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Cortical Hypoactivation During Resting EEG Suggests Central Nervous System Pathology in Patients with Chronic Fatigue Syndrome

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Abstract

We investigated cognitive impairment to executive function in 50 patients with chronic fatigue syndrome (CFS) and 50 matched healthy controls (HC). Resting state EEG was collected from 19 scalp locations during a 3 minute, eyes-closed condition. Current densities were localized using exact low-resolution electromagnetic tomography (eLORETA). The Multidimensional Fatigue Inventory (MFI-20) and the Fatigue Severity Scale (FSS) were administered to all participants. Independent t-tests and linear regression analyses were used to evaluate group differences in current densities, followed by statistical non-parametric mapping (SnPM) correction procedures. Significant differences were found in the delta (1–3 Hz) and beta-2 (19–21 Hz) frequency bands. Delta sources were found predominately in the frontal lobe, while beta-2 sources were found in the medial and superior parietal lobe. Left-lateralized, frontal delta sources were associated with a clinical reduction in motivation. The implications of abnormal cortical sources in patients with CFS are discussed.

Keywords

Chronic Fatigue Syndrome; Myalgic Encephalomyelitis; EEG; eLORETA; MFI-20; arousal; neuroinflammation

1. Introduction

Despite the number of studies examining central fatigue in patients with chronic fatigue syndrome (CFS), many challenges remain. Most common challenges faced by researchers are how to characterize temporally fluctuating symptom severity and heterogeneity in CFS samples (Chaudhuri and Behan, 2004; Thomas and Smith, 2009). A recent meta-analysis of

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fifty studies including a total of 1,544 patients with CFS found cognitive symptoms including deficits in memory, attention, and reaction time (Cockshell and Mathias, 2010). As one example, Thomas and Smith (2009) studied 307 patients with CFS and related illness severity to performance decrements in information processing speed, free memory recall, and freedom from distraction. A number of studies have indicated that neuropsychological deficits in CFS do exist and appear to be independent of co-morbid psychiatric disorders (Claypoole et al., 2007; Constant et al., 2011; DeLuca et al., 1997; Sandman et al., 1993).

Central involvement in symptoms of CFS has been substantiated by structural and functional neuroimaging findings. Structurally, CFS has been associated with bilateral white matter atrophy, diffusion tensor imaging changes in the right arcuate fasciculus (Zeineh et al., 2015), as well as reduced grey matter volume and leukoaraiosis in the frontal cortex, limbic areas, basal ganglia, thalami, and brainstem (Barnden et al., 2015; Barnden et al., 2011; de Lange et al., 2005; Lange et al., 1999; Puri et al., 2012). Functionally, measures of central fatigue¹ in CFS correlate with reduced cerebral metabolism and reduced cortical blood flow (Biswal et al., 2011; Costa et al., 1995; MacHale et al., 2000; Schwartz et al., 1994; Tirelli et al., 1998; Yoshiuchi et al., 2006). Tirelli et al. (1998) found that hypometabolism in the brainstem distinguished non-depressed patients with CFS from patients with major depressive disorder only. More recently, neuroinflammation in specific areas of the brain in patients with CFS was associated with the severity of neuropsychological symptoms (Nakatomi et al., 2014). Further, blood-oxygen-level-dependent functional MRI (BOLD fMRI) studies have demonstrated marked differences in frontal and parietal regions involving working memory, executive functioning, attention, and motor planning (Cook et al., 2007; Lange et al., 2005). Examining regions of interest pertaining to working memory, Lange et al. (2005) found that patients with CFS had more widespread activation compared to health controls during a verbal working memory task, suggesting that compensatory mechanisms could likewise contribute to cognitive symptoms. Furthermore, decreased functional connectivity has been found in primary neurocognitive networks (Boissoneault et al., 2015; Gay et al., 2015; Zinn et al., 2016b). Aberrant connectivity, in turn, might contribute to slowed information processing speed and possibly deregulation in other aspects of cognitive function. Tanaka et al. (2006) observed that patients had reduced responsiveness of the auditory cortices to transient, short-lived, noise reduction measured while performing a fatigue-inducing continual visual search task. In addition, the rate of this attenuation was positively correlated with the subjective sensation of fatigue as measured using a fatigue visual analogue scale, immediately before the magnetic resonance imaging session. Small sample sizes are a limitation in many of these studies. Together, findings suggest there are significant, albeit nonspecific brain abnormalities in patients with CFS (Barnden et al., 2011; Lange et al., 2005; Okada et al., 2004; Puri et al., 2012; Siessmeier et al., 2003; Tirelli et al., 1998).

Quantitative electroencephalography (qEEG) is a measure of global arousal and sleep (Thatcher, 2012), evidenced by its use in polysomnography, epilepsy (Ropper and Samuels,

¹Central fatigue differs from fatigue in that it involves not only physical exhaustion, but also mental exhaustion. Patients experience constant exhaustion, problems with visual/motor tasks, word-finding, anomia and aphasia, disturbed sleep patterns with all symptoms fluctuating Chaudhuri, A., Behan, P.O., 2004. Fatigue in neurological disorders. *The Lancet* 363, 978–988..

2009), and in aiding diagnosis of numerous neuroinflammatory conditions (Westmoreland, 2005). The high temporal resolution of qEEG measurements allow the detection of subtle differences in speed and efficiency in spontaneous neuronal communication or the relay of information via timing of oscillatory patterns generated in various cortical and subcortical areas (Buzsaki, 2006; Steriade, 2005; Thatcher, 2012). The frequency, phase, and amplitude of band-limited EEG oscillations relates to the specific information processing taking place at multiple spatiotemporal scales at any given moment (Le Van Quyen, 2011). Several qEEG studies on patients with CFS have suggested that global brain dysregulation of abnormal oscillations may be exerting a downward influence on cognition. For example, using a single electrode at Cz (central midline placement) during eyes-closed and serial sevens conditions, Billiot et al. (1997) found that patients had increased theta during both conditions compared to age-matched healthy controls (HCs). Peak alpha frequency, thought to be a measure of cognitive vigilance (Angelakis et al., 2004), was also reported as negatively associated with fatigue ratings (Billiot et al., 1997). In a single case study using 19-channel EEG, Hammond (2001) found increased theta activity anteriorly in the left frontal lobe, which correlated with fatigue symptoms. Impaired sleep homeostasis was found in a sleep study that reported attenuated delta power in patients with CFS during slow-wave (delta-associated) stages of sleep (Decker et al., 2009). Insufficient delta sleep could produce significant cognitive impairment affecting primary executive functions during wakefulness.

