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

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

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 ≥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.

Keywords
Exercise, Symptoms, Brain, Cognitive performance

Disciplines
Biomechanics | Exercise Science | Kinesiology | Kinesiotherapy | Movement and Mind-Body Therapies

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

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A B S T R A C T

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.

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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; VO$_2$, Carbon Dioxide Production; Ve, Ventilation; VO$_2$, Oxygen Consumption.

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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 (Nijss et al., 2008; VanNess et al., 2010; White et al., 2010; Meeus et al., 2011; Meyer et al., 2013; Kees et al., 2015), alters cardiorespiratory responses to exercise (Cook et al., 2012; Snell et al., 2013), impairs pain regulation (Van Oosterwijk et al., 2010; Van Oosterwijk et al., 2011), impacts immune function markers (e.g. cytokines, complement 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 (Nijss 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.
2.4. Baseline data collection and symptom assessment

Questionnaires completed at baseline included the: 1) DePaul Symptom Questionnaire (DSQ; [Jason et al., 2015]), 2) Medical Outcomes Survey Short-Form-36 (SF-36; [McHorney et al., 1994]), 3) Profile of Mood States (POMS; [McNair et al., 1981]) and clinical symptom data. These instruments were intended to characterize the sample and provide covariate data for neuroimaging analyses. The clinical symptom data included ratings of the degree to which participants indicated that the symptoms of PEM, unrefreshing sleep, muscle pain, joint pain, memory/concentration problems, headaches, muscle weakness and swollen or tender lymph nodes were a “problem” for their illness during the last month. Ratings occurred across a 1 to 5 likert-type scale (1 = Never a problem; 2 = A mild problem; 3 = A substantial problem; 4 = A severe problem; 5 = A very severe problem). In addition, the POMS and ten visual analogue scales (VAS) derived from key symptoms contained in the CDC symptom inventory (ex., fatigue after exertion, muscles aches, memory problems; see Table 3 for full symptom list) (Wagner et al., 2005) were administered pre-exercise and immediately and 24-h post-exercise to measure mood and symptom changes associated with acute exercise (i.e. PEM).

2.5. Exercise testing

Participants completed 30 min of exercise on an electronically-braked cycle ergometer (Lode Corival, Lode B.V., Groningen, The Netherlands). Exercise intensity was set at 70% of the participant’s age-predicted maximal heart rate. Exercise began at 20 Watts and the intensity of exercise was gradually increased until the participants reached their target heart rate (HR). Once the target HR was reached (~4 min), the participants completed 25 min of steady-state exercise at the target intensity. Exercise intensity was maintained by making minor Watt adjustments throughout the 25-min session. Exercise ended with a 3-min active recovery period at 20 Watts. Ratings of perceived exertion (RPE) and leg muscle pain were measured at 5-min intervals during exercise using validated scales (Borg, 1982; Cook et al., 1997).

Measurements of oxygen consumption (VO2), carbon dioxide production (VCO2), minute ventilation (Ve), HR and work rate (Watts) were recorded continuously during exercise using a metabolic cart (TrueOne® 2400 Parvomedics, Sandy, UT) and a 2-way non-rebreathing valve (Hans-Rudolph, Kansas City, MO). The flow meter was calibrated prior to exercise by making multiple comparisons to a three-liter piston syringe. O2 and CO2 sensors were calibrated by the presentation of known gas concentrations. Lactate measurement (Nova Lactate Pro, Nova Biomedical, Waltham, MA) occurred at minutes 1, 15 and 30 of the exercise session.

2.6. Functional brain imaging procedures

All functional and anatomical magnetic resonance images were collected on a 3-Tesla GE Discovery MR750 scanner (GE Health Systems, Waukesha, WI). Following the localizer scan and high-order shimming, high-resolution functional T2* echo-planar blood oxygen level dependent images were obtained with an eight-channel transmit-receive head coil. Functional image acquisition procedures were obtained with a gradient echo sequence (TR 2000 ms, TE 25 ms, flip angle 60°) and consisted of 40 sagittal slices with thickness 4 mm and no gap, yielding coverage of the whole brain. The acquisition matrix was 64 x 64 and the filed-of-view was 24 cm, delivering an in-plane voxel resolution of 3.75 x 3.75 x 5 mm. High-resolution T1-weighted anatomical acquisitions (TR 9 ms, TE 1.7 ms, FOV 24 cm, flip angle 10°) consisted of 128 axial slices with a matrix of 256 x 256, each 1.2 mm thick.

