current density in patients was significantly lower in the delta and theta frequency bands. After 24 hours, however, patients demonstrated a significant reduction in current density across all frequency bands.

A significant effect of group was found, indicating that the differences between patients with ME/CFS and HCs were statistically different, $\tau^2 = .464$, $F(6, 395) = 30.54$, $p < .001$, $\eta^2 = .32$, as well as the interaction of time and group, $\tau^2 = .457$, $F(2, 399) = 91.17$, $p < .001$, $\eta^2 = .31$. Current density and time interaction was significant with a medium effect size, $\tau^2 = 1.106$, $F(12, 389) = 32.6$, $p < .001$, $\eta^2 = .50$. Finally, there was a significant triple interaction effect of current density and time and group, $\tau^2 = .732$, $F(12, 389) = 23.72$, $p < .001$, $\eta^2 = .42$ (Figures 1, 2, 3).

Next, multilevel logistic regression analyses with a random intercept were conducted to estimate the association between the outcome of current density and variables of interest (time and experimental group), which differed according to each frequency band. Multivariate Hotelling's τ^2 *F*-tests from repeated measures analysis of covariance and odds ratios from logistic regression models were used to assess whether the seven prespecified frequency bands in the study were significant by time and experimental group. Adjusted odds ratios (ORs) and 95% confidence intervals are reported and Bonferroni correction was applied to all comparisons with adjusted *p* values being reported. The adjusted odds ratios for the likelihood of abnormal current density within each frequency band at each time was estimated for the patients with ME/CFS, using Time 1 as the referent. The final model fit was significant, $\chi^2(14) = 88.140$, $p < .001$ (Table 2). Notable changes occurred in the Alpha-1 band, where the odds of dysfunction increased more than two-fold from 7.3 to 16.4 between Time 2 and Time 3 (OR = 16.392). Similarly, the odds ratio increased nearly five-fold from 3 to 14.3 in the Beta-1 band (OR = 14.304).

Table 2
*Results of Multilevel Logistic Regression Analysis**

	Frequency Band	Odds Ratio	95% Confidence Interval Lower Bound	95% Confidence Interval Upper Bound
Time 2 (Posthandgrip)	Delta	0.500	0.294	0.850
	Theta	1.208	0.633	2.307
	Alpha-1	7.324	2.050	26.507
	Alpha-2	0.090	0.022	3.710
	Beta-1	3.008	1.286	7.035
	Beta-2	0.169	0.075	0.383
	Beta-3	2.929	1.838	4.668
Time 3 (24 hours)	Delta	1.387	0.831	2.314
	Theta	0.422	0.221	0.806
	Alpha-1	16.392[a]	4.471	60.092
	Alpha-2	0.018	0.004	0.078
	Beta-1	14.304[a]	5.820	35.153
	Beta-2	0.077	0.033	0.177
	Beta-3	2.731	1.658	4.498

* Effects of patients with ME/CFS only at Times 2 and 3 (Time 1 as the referent).
[a] The odds of CAN dysfunction in the Alpha-1 frequency band for patients with ME/CFS is 7.3 times higher than healthy controls at Time 2, while that odds more than doubled at Time 3 (odds ratio = 16.4). A similar odds increase can be seen in Beta-1.

Discussion

The present study aimed to quantify the effects of physical exertion on central autonomic function in ME/CFS using eLORETA. The principal finding was a significant time and frequency-dependent pattern of CAN perturbation in the patient group, relative to the HC group. Baseline current density in the patient group was significantly lower in the Alpha and Beta frequency bands, but marginally higher in the Delta band. At Time 2 (posthandgrip), significant physiological changes emerged within both groups: ME/CFS current density was reduced, while HC current density was elevated. This discrepancy between groups occurred in all frequency bands, except Delta. After 24 hours, however, the difference between groups became more pronounced. The ME/CFS group showed a greater reduction in current density whereas the HCs had further increased across all frequency bands.

Secondarily, we found that the odds of CAN dysfunction between Times 1 and 2 and Times 1 and 3 were greater in the Alpha-1 and Beta-1 frequency bands. Different oscillatory frequencies have dissimilar physiological significance, and they represent the temporal modulation of parallel information processing occurring at multiple levels with cyclic variations of intrinsic excitability between different neuronal populations (Buzsáki & Watson,

2012). The timings of the Alpha-1 band have been shown to influence the gating of incoming streams of sensory information that influence task performance (Busch et al., 2009). Thus, a greater likelihood of Alpha-1 dysfunction in patients suggests they are prone to experience problems with central drive mechanisms that influence sensorimotor processing of fatigue during physical exercise. Likewise, the Beta band (~13–30 Hz) is arrhythmic, low voltage activity associated with alertness, and studies have demonstrated its role in cognitive processing of attention and working memory (Heister et al., 2013; Palva et al., 2005). Higher odds ratios in Beta-1 (~13–18 Hz) activity might be a reflection of persistent cognitive deficits associated with ME/CFS (Cockshell & Mathias, 2014; Güntekin et al., 2013).

Together, these results are consistent with the characteristic stamina loss and behavioral worsening of symptoms in PEM after 24 hours and they extend previous investigations showing aberrant CNS signaling followed by fatigue-inducing voluntary motor tasks (Benwell et al., 2006; Hilty, Jäncke, et al., 2011; Schillings et al., 2005; Siemionow et al., 2004; Zwarts et al., 2008). Our prediction that the HC group would return to baseline after 24 hours was not confirmed, and their current density was even higher. One possible explanation involves the modification of homeostatic mechanisms that initiate physiological changes in excitatory drive and motor control of ANS outflow. According to a central fatigue model (Amann & Calbet, 2008), planning, execution, and control of voluntary muscle tasks are regulated by alterations to neurotransmitter levels and O_2 delivery which are governed by homeostatic mechanisms in the CNS in response to physical challenge. The isometric handgrip task is known to elicit sympathetic activity which stimulates the baroreceptors in the sinoatrial node of the heart through activation of the nucleus tractus solitarius (NTS; Topolovec et al., 2004). The NTS, in turn, innervates the locus coeruleus (LC) of the rostral pons of the brainstem, a nucleus which is the primary source of norepinephrine (NE) in the brain (Sharma et al., 2010). NE promotes an enhanced signal/noise ratio in sensorimotor processing and ascending arousal system responses and, acting through thalamic nuclei and sensory cortices, mediates gating and tuning influences in coordinating experience-dependent alterations to pain processing, motor control, and local blood flow (Cutsforth-Gregory & Benarroch, 2017). Consistent with central fatigue, the handgrip task was demonstrated to activate the mid/anterior insula which processes nociceptive cues to homeostatic disturbances (Hilty, Jäncke, et al., 2011). The insula processes interoception and has extensive connections with the hypothalamus for the regulation of neuroendocrine responses to physical stimuli (Allen et al., 1991). Basal cortisol has been consistently reported to be significantly lower in patients with ME/CFS (Demitrack et al., 1991; Papadopoulos & Cleare, 2012; Parker et al., 2001; Van Den Eede et al., 2007) possibly leading to reductions in cortical activity we found.

To date, this is the first study using eLORETA to examine CAN structures that may underlie disturbances in PEM. However, this was a pilot study intended to provide groundwork for a larger scale study without sample size limitations. Thus, given the small sample size of each group, the differences found here must be interpreted with caution. In addition, only diffuse changes in CAN activity were reported here, but a larger study would have potential to evaluate differences in activity for each separate region of interest. Moreover, the inclusion of autonomic measures in future studies would be beneficial to making stronger association of CAN disturbances with autonomic dysfunction in ME/CFS. Next, we recognize that eLORETA source estimations are restricted to cortical regions of interest and several subcortical regions of the CAN (thalamus, red nucleus, cerebellum) were excluded from the analyses. However, findings of cortical pathology implicate these subcortical structures due to their reentrant circuitry with cortico-subcortical fibers. Finally, significant changes to baseline current density were found in both groups after 24 hours, and future studies could include additional follow-up EEG recordings made at 48 and 72 hours to capture the pace and duration of patient recovery patterns and eventual return to baseline.

In conclusion, this study offers important preliminary evidence for CAN involvement in the episodic manifestations of PEM in patients with ME/CFS. If confirmed, the CAN current density may serve as an index of PEM for aiding diagnosis and treatment outcomes. Furthermore, this study demonstrates the feasibility of eLORETA as a practical tool for investigating PEM and revealing the neuropathic mechanisms in ME/CFS.

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None of the authors have potential conflicts of interest to be disclosed.

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NeuroRegulation

Transcranial Direct Current Stimulation (tDCS) Improves Empathy and Recognition of Facial Emotions Conveying Threat in Adults with Autism Spectrum Disorder (ASD): A Randomized Controlled Pilot Study

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Abstract

Introduction: Empathy is critical for human interactions to become shared and meaningful, and it is facilitated by the expression and processing of facial emotions. Deficits in empathy and facial emotion recognition are associated with individuals with autism spectrum disorder (ASD), with specific concerns over inaccurate recognition of facial emotion expressions conveying a threat. Yet, the number of evidenced interventions for facial emotion recognition and processing (FERP), emotion, and empathy remains limited, particularly for adults with ASD. Transcranial direct current stimulation (tDCS), a noninvasive brain stimulation, may be a promising treatment modality to safely accelerate or enhance treatment interventions to increase their efficacy. **Methods:** This study investigates the effectiveness of FERP, emotion, and empathy treatment interventions paired with tDCS for adults with ASD. Verum or sham tDCS was randomly assigned in a within-subjects, double-blinded design with seven adults with ASD without intellectual disability. Outcomes were measured using scores from the Empathy Quotient (EQ) and a FERP test for both verum and sham tDCS. **Results:** Verum tDCS significantly improved EQ scores and FERP scores for emotions that conveyed threat. **Conclusions:** These results suggest the potential for increasing the efficacy of treatment interventions by pairing them with tDCS for individuals with ASD.

Keywords: transcranial direct current stimulation; autism spectrum disorder; right temporoparietal junction; empathy; threat; facial emotion recognition; randomized controlled pilot study

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Introduction

Empathy refers to a group of socioemotional competencies that allow for perception, understanding, and affective response to the thoughts, desires, beliefs, intentions, emotions, and knowledge of other individuals (Decety & Svetlova, 2012). Empathy is critical for human interactions to become shared and meaningful (Batson, 2011), and it is often facilitated through the expression and processing of facial emotions (Clark et al., 2008). Deficits in both empathy (Blair, 2005; Reichow & Volkmar, 2010) and facial emotion recognition are associated with individuals with autism spectrum disorder (ASD; Baron-Cohen et al., 2009), with specific safety concerns over inaccurate recognition of facial emotion expressions conveying a threat (Ashwin et al., 2007; Krysko & Rutherford, 2009).

ASD is the fastest-growing neurodevelopmental disorder in the United States (CDC, 2016). Zablotsky et al. (2019) showed that the prevalence of ASD has more than doubled from 2009 to 2017, to as many as 1 in 40 children. While social interaction deficits are a key diagnostic feature for ASD (APA, 2013), Baron-Cohen and Wheelwright (2004) demonstrated that individuals with ASD who possess higher empathy abilities also show improved social relationships and overall social functioning, highlighting the need for more effective and efficient treatment interventions for improving empathy-related skills. One such skill involves the processing of facial of emotions (Baron-Cohen et al., 1995), which remains a challenge in ASD even when controlling for gender, verbal ability, and age. The impact of this challenge is pervasive as it impairs the initiation and maintenance of meaningful relationships (Reichow & Volkmar, 2010) and contributes to isolation, substance use, and depression (Hedley et al., 2016; Hofvander et al., 2009).

Currently, evidence-based treatment interventions that target empathy and facial emotion recognition abilities include computer-based, interactive formats for recognizing complex emotions and mental states (Golan & Baron-Cohen, 2006), utilizing a visual framework and video-feedback (Kern Koegel et al., 2016), and using a caregiver-mediated, manualized intervention for improving empathy and social cognition (Laugeson et al., 2015). While there are reports of positive effects from these approaches, the number of evidenced interventions remains scarce, particularly for adults with ASD, indicating a need to pursue additional interventions to increase efficacy.

One potential way to improve the efficacy of facial emotion recognition and empathy interventions utilizing a computer-based, interactive format is to pair these interventions with transcranial direct current stimulation (tDCS; Gill et al., 2015). Studies utilizing tDCS in neurotypical individuals have demonstrated improvements on empathy-related tasks, such as perspective taking and evaluation of self against others (Santiesteban et al., 2012), inferring others' mental states when identifying deception (Sowden et al., 2015), or when making moral judgments (Ye et al., 2015). Improvements in recognizing facial emotions have been demonstrated after tDCS was applied over the cerebellum (Ferrucci et al., 2012), the right orbital frontal cortex (Willis et al., 2015), and over the superior temporal cortex (Boggio et al., 2008). However, the singular task of recognizing a facial emotion requires less in-depth analysis of emotional perceptual stimuli than what is required for facial emotion recognition that also incorporates the processing of that emotion and the development of empathy (Adolphs, 2003; Krysko & Rutherford, 2009).

To target these multiple processes, the right temporoparietal junction (rTPJ) may be optimal for stimulation, because of the rTPJ's role as part of a large-scale neural network for social cognition (Kennedy & Adolphs, 2012). The rTPJ contributes lower-level processing of environmental sensory-perceptual stimuli, such as discriminating between self and others, as well as higher-level social-cognitive processing, such as perspective-taking, empathy, theory of mind (ToM; Decety & Lamm, 2007) emotion verbal fluency (Esse Wilson, Trumbo, et al., 2018), and social functioning (Esse Wilson, Quinn, et al., 2018). The rTPJ is also specifically associated with deficits in empathy and ToM in individuals with ASD (Lombardo et al., 2011). Anodal (increases cortical excitability) tDCS applied over the rTPJ in neurotypical individuals shows improved social functioning on tasks for perspective taking and evaluation of self against others (Santiesteban et al., 2012). These findings suggest that altering the cortical excitability of the rTPJ with tDCS may influence performance on tasks used during social cognition. Further, impaired facial emotion recognition and processing (FERP) has been shown to affect the typical processing of threat-based facial expressions (e.g., anger, fear), more so than other emotions (e.g., happiness, sadness, surprise, disgust; Ashwin et al., 2007; Krysko & Rutherford, 2009), suggesting a lack of vigilance and self-preservation may be a concern for individuals with ASD (Ohrmann et al., 2007). However, there are currently no studies examining the use of tDCS with individuals with ASD paired with treatment interventions for empathy and FERP, including recognition of threatening facial expressions.

The objective of the present study was to conduct a randomized controlled pilot study to investigate the feasibility of combining anodal tDCS over the rTPJ paired with a computer-based interactive FERP, emotion, and empathy intervention, and to evaluate the result of the stimulation on measures of the Empathy Quotient (EQ; Baron-Cohen & Wheelwright, 2004) and a FERP test with adults with ASD. We anticipate that this pilot study will provide a basis for a future randomized controlled trial. We hypothesize that participants will demonstrate (a) higher scores on the EQ, (b) a reduction of

inaccurate identifications on a FERP test for threat expressions, and (c) increased accuracy on the FERP test overall, after receiving verum tDCS compared to sham tDCS.

Methods

Participants

Study procedures were approved by the local Internal Review Board (IRB), the Human Research Protections Office of the University of New Mexico (UNM). Each participant also completed an informed consent process and provided signed consent before their participation in the study. Seven right-handed, English-speaking adults with mean age of 26.1 years (five males; two females; see Table 1 for complete demographics) with ASD met the study inclusion criteria and completed both sessions of the study. Participants were recruited by word of mouth and flyer postings at the UNM campus, the UNM Accessibility Resource Center, and through a posting to the Autism Speaks *Participate in Research* webpage.