Exact low resolution electromagnetic tomography (eLORETA) is an inverse solution for estimating the current sources of electrical activity from scalp potential recordings. This technique provides a way to investigate spatial locations of the brain associated with symptoms in CFS (Pascual-Marqui et al., 2011; Zinn et al., 2016a). Using low-resolution electromagnetic tomography (LORETA), Sherlin et al. (2007) investigated 17 pairs of monozygotic twins discordant for CFS during the resting-state (eyes-closed condition) and found increased delta current density in the left uncus and parahippocampal gyrus in twins with CFS compared to healthy co-twins. Increased theta current density was also revealed in the cingulate gyrus and right superior-frontal gyrus of the affected twins. Flor-Henry et al. (2010) used the BK-Beamformer technique to localize current source density in patients with CFS during the eyes-open and spatial cognitive conditions. A primary finding of this study was that patients had significant differences in alpha and beta (14–20 Hz) current density compared to HCs. Other frequency bands were not explored in that study.

Although previous source analysis studies of CFS yielded promising findings (Flor-Henry et al., 2010; Sherlin et al., 2007), they had some limitations. For example, the unregularized version of LORETA was used by Sherlin et al. (2007) but eLORETA provides greater localization accuracy at higher spatial resolution (Grech et al., 2008; Pascual-Marqui et al., 2011). Furthermore, Flor-Henry et al. (2010) did not relate their findings to fatigue measures. The present study addressed these limitations using eLORETA to examine regions of interest (ROIs) and their possible associations with self-reported symptoms of central fatigue. We hypothesized that patients with CFS, in comparison to HCs, would show elevations of current density in slow-wave frequency bands (e.g. delta and theta) in frontal regions, and these elevations would be related to clinical self-report measures of central fatigue.

2. Materials and Methods

2.1 Participants

Fifty patients with CFS and 50 HCs were matched by age, gender, educational level, and ethnicity, ranging in age from 28 years to 74 years ($M = 52$; $SD = 11.5$) (see Table 1 for sample demographics). The ratio of females to males was nearly 3:1 (females = 76). Patients were recruited using current, past-study, and wait-listed patients from the Stanford CFS clinic. HCs were recruited through online advertising and from past studies. Patients with CFS were identified by the Fukuda et al. (1994) criteria within 6 months prior to participation through clinical diagnosis. Inclusion and exclusion criteria—absence of known neurological disorders, seizure activity, brain trauma, psychiatric, or physical diseases different than CFS—were assessed during telephone screening. Participants with neurological or psychiatric conditions were also excluded on the basis of medications they reported as currently taking due to medication effects in the EEG (e.g. anxiolytics, antidepressants, sedatives, etc.). HCs were included if they had no exclusionary medical disorders and no abnormal physical functioning. None of the participants had taken medications for 24 hours before testing.

2.2 Behavioral measures

Participants completed behavioral measures before the EEG session was conducted. The study participants completed two measures of fatigue, the Multidimensional Fatigue Inventory (MFI-20) (Smets et al., 1995) and the Fatigue Severity Scale (FSS) (Krupp et al., 1989). The MFI-20 is a 20-item self-report inventory to measure fatigue that has been used for assessment of central fatigue in CFS patients (Lin et al., 2009; Reeves et al., 2005). It demonstrates excellent reliability and validity in CFS samples with an average Cronbach's alpha of .84 (Lin et al., 2009) and includes 5 subscales with the following dimensions: general fatigue, physical fatigue, mental fatigue, reduced motivation, and reduced activity. Each subscale has four items based on a 5-point Likert scale; scoring on each subscale ranges from 4 to 20, with higher scores showing greater fatigue. The FSS is a 9-item questionnaire commonly used to assess fatigue with questions scored from 1 to 7 using a Likert scale. The FSS has demonstrated high internal consistency with a Cronbach's alpha of .92 for a sample of MS patients (Lerdal et al., 2007). Originally developed to measure fatigue in multiple sclerosis and SLE, the FSS has been utilized in a number of diverse medical populations such as patients experiencing esophagitis (Song et al., 2013), neck pain (Takasaki and Treleaven, 2013) and post-stroke fatigue (Tang et al., 2013).

2.3 EEG recordings

Resting EEG was recorded for 3 minutes for all participants using the Discovery 19-channel acquisition amplifier (BrainMaster Technologies, Bedford, Ohio) with Neuroguide (Applied Neuroscience, Inc.) software (version 2.7.4) from 19 scalp electrodes positioned according to the international 10/20 system using standardized electrode caps (Jurcak et al., 2007) with a linked-ears reference. EEG data were recorded at 256 Hz sampling rate and filtered offline from 1–30 Hz. Participants were seated in an upright position in a padded chair and the examination room was well-lit. During cap preparation, impedances for all electrode sites were maintained below 5 k Ω . To minimize circadian effects, all recording sessions took

place between the hours of 11:00 a.m. and 3:00 p.m. Prior to recording, participants were shown their own raw EEG signals in real-time so they could observe raw changes produced by ocular artifacts upon being asked to blink their eyes several times as well as muscular artifact produced when asked to clench their teeth and tense their forehead muscles. Participants were subsequently instructed to remain alert while keeping their eyes closed until the recording session had ended. Vigilance was continuously controlled for during the recording period as the EEG signal was continuously being monitored for emerging signs of drowsiness. Test-retest and split-half reliability coefficients for selected EEG were computed by Neuroguide and kept above .95 as a vigilance test of comparative similarity between different parts of the EEG record. The first 10 seconds of artifact-free EEG at the beginning of each record was used as a template for an automated algorithm in Neuroguide software to remove the spatial and temporal EEG signatures of eye-movement, muscle artifact, and drowsiness. An expert EEG technician, who was blinded during the data acquisition and artifact rejection process, visually inspected each record and manually removed any remaining artifacts. For each participant, at least 60 seconds of artifact-free EEG was selected from each record and exported to text files split into 2-second segments with a 75% cosine taper window (Serman and Kaiser, 2000). Frequency bands were defined as follows: delta (1–3 Hz), theta (4–7 Hz), alpha (8–12 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).