Functional MRI (fMRI) of the brain were obtained during performance of: 1) a fatiguing cognitive task – the Paced Auditory Serial Addition Task (PASAT), 2) a non-fatiguing cognitive task – simple number recognition, and 3) a non-fatiguing motor task – finger tapping (as described in Cook et al., 2007). For the finger-tapping task, participants were instructed to open and close their right hand, bringing their four fingers in contact with their thumb, at the same rate (2 Hz) as a flashing crosshair. For the simple auditory monitoring task, participants were instructed to listen to a series of numbers ranging from “one” to “ten” and to press a button when they hear the number “seven.” Each number was presented for 1500 ms and separated by 500 ms. Both tasks consisted of four 30-s on-periods preceded and followed by 30-s off-periods for a total duration of 4 min and 30 s. For the auditory monitoring task, twenty events were presented during each 30-s on-period. Of these, seven events (35%) were correct targets (i.e., the number 7). Task performance was quantified as the number of correct responses. Images were viewed through fMRI-compatible fiber optic goggles (Avotec Inc., Way Stuart, FL). Auditory stimuli (i.e. numbers) were delivered using a pneumatic headphone system (Avotec Inc., Way Stuart, FL) using a digital equalizer. A modified version of the PASAT (Tombaugh, 2006) was used to induce feelings of mental fatigue during fMRI scanning (as described in: Cook et al., 2007). Participants listened to a series of numbers ranging from “one” to “nine”. They were instructed to continually and silently add the first number to the second, the second number to the third and so on and to press the button whenever two consecutive numbers sum to the number 10. Each number was presented for 1500 ms and was separated by 500 ms. The task occurred in three separate segments and consisted of three 4-min and 30-s on-periods and five 30-s off-periods for a total of 16 min. One hundred and twenty events were presented during each three-minute on-period. Of these, forty-two (35%) were correct targets (i.e. two numbers summing ‘10’). As a secondary task, participants were instructed that in addition to listening to the numbers presented as part of the PASAT, they were to visually focus on a set of three boxes that contained rapidly (every 500 ms) and randomly changing numbers. The rate at which the visual numbers were presented was intentionally made too rapid for any arithmetic and was purely intended to distract and interfere with the primary auditory task, thereby, increasing the complexity and attentional demands of the task and inducing greater mental fatigue. Thus, the participants were instructed to listen to the numbers presented through the headphones and perform the serial addition task on these auditory numbers, while simultaneously focusing visually on the numbers scrolling on the screen. The numbers of correct, incorrect and omitted responses were measured using E-Prime (Psychological Software Tools, Inc., Sharpsburg, PA) and used to determine task performance. Ratings of mental fatigue (VAS) were obtained immediately prior to and following each task block.

2.7. Data processing & analysis

Subject characteristics and self-report data for ME/CFS and control participants were examined using descriptive statistics, including the Cohen’s d effect size metric (Cohen, 1988). Cognitive performance and mental fatigue data collected during scanning were analyzed using Group (ME/CFS & control) x Time (Pre and Post Exercise) x Block (1, 2 and 3) mixed model analysis of variance with repeated measures. Average cardiorespiratory, perceptual and performance of: 1) a fatiguing cognitive task – the Paced Auditory Serial Addition Task (PASAT), 2) a non-fatiguing cognitive task – simple number recognition, and 3) a non-fatiguing motor task – finger tapping (as described in Cook et al., 2007). For the finger-tapping task, participants were instructed to open and close their right hand, bringing their four fingers in contact with their thumb, at the same rate (2 Hz) as a flashing crosshair. For the simple auditory monitoring task, participants were instructed to listen to a series of numbers ranging from “one” to “ten” and to press a button when they hear the number “seven.” Each number was presented for 1500 ms and separated by 500 ms. Both tasks consisted of four 30-s on-periods preceded and followed by 30-s off-periods for a total duration of 4 min and 30 s. For the auditory monitoring task, twenty events were presented during each 30-s on-period. Of these, seven events (35%) were correct targets (i.e., the number 7). Task performance was quantified as the number of correct responses. Images were viewed through fMRI-compatible fiber optic goggles (Avotec Inc., Way Stuart, FL). Auditory stimuli (i.e. numbers) were delivered using a pneumatic headphone system (Avotec Inc., Way Stuart, FL) using a digital equalizer. A modified version of the PASAT (Tombaugh, 2006) was used to induce feelings of mental fatigue during fMRI scanning (as described in: Cook et al., 2007). Participants listened to a series of numbers ranging from “one” to “nine”. They were instructed to continually and silently add the first number to the second, the second number to the third and so on and to press the button whenever two consecutive numbers sum to the number 10. Each number was presented for 1500 ms and was separated by 500 ms. The task occurred in three separate segments and consisted of three 4-min and 30-s on-periods and five 30-s off-periods for a total of 16 min. One hundred and twenty events were presented during each three-minute on-period. Of these, forty-two (35%) were correct targets (i.e. two numbers summing ‘10’). As a secondary task, participants were instructed that in addition to listening to the numbers presented as part of the PASAT, they were to visually focus on a set of three boxes that contained rapidly (every 500 ms) and randomly changing numbers. The rate at which the visual numbers were presented was intentionally made too rapid for any arithmetic and was purely intended to distract and interfere with the primary auditory task, thereby, increasing the complexity and attentional demands of the task and inducing greater mental fatigue. Thus, the participants were instructed to listen to the numbers presented through the headphones and perform the serial addition task on these auditory numbers, while simultaneously focusing visually on the numbers scrolling on the screen. The numbers of correct, incorrect and omitted responses were measured using E-Prime (Psychological Software Tools, Inc., Sharpsburg, PA) and used to determine task performance. Ratings of mental fatigue (VAS) were obtained immediately prior to and following each task block.

