Brain, Behavior, and Immunity 62 (2017) 87–99

Contents lists available at ScienceDirect

Brain, Behavior, and Immunity

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

Full-length Article

Neural consequences of post-exertion malaise in Myalgic Encephalomyelitis/Chronic Fatigue Syndrome

Dane B. Cook [a,b,*], Alan R. Light [c], Kathleen C. Light [c], Gordon Broderick [d], Morgan R. Shields [b], Ryan J. Dougherty [b], Jacob D. Meyer [b], Stephanie VanRiper [b], Aaron J. Stegner [b], Laura D. Ellingson [e], Suzanne D. Vernon [f]

[a] William S. Middleton Memorial Veterans Hospital, Madison, WI, United States
[b] University of Wisconsin – Madison, Madison, WI, United States
[c] University of Utah, Salt Lake City, UT, United States
[d] Nova Southeastern University, Fort Lauderdale, FL, United States
[e] Iowa State University, Ames, IA, United States
[f] Bateman Horne Center, Salt Lake City, UT, United States

ARTICLE INFO

Article history:
Received 11 November 2016
Received in revised form 1 February 2017
Accepted 13 February 2017
Available online 17 February 2017

Keywords:
Exercise
Symptoms
Brain
Cognitive performance

ABSTRACT

Post exertion malaise is one of the most debilitating aspects of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome, yet the neurobiological consequences are largely unexplored. The objective of the study was to determine the neural consequences of acute exercise using functional brain imaging. Fifteen female Myalgic Encephalomyelitis/Chronic Fatigue Syndrome patients and 15 healthy female controls completed 30 min of submaximal exercise (70% of peak heart rate) on a cycle ergometer. Symptom assessments (e.g. fatigue, pain, mood) and brain imaging data were collected one week prior to and 24 h following exercise. Functional brain images were obtained during performance of: 1) a fatiguing cognitive task – the Paced Auditory Serial Addition Task, 2) a non-fatiguing cognitive task – simple number recognition, and 3) a non-fatiguing motor task – finger tapping. Symptom and exercise data were analyzed using independent samples t-tests. Cognitive performance data were analyzed using mixed-model analysis of variance with repeated measures. Brain responses to fatiguing and non-fatiguing tasks were analyzed using linear mixed effects with cluster-wise (101-voxels) alpha of 0.05. Myalgic Encephalomyelitis/Chronic Fatigue Syndrome patients reported large symptom changes compared to controls (effect size $\geq$0.8, $p < 0.05$). Patients and controls had similar physiological responses to exercise ($p > 0.05$). However, patients exercised at significantly lower Watts and reported greater exertion and leg muscle pain ($p < 0.05$). For cognitive performance, a significant Group by Time interaction ($p < 0.05$), demonstrated pre- to post-exercise improvements for controls and worsening for patients. Brain responses to finger tapping did not differ between groups at either time point. During number recognition, controls exhibited greater brain activity ($p < 0.05$) in the posterior cingulate cortex, but only for the pre-exercise scan. For the Paced Serial Auditory Addition Task, there was a significant Group by Time interaction ($p < 0.05$) with patients exhibiting increased brain activity from pre- to post-exercise compared to controls bilaterally for inferior and superior parietal and cingulate cortices. Changes in brain activity were significantly related to symptoms for patients ($p < 0.05$). Acute exercise exacerbated symptoms, impaired cognitive performance and affected brain function in Myalgic Encephalomyelitis/Chronic Fatigue Syndrome patients. These converging results, linking symptom exacerbation with brain function, provide objective evidence of the detrimental neurophysiological effects of post-exertion malaise.