2.4 eLORETA Source Analysis

Scalp surface EEG recordings were analyzed using eLORETA to estimate the 3-dimensional distribution of current densities for a full brain volume consisting of 6,239 voxels of unambiguous grey matter at 5 mm³ spatial resolution (see Table 2) (Pascual-Marqui, 2007; Pascual-Marqui et al., 2011). eLORETA represents an improvement over previously well-established and related tomographies referred to as LORETA (Pascual-Marqui et al., 1994) and sLORETA (Pascual-Marqui, 2002). LORETA has been validated in studies of neurological disorders (Babiloni et al., 2006; Babiloni et al., 2010; Itoh et al., 2011; Mientus et al., 2002; Spironelli et al., 2011; Thatcher et al., 2001; Velikova et al., 2010) including CFS (Sherlin et al., 2007). Furthermore, high correlations have been shown between LORETA and other modalities, such as fMRI (Mulert et al., 2004; Vitacco et al., 2002), structural MRI (Worrell et al., 2000), and PET (Dierks et al., 2000; Pizzagalli et al., 2004; Zumsteg et al., 2005). LORETA validation is also supported by the localization findings obtained from invasive, intracranial recordings in humans, as established with several epilepsy studies in cognitive ERPs (Volpe et al., 2007; Zumsteg et al., 2006a; Zumsteg et al., 2006b).

Functional current density analysis was performed using the LORETA-KEY software package provided by the Key Institute for Brain-Mind Research, University Hospital of Psychiatry, Zurich at <http://www.uzh.ch/keyinst/loreta.htm>. Computations of cortical current density are restricted to unambiguous cortical grey matter coordinates co-registered to the Montreal Neurologic Institute (MNI) average of 305 MRI brains (MNI 152 template). The eLORETA software reports MNI coordinates for the significantly active ROIs while anatomical labels established by von Brodmann in 1909 and referred to as Brodmann areas are based on “corrected” Talairach space (Lancaster et al., 2000; Talairach and Tournoux,

1988). Implementation of eLORETA is based on a realistic head model (Fuchs et al., 2002). A detailed description of this inverse solution together with the proof of its zero-error localization property are described in Pascual-Marqui (2007); Pascual-Marqui et al. (2011).

2.5 eLORETA Statistics

The LORETA-KEY software package was used to evaluate group differences in current density, and to generate 3-D statistical maps. To control for global experimental effects, a subject-wise normalization was performed, scaling the data for each subject by dividing the value of every single voxel by the total power of all voxels of each image. The normalized data were log-transformed and voxel-wise independent sample tests of eLORETA current density power were performed across all voxels for each frequency band (using the log F -ratio). To control for Type 1 error, significant voxels were identified using a statistical non-parametric mapping (SnPM) procedure (Nichols and Holmes, 2002). SnPM uses the data to produce the empirical probability distribution of the “maximal statistic” at the 95th percentile under the null hypothesis. A total of 5,000 randomizations were used to determine the critical threshold value at the .05 alpha level. This strategy for finding the critical threshold value empirically corrects for multiple comparison testing (i.e., for the collection of tests performed for all voxels, and for all discrete frequencies) without reliance on the assumption of Gaussianity. Nichols and Holmes (2002) describe the properties of the method in detail, including its non-parametric nature and how it properly controls for Type I error. The critical threshold value was entered into the “scale-max” of the LORETA viewer for showing the “surviving voxels” consisting of color-coded significant statistic values (any statistic value exceeding this threshold with their null hypotheses was rejected). In addition to single threshold tests, SnPM procedures also simultaneously perform supra-threshold cluster-size tests (cluster statistics) which return the corrected p -values for each suprathreshold cluster in the observed statistic image. Cluster-based inference has greater sensitivity over the single-voxel test while having lower specificity. Statistical maps were then further analyzed using IBM SPSS Version 22 to obtain tables of summary results and analyze regression data correlation coefficients for scatterplots.

3. Results

3.1 Demographics

Participants were matched by age, sex, educational level, and ethnicity and there were no significant differences between CFS participants and HCs across these variables (Table 1). However, the clinical variables measured by the MFI-20 and FSS were all significantly different between groups (Table 2). Mann-Whitney U tests and median tests were conducted to determine significance level between groups.

3.2 Source analysis using eLORETA

Delta current density findings—To capture the spatial extent of cortical source activations, statistical images were assessed for cluster-wise significance (Nichols and Holmes, 2002). Table 3 lists all the regions of interest that were analyzed.

Independent sample t-tests were conducted to compare current densities between patients with CFS and HCs, revealing a large spatially significant cluster of increased delta current density in the CFS group (Figures 1, 2), log-*F*-ratio threshold $t_{\text{MAX}} = 0.374$, $p = .028$; the largest .05 FWE-corrected critical cluster size of 1353 voxels encompassing 48 percent of the frontal lobe bilaterally, 75 percent of the left frontal lobe, and 22 percent of the limbic lobe, and nearly 10 percent of the left temporal lobe; a few voxels were found in the post central gyrus of the parietal lobe (Supplementary Figure 1a,c). No significant differences were found in the occipital lobe. Maximal values of delta current density were found in the left superior frontal gyrus, left middle frontal gyrus, as well as the left sub-gyral (Table 4). ROIs with highest percentage of significant delta sources included the bi-lateral anterior cingulate, left inferior frontal gyrus, and the orbital gyrus (Supplementary Figure 2).

