Biological Psychology 136 (2018) 87–99

Contents lists available at ScienceDirect

Biological Psychology

journal homepage: www.elsevier.com/locate/biopsycho

Cortical hypoactivation during resting EEG suggests central nervous system pathology in patients with chronic fatigue syndrome

M.A. Zinn[a], M.L. Zinn[a], I. Valencia[b], L.A. Jason[a,*], J.G. Montoya[b]

[a] Department of Psychology, Center for Community Research, DePaul University, 990 West Fullerton Ave., Suite 3100, Chicago, IL 60614, USA
[b] Department of Medicine, Division of Infectious Diseases, Stanford University School of Medicine, Stanford, CA, USA

ARTICLE INFO

Keywords:
Chronic fatigue syndrome
Myalgic encephalomyelitis
EEG
eLORETA
MFI-20
Arousal
Neuroinflammation

ABSTRACT

We investigated central fatigue 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 min, 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.

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 & Behan, 2004; Thomas & Smith, 2009). A recent meta-analysis of fifty studies including a total of 1544 patients with CFS found cognitive symptoms including deficits in memory, attention, and reaction time (Cockshell & 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, Johnson, Ellis, & Natelson, 1997; Sandman, Barron, Nackoul, Goldstein, & Fidler, 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., 2011; Barnden, Crouch, Kwiatek, Burnet, & Del Fante, 2015; de Lange et al., 2005; Lange et al., 1999; Puri et al., 2012). Functionally, measures of central fatigue[1] in CFS correlate with reduced cerebral metabolism and reduced cortical blood flow (Biswal, Kunwar, & Natelson, 2011; Costa, Tannock, & Brostoff, 1995; MacHale et al., 2000; Schwartz et al., 1994; Tirelli et al., 1998; Yoshiuchi, Farkas, & Natelson, 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, O'Connor, Lange, & Steffener, 2007; Lange et al., 2005). Lange et al. (2005) found that patients with CFS had more widespread activation compared to healthy controls (HC) during a verbal working memory task, suggesting that compensatory mechanisms could be contributing to cognitive symptoms. Furthermore, decreased functional connectivity has been found in primary neurocognitive networks (Boissoneault et al., 2015; Gay et al., 2015; Zinn, Zinn,

* Corresponding author.
E-mail address: ljason@depaul.edu (L.A. Jason).

[1] Central 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.

https://doi.org/10.1016/j.biopsycho.2018.05.016
Received 29 July 2017; Received in revised form 29 March 2018; Accepted 20 May 2018
Available online 23 May 2018
0301-0511/

& Jason, 2016b). Aberrant connectivity, in turn, might contribute to slowed information processing speed and disruption to other aspects of cognitive function. For example, Tanaka et al. (2006) observed that patients had decreased responsiveness of the auditory cortices while performing a fatigue-inducing continual visual search task. The rate of attenuated activity was positively associated with the perceived level of fatigue. 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, Tanaka, Kuratsune, Watanabe, & Sadato, 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 & Samuels, 2009), and for aiding diagnosis of numerous neuroinflammatory conditions (Westmoreland, 2005). The high temporal resolution of qEEG measurement will allow the detection of subtle differences in spontaneous neuronal communication or the relay of information via timing of oscillatory patterns generated by post-synaptic potentials of cortical pyramidal neurons (Buzsaki, 2006; Steriade, 2005; Thatcher, 2012). The frequency, phase, and amplitude of the oscillations relate to specific levels of 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 HCs. Peak alpha frequency, thought to be a measure of cognitive vigilance (Angelakis, Lubar, Stathopoulou, & Kounios, 2004), was also reported as negatively associated with fatigue ratings (Billiot, Budzynski, & Andrasik, 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, Tabassum, Lin, & Reeves, 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 cortical sources of current density from scalp electric potentials. This technique provides a way to investigate spatial locations of the brain associated with symptoms in CFS (Pascual-Marqui et al., 2011; Zinn, Zinn, & Jason, 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 was that patients had significant differences in the alpha (8–13 Hz) and beta (14–20 Hz) bands compared to HCs. However, other frequency bands were not explored in that study.

Although previous source analysis studies of CFS yielded promising findings (Flor-Henry, Lind, & Koles, 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.

Table 1
Demographic characteristics of all participants matched by age, sex, educational level, and ethnicity[a].

Variable	CFS (n = 50) M (SD)	HCs (n = 50) M (SD)	Sig.
Age, years	51.8 (11.5)	52.1 (11.5)	n.s.
	% (n)	% (n)	
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)	

[a] n.s. = not significant; CFS = chronic fatigue syndrome; HC = healthy control.

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 University 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, anti-depressants, 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 h 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, Garssen, Bonke, & De Haes, 1995) and the Fatigue Severity Scale (FSS) (Krupp, LaRocca, Muir-Nash, & Steinberg, 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 0.84 (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