NeuroRegulation

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

Citation: Zinn, M. A., Zinn, M. L., & Jason, L. A. (2021). Central autonomic network disturbance in myalgic encephalomyelitis/chronic fatigue syndrome: A pilot study. *NeuroRegulation*, *8*(2), 73–86. https://doi.org/10.15540/nr.8.2.73

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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.

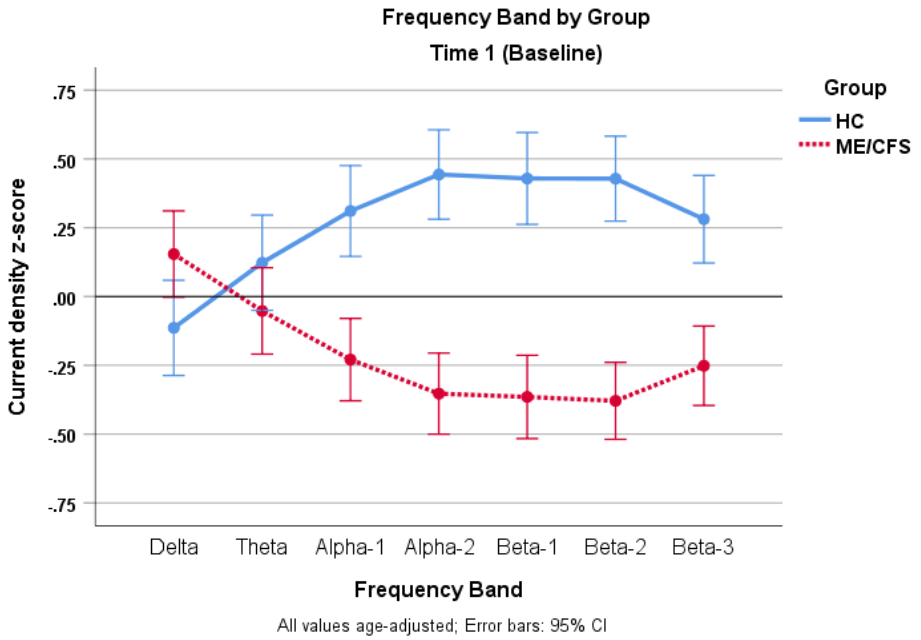
To evaluate group differences in current density for each frequency band at pretest, posttest, and 24 hours (see Figures 1, 2, 3), a mixed multivariate analysis of variance was conducted (age was entered as a covariate). Hotelling's τ^2 was employed to describe multivariate tests due to its inherent

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)		

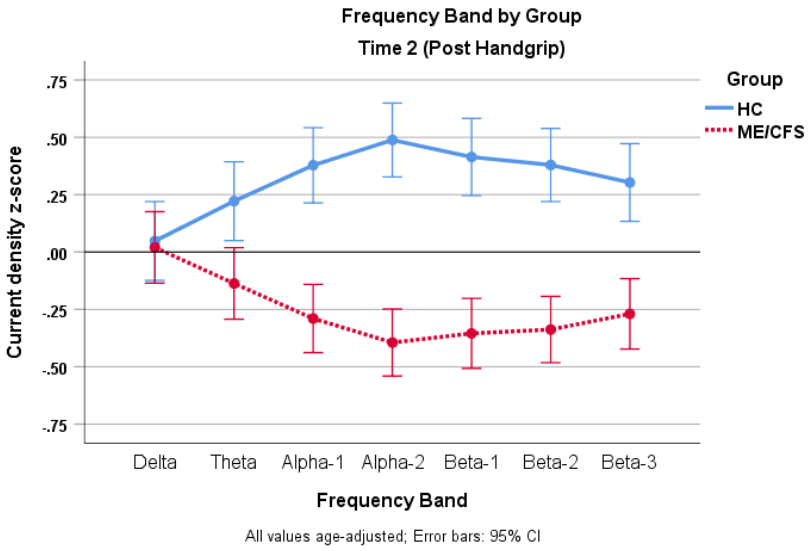
[a] Unpaired Mann-Whitney U test
[b] χ^2 test

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



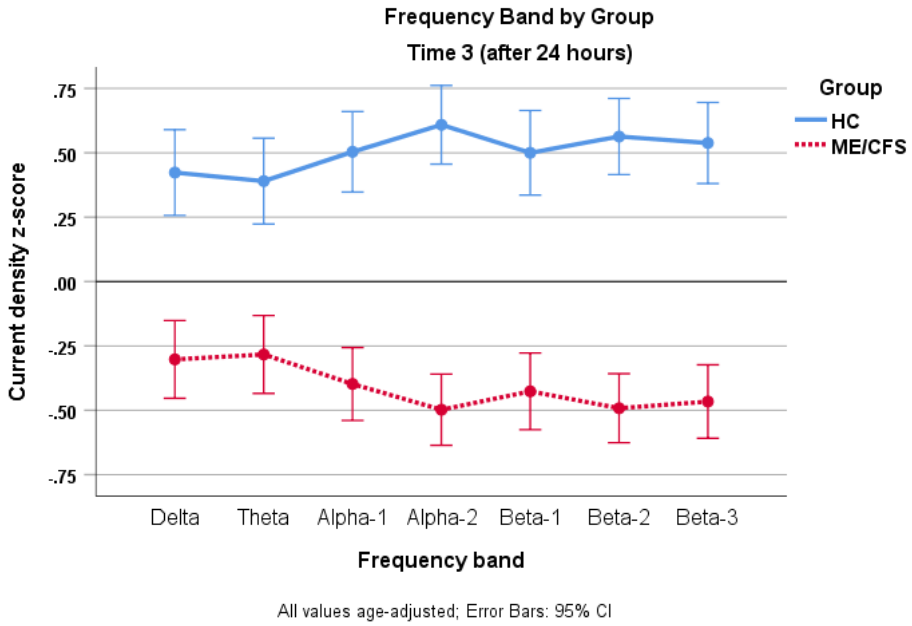
Note. Comparisons for each frequency band were evaluated as follows: Delta, p = .052; Theta, p = .171; Alpha-1, p < .001; Alpha-2, p < .001; Beta-1, p < .001; Beta-2, p < .001; Beta-3, p < .001.

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.

Author Note

Sponsored by DePaul University. There were no sources of funding for this study.

Author Disclosure

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

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Received: February 26, 2021
Accepted: April 8, 2021
Published: June 30, 2021