Beta-2 current density findings—Patients with CFS evidenced lower current density for beta-2 in posterior medial frontal gyrus, supplementary region to the primary motor cortex (Figure 3), log-*F*-ratio cluster-defining threshold $t_{\text{MAX}} = -.436$, $p = .024$; the .05 FWE-corrected critical cluster size was 27 voxels. Decreased beta-2 also occurred in a larger cluster of voxels which included the left medial frontal gyrus, bi-lateral paracentral lobule, bi-lateral pre/post central gyrus, bi-lateral cingulate gyrus, bi-lateral precuneus, bi-lateral sub-gyral, left inferior parietal lobule, and bi-lateral superior parietal lobule (Table 5), log-*F*-ratio cluster-defining threshold $t_{\text{MAX}} = -.374$, $p = .028$; the largest .05 FWE corrected critical cluster size was 380 voxels. No significant beta-2 current densities were found in the occipital lobe. In contrast to delta sources, which were nearly absent in the parietal lobe, beta-2 sources were found bilaterally in 18 percent of the parietal lobe and only 6 percent of the frontal lobe; 40 percent of those voxels found in the frontal lobe were in midline ROIs (Supplementary Figure 1b,d).

Associations between delta current density and fatigue scales—Linear regression analyses, which included both groups, revealed that delta current density was positively associated with scores of the MFI-20 reduced motivation subscale (Figure 4), critical voxel-wise threshold $r = 0.364$, $p = .008$, FWE corrected at .05 level, and $r = .403$, $p = .008$, FWE corrected at 0.01 level. The significant delta sources were confined to the left hemisphere in portions of the frontal, limbic, temporal, and parietal lobes as well as sub-lobar ROIs (Table 6). Maximal delta sources were found in the left precentral gyrus and left inferior frontal gyrus (BAs 44, 45 or Broca's area shown in Figure 4). Significant voxels were also found in left post-central gyrus, superior/middle temporal gyrus, left superior/middle frontal gyrus, left orbital gyrus (BAs 11, 47), left anterior cingulate (BA 32), and left insula (BAs 13, 45) (Table 6, Figure 4). No significant relationships were found between current density and the MFI-20 total composite score ($r = .329$, $p = .12$), general fatigue ($r = .372$, $p = .34$), physical fatigue ($r = .326$, $p = .174$), reduced activity ($r = .332$, $p = .303$), mental fatigue subscale scores ($r = .333$, $p = .37$). Likewise, there was no association between current density and the FSS questionnaire, though it approached significance ($r = .326$, $p = .06$). Likewise, regression analyses were performed on just the healthy control group and no associations were found with the MFI-20 ($r = .557$, $p = .52$) and the FSS ($r = .694$, $p = .619$). All non-significant regression tests were FWE corrected at the .05 level. No significant relationships were found in other frequency bands.

4. Discussion

The key aims of our study were to investigate electrophysiological correlates of CFS and associated central fatigue using source localization of EEG signals in 50 patients and 50 matched HCs. We report a critical gap in the CFS literature by examining the entire brain using electrophysiological source analysis. In accomplishing our goals, we found generalized delta band current density in many frontal ROIs of patients with CFS in comparison to HCs. We also found a focal subset of left prefrontal delta sources associated with higher scores of the MFI-20 reduced motivation subscale. Finally, we found that patients with CFS demonstrated lower beta-2 band current density in the somatomotor cortex (precentral & postcentral gyri, paracentral lobule), superior parietal lobe, and medially in the precuneus and posterior cingulate.

Our finding of topographically widespread delta sources in the frontal lobe may have important etiological implications for understanding CFS. Delta oscillations are slow waves that arise through intracortical interactions and cortico-thalamic synchronization with the thalamic nucleus reticularis (Steriade et al., 1990; Steriade et al., 1993). While delta is prominent during slow-wave sleep, it is blocked primarily by cholinergic output during wakefulness to facilitate higher frequencies (beta, gamma) involved in higher-order cognitive processing (Bressler and Kelso, 2001; Knyazev, 2012). For example, hierarchical cross-frequency coupling during the delta phase was shown to modulate the power of higher frequencies during attentional selection (Lakatos et al., 2008). Pathologic cortical delta waves may result from damage in the midbrain and localized white matter lesions (Gloor et al., 1977; Schaul, 1990; Schaul et al., 1981) and brain inflammatory conditions (Westmoreland, 2005). Indeed, our finding of abnormal delta activity in patients with CFS is also consistent with delta findings related to other neurological diseases such as Alzheimer's disease, Parkinson's disease, and multiple sclerosis (Babiloni et al., 2013; Babiloni et al., 2016; Nishida et al., 2011).

The next finding in our study was lower beta-2 band activity among patients. The EEG beta frequency is a desynchronized (arrhythmic), low voltage activity ranging from 13–30 Hz, primarily generated by small feedback loops between thalamic relay cells, the nucleus reticularis and pyramidal cells with small inhibitory neurons positioned closely to the pyramidal neurons (Thatcher, 2012). Significantly reduced beta activity has been associated historically with focal neurological damage and mild cognitive impairment (Guntekin et al., 2013; Ueda et al., 2013), Parkinson's disease (Fonseca et al., 2013) and is one diagnostic criteria used to detect cognitive impairment immediately after cerebral hemorrhage and during diagnosis of mild cognitive impairment (Ueda et al., 2013; Zeng et al., 2013). Beta activity has been shown to be positively correlated with arousal, increases with improved working memory (Heister et al., 2013; Palva et al., 2005) and decreases during conditions of burnout (van Luijckelaar et al., 2010). There are only a few studies examining beta power in CFS (Decker et al., 2009; Guillemineault et al., 2006), both of which found decreased beta activity during several stages of sleep. The ROIs indicating reduced beta sources in our study may provide an electrophysiological basis for reduced central drive in CFS involving psychomotor slowing (Claypoole et al., 2007; Van Den Eede et al., 2011), persistent motor fatigue, and impaired cortical motor area excitability (Gaudino et al., 1997; Majer et al.,

2008; Prasher et al., 1990; Siemionow et al., 2004) known to be impaired in the multifaceted CFS phenotype.