Procedure

Participants attended two sessions spaced 7 days apart at the UNM Psychology Clinical Neuroscience Center and followed the procedure of our previous study examining tDCS with social functioning and social cognition (Esse Wilson, Trumbo, et al., 2018). Similar to that study, participants were screened for ASD with the Autism Quotient (AQ; Baron-Cohen et al., 2001), a reliable instrument that measures the degree adults with normal intelligence display social/behavioral traits associated with ASD (Hoekstra et al., 2008; Ruzich et al., 2015). The AQ has been found to demonstrate good psychometric properties and to adequately distinguish people with ASD from those without ASD (Lundqvist & Lindner, 2017; Zhang et al., 2016). Additionally, based on research demonstrating that 80% of adults with ASD with normal or above cognitive functioning score a 32 or above on the AQ (Baron-Cohen et al., 2001), we required a score of 32 or higher on the AQ for study participation. Last, participants were screened for right-handedness with the Edinburgh Handedness Inventory (Oldfield, 1971) and for cognitive function with the Shipley-2 (Shipley et al., 2009). The Shipley-2 is a standardized measure that provides standard scores with a mean of 100 and a standard deviation of 15. Thus, a standard score of 70 is two standard deviations below the mean on the Shipley-2. For this reason, we determined that a standard score of 70 or higher was required on the Shipley-2 for study participation.

Two pretreatment-intervention tests were administered in randomized order: (1) The Empathy Quotient (EQ; Baron-Cohen & Wheelwright, 2004) and (2) a FERP test.

The EQ is a 60-item measure for global empathy (Baron-Cohen & Wheelwright, 2004; Lawrence et al., 2004) consisting of statements about empathic skills which are rated on a 4-point Likert scale (*strongly agree*, *slightly agree*, *slightly disagree*, and *strongly disagree*). It has shown validity and reliability for measuring cognitive empathy, emotional reactivity, and social skills, both trait and state components of empathy, processes of empathy (Reniers et al., 2012), and an individual's beliefs about their own empathy. The EQ also encompasses differing aspects of empathy, such as empathic concern and perspective taking.

The FERP test consisted of 48 trials where participants viewed neutral and emotional photographic images taken from the NimStim set of normed, multicultural male and female facial emotion expressions (Tottenham et al., 2009). We designed the FERP test using a neutral-emotion-neutral presentation of faces (Matsumoto & Hwang, 2011) with each trial first presenting a face showing a neutral expression for 1000 ms, followed by an emotional image of the same face presented for 1000 ms showing one of the six facial emotion expressions of sadness, happiness, fear, surprise, disgust, or anger (Ekman, 2003), followed by another 1000 ms of the same face in a neutral expression. The participant was then asked to identify from a multiple-choice list which of the six emotions had been presented. The goal of the FERP test design was to access participants' higher-level, emotion-based cognitive processes, rather than measuring participants' abilities to identify "microexpressions" (facial emotions presented for < 250 ms) or participants' ability to use compensatory strategies for facial emotion recognition (Harms et al., 2010), which may have occurred if facial emotions were presented for > 1000 ms.

After pretreatment-intervention tests were completed, we followed the same procedures for administration of tDCS as developed in Esse Wilson, Trumbo, et al. (2018). Verum tDCS was applied over the rTPJ at 2.0 mA for 30 min, and sham tDCS was delivered with a current that increased from 0 to 2.0 mA during 20 s, then decreased to 0 mA after 30 s. The stimulation was delivered through two square 11 cm^2 saline-soaked sponge electrodes (neuroConn DC-STIMULATOR MR, neuroCare

Table 1

Participants Demographics, History, and Characteristics

Demographics	
n	7
Gender (M/F)	5/2
Age, mean years (*SD*, range)	26.1 (18–58)
History	
Category name	# of participants reporting (% of total)
Depression	4 (57)
Anxiety	4 (57)
Attention deficit	1 (14)
Hospitalization for psychiatric disorder	0 (0)
Current medication use:	
Depression	2 (29)
Anxiety	0 (0)
Illicit drug user	0 (0)
Caffeine	
Regular user	2 (29)
Used during study	2 (29)
Cigarette or other nicotine	
Regular user	0 (0)
Used during study	0 (0)
Alcohol	
Regular user	2 (29)
Used during study	0 (0)
Characteristics	
AQ score mean (*SD*)	36.14 (3.89)
Shipley-2 standard score mean (*SD*)	97 (16.95)

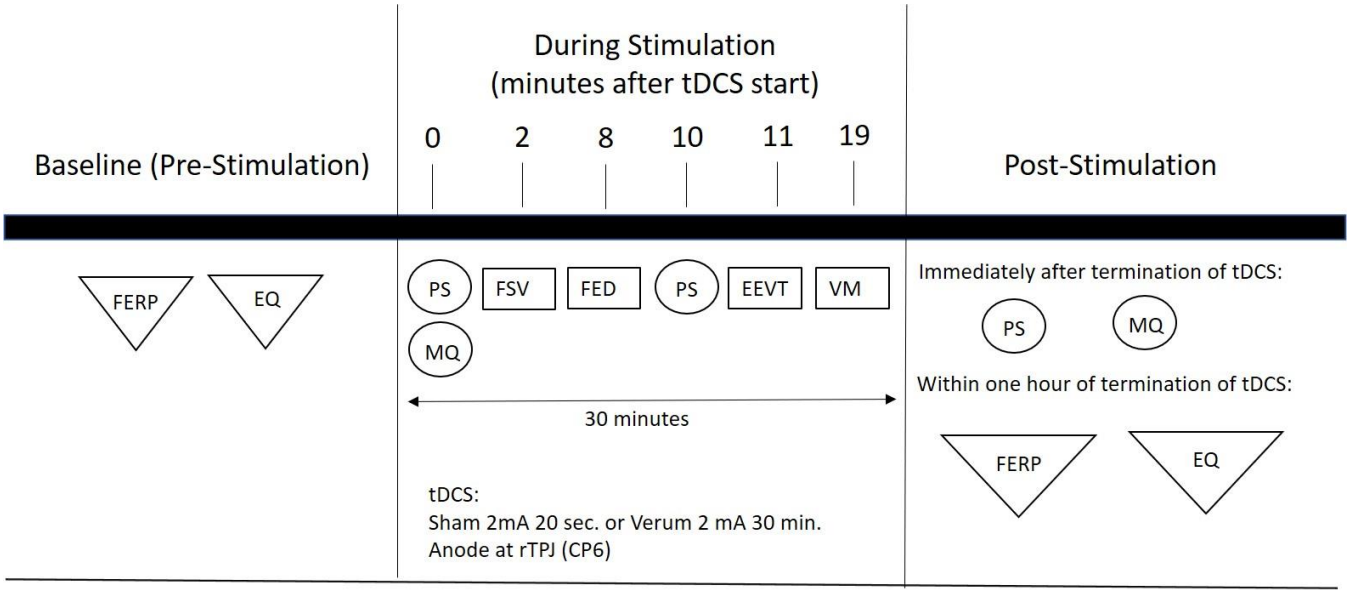
M/F = male/female; *SD* = standard deviation; tDCS = transcranial direct current stimulation; AQ = Autism Quotient

Group, Munich, Germany) with anode over CP6 (10–10 EEG system) and cathode over the ipsilateral deltoid. Participants randomly received either verum or sham tDCS during each of the two experimental sessions. If a participant was randomly assigned to receive sham tDCS in the first session, then they received verum tDCS in the second session, and vice versa. Both the assessing researcher and the participant were blinded as to which condition the participant was in until after the completion of the second visit. Blinding was accomplished through the use of a unique code for each participant that was programmed into the neuroConn stimulator by a coauthor who did not participate in assessment.

Verum and sham tDCS were paired with computer-based, interactive FERP, emotion, and empathy interventions that included video modeling depicting the use of conversation rules across a variety of social situations, facial emotion recognition training, and complex emotion and empathy training utilizing empathy words, photos, and embedded narrated short videos. Additionally, administration of two questionnaires during both verum and sham tDCS was completed: (1) a mood questionnaire (MQ) administered twice to detect any mood changes

(given within first minutes of stimulation and immediately after termination of stimulation), and (2) a physical sensations (PS) questionnaire to detect levels of itching, heat, and tingling (taken at three separate time points—first minutes of stimulation, approximately 10 minutes after start of stimulation, and immediately after termination of stimulation). After receipt of tDCS and interventions, administration of the EQ and FERP test were completed. A timeline summarizing study's prestimulation, stimulation, and poststimulation activities is depicted in Figure 1.

Figure 1. *Timeline Summarizing Study's Prestimulation, Stimulation, and Poststimulation Activities*.



Note. Items in triangles are measures where FERP = Facial Emotion and Recognition and Processing test, and EQ = Empathy Quotient; items in circles are questionnaire assessments, PS = physical sensation questionnaire and MQ = mood questionnaire; and items in rectangles refer to treatment tasks where FSV refers to faces and shapes viewing, FED to facial emotion detection, EEVT to emotion and empathy video treatment, and VM to video modeling.

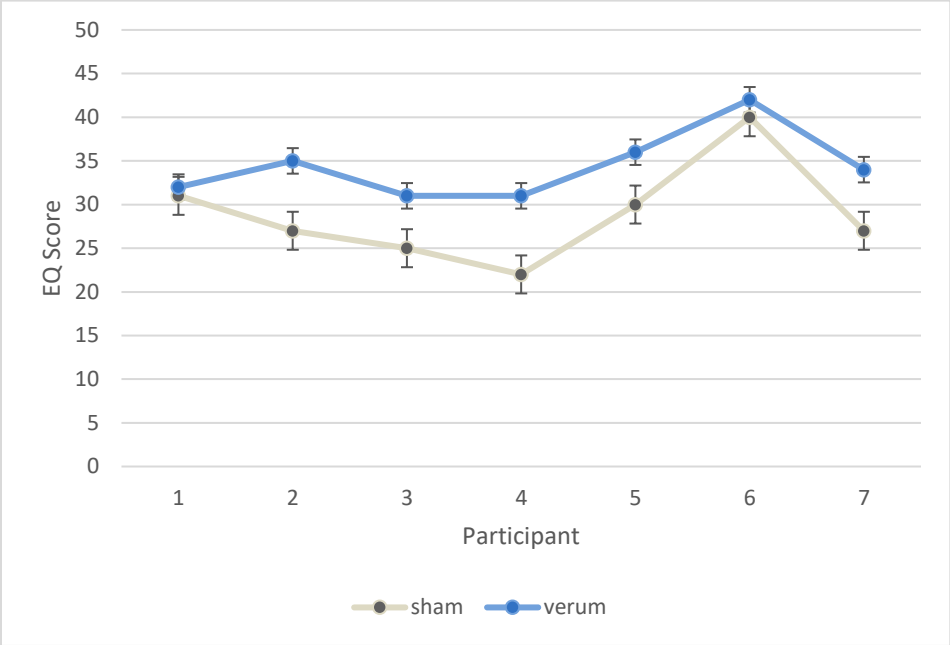
Statistical Analysis

Due to the high level of heterogeneity in the ASD population (Jeste & Geschwind, 2014), we used a within-subjects, repeated-measures design, which allowed participants to act as their own controls over the two randomly assigned (one verum, one sham), double-blinded sessions. A Wilcoxon signed-rank test was utilized to examine if group differences existed (verum tDCS, sham tDCS). This test is considered nonparametric, so minimal assumptions needed to be made about the data, such as it being normally distributed, and it is well-suited for repeated measures with paired data (Whitley & Ball, 2002). Analyses were two-tailed with an alpha level set at 0.05.

Results

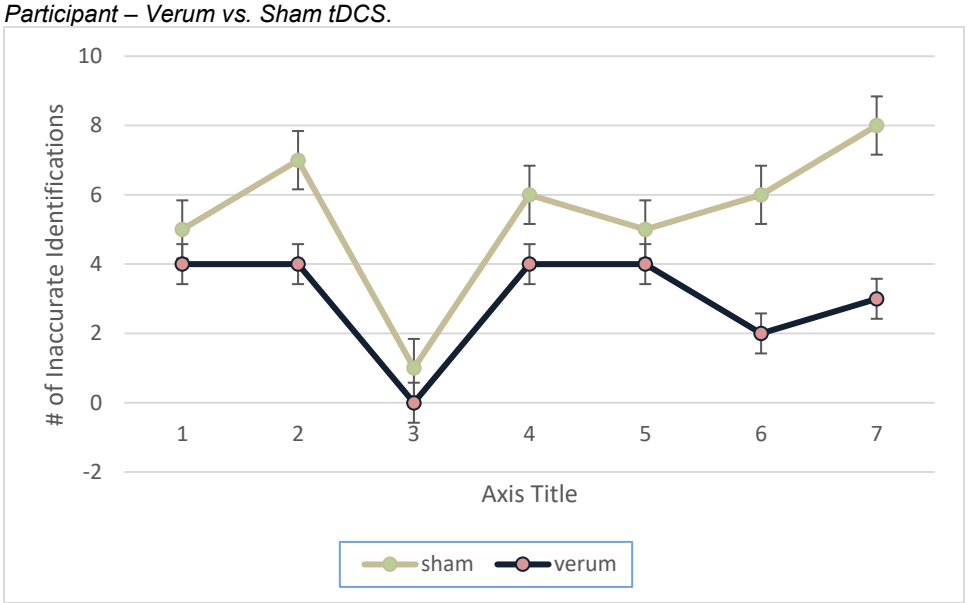
Of the seven participants who participated in the study, all met screening criteria and completed both visits for the study. No significant changes in mood from the MQ or pain from the PS questionnaires were reported from either the verum or sham tDCS sessions. Additionally, examination of mean participant rating scores from the PS questionnaire assessing tingling, burning, and itching sensations showed no significant differences when comparing verum to sham sessions (p = .39). Participants received a significantly higher score on the EQ, $Z = -2.366$, $p < .02$, $r = .68$, and had significantly less inaccurate identifications of threatening facial emotion expressions, $Z = -1.90$, $p < .02$, $r = .55$, after receiving verum tDCS compared to sham tDCS. Differences approached significance for overall accuracy in identifying the basic six emotions when comparing verum to sham tDCS, $Z = -1.61$, $p < .06$. Findings for the EQ and inaccurate identifications of threatening facial emotion expressions are depicted in Figures 1 and 2.

Figure 1. *EQ Scores by Participant – Verum vs. Sham tDCS.*



Note. Participants scored significantly higher on the Empathy Quotient after receipt of verum tDCS compared to sham tDCS ($p < .02$). Verum and sham scores are shown for each participant. EQ = Empathy Quotient; tDCS = transcranial direct current stimulation.

Figure 2. *Number of Inaccurate Identifications of Threatening Facial Expressions by Participant – Verum vs. Sham tDCS.*



Note. Participants made significantly less inaccurate identifications of threatening facial emotion expressions in the verum tDCS condition compared with the sham tDCS condition ($p < .02$). Verum and sham scores are shown for each participant. tDCS = transcranial direct current stimulation.

Discussion

The present randomized controlled pilot study compared the effects of tDCS applied over the rTPJ in verum (2.0 mA for 30 min) and sham conditions (2.0 mA for 20 s then decreased to 0 mA after 30 s) in adults with ASD who are not intellectually disabled as they completed computer-based, interactive emotion, and empathy interventions. The measures used to compare these two conditions included the EQ (measuring global empathy) and a FERP test (measuring overall recognition accuracy from briefly presented facial emotion expression images, as well as accuracy on recognition of threat expressions). It was hypothesized that participants would demonstrate (a) higher scores on the EQ, (b) less inaccurate identifications on the FERP test for threat expressions, and (e) increased accuracy on the FERP test as a whole, after receiving verum tDCS compared to sham tDCS. Our hypothesis was correct for (a) and (b) with participants scoring significantly higher on the EQ, and also reducing the number of inaccurate identifications for threat expressions on the FERP test after verum tDCS when compared to sham tDCS. Our hypothesis for (c) was found incorrect, although differences approached significance. These findings provide support for a preliminary model for the use of computer-based interactive FERP, emotion, and empathy interventions paired with tDCS applied over the rTJP for reducing inaccurate identifications of facial expressions depicting threat (fear, anger) and for increasing empathy skills.

The results of our study suggest that the efficacy of treatment interventions can be improved when using tDCS to modulate neural processing while simultaneously completing interventions that target the building of skills for FERP and emotion and empathy processing. Our findings corroborate studies demonstrating that some individuals with ASD show improvement on measures of facial emotion recognition after they develop skills specific to this task, despite a continued underlying presence of atypical neural processing (Harms et al., 2010; Krysko & Rutherford, 2009). In our study, we capitalized on the relationship of FERP to empathy (Clark et al., 2008) during the receipt of treatment intervention, while also utilizing tDCS over the rTPJ to additionally target underlying neural processing.