Abbreviations: AFNI, Analysis of Functional Neuroimages; CDC, Centers for Disease Control; CCC, Canadian Consensus Criteria; DSQ, DePaul Symptom Questionnaire; fMRI, Functional MRI; GWI, Gulf War Illness; HR, Heart Rate; ME/CFS, Myalgic Encephalomyelitis/Chronic Fatigue Syndrome; MNI, Montreal Neurological Institutes; PASAT, Paced Auditory Serial Addition Task; PEM, Post-exertion malaise; POMS, Profile of Mood States; RER, Respiratory Exchange Ratio; RPE, Ratings of Perceived Exertion; SF-36, Medical Outcomes Survey Short-Form-36; START, Stress Test Associated Reversible Tachycardia; STOPP, Stress Test Occurring Phantom Perception; TMD, Total Mood Disturbance; U.S., United States; VAS, Visual Analogue Scale; VCO_2, Carbon Dioxide Production; Ve, Ventilation; VO_2, Oxygen Consumption.

* Corresponding author at: Department of Kinesiology, University of Wisconsin – Madison, 2000 Observatory Drive, Madison, WI 53706, United States.
E-mail address: dane.cook@wisc.edu (D.B. Cook).

http://dx.doi.org/10.1016/j.bbi.2017.02.009
0889-1591/Published by Elsevier Inc.

1. Introduction

Post-exertion malaise (PEM) is a debilitating condition and a central characteristic of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) (Institute of Medicine (U.S.). Committee on the Diagnostic Criteria for Myalgic Encephalomyelitis and Institute of Medicine (U.S.). Board on the Health of Select Populations, 2015). Characterized by symptom exacerbation across a host of domains (e.g. fatigue, pain, cognition), PEM is perhaps the most incapacitating aspect of this vexing disease (Fukuda et al., 1994; Carruthers et al., 2003). Unfortunately, the biological mechanisms that underlie this phenomenon are not well-understood.

Under controlled laboratory settings, acute exercise has proven a useful model to study PEM. Both maximal and submaximal exercise protocols have been employed to determine effort-associated changes across a multitude of perceptual and physiological outcomes. These studies have demonstrated that acute exercise worsens symptoms of ME/CFS (Nijs et al., 2008; VanNess et al., 2010; White et al., 2010; Meeus et al., 2011; Meyer et al., 2013; Keech et al., 2015), alters cardiorespiratory responses to exercise (Cook et al., 2012; Snell et al., 2013), impairs pain regulation (Van Oosterwijck et al., 2010; Van Oosterwijck et al., 2011), impacts immune function markers (e.g. cytokines, compliment c4, natural killer cells, receptors) (Broderick et al., 2011; Light et al., 2011; Meyer et al., 2013) and may change gut microbiome interactions (Shukla et al., 2015). It is clear from these studies that PEM influences multiple physiological systems. One system that has received limited attention with respect to PEM, is the central nervous system (Nijs et al., 2012), particularly brain function.

There is considerable evidence demonstrating that ME/CFS has both structural and functional brain consequences. Cross-sectional data have shown that ME/CFS patients have reduced resting brain blood flow (Yoshiuchi et al., 2006; Biswal et al., 2011), differing connectivity among brain regions (Kim et al., 2015; Boissoneault et al., 2016; Gay et al., 2016), alterations of whole brain metabolism and for metabolites such as lactate and n-acetyl aspartate (Brooks et al., 2000; Siessmeier et al., 2003; Murrough et al., 2010), reduced gray and white matter volume (Lange et al., 2001; Okada et al., 2004; De Lange et al., 2005; Puri et al., 2014), increased presence of white matter lesions (Lange et al., 1999; Cook et al., 2001), increased neuroinflammation (Nakatomi et al., 2014) and altered brain function during cognition (De Lange et al., 2004; Lange et al., 2005; Cook et al., 2007). However, the influence of PEM on many of these brain-derived outcomes remains unexplored.