Our analyses of the FSS and the MFI-20 with current density provided only one statistically significant relationship, outlining a possible discontinuity in measuring fatigue and brain activation in CFS. It is well-known that the fatigue in CFS is atypical and is not the same fatigue that healthy people experience, rendering the idea of measuring CFS fatigue speculative. The factors underlying the type of fatigue in CFS have not received adequate attention. When evaluated without brain activation, there was a highly significant difference between patients with CFS and HC's for both fatigue scales, elucidating the idea that the scales themselves do provide information about fatigue. However, when evaluated with brain activation, only the reduced motivation subscale in the MFI-20 was significant. The MFI-20 is known to measure central fatigue but given the lack of literature about central fatigue in CFS, our results suggest a knowledge gap outlined here that warrants further exploration.

The reduced motivation subscale of the MFI-20 was associated with multiple areas of left lateralized delta slowing including the left superior/middle/inferior frontal gyri, pre-central gyrus, orbitofrontal gyrus, anterior cingulate, insula, and the superior/middle temporal gyri. The striking lateralization of our findings further supports prior hypotheses regarding the left forebrain's role in both physical and mental energy management (Craig, 2005). Maxima were found in the inferior frontal gyrus (Broca's area) region which involves verbal memory retrieval and matching auditory/visual stimuli to motor planning involving speech production (Skipper et al., 2007). The focal identification of Broca's area extends to nearby surrounding brain tissue via U-shaped fibers, but it also includes Wernicke's area via white fiber tracts of the arcuate fasciculus (Catani and ffytche, 2005). Motivational difficulties are strongly tied to dysfunction in frontal-subcortical circuits and limbic processing which can interfere with cognitive and motor function (Brown and Pluck, 2000). For example, the dorsolateral prefrontal cortex (Brodmann areas 9 and 46) is involved in the complex circuitry for motivation with projections to the basal ganglia, thalamus, and brainstem (Ghoshal et al., 2011). Motivation is a component of a work output model of fatigue proposed by Chaudhuri and Behan (2004) and, according to the model, the level of perceived exertion is increased when there is insufficient limbic input to sensorimotor signaling pathways that control voluntary movement. Remarkably, neurobehavioral deficits of voluntary action can occur based on paralimbic abnormalities we found, elucidating motivation as a functionally significant dimension of fatigue in patients with CFS.

4.1 CFS and Amotivational States

Abnormality in the orbitofrontal gyrus, anterior cingulate, and insula provides support for the occurrence of amotivational states in CFS. These states can present on a clinical spectrum ranging from apathy to abulia ("loss of will") to akinetic mutism (extreme passivity with no movement or speech) (Filley, 2010). The orbitofrontal gyrus is involved in self-initiated behavior and disruption to this region—or connections between—is associated with a clinical reduction in volition (Levy, 2012; Ropper and Samuels, 2009). Likewise, the anterior cingulate plays a pivotal role in attention, working memory, and conflict resolution, and regulation of emotional/motivational responses (Pastotter et al., 2010). In patients with

CFS, abnormality in the ventral portion of the anterior cingulate was linked to slower reaction times and fewer correct responses (de Lange et al., 2004). Finally, the insula is a heterogeneous structure with several subdivisions that mediate tasks involving motor association, affective processing, and it is the primary area for viscerosensory representations of the body's internal physiological state (e.g., bodily arousal) and feelings, consistent with the James-Lange emotion theory predicting subjective fatigue (Critchley and Harrison, 2013; Uddin et al., 2014). In addition to having many connections to amygdaloid nuclei, the insula plays an important role in autonomic regulation of the heart and gastrointestinal tract (Augustine, 1996). Joint activation of the insula, orbital frontal cortex, and the anterior cingulate forms a highly interconnected core system for task-dependent control of goal-directed behavior. Sensory processing of motivationally salient information is currently the focus of investigation as part of the salience network which provides dynamic switching among other primary functional networks (Menon, 2011; Menon and Uddin, 2010). Together, our findings in regions of the paralimbic cortex including the left anterior cingulate, insula, and orbital frontal gyrus, coupled with broader pathology of the left prefrontal cortex, suggest that patients with CFS may have diminished capacity for homeostatic control and awareness of internal body states, which may in turn inhibit their ability to initiate and sustain purposeful actions.

4.2 CFS Symptoms and the Ascending Reticular Activating System

Some of the earliest appearing clinical correlates in abnormal brain rhythm disturbances appear behaviorally as problems in arousal (Ropper and Samuels, 2009). Complex modulatory mechanisms of subcortical structures and top-down influence of the cortex may elucidate understanding of central fatigue in CFS. The ascending reticular activating system (ARAS) is generally responsible for facilitating human consciousness, arousal levels, and sleep/wake transitions (Paus, 2000) and has been previously hypothesized as a unifying neuroanatomical abnormality to explain CFS symptoms (Dickinson, 1997). In the ARAS, various monoaminergic nuclei in the brainstem produce acetylcholine, norepinephrine, serotonin, and dopamine, together with hypothalamic orexin and efferent fibers from thalamic and basal forebrain structures to help modulate arousal levels and sleep/wake transitions; this occurs through both direct neuronal projections as well as through modulation of thalamocortical circuits (Saper et al., 2010; Wulff et al., 2010). Our findings appear to indicate a pattern of diminished cortical excitation in patients with CFS which may be an objective sign of lower arousal levels when the ARAS is weakened (Jones, 2009). Destabilization of the mutual antagonistic balance of any or all of these ARAS systems can disrupt brain state transitions, causing rapidly shifting fluctuations in symptomology found to be co-morbid in many brain pathologies (Wright et al., 2012; Wulff et al., 2010). Studies which have demonstrated that down-regulation of serotonin receptors (Cleare et al., 2005; Yamamoto et al., 2004) and reduced acetylcarnitine uptake in CFS (Kuratsune et al., 2002) are additional neurobiological indicators of ARAS destabilization. Disturbance to the ARAS would likely result in broader impairments of executive functioning through aberrant information processing speed, psychomotor responsiveness, reaction times, and memory consolidation that is consistent with neuropsychological findings in CFS (Berridge and Waterhouse, 2003; Claypoole et al., 2007; Cockshell and Mathias, 2010; Joyce et al., 1996; Thomas and Smith, 2009).