Because facial expressions convey emotion, previous studies utilizing tDCS have targeted brain regions known for facial emotion recognition, such as the right orbitofrontal cortex (Willis et al., 2015), the superior temporal cortex (Boggio et al., 2008), or the posterior superior temporal sulcus (Harms et al., 2010). While anger and fear facial expressions may also implicate these brain regions, the rTPJ is specifically implicated in handling the higher-level social-cognitive information necessary for processing complex emotions (Decety & Lamm, 2007). This led our study to choose the rTPJ as a stimulation site for tDCS for processing emotions, including the complex social-cognitive construct of threat. This is an extension of previous research utilizing tDCS over the rTPJ to improve emotion processing during emotion verbal fluency tasks with adults with ASD (Esse Wilson, Trumbo, et al., 2018). Future directions may utilize tDCS over the rTPJ with individuals with ASD to examine emotion processing of facial and body expressions, as well as emotion-based words and phrases, that convey threat. Additionally, future research may incorporate tDCS applied over other brain regions, such as the orbitofrontal cortex, the superior temporal cortex, or the posterior superior temporal sulcus, in conjunction with treatment interventions for social functioning and social cognition. While the present study includes empathy and FERP measures, future studies might also investigate utilizing measures specific to ToM. Additionally, future work may also apply to other groups with deficits in socioemotional processes, such as individuals with fetal alcohol spectrum disorder.

This effort was completed as a randomized controlled pilot study on the feasibility and potential efficacy of combining tDCS paired with FERP, emotion, and empathy interventions. Participants in our study self-identified as having ASD, with a score of 32 or higher required on the AQ for participation. Future pilot studies might also confirm diagnosis with a standardized clinical assessment tool. Last, use and safety of tDCS with children suggests that this approach may be extended to adolescents with ASD (Ciechanski & Kirton, 2017; Palm et al., 2016).

Conclusions

Our study supports the feasibility and efficacy of utilizing anodal tDCS over the rTPJ during a computer-based interactive FERP, emotion, and empathy intervention with adults with ASD without an intellectual disability. All participants completed the study tasks of both sessions, as well as pre- and postassessments. Additionally, PS questionnaires were given to participants during receipt of tDCS to assess levels of tingling, burning, and itching sensations, with no adverse events reported. Verum or sham tDCS was randomly assigned in a within-subjects, repeated-measures, double-blinded design

over two visits separated by 1 week. Outcomes were assessed using the EQ and a FERP test. Paired data were analyzed to examine if group differences existed when comparing verum to sham tDCS. It was predicted that differences would be found when comparing EQ and FERP scores for verum and sham tDCS. Participants received a significantly higher score on the EQ and had significantly less inaccurate identifications of threatening facial emotion expressions after receiving verum tDCS compared to sham tDCS. These findings are consistent with a role for the rTPJ in empathy and FERP in adults with ASD and provide optimism for the use of tDCS paired with FERP, emotion, and empathy interventions.

Author Declaration

Sandia National Laboratories is a multimission laboratory managed and operated by National Technology and Engineering Solutions of Sandia, LLC, a wholly owned subsidiary of Honeywell International, Inc., for the U.S. Department of Energy's National Nuclear Security Administration under contract DE-NA0003525. Opinions expressed are those of the authors and not necessarily those of the U.S. Government. Sandia Laboratory approval number SAND2021-6043 J.

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NeuroRegulation

Mobile Evaluation of Heart Rate Variability Using the Diver's Reflex

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Abstract

Introduction. Heart rate variability (HRV) is considered a marker of autonomic nervous system (ANS) function and a biomarker of interest in evaluating nervous system function following traumatic brain injury. This study validates prior research with larger sample sizes and proposes a model for establishing baseline HRV reactivity in healthy participants. **Methods.** Sixty-two healthy collegiate athletes were recruited for this study. Following informed consent, they were evaluated supine using the Elite HRV CorSense monitor and platform to record low frequency/high frequency (LF/HF) ratio and root means square of successive differences (RMSSD) over 5 min. A bag of ice was placed on their face, then RMSSD and LF/HF ratio were collected over three successive 1-min intervals. **Results.** RMSSD was elevated at 1 and 2 min (+47.4 ms, $p < .0001$; +16.5 ms, $p = .014$) following face cooling and fell to baseline at 3 min (+4.6 ms, $p = .52$). LF/HF ratio decreased following face cooling at 2 and 3 min (change from rest %: 2 min, −33%, $p = .007$; 3 min, −50%, $p = < .0001$). **Conclusion.** The Elite HRV platform can detect an elevation in RMSSD in the first minute following face cooling with a return to baseline in the second and third minutes. It can also detect a consistent decrease in LF/HF following face cooling.

Keywords: HRV; RMSSD; LF/HF; concussion; CorSense

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Introduction

Heart rate variability (HRV) is defined as the fluctuation in time intervals per heartbeat (Shaffer & Ginsberg, 2017). HRV that is too low reflects impaired adaptability of the cardiorespiratory system to stress, whereas HRV that is too high can be indicative of pathologic states which can confer an elevated risk of mortality (Stein et al., 2005). Clinically HRV has been used to evaluate patients with serious arrhythmias or other high mortality cardiac conditions to predict cardiac function in conjunction with other clinical markers (Kleiger et al., 2005). Of particular interest to sports medicine is HRV's role as a marker of autonomic dysfunction in cases of concussion, as research is demonstrating HRV could be used to quantitively evaluate autonomic recovery from brain injury (Gall et al., 2004; Katz-Leurer et al., 2010; Senthinathan et al., 2017; Vistisen et al., 2014).

The term "HRV" refers to a set of data acquired from a reading that includes RR-intervals, root means square of successive differences (RMSSD), low frequency/high frequency (LF/HF) ratio, and many others (Shaffer & Ginsberg, 2017). RMSSD and the LF/HF ratio have been shown to be different between healthy and postconcussion subjects and so are the focus of this study (Johnson et al., 2018; Senthinathan et al., 2017). RMSSD reflects the individual beat-to-beat variances in heart rate over a measured interval and has been shown to estimate autonomic nervous system (ANS) effects on HRV (Shaffer & Ginsberg, 2017). The LF/HF ratio measures the relative power of the LF and HF bands in spectral analysis of HRV (Shaffer & Ginsberg, 2017). The LF portion (0.04–0.15 Hz) is controlled

by both the sympathetic (SNS) and parasympathetic nervous system (PNS), while the HF portion (0.15–0.40 Hz) is predominantly controlled by the PNS alone (Shaffer & Ginsberg, 2017).

Following a concussion, the decision to return to play is a complicated one made jointly by athletes, coaches, and clinicians. Current guidelines suggest return to play is appropriate when symptom scores, neurologic evaluation, and cognitive activity all return to baseline (Patricios et al., 2018). Most adolescent and collegiate athletes recover from an uncomplicated concussion in 7 to 10 days (Leddy et al., 2012). Unfortunately, for some athletes, symptoms may persist after the return to play decision is made and can possibly progress into postconcussive syndrome where symptoms prevent the athlete from playing for months after their injury (Miranda et al., 2018). Autonomic and vestibular deficits in particular have been shown to persist in some athletes even after return to play decisions have been made (Blake et al., 2016; Collins et al., 2016; Esterov & Greenwald, 2017). Because HRV is a reflection of the ANS it can be used as an objective marker to measure physiologic recovery especially when there is a baseline prior to injury for comparison.

One limitation to the use of HRV is the time and equipment required to collect this data. Raw HRV data is traditionally collected using an echocardiogram (ECG), then reflected in mathematic calculations either by hand or with software. Several products have been commercialized to streamline this process without a traditional ECG including chest bands, wristbands, and one-lead finger ECG scanners. These have been shown to adequately reflect changes in HRV despite not having the same accuracy as a traditional ECG (Guzik et al., 2018; Perrotta et al., 2017).

The device used in this study was the Elite HRV CorSense monitor. This product is a one-lead ECG that clips on to the subject's index finger. The device is operated via a user-friendly smartphone application available both on iOS and Android phones. It is relatively low cost and calculates the data metrics for HRV within the application giving the user a readout within a minute once a session is completed. This eliminates the need for external software processing. It does not provide a raw rhythm strip like a traditional ECG. The monitor and application are highly mobile, allowing for evaluation away from a medical center.

Other studies that evaluate the adaptive autonomic response to stress have used cardiovascular exercise, resistance training, standing, and exacerbation of the "diver's reflex" as possible stressors (Blake et al., 2016; Gall et al., 2004). The diver's reflex is the transient autonomic response to a cold substance to thermoreceptors located in the face and hands. Prior studies have shown a noticeable change in HRV via RMSSD when comparing the value before, during, and after this reflex using a traditional three-lead ECG (Johnson et al., 2018; Leddy et al., 2017; Leddy et al., 2012). These changes have been appreciable within one minute of exposure, making it an ideal test to monitor the ANS response to a stressor rapidly.

This study is the normative arm of a project originally developed to study athletes before and after concussion. Due to the COVID-19 pandemic only normative data is published here because all athletics were halted at the peak of the pandemic, which prevented sports-related concussions from occurring. Nunan et al. (2010) compiled a systematic review of 44 published articles establishing normative short-interval HRV data in healthy adults. These data were primarily collected with three-lead ECGs or Holter monitoring. The participants in this study also cover the entire age spectrum and have disparate baseline levels of physical activity. The Johnson study discussed above also has sample size < 20 and focus on females only (Johnson et al., 2018). This study establishes normative data for ambulatory short-interval HRV recording in college-age men and women with high levels of baseline physical activity using equipment that may be more accessible than a three-lead ECG or Holter monitor in an ambulatory setting. These norms may be useful for athletic trainers, clinicians, or researchers wishing to assess HRV for training or recovery purposes with an accessible and fast method (Dong, 2016).

The goal of this study is to evaluate the utility of the Elite HRV CorSense monitor in detecting a change from baseline using the diver's reflex as a stressor. Our hypothesis is that the diver's reflex produces a sympathetic response from the ANS that can be detected by the RMSSD and LF/HF data in the first minute and then return to baseline as previously shown in other studies (Johnson et al., 2018). If an appreciable difference is detected, this would provide validity for future studies to use the Elite HRV CorSense monitor to rapidly measure HRV rather than a traditional ECG.

Methods

Participants

Sixty-two participants (35 men and 27 women) from Western Michigan University (WMU) football, baseball, softball, basketball, soccer, and volleyball teams were included in this study (Table 1). Demographic information was not collected. Participants were excluded from the study if they were under the age of 18.

The study protocol was jointly approved by the Institutional Review Boards (IRBs) at both Western Michigan University Homer Stryker M.D. School of Medicine (WMed) and WMU. The target athletes were asked to participate in the study following their presports physical in the WMU Health Center. There was an informed consent process approved by both boards prior to initiation of the protocol described below. All participants who opted-in provided written informed consent and were informed there was no compensation for participation in this study.

Table 1

Participant Demographic Information

Team	Frequency	Percent	Sex	Frequency	Percent
Football	18	29.0	Male	27	43.6
Men's Baseball	1	1.6			
Men's Basketball	1	1.6			
Men's Soccer	15	24.2			
Women's Basketball	1	1.6	Female	35	56.5
Women's Soccer	18	29.0			
Women's Softball	2	3.2			
Women's Volleyball	6	9.7			

Study Design

This was a cross-sectional study, performed in a single session with each participant. For the participants who opted-in, a researcher described the study, an information sheet was provided, and written consent was obtained. The researcher then led the participant through HRV monitoring at rest and then with face cooling (FC) using an Elite HRV CorSense monitor.

Protocol

The participants were asked to find a comfortable position with eyes closed and the Elite HRV CorSense monitor was placed on the index finger of the participant's choice. A 5-min at-rest reading was recorded, then FC was achieved by placing a pliable 2 L plastic bag of ice on the forehead, eyes, and cheeks of the participant for a total of three continuous readings recorded at 1-min intervals. During recording sessions no additional instruction was provided for respiratory pattern.

Elite HRV CorSense Monitor

The CorSense HRV monitors were purchased from the Elite HRV company for use for this project. Readings were collected through the Elite HRV application for mobile devices. The RMSSD and LF/HF data were collected for each reading from the application. Per the Elite HRV website, the platform applies the RMSSD calculation to its recorded R-R intervals via industry standard and defines waves 0.04–0.15 Hz as LF and waves 0.15–0.40 Hz as HF.

Limitations

Demographic information including mental health about the athletes was not collected, and sex was inferred from the athletic team of the participant. There were some technical issues with connecting CorSense HRV monitors to mobile devices, sometimes interfering with data collection times. Much of the detailed information about how Elite HRV specifically calculates RMSSD and LF/HF is proprietary information, and any studies this company has performed verifying the accuracy and precision of their monitors are not public information.

Statistical Analyses

All data analysis was completed in SAS v9.4 (Cary, NC). Repeated-measure general linear models (GLMs) were used to analyze the relationship of the two outcome measures, RMSSD and LF/HF ratio, to possible predictors including condition (with four levels: at rest, first minute, second minute, and third minute of FC) as well as sex. Sex was tested as a possible predictor in a model that controlled for condition. Due to the positive outliers and right-skew of the LF/HF ratios (Figure 1), the GLM for this outcome measure used the log transformation,

which better conformed to the normality assumption of GLMs. A Bonferroni-adjusted significance level of 0.0167 was used for the tests for change in HRV from rest at 1, 2, and 3 minutes of FC. In order to compare our estimates to the reference values for RMSSD, LF/HF, and Log LF/HF provided by Nunan et al., we calculated our mean and their mean as a percentage of their mean and used the standard deviation they provided in order to calculate a standardized difference (Table 2; Nunan et al., 2010).

Ethical Considerations

A research ID was generated for all participants in order to deidentify their data. All data were entered into our database using the participant's research ID. No coaching or training staff had access to the participants' raw or deidentified data.

Results

RMSSD

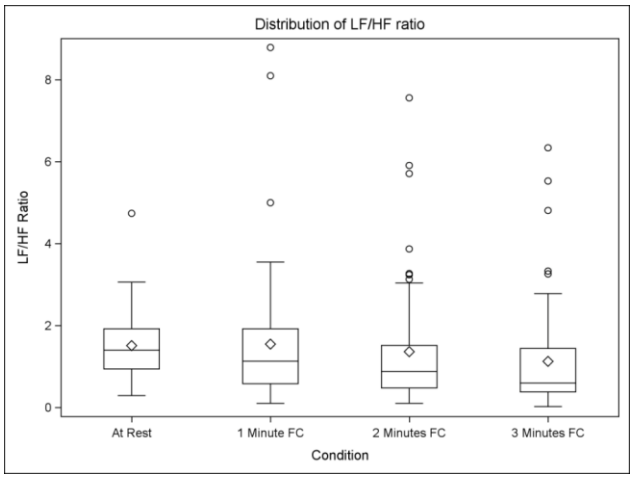
Time after FC initiation was a significant predictor of RMSSD (p < .0001, Figure 2). The overall mean (*SD*) RMSSD at rest was 91 (6.1) ms. RMSSD increased to 138.2 (6.1) ms after 1 minute of FC, then dropping to 107.0 (6.1) ms at 2 minutes of FC, and dropping again to 94.8 (6.2) ms at 3 minutes of FC (Table 3). The elevated RMSSD at 1 and 2 minutes of FC were both significant changes from RMSSD at rest, but not at 3 minutes. Controlling for time after FC initiation, sex was not found to be a significant predictor of RMSSD (p = .3).