The purpose of the present investigation was to determine the influence of acute exercise on symptoms, cognitive performance and brain function during both fatiguing and non-fatiguing tasks in patients with ME/CFS and healthy controls. This study is an extension of our prior work that demonstrated greater brain activity during a mentally-fatiguing cognitive task for ME/CFS patients compared to controls (Cook et al., 2007). We hypothesized that ME/CFS patients would exhibit augmented brain responses to a fatiguing cognitive task, but would not differ from controls during non-fatiguing motor (finger tapping) or simple cognitive (auditory monitoring) tasks (a replication of our prior work). Further, we hypothesized that exercise would result in an exacerbation of symptoms, reduced cognitive performance and further increases in brain activity during fatiguing cognition for ME/CFS patients but not controls.

2. Materials and methods

2.1. Participants

This study consisted of 15 female ME/CFS patients and 15 female healthy controls matched on age (±3 years), height (±2 inches), weight (±5 lb) and physical activity (based on the methods of Meyer et al., (Meyer et al., 2013)). Briefly, we paired healthy controls with patients by inquiring about physical activity habits during the phone screen interview. Participants were asked to report their general physical activity patterns and whether they were more or less active than their peers. Overall, sedentary controls were sought unless a ME/CFS patient reported being physically active (n = 2). In this case, a physically active control was chosen as a match. Participants were recruited for a submaximal exercise, gene expression and brain imaging study. The data presented here include baseline characteristics, pre- and post-exercise symptoms, cognitive performance and brain responses to fatiguing and non-fatiguing cognitive and motor tasks.

2.2. Inclusion and exclusion criteria

ME/CFS participants were required to meet both Centers for Disease Control (CDC) (Fukuda et al., 1994) and Canadian Consensus Criteria (CCC) (Carruthers et al., 2003) case definition criteria. Confirmation of diagnosis was obtained both by a letter from their doctor confirming that they met both CDC and CCC criteria and completion of the DePaul Symptom Questionnaire at study entry (Brown and Jason, 2014). The DePaul symptom questionnaire contains diagnostic algorithms that are based on items meant to represent case definition criteria of ME/CFS, and the questionnaire was specifically developed to assess both CDC and CCC criteria (Jason et al., 2013a). It has also demonstrated good test-retest reliability and sensitivity (Jason et al., 2015; Strand et al., 2016). Participants were excluded for: 1) current use of immunomodulatory medications or antibiotics in the past 6 weeks, 2) self-report or physician confirmed diagnosis (present) of psychosis, major depression with psychotic or melancholic features, bipolar disorders, anorexia or bulimia nervosa; alcohol or substance abuse within the past 2 years, 3) fatigue sufficient to impair functioning or preclude exercise testing (e.g. bed-bound), 4) cardiovascular conditions that would preclude engaging in submaximal exercise and 5) any contraindications for the MRI environment (e.g. ferrous metal in the body). In addition, controls were required to be healthy and free from active illness. Controls were asked to indicate their health status and ability to exercise at screening and health status was confirmed verbally on each day of testing to ensure that neither ME/CFS nor controls had an acute illness (e.g. common cold) on the day of testing. Finally, all participants were asked to refrain from structured exercise for the 48-h period prior to each testing day and this was confirmed verbally with the participant upon arrival to the laboratory for testing.

2.3. Experimental procedures

Participants reported to the Exercise Psychology Laboratory at the University of Wisconsin – Madison for symptom assessment and for the exercise testing procedures. Functional neuroimaging procedures were performed at the Waisman Center's Laboratory for Brain Imaging and Behavior. Participants completed three days of testing. Day 1 involved baseline symptom data collection and functional brain imaging of both fatiguing and non-fatiguing tasks. Day 2 occurred approximately one-week following baseline data collection, and consisted of symptom measurement and exercise testing. Day 3 occurred 24-h post-exercise, and consisted of symptom measurement and a repetition of the functional brain imaging procedures that were performed on the first day of testing. All study procedures were approved by the institutional review board of the University of Wisconsin – Madison and all participants provided informed consent according to the Declaration of Helsinki prior to testing.