The viral-lesion hypothesis is supported in earlier imaging studies (Costa et al., 1995; Tirelli et al., 1998) showing brainstem hypometabolism and, more recently, grey/white matter abnormalities in the midbrain (Barnden et al., 2011). Dickinson (1997) reviewed the viral-lesion hypotheses in detail, hypothesizing that a previous viral infection could cause multiple small lesions in the ARAS. Due to its densely compact size, even microscopic damage to the brainstem can lead to severe loss of consciousness and voluntary movement (Lambert et al., 2013). For example, post-polio syndrome is an example where lesions in the ARAS are known to exist (Bartels and Omura, 2005; Bruno et al., 1994; Bruno et al., 1991). Regional blood flow is shown to be reduced in CFS, supported by changes found in neuronal activity. Further evidence is provided by orthostatic intolerance found in CFS (Natelson et al., 2007). Thus, a damaged ARAS may explain findings in CFS sleep disturbance and chronic/episodic fatigue during wakefulness related to delta findings in our study.

4.3 Limitations

Among the limitations of this study, eLORETA analyses were limited to study of cortical function and we could not directly examine subcortical structures such as the basal ganglia and brainstem. However, brain architecture consists of millions of interacting cortico-subcortical loops and evidence of cortical pathology indirectly implicates re-entrant loops from subcortical systems which give rise to overall cortical function (Koziol and Budding, 2009). Secondly, there were no objective neuropsychological measures used in this study and future work combining a neuropsychological test battery with eLORETA may be valuable for exploring associations with clinical variables. Finally, given that delta asymmetry has also been associated with depression and anxiety, future studies should incorporate these measures as well as apathy scales.

Conclusions

Overall, the present study revealed a pattern of global central nervous system hypoactivation in patients with CFS. Most research points to a common finding of cognitive slowing in CFS and we identified this with quantifiable increases in delta and decreases in beta-2 frequency bands. Focal increases in delta sources in regions with language and limbic underpinnings were related to a reduced motivation factor of fatigue. Our findings add to the existing literature demonstrating evidence of central nervous system involvement in patients with CFS. Identifying the subtle aspects of brain dysfunction underscores the need for studies of CFS examining EEG signals that reflect cellular electrical conductivity without time-delay and different frequency bands for added information about synchronous brain region activities. Finally, our study demonstrates that eLORETA is a promising tool for recognizing CFS pathogenesis in spatial locations of the brain on a time scale of milliseconds (Pascual-Marqui et al., 2011; Zinn et al., 2016a).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Fig. 1.

Delta band results of eLORETA independent groups analysis showing greater current density in patients with CFS compared to HCs during the eyes-closed resting condition. Yellow color represents significant cluster activations that were found. Orthogonal views are displayed. A. anterior; P. posterior; L. left hemisphere; R. right hemisphere; L. left hemisphere. Axial, sagittal, and coronal slices shown on Colin27 T2 MRI template (right = right) with MNI coordinates

Fig. 2.

Delta band results of eLORETA independent groups analysis showing greater current density in patients with CFS compared to HCs during the eyes-closed resting condition. Yellow color represents significant cluster activations that were found. Axial views are displayed which correspond to cortical depth in these findings. A. anterior; P. posterior; L. left hemisphere; R. right hemisphere; L. left hemisphere. Axial, sagittal, and coronal slices shown on Colin27 T2 MRI template (right = right) with MNI coordinates

Fig. 3.

Beta-2 band results of eLORETA independent groups analysis revealed decreased current density in patients with CFS compared to HCs during the eyes-closed resting condition.

Blue color represents significant negative cluster activations that were found. Orthogonal views are displayed. A. anterior; P. posterior; L. left hemisphere; R. right hemisphere; L. left hemisphere. Axial, sagittal, and coronal slices shown on Colin27 T2 MRI template (right = right) with MNI coordinates

Fig. 4.

Results of eLORETA regression analyses revealed that current density for the delta band was positively associated with scores on the MFI-20 reduced motivation subscale red-coded for $p < .05$ and yellow-coded for $p < .01$ level, critical voxel threshold $r = .403$, $p = .008$, FWE corrected. Axial, sagittal, and coronal slices with eLORETA solutions were projected onto Colin27 T2 MRI template (right=right) with MNI coordinates. Of the nine scatterplots, highly significant associations (*) were found in the left precentral gyrus and the inferior frontal gyrus (BA 44, or Broca's area). See table 5 for complete regions of interest and BAs. The difference between patients with CFS (blue) and HCs (red) in all scatterplots was significant at $p < .001$.

Table 1

Demographic characteristics of all participants matched by age, sex, educational level, and ethnicity *

Variable	CFS (<i>n</i> = 50)	HCS (<i>n</i> = 50)	Sig.
	<i>M</i> (<i>SD</i>)	<i>M</i> (<i>SD</i>)	
Age, years	51.8 (11.5)	52.1 (11.5)	n.s.
	% (<i>n</i>)	% (<i>n</i>)	
Sex			n.s.
Female	76 (38)	76 (38)	
Male	24 (12)	24 (12)	
Education			n.s.
High school	2 (1)	8 (4)	
Bachelors/Masters	72 (36)	72 (36)	
Ph.D.	4 (2)	4 (2)	
Other	22 (11)	16 (8)	
Ethnicity			n.s.
Asian	4 (2)	6 (3)	
Black	2 (1)	6 (3)	
Hispanic	2 (1)	6 (3)	
White	92 (46)	80 (40)	
Other	0 (0)	2 (1)	