Table 2

Our Mean RMSSD and LF/HF Ratio for the "At Rest" Condition Compared to the Reference Ranges Outlined in Nunan et al. (2010)

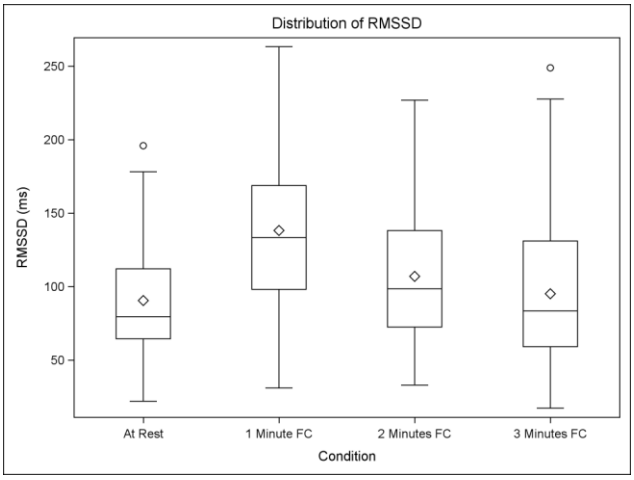
Measure	Our Mean	Nunan Reference Mean	% Difference	Normalized Difference	Nunan Range of Means
RMSSD	91	42	117%	3.3	19–75
LF/HF Ratio	1.5	2.8	−46%	−0.5	1.1–11.6
Log LF/HF Ratio	0.26	0.69	−62%	0.6	−2.14

Figure 1. *Distribution of LF/HF Ratio as a Function of Condition*.



Note. "At rest" refers to the 5-min period of rest prior to face cooling (FC). Each subsequent column refers to the end of the interval at which data was collected. Therefore, 1 minute FC reflects HRV during 0 to 1 minutes of FC, 2 minutes FC refers to 1 to 2 minutes, and 3 minutes FC refers to 2 to 3 minutes. Diamond boxes refer to the mean and open circles are outliers. Table 3 lists LF/HF ratio changes and their comparisons to rest with statistical significance.

Figure 2. *Distribution of RMSSD as a Function of Condition*.



Note. "At rest" refers to the 5-min period of rest prior to face cooling (FC). Each subsequent column refers to the end of the interval at which data was collected. Therefore, 1 minute FC reflects HRV during 0 to 1 minutes of FC, 2 minutes FC refers to 1 to 2 minutes, and 3 minutes FC refers to 2 to 3 minutes. Diamond boxes refer to the mean and open circles are outliers. Table 3 lists RMSSD changes and their comparisons to rest with statistical significance.

Table 3
Minute of FC Compared to "At Rest" for RMSSD and Raw LF/HF

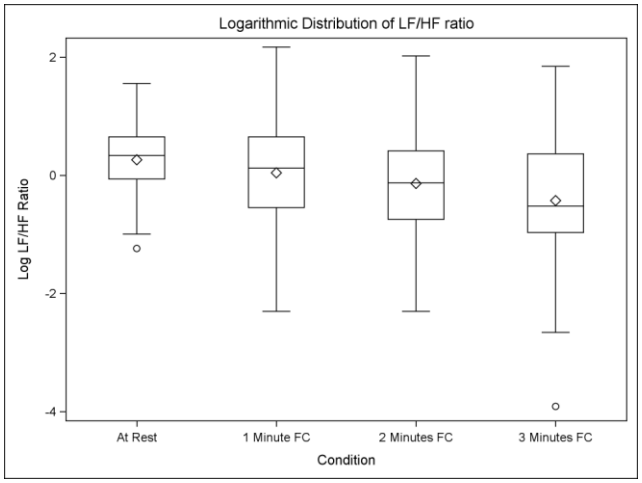
	RMSSD		LF/HF	
	Change from rest (ms)	*p-value*	Change from rest (%)	*p-value*
Minute 1	47.7	< .0001*	−20	.13
Minute 2	16.5	.014*	−33	.007*
Minute 3	4.3	.52	−50	< .0001*

*$p < .05$

LF/HF

The GLM estimates the mean of the Log LF/HF. Consequently, the LF/HF mean estimates, obtained by exponentiating the GLM estimates, represent geometric means. Time after FC initiation was a significant predictor of Log LF/HF ratio ($p < .0001$, Figure 3). The overall mean LF/HF ratio at rest was found to be 1.5 (1.1); mean Log LF/HF ratio at rest was 0.26 (Table 2). LF/HF ratio decreased to 1.04 (1.1) at 1 minute of FC and continued decreasing to 0.88 (1.1) at 2 minutes of FC and 0.65 (1.1) at 3 minutes of FC. The decreased LF/HF ratios at 2 and 3 minutes of FC were both significant changes from rest, but not at 1 minute. Controlling for time after FC initiation, sex was not found to be a significant predictor of Log LF/HF ($p = .48$).

Figure 3. *Distribution of Log LF/HF by Condition*.



Note. Logarithmic distribution was used due to positive outliers and right skew of the raw LF/HF ratio in Figure 2. Log LF/HF better conformed to the normality assumption in generalized linear models. "At rest" refers to the 5-min period of rest prior to face cooling (FC). Each subsequent column refers to the end of the interval at which data was collected. Therefore, 1 minute FC reflects HRV during 0 to 1 minute of FC, 2 minutes FC refers to 1 to 2 minutes, and 3 minutes FC refers to 2 to 3 minutes. Diamond boxes refer to the mean and open circles are outliers.

Discussion

The primary findings from this study were that the Elite HRV CorSense monitor was able to detect changes in RMSSD and the LF/HF ratio from rest over 3 min of FC in healthy athletes. RMSSD increased from rest with FC at 1 min, then fell back to baseline at 2 and 3 min. LF/HF ratio steadily decreased from rest becoming statistically significant beginning at minute 2 of FC. These findings were also consistent across sex; male and female athletes had similar trends in RMSSD and LF/HF ratio over the 3-min FC interval. These data support the use of short intervals (1 and 5 min) to monitor RMSSD and LF/HF in college aged athletes using the Elite HRV CorSense monitor.

Our study shows that a baseline can be established for RMSSD and LF/HF ratio using the Elite HRV CorSense monitor and their platform in under 10 minutes. Our methods could be used as a framework for future studies interested in evaluating HRV in the setting of traumatic brain injury (Johnson et al., 2018). The major benefit of a brief protocol is that baselines can be collected for a large group of athletes prior to injury, so each athlete can act as their own control postconcussion; previous studies on HRV with respect to concussion have failed to collect a baseline set of HRV metrics prior to concussion for their subjects.

Having a brief protocol is not without limitations. A 5-min recording time was chosen for our at-rest reading time because it has been accepted in the field as adequate for short-term evaluation of RMSSD and the LF/HF ratio (Shaffer & Ginsberg, 2017). The 1-min recording time with FC was chosen because the diver's reflex is a transient increase in cardiac PNS activity lasting about 1 to 2 minutes, and so a shorter reading was required in order to capture this (Johnson et al., 2018). This means that recordings of variable lengths were compared to each other which is nonideal as longer recordings capture more HRV (Shaffer & Ginsberg, 2017). Our study demonstrates that despite this complication, a statistical difference between variables was still demonstrated and is a sufficient tool for evaluating HRV in this setting. Of note, LF and HF have established minimum recommended recording times of 2 min and 1 min, respectively, and are less consistent in short reading sessions as a 1-min reading could only capture two to nine cycles in

the LF band, but unfortunately the diver's reflex is not sustained long enough to be captured in a longer reading time (Abhishekh et al., 2013; Berkoff et al., 2007).

An interesting—and counterintuitive—finding of our study was that while RMSSD and LF/HF ratio are both considered markers of HRV, their patterns of change with FC are different. Where the RMSSD was significantly different from rest for the first and second minutes of FC only, LF/HF ratio was significantly different for the second and third minutes, but not for the first. Similar findings were shown in a study by Schipke and Pelzer (2001) who also used the diver's reflex to evaluate HRV through gradual immersion into a pool (Schipke & Pelzer, 2001). Their study demonstrated that the HF band, which is more reflective of PNS activity, had a more significant change in each stage than the LF band. This led to a decrease in LF/HF ratio in each stage as the participant progressed to full immersion into the pool. We propose that in an analogous way, prolonged FC leads to a gradual increase in HF band through PNS activation, leading to a drop in LF/HF after the first minute of FC.

Some confounding factors that have been shown to affect HRV include sex, race, prior medical history, recent alcohol or other substance use, and certain medications (Shaffer & Ginsberg, 2017). In this study we recruited athletes of both sexes to make our comparisons and found that sex was not a statistically significant confounding variable. We did not, however, separate or screen our subjects for any of the other confounding variables listed above. A comprehensive screen was beyond the scope of our proposal, though important to consider are the temporal factors such as a subject's current medication profile and recent substance use which could transiently affect a subject's baseline. Comparing values following disease to a baseline would ideally be done in similar conditions, and it becomes important to consider how these transient factors could manipulate a subject's baseline or postinjury readings.

Elite HRV and other commercial products have garnered criticism that their platforms and devices may not be as accurate as the three-lead ECG used in many other prior studies (Garabelli et al., 2017; Guzik et al., 2018; Perrotta et al., 2017). When comparing our mean data at rest to the reference range described in Nunan et al. (2010; Table 2), our RMSSD falls outside the range of reported means, but our LF/HF ratio and the log transform are within the range of literature values. On one hand, these data may be reflective of the population differences between the young active adults in our study versus the broad scope of Nunan et al. (2010). On the other hand, it may validate the criticism that Elite HRV is not as accurate at measuring RMSSD as a three-lead ECG. Given this discrepancy, the raw values cannot be compared between devices without further research. However, our study does demonstrate that the Elite HRV device is precise enough to detect changes based on condition, and so we would recommend use of Elite HRV when this is the aim. Caution must be taken when comparing HRV metrics between an ECG and a commercial product, and any clinical management of serious conditions affecting mortality should be evaluated with a standard ECG over a 24-hour period rather than the shorter epochs described here. It has not been apparent to our group that the commercial products described in this paper have been explored enough to have utility outside of exercise and sports physiology.

The American Medical Society of Sports Medicine official position statement on concussion from 2019 supports the use of subsymptomatic exercise to expedite recovery from concussion in subjects that can tolerate it (Harmon et al., 2019). This field has begun investigating biologic markers as well as physiologic markers such as HRV (McCrea et al., 2017). Due to the heterogenous nature of concussion, it is likely that HRV would not be a metric to track in all concussions, but instead those with significant autonomic deficits following injury. Having the ability to monitor HRV without an ECG would reduce effort required for researchers, patients, and clinicians to use HRV as a tool in the recovery process.

Conclusion

The Elite HRV CorSense monitor was able to detect a rise in RMSSD from rest with 1 min of FC, and a subsequent fallback to baseline afterwards. This provides a time-efficient and user-friendly framework to measure the adaptive response of the ANS to stressors such as FC, and further research should be done to characterize these changes from baseline in conditions where the ANS is impaired. These data could be used as a reference for researchers and clinicians in evaluating HRV following traumatic brain injury to evaluate the ANS.

Author Disclosure

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Trademarked Equipment Used

Elite HRV CorSense monitor and platform from Elite HRV out of Asheville, NC.

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NeuroRegulation

A Meta-Analysis of the Effect of Neurofeedback on Depression

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Abstract

This meta-analytical study examined the effect of neurofeedback (NF) on decreasing depression. The main finding of the meta-analysis was that NF resulted in a large (g = −0.91) decrease in depression. This finding can be explained through the various roles of brainwave oscillations in terms of both the formation and persistence of depression and the development of oscillatory patterns less compatible with depressive states. One plausible mechanism for NF's depression-reduction effect is that of the approach-withdrawal model as related to not only the asymmetrical activation of the frontal regions but also the hypoactivity of the amygdala. Future research might uncover other possible explanations for NF's observed efficacy as a means of reducing depression. The findings of the study provide some support for the utilization of NF as either a complement to the pharmaceutical treatment of depression or, given its effect size, a standalone therapy. However, because NF research base is immature in comparison to the research base on pharmaceutical antidepressants, additional analysis remains necessary.

Keywords: neurofeedback; depression; biofeedback; arousal-withdrawal model; frontal alpha asymmetry; amygdala

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Introduction

In 2017, 264 million people globally had some form of depressive disorder (James et al., 2018). The prevalence of major depressive disorder (MDD) has been between 4 and 4.7% from 1990 onwards (Baxter et al., 2014). Depression is a costly disease in terms of its impacts on (a) medical expenses, particularly in the case of treatment-resistant depression (TRD; Shin et al., 2020); (b) workplace productivity (Bubonya et al., 2017); and (c) decreased quantity and quality of life (Jia et al., 2015). For these and other reasons, there is an abiding public health interest in decreasing the prevalence and intensity of depression.

Globally, pharmaceutical treatments of depression are common (Shin et al., 2020), but there is also growing evidence for the potential efficacy of nonpharmaceutical treatments such as psychotherapy, meditation/mindfulness, and biofeedback (BF), as in the form of neurofeedback (NF). Nonpharmaceutical approaches are particularly promising in cases of TRD, which are both more costly (Shin et al., 2020) and, by definition, more difficult to resolve through accepted treatments. Increasing interest in nonpharmaceutical approaches to treating depression has resulted in numerous studies on the possible effectiveness of NF as a depression-reducing modality.

As the body of studies on NF grows, a meta-analysis is capable of providing a more accurate estimate of the effect of NF on depression while also isolating themes related to the effectiveness of NF that require additional research attention. The two purposes of this meta-analysis are to (a) calculate a Hedges' g measure of effect size for the effect of NF

on depression symptom reduction and (b) discuss possible reasons for the observed effectiveness of NF as a nonpharmaceutical approach to the reduction of depression. The results are of interest as not only a contribution to the meta-analytical literature on NF but also as a means of identifying and discussing the theoretical reasons for NF's possible antidepressant properties.

Methods

Study data were collected with the objective of deriving a point estimate and accompanying 95% confidence interval (*CI*) for the effect of NF on depression, as measured by Hedges' *g*, a commonly preferred measure of effect size (Peng & Chen, 2014). Figure 1 below is the PRISMA flow diagram for the meta-analysis, with the primary database source for articles being PUBMED. The primary reason for study exclusion was failure to report both depression means and standard deviations for before- and after-NF conditions.

Results

Table 1 below contains a summary of the included studies (k = 11). Some studies contained more than one NF protocol, allowing more than one result to be extracted. The Beck Depression Inventory (BDI-II; Beck et al., 1996) was used in all but one of the included studies.

Figure 1. *PRISMA Flow Diagram for Meta-analysis*.

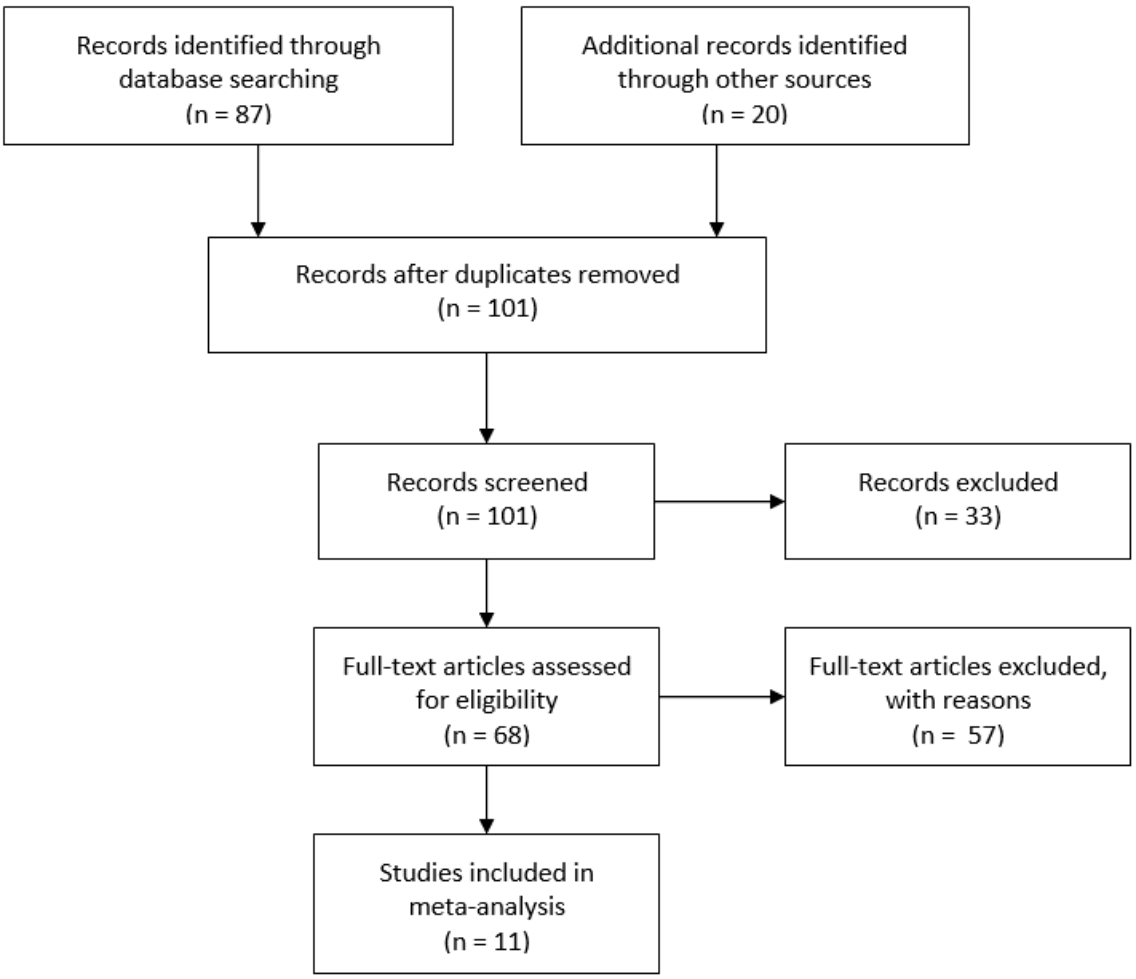


Table 1

Summary of Studies in Meta-Analysis

Citation	Depression (D) Measure	D Before NF: *M* (*SD*)	D After NF: *M* (*SD*)	Sample Size (Control) and Description	NF Protocol
Yu et al. (2020)	BDI-II	24.90 (8.25)	16.80 (9.24)	14 (Chinese university students)	10-11 Hz uptraining, Fp1 & Fp2
Young et al. (2017)	BDI-II	27.20 (10.70)	16.10 (9.70)	18 (American adults)	rftMRI-NF
Takamura et al. (2020)	BDI-II	28.70 (8.57)	17.20 (6.12)	6 (Japanese adults)	rftMRI-NF
Wang et al. (2019)	BDI-II	30.25 (8.39)	19.83 (12.02)	24 (Chinese adults)	Alpha asymmetry
Wang et al. (2019, second protocol)	BDI-II	29.17 (11.47)	17.83 (11.20)	23 (Chinese adults)	High beta downtraining
Zotev et al. (2020)	POMS Depression	15.40 (14.00)	7.75 (10.10)	16 (American adults)	rtfMRI-NF
Cheon et al. (2016)	BDI-II	25.25 (7.91)	14.63 (10.98)	20 (South Korean adults)	ATR + beta downtraining
Choi et al. (2011)	BDI-II	22.75 (12.35)	9.08 (6.92)	12 (South Korean adults)	Alpha asymmetry
Harris et al. (2021)	BDI-II	10.55 (9.66)	5.64 (6.86)	11 (American adults)	Unspecified
Hou et al. (2021)	BDI-II	20.23 (10.47)	12.08 (7.33)	13 (Chinese adults)	Alpha asymmetry, left parietal lobe
Hou et al. (2021, second protocol)	BDI-II	17.69 (7.24)	10.31 (5.98)	13 (Chinese adults)	Alpha asymmetry, right parietal lobe
Mennella et al. (2017)	BDI-II	9.75 (12.38)	6.00 (7.90)	16 (Italian adults)	Alpha asymmetry
Kim & Kim (2015)	BDI-II	27.43 (7.66)	20.21 (7.23)	14 (South Korean adults)	Unknown

In the random effects model, the effect of NF on depression was observed to be $g = -0.91$ (−1.11, −0.70), and this effect was significant at $p < .01$. This g value constitutes an effect that Cohen (2013) described as large and supports the claim that neurofeedback is an effective means of decreasing the symptoms of depression.

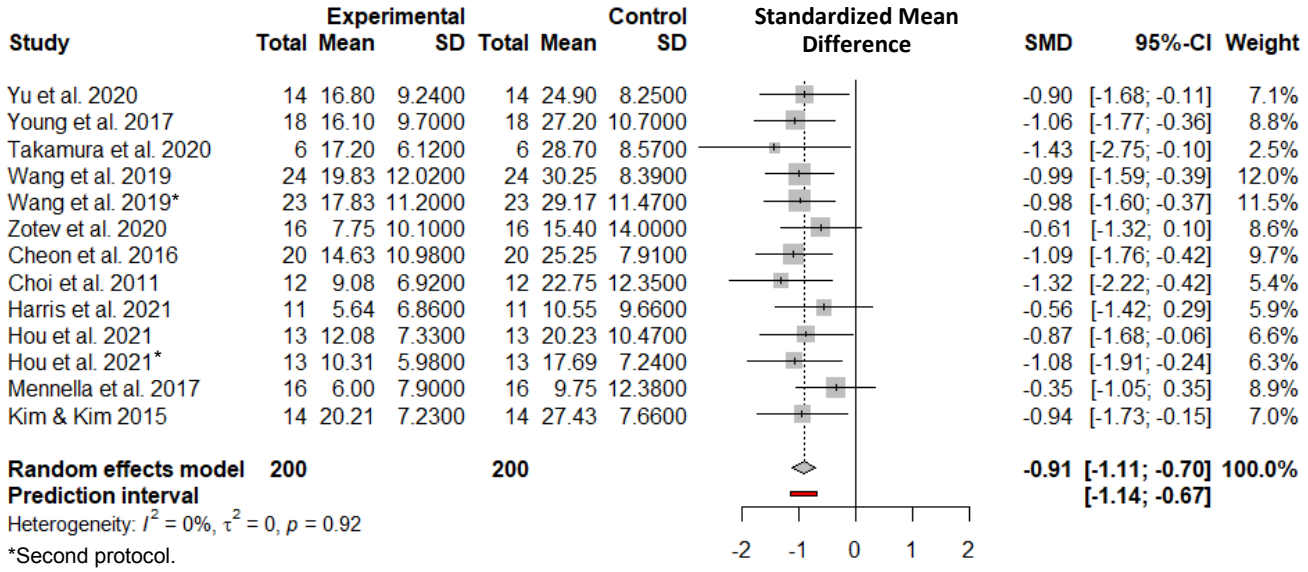
Discussion

One means of approaching the discussion is to explore how and why the following NF protocols might be effective in terms of reducing depression. In addition, particular interest should be paid to the potential role of any specific regions of the brain to which these protocols are directed. The overarching objective of this discussion is to explain the context for the meta-analytical findings and their identification of a large effect of NF on depression reduction. However, such a discussion should also be framed in the context of the standard biomedical account of depression and its treatment, primarily through pharmaceutical means

Pharmaceuticals, Depression, and the New Physics of the Brain

An appropriate means of framing any discussion of the role of pharmaceuticals in depression reduction is to summarize the major subclasses of drugs that serve as antidepressants prior to discussing the possible mechanisms for the effectiveness of such drugs. Lenart and Fekete (2021, p. 286) provided a classificatory scheme that distinguishes between (a) typical antidepressants (comprising monoamine oxidase inhibitors; tricyclic antidepressants; selective serotonin reuptake inhibitors, or SSRIs; and serotonin-norepinephrine reuptake inhibitors, or SNRIs); and (b) atypically antidepressants (including tetracyclic antidepressants; norepinephrine-dopamine reuptake inhibitors, or NDRIs; norepinephrine reuptake inhibitors, or NRIs; and serotonin antagonists). Lenart and Fekete, who were particularly interested in angiotensin receptor blockers (ARB) as antidepressants, noted that this class of pharmaceutical has a suite of anti-inflammatory, antiapoptopic, and antioxidative properties that are cumulatively neuroprotective.

Figure 2. *Forest Plot, Random Effects Model, Pooled Hedges* g *for Meta-analysis*.



However, summarizing the state of knowledge in 2021, Lenart and Fekete concluded both that there is no integrated and comprehensive account of depression's underlying pathological mechanisms and that "medications are only partially effective" (Lenart & Fekete, 2021, p. 288).

Notable in Lenart and Fekete's (2021) summary is the identification of many classes of pharmaceuticals, some with highly distinct mechanisms of action. The rationale for the existence of several possible pharmaceutical strategies for treating depression is the complexity of depression itself. To begin with, depression can involve different structures, functions, and pathologies within the brain—for instance, as Kim (2015, p. ix) noted, hypoactivity in the hypothalamic-pituitary-adrenal (HPA) axis is correlated more with atypical depression, whereas hyperactivity of the HPA is correlated more with the melancholic subtype of depression. More generally, Kim called attention to the complementary validity of cognitive, biomolecular, and quantum-physical perspectives (see Schwartz et al., 2005) in understanding depression. These perspectives are, as Kim noted, entangled with various complexities in gene-environment interactions that are specific to individuals who are depressed or at risk for depression.

As both Kim (2015) and Lenart and Fekete (2021) noted, there is consensus on the complexity of depression. Schwartz et al.'s (2005) discussion of quantum physics in relation to neuroscience is relevant to the complexity of any mental disease state. Schwartz et al. noted that the brain cannot be modeled in alignment with the assumptions made by classical physics; quantum physics introduces elements of uncertainty, complexity, and agent choice that prevent, in principle, the application of simple brain-state modeling and the nomological reduction of certain pathologies to certain states of the brain.

Schwartz et al.'s (2005) invocation of the relevance of quantum physics to neuroscience is intended to clarify, not obscure, the neuroscientific research paradigm as it applies to mental illnesses such as depression. Schwartz et al. noted that the function of the brain along quantum-physical as well as classical physical principles means that there are likely to be parallel structures and functions in place of single, reductive pathophysiological pathways. In other words, as Kim (2015) also noted, there will likely never be a single account of depression; it would be more apt to conceptualize depressions in place of depression, with each depression due to various and possibly unique combinations of genetic predisposition, environmental characteristics, agent choice, cognitive strategies, biomolecular function, and structural properties of different parts of the brain.

The pharmaceutical view of treating depression has gone through three phases. In the first phase, the accompanying biomedical paradigm was reductive, with the presumption being that depression is a brain state, or an array of brain states, arising from

properties of the brain that can be pharmaceutically acted on and cured (Kelly, 2020). In the second phase, TRD and the accumulation of data gave rise to a more complex view of pharmaceutical treatment, one in which a purely reductionistic and mechanistic view of psychopharmacology was challenged (Young & Moulton, 2020). In the third phase, there is a general acknowledgement (Lenart & Fekete, 2021) that (a) depression is complex, (b) pharmaceutical approaches are at least partially effective, and (c) there is no unified explanatory account of the effectiveness or ineffectiveness of different pharmacological approaches.

The fundamental existence of uncertainty and parallelism (Schwartz et al., 2005) in neuroscience as a result of quantum-physical challenges to the classical model of physics is not an argument for abandoning the search for physical laws, models, and methods that apply to the brain. However, one result of the paradigm shift in physics (and in neuroscience by way of physics) should be, as Schwartz et al. implied, an epistemic and methodological humbleness in the study of the brain. In a many-paths account of depression such as that of Kim (2015), there is ample room for different ways of studying and treating depression—including, but not limited to, various discrete and overlapping cognitive, molecular, computational, therapeutic, and pharmacological approaches and stances, leading to a multifactorial treatment approach (Sathappan et al., 2019). In such an approach, the guiding research question is not whether nonpharmaceutical approaches to depression work *per se*; rather, the question is how effective such approaches can be measured to be in terms (such as the *g* or *d* measures of effect size) comparable to pharmaceutical approaches.

NF Protocols and Depression

One of the most widely attested NF protocols for the reduction of depression involves frontal alpha asymmetry reduction. There is also evidence for the effectiveness of real-time fMRI-based NF. Finally, less common NF protocols for depression reduction have also been proposed. The evidence and rationale for several NF protocols are discussed below.

Frontal alpha asymmetry is a state in which there is more activity in the left frontal cortex vis-à-vis the right frontal cortex (Harmon-Jones, 2003). Relatively higher left frontal cortical activity is, in turn, associated with positive affect, whereas relatively higher right frontal cortical activity is associated with negative affect (Tomarken et al., 1992). Frontal alpha asymmetry thus either causes, or is correlated with, the predominance of negative over positive affect. Harmon-Jones in particular is associated with a refinement of this hypothesis, suggesting (Harmon-Jones, 2003; Harmon-Jones et al., 2010) that frontal activation asymmetry should not be understood in terms of affect. This version of the asymmetry hypothesis in relation to emotion and behavior rests on the claim (perhaps first advanced by Davidson, 1992) that greater activation of the left frontal cortex is associated with greater approach motivation, which can include negative and positive affects. On the other hand, a predominance of the right frontal cortex indicates withdrawal motivation.

Both of these explanatory accounts of frontal asymmetry are relevant to depression. In the older account (Tomarken et al., 1992), frontal asymmetry is a marker of depression insofar as negative affects predominant over positive affects. In the newer account (Harmon-Jones, 2003; Harmon-Jones et al., 2010), frontal asymmetry's role in depression is to promote withdrawal over approach. Both of these accounts complement the American Psychological Association's (APA, 2013) description of the symptomatology of depression. According to the APA, depression combines negative affects (such as mood) with a lack of arousal (as related to thought and behavior) and withdrawal from hitherto pleasurable activities. However, even though the affect-based account of frontal asymmetry appears to be compatible with the symptomatology of depression, it is the approach- and withdrawal-related account of frontal asymmetry that has come to be accepted in the context of applied psychology (Briesemeister et al., 2013). Briesemeister et al. (2013) conducted a meta-analysis of psychological experiments and found that frontal alpha asymmetry existed in 73.4% of scenarios in which subjects were confronted with an approach/withdrawal task, but only in 19.6% of scenarios in which no task was present.

If frontal alpha asymmetry is associated with increased withdrawal or negative affect, then increased frontal alpha symmetry should be associated with increased arousal or positive affect, which, in turn, should be associated with a reduction in depression symptoms. However, the meta-analysis conducted by Van Der Vinne et al. (2017) did not find a statistically significant effect of the existence of frontal alpha asymmetry on the diagnosis of depression, raising an important question about whether frontal alpha asymmetry has diagnostic validity with respect to MDD and other depression-related disorders. On the other hand,

several of the studies cited by Briesemeister et al. (2013) suggested that frontal alpha asymmetry has predictive validity with respect to depression. In addition, diagnostic validity can be treated separately from the experimental question of whether, in the presence of treatment for depression, frontal alpha asymmetry is observed to decline.

Frontal alpha asymmetry, being measurable through electroencephalograms (EEG) collected in the context of NF research and interventions, can be reviewed in light of several of the studies included in the statistical meta-analysis whose results are presented above. Before such a discussion, it should be noted that there is a possible ambiguity in how the concept of asymmetry is approached. In some measurement approaches, an asymmetry increase is coded so as to reflect the reduced activation of the right frontal area; here, an asymmetry increase has the same functional meaning as an asymmetry decrease, that is, the state of the left and right frontal areas converging rather than diverging. Increasing asymmetry can mean reducing the activation of the right frontal area relative to the left, and decreasing asymmetry can mean achieving a state in which the left and right frontal areas converge in activation. Thus, even though the same underlying phenomenon is being measured, the manner in which it is conceptually and operationally approached can result in ambiguities in terminology. For the sake of clarity, the concept of asymmetry decrease has been applied to the various NF studies on this topic, with an asymmetry decrease representing the convergence of hyperactivated right frontal areas to the activation levels of left frontal areas.

Wang et al. (2019) reported that 4 out of 7 subjects who received NF designed to reduce frontal alpha asymmetry experienced a symmetry reduction, whereas the remaining participants experienced increased asymmetry. Wang et al. coded asymmetry reduction as an increase in the relative activation of alpha in the right frontal lobe. One of the special points in interest in Wang et al.'s study is that the individuals who experienced frontal alpha asymmetry reduction were also those who experienced a significant decline in depression; the individuals who did not experience frontal alpha asymmetry reduction also did not report a decline in depression. This finding was not reflected in Mennella et al.'s (2017) study, in which changes in frontal alpha asymmetry were not correlated with depression. However, unlike Wang et al., Mennella et al. did not analyze high responders to frontal alpha asymmetry reduction as a separate subclass, which would have disclosed whether individuals with marked reductions in frontal alpha asymmetry subsequent to NF also happen to report significantly lower depression scores.