* n.s. = not significant; CFS = chronic fatigue syndrome; HC = healthy control

Table 2

Results of clinical variables for all participants *

Variable	CFS (<i>n</i> = 50)	HCS (<i>n</i> = 50)	Sig.
	<i>M</i> (<i>SD</i>)	<i>M</i> (<i>SD</i>)	
MFI-20 Total Score	76.4 (7.54)	30.5 (8.68)	< .001
MFI-20 General Fatigue	17.8 (.353)	6.28 (.333)	< .001
MFI-20 Physical Fatigue	16.66 (.406)	6.36 (.315)	< .001
MFI-20 Reduced Activity	15.40 (.442)	5.72 (.246)	< .001
MFI-20 Reduced Motivation	11.78 (.501)	5.82 (.269)	< .001
MFI-20 Mental Fatigue	14.42 (.491)	6.32 (.315)	< .001
FSS Score	8.18 (.135)	2.47 (.156)	< .001

* CFS = chronic fatigue syndrome; HC = healthy control; MFI = Multidimensional Fatigue Inventory; FSS = Fatigue Severity Scale.

Table 3

Complete eLORETA 3-D Solution Space: Brain lobes, Regions of Interest, and Corresponding Brodmann Areas

Lobe	Region of interest	Brodmann area
Frontal	Cingulate Gyrus	6, 32
	Extra-Nuclear	47
	Inferior Frontal Gyrus	6, 9, 10, 11, 13, 44, 45, 46, 47
	Medial Frontal Gyrus	6, 8, 9, 10, 11, 25, 32
	Middle Frontal Gyrus	6, 8, 9, 10, 11, 46, 47
	Orbital Gyrus	11, 47
	Paracentral Lobule	3, 4, 5, 6, 31
	Postcentral Gyrus	3, 4
	Precentral Gyrus	4, 6, 9, 43, 44
	Rectal Gyrus	11
	Sub-Gyral	6, 8, 9, 10
	Superior Frontal Gyrus	6, 8, 9, 10, 11
Temporal	Angular Gyrus	39
	Fusiform Gyrus	19, 20, 36, 37
	Inferior Frontal Gyrus	13
	Inferior Temporal Gyrus	19, 20, 21, 37
	Insula	41
	Middle Temporal Gyrus	19, 20, 21, 22, 37, 38, 39
	Sub-Gyral	13, 20, 21, 37, 39
	Superior Occipital Gyrus	39
	Superior Temporal Gyrus	13, 21, 22, 38, 39, 41, 42
	Supramarginal Gyrus	40
	Transverse Temporal Gyrus	41, 42
Parietal	Angular Gyrus	39
	Inferior Parietal Lobule	7, 39, 40
	Paracentral Lobule	4, 7
	Postcentral Gyrus	1, 2, 3, 5, 7, 40, 43
	Precentral Gyrus	4
	Precuneus	7, 19, 31, 39
	Sub-Gyral	2, 7, 40
	Superior Parietal Lobule	5, 7, 40
	Supramarginal Gyrus	39, 40
Occipital	Cuneus	7, 17, 18, 19, 23, 30, 31
	Fusiform Gyrus	18, 19, 37
	Inferior Occipital Gyrus	17, 18, 19
	Inferior Temporal Gyrus	37

Lobe	Region of interest	Brodmann area
	Lingual Gyrus	17, 18, 19
	Middle Occipital Gyrus	18, 19, 37
	Middle Temporal Gyrus	19, 22, 37
	Parahippocampal Gyrus	37
	Precuneus	18, 23, 31
	Superior Occipital Gyrus	19
Limbic	Anterior Cingulate	10, 24, 25, 32, 33
	Cingulate Gyrus	23, 24, 31, 32
	Inferior Temporal Gyrus	20
	Paracentral Lobule	31
	Parahippocampal Gyrus	19, 20, 27, 28, 30, 34, 35, 36, 37
	Posterior Cingulate	18, 23, 29, 30, 31
	Precuneus	31
	Sub-Gyral	19, 31
	Uncus	20, 28, 32, 36, 38
Sub-lobar	Extra-Nuclear	13, 47
	Insula	13, 22, 40, 41, 45, 47

Table 4

Delta Band Results of eLORETA Independent Groups Analysis*

Lobe	Side	Region of interest	Brodmann area	MNI coordinates			Max. log-F- ratio	Cluster size (voxels)
				X	Y	Z		
Frontal	L	Cingulate Gyrus	6, 32	-15	25	40	.584	7
	R	Cingulate Gyrus	6, 32	5	25	40	.482	5
	L	Inferior Frontal Gyrus	6, 9, 10, 11, 13, 44, 45, 46, 47	-40	55	5	.550	172
				10	40	-20	.383	1
	R	Inferior Frontal Gyrus	11	-20	35	25	.565	110
	L	Medial Frontal Gyrus	6, 8, 9, 10, 11, 25, 32	5	35	45	.506	100
	R	Medial Frontal Gyrus	6, 8, 9, 10, 11, 32	0	40	45	.530	17
	M	Medial Frontal Gyrus	6, 8, 9, 10	-25	45	40	.622	214
	L	Middle Frontal Gyrus	6, 8, 9, 10, 11, 46, 47	30	35	50	.466	54
	R	Middle Frontal Gyrus	6, 8, 9, 10	-10	55	20	.521	15
	L	Orbital Gyrus	11, 47	5	50	-20	.452	9
	R	Orbital Gyrus	11	-30	20	40	.580	75
	L	Precentral Gyrus	4, 6, 9, 44	-5	55	-25	.511	12
	L	Rectal Gyrus	11	5	55	-25	.463	5
	R	Rectal Gyrus	11	-25	30	35	.594	4
	L	Sub-Gyral	6, 8, 9, 10	15	25	45	.456	1
	R	Sub-Gyral	8	5	35	55	.511	126
Temporal	R	Superior Frontal Gyrus	6, 8, 9, 10, 11	-25	40	45	.623	154
	L	Superior Frontal Gyrus	6, 8, 9, 10, 11	0	35	50	.535	6
	M	Superior Frontal Gyrus	6, 8				Total:	1089
Temporal	L	Middle Temporal Gyrus	21	-55	10	-25	.417	14
	L	Superior Temporal Gyrus	22, 38	-45	25	-20	.475	65
							Total:	79
Parietal	L	Postcentral Gyrus	3	-55	-15	50	.389	4
							Total:	4