Research on the various possible interrelationships between depression, frontal alpha asymmetry, and NF is in its relative infancy. However, a review of the NF literature suggests that front alpha symmetry reduction is, by means of arousal-withdrawal theory (Davidson, 1992), a plausible mechanism for reducing depressive symptoms. Another commonly utilized NF approach to depression reduction, rtfMRI-NF, also deserves close consideration because of the frequency with which it has been applied in NF practice.

In discussing the neurophysiological basis for rtfMRI, Young et al. (2017) cited the importance of the amygdala, which, as they noted, is overactivated relative to negative stimuli and less activated with respect to positive stimuli (Suslow et al., 2010; Victor et al., 2010), resulting in an overall hypoactive state in depression. Young et al. cited two prior rtfMRI-NF-based interventions in which depression reduction appears to have been achieved by means of stimulating increased activity in the amygdala. In their baseline analysis, Young et al. first confirmed that the amygdala was hemodynamically hypoactive among depressed patients, then confirmed that amygdala regulation increased significantly among participants in the rtfMRI-NF group. Because depression decreased significantly among those exposed to rtfMRI-NF, Young et al. drew the conclusion that the primary mechanism for depression reduction was increased activation of the amygdala.

The arousal-withdrawal model (Davidson, 1992) of depression can explain the results obtained by Young et al. (2017)—as well as the results obtained by Takamura et al. (2020) and Zotev et al. (2020), which were also obtained in the context of a hypothesis about amygdala hypoactivity as a correlate and substrate of depression. The hypoactive amygdala is, in essence, both a cause and an epiphenomenon of withdrawal and disengagement. If so, then rendering the amygdala more active through rtfMRI-NF has the potential to reduce depression, as found in the recent research (Takamura et al., 2020; Young et al., 2017; Zotev et al., 2020). The theoretical story appertaining to NF, depression, and amygdala is, in this way, just as explanatorily compelling as the narrative that links NF, depression, and frontal asymmetry.

Conclusion

Depression is perhaps the most widespread mental illness or disorder in the world (James et al., 2018) and is responsible for immense economic, social, and individual costs (Bubonya et al., 2017; Jia et al., 2015; Shin et al., 2020). Although there is consensus on the need to reduce depression, the question of how to achieve this reduction is increasingly open to challenge, redefinition, and exploration. Although there is no doubt that, on the whole, antidepressant pharmaceuticals work (Young & Moulton, 2020), there is also compelling evidence that nonpharmaceutical interventions work (Kim, 2015). The contribution of this study was to demonstrate that NF is also an effective depression-reducing modality through the calculation of a pooled effect size, *g*, for numerous studies on depression and NF. In addition, the discussion of the underlying explanations for the efficacy of NF in this context called attention to the relevance of the arousal-withdrawal model of depression as it applies to frontal asymmetry and the activation of the amygdala. The effectiveness of NF against depression is not only observationally attestable through meta-analysis but theoretically describable through existing, well-supported models of depression and brain function. However, given the immaturity of the research base on NF, more work is necessary to deepen the claim for the effectiveness of this modality as either an alternative or a complement to pharmaceutical antidepressants.

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NeuroRegulation

Effect of Transcutaneous Spinal Direct Current Stimulation (TsDCS) Combined with Other Therapies on Walking Capacity in Patients with Neurological Disorders: A Systematic Review

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Abstract

Introduction: Neuromodulation has been used for walking difficulty as a therapeutic approach and, as transcutaneous spinal direct current stimulation (TsDCS) is emerging as a novel tool for patients with neurological disorders when combined with transcutaneous direct current stimulation (tDCS) and/or gait training, it seems to have a promising effect; therefore, a systematic review may provide a better insight into the efficacy of the results. This systematic review aims to assess the effects of TsDCS when applied in combination with different therapies in neurological disorder patients**. Methods**: Databases (Pubmed, CENTRAL, and Web of Science) were used for searching studies since inception. With the guidance of reviewers, one author extracted data. Two independent reviewers assessed qualities of the randomized controlled trials (RCTs). **Results**: Five studies from an initial yield of 256 studies met the inclusion criteria. TsDCS might improve walking capacity when combined with tDCS and/or gait training in stroke (TsDCS with gait training and tDCS), cerebral palsy (tDCS with gait training), and cerebellar ataxia (TsDCS with tDCS). **Conclusion:** The result suggests that more studies are needed for concluding the therapeutic potential. Future studies should emphasize standard stimulation protocol and determining its efficacy in other outcome parameters of gait and in patients with different neurological disorders.

Keywords: transcutaneous spinal cord stimulation; noninvasive spinal direct current stimulation; gait; walking; locomotion

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Introduction

In the last decades, noninvasive brain stimulation (NIBS) has evolved to become a valuable tool in both basic and clinical neuroscience. Various methods of NIBS such as transcutaneous direct current stimulation (tDCS), transcranial magnetic stimulation (TMS), and transcranial electrical stimulation (TES) have been widely used for diagnostic, prognostic, and even therapeutic applications in a broad range of neurological and psychiatric disorders. The rationale for using NIBS techniques lies in the possibility to modulate, in a targeted manner, the activity of different cerebral and cerebellar cortical regions, as well as the functional connections between these areas and distant brain regions, also including subcortical structures (Cosentino et al., 2018). When it comes to neurorehabilitation interventions, the improvement of the gait of the patient is an important consideration, as locomotion is the most affected factor as well as the main complication in neurological disorders which further hampers the resettlement of social and

professional aspects of human lives (de Paz et al., 2019). The neural circuitry involved in the different aspects of gait control is very complex and includes the basal ganglia-cortical loops, the cerebellum, and structures of the brainstem and the spinal cord. This is why different approaches of NIBS have been suggested for the treatment of gait disorders in a variety of neurological disorders including Parkinson's disease, stroke, cerebellar ataxia, multiple sclerosis, cerebral palsy, and spinal cord injury (Cosentino et al., 2018). Preceding studies on the result of tDCS on gait and lower limb function have been indecisive, maybe because of the inability of tDCS to stimulate the lower limb representation in homunculus in reaching the locomotor network (Awosika et al., 2019).

The use of noninvasive modulation of spinal neurons by transcutaneous spinal direct current stimulation (TsDCS) has been variously described. In healthy people, cathodal TsDCS was recently found to improve motor unit recruitment, likely consequent to GABAergic system inhibition and direct postsynaptic neuron overexcitation, and it has been proposed as a novel therapeutic tool for managing conditions in which motor unit recruitment is reduced (Picelli et al., 2015). The segmental spinal physiology, ascending lemniscal and nociceptive pathway can be stimulated by applied direct current stimulation over the T11 spinal region so it can be viable for improving locomotor learning (Awosika et al., 2019). As well established, neuromodulation can be done at different levels of the spinal column according to the task. For example, at T11–T12 lower extremity movement is elicited as here lie the CPGs; stimulation at T10–T11 tends to improve the quadriceps activity, while neuromodulation at T12–L1 stimulates the hamstring muscle activity (Megía García et al., 2020). At the spinal level, transcutaneous spinal stimulation increases spinal reflex activity similar to that obtained with epidural stimulation. Compared to TsDCS which is noninvasive, invasive spinal stimulation has more localized effects, but both of them activate posterior root fibers and stimulate the same region. Therefore, noninvasive nature along with other similar advantages (like that of invasive stimulation) makes the use of TsDCS more demanding and widely acceptable in clinical research (Shapkova et al., 2020). In the context of searching, methods for modulation of the spinal locomotor circuitry TsDCS can be used with other interventions for improving its efficacy, which might be limited when used alone, and can entrain the activity-dependent plasticity of spinal neuronal networks (Shapkova et al., 2020).

As locomotion is one of the major complications in patients with neurological disorders and referring to neuromodulation as an intervention, tDCS has been used for motor rehabilitation in various conditions and has prominently proven to be effective in upper extremity rehabilitation; unlike lower limb rehabilitation, this can be due to the inability of tDCS to stimulate the lower limb representation in homunculus in reaching the locomotor networks comparative to upper limb, so transcutaneous spinal stimulation has recently been introduced as a therapeutic novel approach which works on stimulating the central pattern generators (CPGs) and supraspinal networks which may prove to enhance the walking ability for patients with neurological disorders. Hence, this review will provide an insight regarding the combined effects of TsDCS with tDCS and/or gait training used for locomotion rehabilitation. Therefore, the main aim of this review is to compare the combined effects of TsDCS along with tDCS and/or gait training on locomotor ability.

Methods

Search Strategy

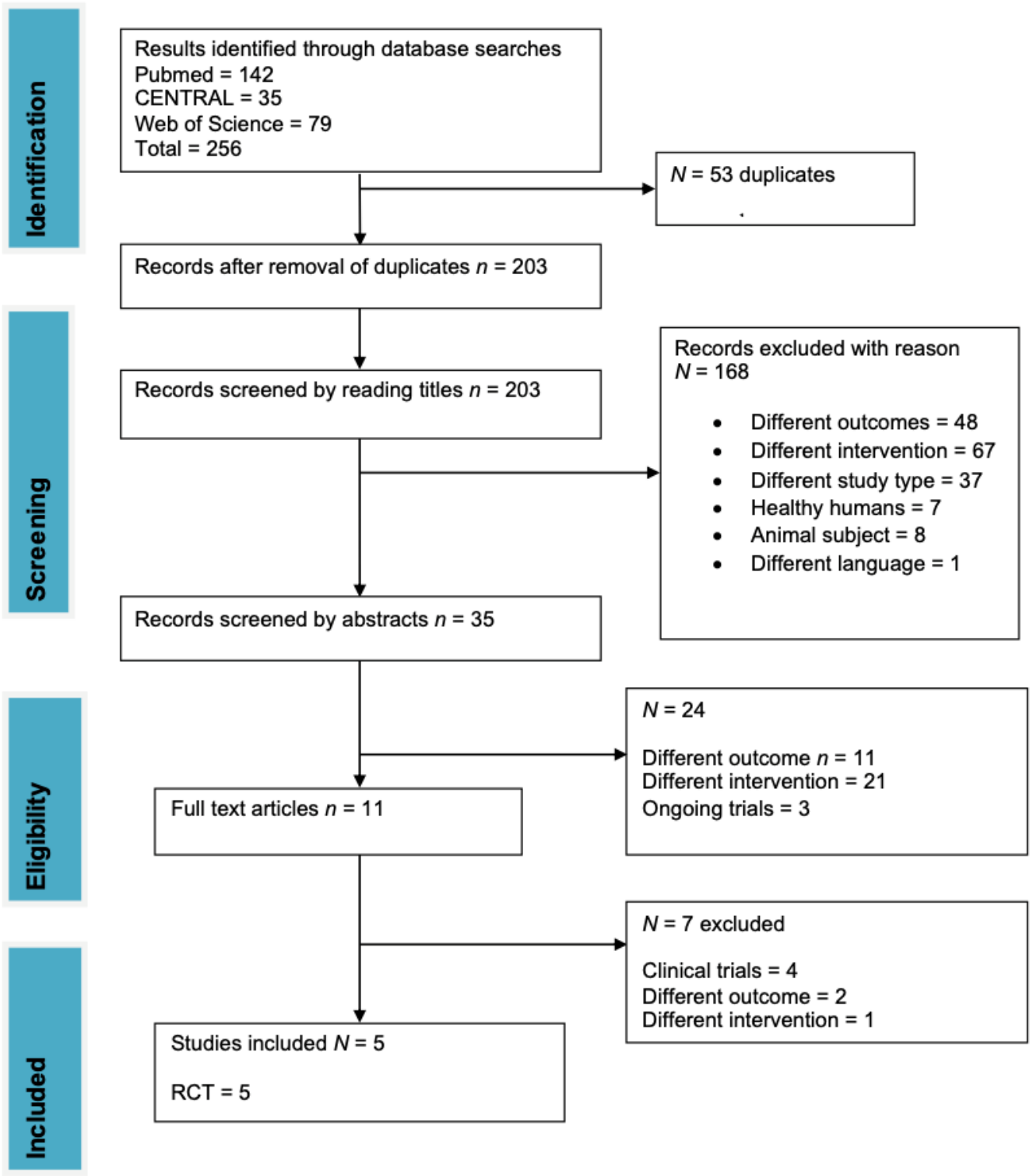
This review was done as per the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. It is registered in Prospero with the registration number CRD42021235579. We developed a search strategy to identify studies that elucidated the effects of TsDCS combined with different therapies on locomotor ability in neurological disorders. A systematic search was performed on the electronic databases MEDLINE (accessed via PubMed), CENTRAL (Cochrane Library Central Register of Controlled Trials), and Web of Science, starting from the earliest records available. Random Search items used were a combination of keywords (i.e., TsDCS, transcutaneous spinal cord stimulation, noninvasive spinal direct current stimulation, gait, walking) entered in various combinations. The keywords were combined with Boolean operators "OR" and "AND" to yield more focused results. The PRISMA flowchart is depicted in Figure 1.

Eligibility Criteria

Criteria for inclusion comprised of randomized controlled trials (RCTs) published in the English language. Subjects had to be diagnosed with the pathology of the central nervous system. Studies using TsDCS combined with other interventions and having locomotor parameters as outcome measures were included, whereas studies examining the effect of TsDCS on other outcomes such as upper limb

motor function, pain, and spinal reflexes were excluded. Furthermore, research using other forms of invasive spinal stimulation or neuromodulation on healthy subjects and animal models were excluded. No sample size restriction was applied.

Figure 1. *Prisma Flowchart Diagram*.



Quality Assessment of Included Trials

For assessing the quality of all selected RCTs, we have used an 11-point PEDro scale which evaluates the methodological quality. It assesses based on the criteria that each point system is either "Yes" or "No" answers. The scoring is such that 9–10 signifies studies of *high quality*, 6–8 *good quality*, 4–5 *moderate*, and below 4 *poor quality*. Two authors independently assessed the quality of retrieved RCT. Any conflict was resolved by a third author. The total score for the methodological quality is depicted in Table 1.

Data Extraction

Data on the characteristics of the trial (author, year of trial conduction, design, and duration), the participants (information on diagnosed condition), and intervention (the device used, duration, dosimetry, and safety) were extracted and depicted in Table 2, and summarized results are depicted in Table 3.

Table 1

Depicting the Quality of RCTs

Article	Benussi et al., 2018	Picelli et al., 2015	Picelli et al., 2018	Picelli et al., 2019	Solopova et al., 2017
Eligibility Criteria	Yes	Yes	Yes	Yes	Yes
Random Allocation	Yes	Yes	Yes	Yes	Yes
Concealed Allocation	No	Yes	Yes	Yes	Yes
Group Similarity at Baseline	Yes	Yes	Yes	Yes	Yes
Blinding of Subjects	Yes	Yes	No	No	No
Blinding of Therapist	Yes	Yes	Yes	Yes	No
Blinding of Assessor	Yes	No	Yes	Yes	No
Dropouts < 15%	Yes	Yes	Yes	Yes	Yes
Intention to Treat Analysis	Yes	Yes	Yes	Yes	Yes
Between-group Differences Reported	No	Yes	Yes	Yes	No
Point Estimate and Variability Reported	Yes	Yes	No	No	Yes
Total Score	8	9	8	8	6
Quality	Good	Excellent	Excellent	Excellent	Good

Table 2

Showing the Characteristics of the Selected Article

Article	Benussi et al., 2018	Picelli et al., 2015	Picelli et al., 2018	Picelli et al., 2019	Solopova et al., 2017
Pathology; *N* participants	*N* = 20; neurodegenerative ataxia	*N* = 30; stroke	*N* = 20; chronic stroke patients	*N* = 40; supratentorial stroke	*N* = 28 (~9 years); with spastic cerebral palsy
Design	Double-blind, randomized, sham-controlled, crossover trial	A pilot, double-blind, randomized controlled trial	A pilot, single-blind, randomized controlled trial	Single-center, single-blind RCT	Randomized controlled trial

Table 2

Showing the Characteristics of the Selected Article

Area of Application of TsDCS and TsDCS Parameters (Current Density; Duration)	Anode placed on scalp over cerebellum area (2 cm under inion), and cathode placed over spinal lumbar enlargement (2 cm under T11). Constant current of 2 mA.	At T9 to T11, Intensity = 2.5 mA and applied for 20 min during RAGT. Current ramped up to 2.5 mA over a 10-s interval and then similarly ramped down at the end of the stimulation. Current density was 0.071 mA/cm^2 and total charge density was 0.09 C/cm^2.	Intensity = 2.5 mA and applied for 20-min during RAGT (online stimulation), combined with central nervous system stimulation. Cathode placed over spinous process of the 10th thoracic vertebra (from 9th to 11th) and anode placed above shoulder of unaffected hemibody.	Intensity of TsDCS set at 2mA and applied for 20 min during RAGT (online stimulation). For patients allocated to Group 1, cathode positioned over contralesional cerebellar hemisphere.	Transcutaneous SCS delivered using 2.5-cm round electrodes placed midline at T11, and L1 spinous processes as cathodes. Biphasic rectangular 1.0-ms pulses (30 Hz), modulated frequency of 10 kHz were used. Intensity = 10–50 mA for most children.
Interventions	Two arms: Group 1 – TsDCS + tDCS Group 2 – Sham stimulation	Three arms: Group 1 – Anodal tDCS + Sham TsDCS Group 2 – Sham tDCS + Cathodal TsDCS Group 3 – Anodal tDCS + Cathodal TsDCS	Two arms: Group 1 – Anodal tDCS + TsDCS + gait training Group 2 – Cathodal tDCS + TsDCS + gait training	Two arms: Group 1 – Contralesional tDCS + TsDCS Group 2 – Ipsilesional tDCS + TsDCS	Two arms: Group 1 – TsDCS + Locomotor training Group 2 – Locomotor training
Variables	SARA, ICARS, 9-Hole Peg Test, 8-Min Walking Time	6MWT, FAC, MI, AS, SGP	6MWT, selected as a measure of walking capacity; FAC, MI, AS; SGP, evaluated with the GAITRite system	6MWT, FAC, MI, AS, SGP	Modified AS; L-ROM test, as directed by Lokomat software; L-FORCE test of Lokomat software
Duration of Intervention	5 days/week for 2 weeks. A follow-up evaluation was performed at 1 and 3 months with a crossover washout period of 3 months.	Ten 20-min RAGT sessions, 5 days/week (from Monday to Friday) for 2 consecutive weeks	20-min RAGT sessions, 5 days/week, for 2 consecutive weeks	Ten 20-min RAGT sessions, 5 days/week, for 2 consecutive weeks	15 training sessions, combined with TsDCS over 3 weeks

Note. RAGT = robot-assisted gait training; 6MWT = 6-Min Walk Test; FAC = Functional Ambulation Category; MI = Motricity Index leg subscore; AS = Asworth scale; SGP = Spatiotemporal gait parameter; SARA = Scale for Assessment and Rating of Ataxia, ICARS = International Cooperative Ataxia Rating Scale.

Results

We developed a search strategy and included three databases. 256 studies were yielded, out of which 142 were in PubMed, 35 in CENTRAL, and 79 in the Web of Science. After removing 53 duplicates, 203 articles remained. On screening of titles and abstracts, 11 full-text articles were retrieved from the remaining and, finally, 5 were selected as per inclusion criteria. Table 3 shows the most relevant characteristics of selected articles.

Table 3
Showing the Results of Selected RCTs

Article	Results
Benussi et al., 2018	Cerebello-spinal tDCS decreases signs in ataxia patients and restores motor cortex inhibition by cerebellar structures.
Picelli et al., 2015	Anodal tDCS when used with cathodal TsDCS might be beneficial for enhancing the effects of robotic gait training in chronic stroke.
Picelli et al., 2018	Cathodal tDCS over contralateral cerebellar hemispheres when used along with cathodal TsDCS may be beneficial to enhance the effects of robot-assisted gait training in chronic stroke.
Picelli et al., 2019	Cathodal tDCS over contralateral or ipsilateral cerebellar hemisphere when used along with cathodal TsDCS might improve gait with similar effects in both combinations in stroke patients.
Solopova et al., 2017	The gait ability can be significantly enhanced with TsDCS when combined with locomotor training comparative to locomotive training alone.

Participants

The sample that is part of this review was comprised of a total of 141 patients with different types of pathologies: 93 subjects with chronic stroke in three studies (Picelli et al., 2015, 2018, 2019), 28 subjects with cerebral palsy (Solopova et al., 2017), and 20 subjects with neurodegenerative ataxia (Benussi et al., 2018).

Stimulation Patterns and Parameters of TsDCS

In terms of electrode size for TsDCS, it was 23.75 cm^2 (Picelli et al., 2018, 2019), 35 cm^2 (Picelli et al., 2015), 8 × 6 cm^2 (Benussi et al., 2018), and 5 × 8 cm^2 (Solopova et al., 2017), respectively. In three of the studies, the cathode was placed over the spinous processes of the thoracic vertebra (from 9th to 11th) and the anode was placed above the shoulder of the unaffected hemibody (Picelli et al., 2015, 2018, 2019); in the other two studies, the cathode was placed midline at T11 and at L1 spinous processes (Solopova et al., 2017) and was placed over the spinal lumbar enlargement (2 cm under T11; Benussi et al., 2018).

The current intensities for cathodal TsDCS were 2.5 mA (Picelli et al., 2015, 2018, 2019), 10 to 50 mA (Solopova et al., 2017), and 2.0 mA (Benussi et al., 2018), respectively, and current density was 0.071 mA/cm (Picelli et al., 2015, 2018, 2019), whereas the total charge density was 0.09 C/cm^2 (Picelli et al., 2015, 2018, 2019) and 0.042 mA/cm^2 (Benussi et al., 2018) for respective studies. As far as the duration of TsDCS was concerned, the sessions were 20 min for all studies (Benussi et al., 2018; Picelli et al., 2015, 2018, 2019; Solopova et al., 2017).

All of the included studies used TsDCS along with other therapies, such as TsDCS with tDCS and gait training (Picelli et al., 2015, 2018, 2019), cerebellar tDCS with TsDCS (Benussi et al., 2018), and TsDCS with locomotor training only (Solopova et al., 2017).

Combined Therapies Protocol

Transcranial Direct Current Stimulation (tDCS) Parameters. Among the five studies, four combined tDCS with TsDCS (Benussi et al., 2018; Picelli et al., 2015, 2018, 2019). In one study, the electrode size was 7 × 5 cm, 35 cm^2, and the anode was placed on a motor area as per EEG system on ipsilesional area and cathode over another side. For anodal tDCS stimulation, the current intensity was 2 mA for 20 min (along with gait training) and charge density was 0.07 C/cm^2 (Picelli et al., 2015); while in another study, the electrode size was about 4 cm in diameter, 12.56 cm^2 in area, and the anode was placed on the ipsilateral side over the motor cortex (M1), as per EEG only, and the cathode was positioned over the orbit of the other side (Picelli et al., 2018). In another included trial (Picelli et al., 2019), the electrode size was similar to the previously mentioned study (Picelli et al., 2018), but the cathodal electrode was placed over the cerebellar hemisphere while the anode was over the buccinator muscle on the same side (Picelli et al., 2019). The current intensity, which was 2 mA, and the duration of 20 min were the same for all three studies (Picelli et al., 2015, 2018, 2019). In the fourth study, the anode was placed over the cerebellar region (electrode size 7 × 5 cm^2, current density 0.057 mA/cm^2) and used tDCS as an additional therapy with TsDCS (Benussi et al., 2018).

Gait Training Protocol. The gait training was combined in four studies with TsDCS intervention (Picelli et al., 2015, 2018, 2019; Solopova et al., 2017), and in three studies among them, the criteria were similar. The robot-assisted gait training was divided into two parts: first 10% weight was supported for 10 min and speed was 1.5 km/hr, then speed was increased to 2 km/hr and no body weight was supported for the next 10 min (Picelli et al., 2015, 2018, 2019). In one study (Solopova et al., 2017), the duration of locomotor training was 40 min at a treadmill speed of around 1 km/hr and the stimulation was switched off after 20 min.

Sham Group/Other Comparison Group Protocols

In all five selected studies, the experimental group was either compared to the control group (Solopova et al., 2017) or with other intervention groups (sham stimulation or stimulation over the contralateral side; Benussi et al., 2018; Picelli et al., 2015, 2018, 2019). The protocol parameters for sham tDCS in one of the studies was that it was applied for 2 min in starting and 30 s in ramp down fashion at the end at the same intensity as anodal stimulation (Picelli et al., 2015); while in the other two studies, the tDCS placement was over the contralesional side for comparison (Picelli et al., 2018, 2019).

One included study (Benussi et al., 2018) reported the electrode positioning was similar to the experimental group, but the current was ramped down after 5 s. Additionally, a reference group was also included in which TMS was applied on healthy controls. The parameters for TMS were that the coil was placed over the motor cortex area and the handle was directed at 45 degrees laterally and posteriorly to the longitudinal plane (Benussi et al., 2018). While only in a single study, the control group received only locomotor training with Lokomat (Hocoma AG, Switzerland) for 40 min without TsDCS (Solopova et al., 2017) and was compared to the experimental group that received both gait training and TsDCS.

Recorded Variables and Their Effect

Patients were evaluated before treatment (T0), immediately after treatment (primary endpoint; T1), at 2 weeks (T2), and at 4 weeks (T3) of follow-up in three studies (Picelli et al., 2015, 2018, 2019). In another included trial, the assessment was taken as in the first phase, at baseline, at 2 weeks after stimulation, at 1 month, and 3 months (Benussi et al., 2018), while the fifth study evaluated before and after comparisons with no follow-up (Solopova et al., 2017).

Walking Capacity. The most used scales were the 6-Min Walk Test (6MWT; Picelli et al., 2015, 2018, 2019), SARA (Scale for Assessment and Rating of Ataxia), and ICARS (International Cooperative Ataxia Rating Scale; Benussi et al., 2018), and GMFM-88 (Solopova et al., 2017) for evaluating the walking capacity in different neurological conditions. Two studies showed a statistically significant difference between groups at T0, T1, and T2 follow-ups but were not maintained at T3 follow-up (Picelli et al., 2015, 2019). In one included trial (Solopova et al., 2017), the change in total GMFM-88 score was significantly correlated with the increase of walking (dimension E in GMFM-88). Similarly, another study (Benussi et al., 2018) reported improvement in SARA and ICARS scores in terms of gait between groups, but one included trail (Picelli et al., 2018) scoring did not differ between the two groups.

Spasticity. The modified Ashworth scale was used mainly in all included studies for spasticity assessment (Picelli et al., 2015, 2018, 2019; Solopova et al., 2017). In four studies, there was no change in spasticity between groups (Picelli et al., 2015, 2018, 2019; Solopova et al., 2017).

Lower Limb Strength. The lower limb strength was assessed by the Motricity Index (MI) leg subscore in all three studies (Picelli et al., 2015, 2018, 2019). Though in two studies there was no improvement found between the groups at T1–T0, T2–T0, T3 follow-up (Picelli et al., 2015, 2019), in a single study, there was a significantly greater improvement in affected lower limb motricity (Picelli et al., 2018).

The Cadence of Stride and Single/Double Support Ratio. Three studies assessed cadence and single/double ratio by GAITRite system (CIR Systems, Inc., Franklin, NJ; Picelli et al., 2015, 2018, 2019). Though in two studies there was no improvement in cadence and single/double support ratio (Picelli et al., 2018, 2019), in one included study (Picelli et al., 2015), significant differences in cadence were found between the groups at the T1–T0 and T2–T0 follow-ups but not at the T3–T0 evaluation. Also, no significant difference in the ratio between single and double support duration was found between the groups at the T1–T0, T2–T0, and T3–T0 follow-up.

Discussion

This systematic review aimed to determine the effectiveness of TsDCS combined with tDCS and/or gait training on locomotor rehabilitation in neurological disorders. To the best of our

knowledge, this is the first systematic review based on data from 141 participants evaluating the effects of TsDCS with tDCS and/or gait training on gait rehabilitation in patients with neurological disorders. Out of the five RCTs, four studies (Benussi et al., 2018; Picelli et al., 2015, 2019; Solopova et al., 2017) showed that TsDCS along with tDCS and/or gait training improves walking capacity in patients with neurological disorders. However, one study (Picelli et al., 2018) did not show any improvement in walking ability, which is the primary outcome, and regarding the secondary outcomes, there are inconclusive results as not all studies have shown significant changes. Specifically, no improvement in spasticity in was any of the studies (Benussi et al., 2018; Picelli et al., 2015, 2018, 2019; Solopova et al., 2017), while cadence (Picelli et al., 2015) and single and double support ratio (Picelli et al., 2018) showed an improvement in respective studies. Overall, our review suggests that TsDCS helps in improving the efficacy of tDCS with/or gait training for promoting walking ability.

In all included studies, the current intensity of TsDCS ranges from 2.0 to 2.5 mA, except in one study by Solopova et al. (2017), in which it is 10 mA to 50 mA; the treatment session was 20 min in all studies. However, the current density is used in varied patterns. The site for application is from T9 to T11–L1 in all included studies (Benussi et al., 2018; Picelli et al., 2015, 2018, 2019; Solopova et al., 2017) and none of the assessed studies reported adverse effects. TsDCS with anodal tDCS has shown to improve the gait in post-stroke patients, as improvements in walking function have been associated with changes in the activation of cortical areas involved in motor control and strengthening of descending input from the brain (Picelli et al., 2015); while in another study also on stroke population (Picelli et al., 2019), TsDCS was combined with cathodal tDCS and stimulation effects were compared between lesional and contralesional sides. Both have shown to improve walking capacity, and no superiority was found in between ipsilesional and contralesional application of cerebellar tDCS combined with TsDCS, as both equally improve walking ability. This can be due to the peculiar bilateral representation of gait function (walking is associated with activation of the primary motor cortex bilaterally, the supplementary motor area, and somatosensory cortex compared with contralateral M1 focus during isolated arm movements), which is considered (Picelli et al., 2018). Another included study on cerebral palsy patients (Solopova et al., 2017) reported a stable improvement of motor functions in children and, in this study, the TsDCS is combined with gait training and proposes that some functional improvement of the spinal supraspinal networks that control locomotor functions were induced.

No change in spasticity was observed in any of the studies (Benussi et al., 2018; Picelli et al., 2015, 2018, 2019; Solopova et al., 2017). As far as TsDCS mechanism of action is concerned regarding spasticity, one of the included studies by Picelli et al. (2015) reported that TsDCS makes motor neurons more susceptible to activation but less responsive to enhance activity that decreases the interneuronal network. Another outcome measure lower limb motricity (which is used for assessment of lower limb strength) has been improved in one included study (Picelli et al., 2018); improvement in motricity might be because of the cerebellar stimulation combined with TsDCS, which has main effects in bringing the change related to inhibition of thalamocortical pathway which is involved for producing new gait patterns (Picelli et al., 2018).

Although TsDCS mechanism of action is a topic of discussion, a growing body of evidence advocates that TsDCS interferes with cortical, corticospinal, and spinal motor output in humans (Ardolino et al., 2021). TsDCS has been shown to influence the ascending and descending spinal pathways and spinal reflex excitability, with increasing evidence that it can induce prolonged functional neuroplastic changes (Benussi et al., 2018).

It appears that the TsDCS when used with other interventions (tDCS and/or gait training) can elicit adaptive neuroplasticity on spinal stimulation (Benussi et al., 2018). This idea is also in line with the review of Megía García et al. (2020), which indicated that TsDCS is a practicable option for increasing voluntary motor response of the upper and lower limbs, trunk stability, and improvement of function and quality of life of patients with spinal cord injury, even though they have included case series and case report having a low level of evidence. Also, another systematic review of Grecco et al. (2015), considered transcutaneous spinal stimulation as a promising therapeutic tool for patients suffering from spinal cord injury. Our review will add to the current knowledge that, apart from spinal cord injury patients, TsDCS when combined with tDCS and/or gait training can be used to increase the efficacy of therapies used for gait rehabilitation in various neurological disorders.