Lobe	Side	Region of interest	Brodmann area	MINI coordinates			Max. log-F- ratio	Cluster size (voxels)
				X	Y	Z		
Occipital		None	None	--	--	--	--	0
Limbic	L	Anterior Cingulate	10, 24, 32, 33	-15	35	25	.557	54
	R	Anterior Cingulate	10, 24, 32	5	30	30	.451	37
	M	Anterior Cingulate	24, 32, 33	0	50	0	.467	13
	L	Cingulate Gyrus	24, 32	-10	25	35	.552	22
	R	Cingulate Gyrus	32	5	20	50	.471	15
	M	Cingulate Gyrus	24, 32	0	25	35	.494	4
Total:								145
Sub-lobar	L	Extra-Nuclear	13, 47	-35	20	0	.456	6
	L	Insula	13, 45	-30	25	5	.479	30
Total:								36

* eLORETA identified maxima at the .05 level, log-F-ratio cluster-defining threshold $t = .374$, $p = .028$; the .05 FWE-corrected critical cluster size was 1353 voxels. Patients with CFS demonstrated increased delta current density during the eyes-closed condition in these areas (L = Left, R = Right, M = Midline)

Table 5

Beta-2 Band Results of eLORETA Independent Groups Analysis^a

Lobe	Side	Region of interest	Brodmann area	MNI coordinates			Max. log-F-ratio	Cluster size (voxels)
				X	Y	Z		
Frontal	L	Medial Frontal Gyrus	6	-5	-30	60	-432	15
	R	Medial Frontal Gyrus	6	5	-30	65	-437	21
	M	Medial Frontal Gyrus	6	0	-30	60	-436	6
	L	Paracentral Lobule	3, 4, 5, 6, 31	-5	-35	60	-433	29
	R	Paracentral Lobule	3, 4, 5, 6, 31	5	-35	60	-435	30
	M	Paracentral Lobule	4, 5, 6, 31	0	-35	60	-435	17
	L	Postcentral Gyrus	4	-10	-40	60	-425	3
	R	Postcentral Gyrus	4	10	-35	70	-430	2
	L	Precentral Gyrus	4, 6	-15	-35	65	-417	8
	R	Precentral Gyrus	4, 6	10	-30	70	-434	8
	R	Superior Frontal Gyrus	6	15	-15	70	-381	1
Total:							Total:	140
Temporal		none	none	--	--	--	--	0
Parietal	L	Inferior Parietal Lobule	40	-35	-55	60	-386	2
	L	Paracentral Lobule	4	-5	-40	65	-425	2
	R	Paracentral Lobule	4	5	-40	65	-425	2
	L	Postcentral Gyrus	2, 3, 5, 7	-10	-40	70	-419	39
	R	Postcentral Gyrus	2, 3, 5, 7	10	-40	70	-422	39
	L	Precuneus	7, 31	-10	-45	50	-415	44
	R	Precuneus	7	5	-35	45	-407	18
	M	Precuneus	7	0	-45	50	-411	7
	L	Sub-Gyral	7, 40	-20	-50	55	-408	7
	R	Sub-Gyral	7, 40	25	-45	60	-387	4
	L	Superior Parietal Lobule	5, 7	-20	-45	60	-412	37
	R	Superior Parietal Lobule	5, 7	20	-45	65	-405	11
Total:							Total:	212

Lobe	Side	Region of interest	Brodmann area	MINI coordinates			Max. log-F-ratio	Cluster size (voxels)
				X	Y	Z		
Occipital		none	none	--	--	--	--	0
	L	Cingulate Gyrus	31	-5	-40	45	-411	16
	R	Cingulate Gyrus	31	5	-40	45	-403	10
	M	Cingulate Gyrus	31	0	-35	40	-390	2
							Total:	28
Sub-lobar		none	none	--	--	--	--	0

^aPatients with CFS demonstrated lower current density for the beta-2 band during the eyes-closed condition in these areas; log-F-ratio cluster-defining threshold $t = .374$, $p = .028$; the .05 FWE-corrected critical cluster size was 1353 voxels. L = Left, R = Right, M = Midline.

Table 6

Left Hemispheric Results of eLORETA Regression Analysis^a

Lobe ^a	Region of interest	Brodmann area	MNI coordinates			Max. r-value	Total voxels
			X	Y	Z		
Frontal	Inferior Frontal Gyrus	9, 11, 13, 44, 45, 46, 47	-55	5	15	.406**	127
	Medial Frontal Gyrus	32	-20	40	15	.368*	1
	Middle Frontal Gyrus	9, 10, 11, 46, 47	-55	25	25	.384*	64
	Orbital Gyrus	11, 47	-15	40	-25	.373*	5
	Precentral Gyrus	4, 6, 43, 44	-60	10	15	.408**	42
	Sub-Gyral	10	-40	45	0	.365*	1
Temporal	Superior Frontal Gyrus	10, 11	-25	50	-15	.377*	23
						Total:	263
	Middle Temporal Gyrus	21	-60	0	-5	.382*	16
	Superior Temporal Gyrus	22, 38	-55	10	0	.392*	66
	Transverse Temporal Gyrus	42	-60	-10	15	.374*	2
Parietal						Total:	84
	Postcentral Gyrus	3, 43	-55	10	20	.381*	5
Occipital	None	None	--	--	--	--	0
Limbic	Anterior Cingulate	32	-20	45	10	.373*	3
Sub-lobar	Extra-Nuclear	13, 47	-35	20	0	.370*	3
	Insula	13, 45	-45	-5	15	.388*	37
						Total:	40

* Maxima significant at .05 level.

** Maxima significant at .01 level.

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Estimates in the model of the relationship between the reduced motivation subscale of the MFI-20 and the significantly increased eLORETA voxel values in the delta band during the eyes-closed resting state condition.