Limitations of Review

The main limitation of this systematic review is the limited number of trials conducted for a great diversity of outcomes of gait and the pattern of application of stimulation. Also, concluding is a complicated insight as we have studied various neurological pathologies. The numbers of subjects studied are less; nevertheless, larger RCTs must be conducted to demonstrate its full therapeutic potential. All studies have combined intervention with TsDCS, so effects of TsDCS specifically cannot be stated. Promoting neuroplasticity as an outcome for stimulation has been a recent approach and, if results of this approach are confirmed in larger trials, then this crucial therapy might be beneficial as a therapeutic approach for several neurological conditions.

Conclusion

Overall, our review suggests that TsDCS can be used in improving walking ability when combined with tDCS and/or gait training for locomotor rehabilitation, although in few included studies, the effects were not observed in succeeding follow-ups (Picelli et al., 2018, 2019). This discovery can be considered in analyzing the duration of application of TsDCS as an intervention. Also, all the included studies involved patients with different neurological disorders, so accurate magnitude of the effect and result cannot be concluded for one particular disorder; hence, more studies are needed for having a clear picture of the effects of TsDCS on different neurological disorders.

Author Declarations

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NeuroRegulation

Language Rehabilitation of Traumatic Brain Injury Patient by LORETA *Z*-Score Neurofeedback: A Single-Case Study

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Abstract

Traumatic brain injury (TBI) creates a variety of sequelae such as aphasia that can be highly challenging for clinicians when developing rehabilitation interventions. Therefore, the present study aimed to investigate the effectiveness of LORETA *z*-score neurofeedback (LZNFB) on language performance for a 21-year-old male suffering from aphasia following TBI. To this end, LZNFB was applied while focusing on the language network for 15 sessions. The study used an experimental design with a pre–post comparison. Baseline and posttreatment comparisons were made on qEEG/LORETA metrics, aphasia symptoms, working memory, and attention. The results indicated clinical improvements in language, working memory, and attention performances after 15 sessions of LZNFB. Our findings suggest that LZNFB may have the potential to aid language performance among those with TBI.

Keywords: traumatic brain injury; LORETA neurofeedback; language; working memory; attention

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Introduction

Traumatic brain injury (TBI) is an injury to the brain and is typically caused by an acute injury to the head, neck, or face (Brown et al., 2019). The wide array of problems confronting those with TBI includes headache, fatigue, impaired memory, reduced attention, depression, aggression, anxiety, sleep disturbances, and sexual dysfunction (Barth et al., 1983). Several reports indicated that TBI can have lifelong impacts including changes in personality and behavior (Banks, 2007; Jackson et al., 2002).

The consequences of TBI are not limited to those changes but also lead to electroencephalographic (EEG) abnormalities, which can be focal or widespread (Brigo & Mecarelli, 2019; Galovic et al., 2017). Some studies demonstrated quantitative EEG (qEEG) changes in patients with TBI. For example, the attenuated alpha frequency in the posterior region and increased theta activity are the most common qEEG findings of individuals with TBI (Arciniegas, 2011; Lewine et al., 2019). Moeller et al. (2011) reported increased delta and theta bands and a decreased beta band in TBI due to the disruption of the cortical-thalamic network. Higher theta-alpha, theta-beta, and delta-alpha amplitude ratios and reduced EEG coherence were also noted in TBI (Modarres et al., 2017). Developing medical treatments that ameliorate the symptoms of TBI is of great importance, and neurofeedback (NF) is one such method.

A review of the literature shows promise for treating some symptoms of TBI with this modality (Gray, 2017). Ayers (1989) was the first to report positive

effects of NF on TBI-related symptoms, finding improvements in a number of postconcussive symptoms experienced by patients, including decreased energy, depression, irritability, photophobia, attention deficit, dizziness, headache, and short-term memory loss. The role of NF in improving cognitive, behavioral, and physical dysfunctions among patients with TBI has been confirmed in previous studies (Bennett et al., 2018; Brown et al., 2019; Gray, 2017; Gupta et al., 2020; Hershaw et al., 2020; Kaser, 2020; Koberda, 2015a).

Although previous studies have shown that NF can mitigate many symptoms of TBI, they have not specifically focused on language rehabilitation by NF. Nevertheless, language therapy produces clinically significant improvements in functional communication, better mood, and quality of life of people with TBI aphasia. Accordingly, the present study sought to evaluate the efficiency of LORETA *z*-score neurofeedback (LZNFB) to rehabilitate the language deficit in a patient with aphasia following TBI. LZNFB is one of the recent advanced technologies of NF that increases specificity by targeting brain network hubs (e.g., the language network) that are referred to as Brodmann areas. The advantage of using the *z*-score in LORETA NF is the ability to receive instant comparisons using a reference database of healthy individual *z*-scores (Thatcher, 2010). These instantaneous comparisons make it possible to find the link between patients' symptoms and the pertinent Brodmann areas (Thatcher, 2010).

In this study, it was hypothesized that LZNFB intervention could potentially enhance language performance in a patient with aphasia following TBI. To test this hypothesis at least in a single case investigation, 15 sessions LZNFB were applied to the language network.

Methods

Case Description

P.F. was a 21-year-old, right-handed male who suffered from aphasia after trauma. Ten months prior to our assessment, he had an accident, and his head had been hurt at the right inferior frontal area. After being unconscious for one month following the accident, the patient underwent surgery on his head. Table 1 presents the demographic information of the patient when he was hospitalized following the trauma. At the time of the assessment, he was alert and oriented and could follow commands, although his language performance was poor.

Table 1

Demographic Information of P.F When Hospitalized After Trauma

Severity	PTA	Age	LOC	GCS
7	277	21	30	6

Note. The severity index is a number between 1 and 10, indicating the severity of TBI based on discriminant classification. Values in the range of 1 to 3, 3 to 5, and > 5 indicate mild, moderate, and severe head trauma, respectively. PTA: Posttraumatic amnesia; LOC: Loss of consciousness; GCS: Glasgow Coma Scale.

Intervention

Power spectral analyses were performed on 5-min segments of the eyes-closed resting state. An EEG was recorded from 19 scalp locations based on the international 10–20 system of electrode placement using the linked ear as a reference. Using a Medicom amplifier and EEG Studio Acquisition software, qEEG data were collected. In addition, editing and digital analysis of the qEEG data were conducted using NeuroGuide software and a comparative database. The protocol included LZNFB to focus on the language network in the symptom checklist, which was developed with the goal of linking symptoms to the areas of the brain. Brodmann areas (BA) in this language network include 22, 39, 40, 41, 42, 44, and 45. Learning reinforcement in neurofeedback was provided using television shows or animations that increased in size when meeting the difficulty thresholds.

The qEEG/LORETA analysis was completed by NEUROSTAT and NeuroGuide software. The available neurocognitive testing batteries (Persian aphasia battery, Stroop test, digit span, and word/nonword test) were used before and after LZNFB and compared using the Barlow formula. The formula for recovery percentage is as follows:

$$\Delta A = \frac{A2 - A1}{A2}(100)$$

As suggested by Barlow et al. (2007), if the results are greater than 15%, we can conclude that the results are clinically significant and treatment is successful.

Results

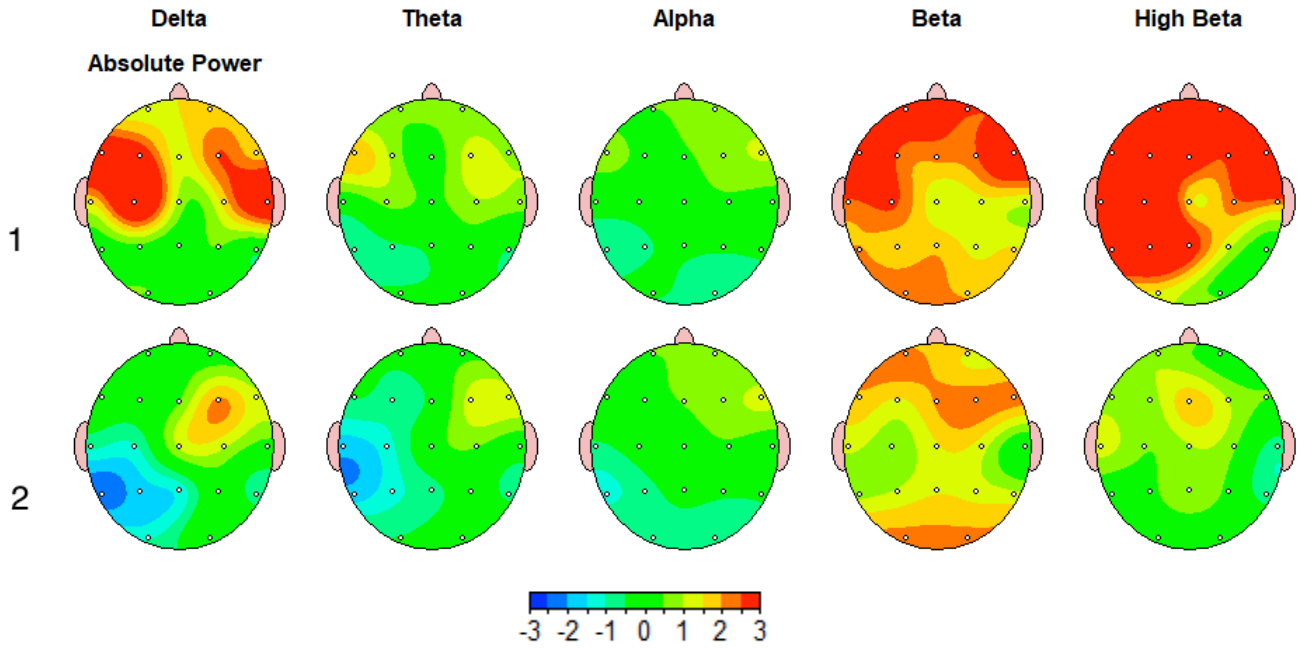
The pretreatment qEEG demonstrated elevated levels of all brain waves except alpha in the frontal and temporal regions. After 20 LZNFB sessions, brain wave amplitudes were closer to values from

the database, as reflected by reduced *z*-scores (Figure 1).

The percentage difference between the baseline and last session of treatment was computed, revealing that the largest changes were found in delta waves at F7 and in high beta waves at F8, T4, T5, C3, and F7 (Table 2).

Our neuropsychological assessments also indicated improvements in the posttreatment score as compared to baseline (Table 3).

Figure 1. *Surface Maps of the Z-score Distribution (Full EEG).*



Note. The qEEG map shows the magnitude of deviations from the normal database using colors. The *z*-score = 0 is defined as normal (green color). Scores less or more than the normal database are displayed by blue and red colors, respectively. EEG: Electroencephalography; 1 = Baseline qEEG; 2 = After 15 LZNFB sessions qEEG.

Table 2
The Largest Differences Between Baseline and Posttreatment

Location	F8	T4	F7	T5	C3	F7
Brain wave	HB	HB	delta	HB	HB	HB
Percentage change	89%	88%	86%	84%	84%	81%

Note. F = Frontal; T = Temporal; C = Central; HB = High beta.

Table 3
Neuropsychological Test Scores Before and After LZNFB

Language test	Language	Pretreatment	Posttreatment	ΔA (%)
	Speed of speech	32.9	53.7	38.7%
	Lexical richness	0.79	0.96	17.7%
	Utterance	11	14	21.4%
	Fluency	6	7	14.2%
	Total word number	39	52	25%

Table 3
Neuropsychological Test Scores Before and After LZNFB

Working memory test	Digit span	6	10	40%
	Word span	6	8	25%
	Nonword span	4	4	0
Stroop test	Correct answers (congruent)	28	48	39%
	Correct answer (incongruent)	21	46	54%

Note. LZNFB: LORETA *Z*-score neurofeedback. Clinically significant differences are shown in red (ΔA% > 15% is clinically significant).

Discussion

This study aimed to analyze the efficacy of LZNFB intervention for the treatment of aphasia following TBI. A qEEG-guided LZNFB protocol was designed for this purpose. Previous studies of TBI rehabilitation by NF have not focused on language performance. This study specifically evaluated the efficacy of LZNFB to rehabilitate the language deficit in a TBI patient. To this end, changes in qEEG/LORETA and aphasia battery metrics after 15 sessions of LZNFB were analyzed, as were changes in working memory and attention scores from pre- to posttreatment. The results showed that fifteen 40-min NF sessions brought the EEG metrics within normal ranges and were effective in improving aphasia symptoms and cognitive performance. The findings of the current case study can be regarded as a promising addition to the treatment planning for TBI-related language problems in the future.

Our findings are consistent with those of previous studies regarding the effectiveness of NF on mitigating TBI symptoms (Bennett et al., 2018; Gray, 2017; Gupta et al., 2020; Kaser, 2020; Rostami et al., 2017).

Effectiveness of LZNFB on the Electrophysiological Outcome

At baseline qEEG demonstrated increased delta, theta, and beta bands at frontal and temporal locations, as well as decreased alpha at the posterior area. Increased delta and decreased alpha bands are known to be directly correlated with cortical metabolism (Szelies et al., 1999). The decreased alpha band at the posterior region and increased theta found in our study have also been seen in other studies (Arciniegas, 2011; Lewine et al., 2019). The increased delta and theta in our study are in line with those of the study of Moeller et al. (2011) and might be due to the disruption of the cortical-thalamic network in TBI. While increased beta occurred in this instance of TBI, it was not found in some similar studies (Leon-Carrion et al., 2008; Tebano et al., 1988). However, some other studies also found increased beta in TBI subjects (Randolph & Miller, 1988; Thornton, 2003), with the researchers concluding that the increased beta was consistently a negative predictor of cognitive performance.

After 20 LZNFB sessions, the qEEG map showed an overall improvement (Figure 1). Our finding of neurological recovery by LZNFB is supported by previous studies that have confirmed its effectiveness in areas such as cerebrovascular accident rehabilitation (Koberda & Stodolska-Koberda, 2014), depression/anxiety and cognitive dysfunction (Koberda, 2015b), addiction (Faridi et al., 2020), attention-deficit/hyperactivity disorder (Koberda et al., 2014), pain management (Koberda et al., 2013), seizure (Koberda & Frey, 2015), and TBI (Koberda, 2015a).

Based on the qEEG analysis, the largest differences between baseline and posttreatment were associated with the F8, F7, T5, and C3 locations (Table 2). The F8 and F7 electrodes correspond to BA 47, which is part of Broca's area and associated with the processing of syntax in oral and sign languages, musical syntax, and semantic aspects of language (Ardila, 2014). The T4 and T5 electrodes correspond to BA 22, which is located at the superior temporal gyrus and is part of Wernicke's area which is involved in speech comprehension. Further, the C3 electrode corresponds to BA 2, which is located in the primary somatosensory cortex, and the main function of this area is the cognitive control of language (Mofrad et al., 2020).

Effectiveness of LZNFB on the Clinical Outcome

Our assessment of the aphasia battery showed that P.F. had clinically significant recovery following treatment with LZNFB (Table 3). The clinical recovery of working memory and attention were also evident (Table 3). Several studies have reported the

relationship between language and working memory (Emmorey et al., 2017; Fitz et al., 2020), as well as language and attention (Galassi et al., 2020; Peach et al., 2017; Vig et al., 2020; Villard & Kiran, 2017; Wang et al., 2019), probably indicating that language is not independent of other cognitive performances; in other words, there is mutual interaction in this regard.

Limitations

This study had some limitations, including the sample size, which was a single case without a control group. Future studies would benefit from a larger sample size to maximize the power and accuracy of their results. In addition, exploring the relationship between TBI severity and LZNFB training effects may be a beneficial focus in the future.

Conclusion

The present preliminary findings suggest that LZNFB may have the potential to aid language performance among those with TBI. It was also found that the rehabilitation of the language network may improve working memory and attention in TBI cases. The result of this case highlights the need for investigating the efficacy of LZNFB not only as a treatment for aphasia but also as a tool for improving cognitive performance more generally.

Author Declaration

The authors declare that they have no grants, financial interests, or conflicts of interest to disclose.

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