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Functional brain imaging analyses were conducted using Analysis of Functional Neuroimages (AFNI) software (Cox, 1996) and all other statistical analyses were performed with SPSS 22.0. Anatomical images were registered to the Montreal Neurological Institutes (MNI) 152 template (Mazziotta et al., 1995) using an affine transformation. For functional data, the initial five time points were discarded from functional analyses due to saturation effects. Data were motion corrected (3dvolreg), de-spiked (3dDespike), slice-time corrected (3dTshift), aligned to the MNI-152 template with a nonlinear warp (ANTS WarpTimeSeriesImageMultiTransform), iteratively blurred to a smoothness of 8 mm full-width, half-maximum (3dBlurToFWHM) and converted to percent signal change. AFNI’s 3dREMLfit program was used to perform linear regression on each participant’s data including separate regressors for the pre-stimulus countdown, task stimuli (i.e. motor and cognitive), and rating period.

Group-level brain imaging analyses were limited to regions of interest that were chosen a priori and that were based on our previous work (Cook et al., 2007). Specifically, we have previously reported PASAT related brain activity for both ME/CFS and control participants in cerebellar, cingulate, frontal, insular, motor, parietal, sensory, and temporal cortices, as well as, the hippocampus and thalamus. Further, mental fatigue was significantly and positively related to activity in cerebellar, cingulate, frontal, motor and temporal cortices and negatively related to activity in the superior parietal cortex. Thus, our regions of interest included 1) motor related activity in the pre-motor, primary motor, supplemental motor and cingulate motor cortices, thalamus and cerebellum, and 2) attention, working memory and executive function related activity in the dorsal prefrontal, inferior frontal, ventrolateral prefrontal, supplemental motor, premotor, superior parietal, inferior parietal, middle and superior temporal, insular and anterior cingulate cortices, cerebellum cuneus and hippocampus.

Brain responses to both fatiguing and non-fatiguing tasks were analyzed using AFNI’s Linear Mixed Effects (3dLME) program with condition (pre- and post-exercise) and group (ME/CFS & control) as the independent variables and brain responses as the dependent variable. To control for multiple comparisons, we thresholded the statistical map at a voxelwise p-value of 0.01 and applied a cluster-size threshold of 101 voxels (7101 mm$^3$), corresponding to a voxelwise alpha of 0.05 as determined by AFNI’s 3dClustSim. Following determination of task-related brain activity, linear regression analyses were conducted to determine relationships between symptoms and brain responses. In addition, exploratory relationships between brain activity during the PASAT post-exercise and metabolic (HR, VO2, VCO2, VE, Watts & lactate) and behavioral (RPE & leg muscle pain) responses during exercise were tested. We used data from the final five minutes of exercise for these analyses as this was representative of a steady-state for both groups and encompassed the majority of the exercise test. For these exploratory analyses, we thresholded the statistical map at a voxelwise p-value of 0.01 and used AFNI’s 3dClustSim to determine the cluster-size threshold ($\alpha = 0.01$).

3. Results

3.1. Participant characteristics

Baseline data are listed in Table 1. As expected, the ME/CFS group was more symptomatic and had overall worse health than the controls. In addition, 11 of 15 ME/CFS participants reported that exercise made their symptoms either substantially, severely or very severely worse, while 4 of the 15 participants reported that exercise either made them mildly worse (n = 2) or not worse (n = 2). For the two participants that reported that exercise did not make them worse, both reported avoiding activities they felt would exacerbate their symptoms. The other most frequently endorsed symptoms that were currently impacting patients included unrefreshing sleep (14 of 15), memory and concentration problems (14 of 15), muscle pain (14 of 15) and headaches (14 of 15).

3.2. Exercise testing outcomes

Cardiorespiratory, lactate and perceptual data measured during exercise are listed in Table 2. ME/CFS and controls had similar HR, respiratory exchange ratio (RER) and lactate responses during exercise. Although both groups exercised at 70% of age-predicted maximal HR, ME/CFS patients exercised at significantly lower absolute Watts and VO$_2$ and reported significantly greater exertion and leg muscle pain ratings compared to controls ($p \leq 0.05$).

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Participant characteristics and ME/CFS symptoms (Mean ± SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ME/CFS</td>
<td>Control</td>
</tr>
<tr>
<td>(n = 15)</td>
<td>(n = 15)</td>
</tr>
<tr>
<td>Age (yrs)</td>
<td>42.7 (11.1) 43.2 (10.4) n/a</td>
</tr>
<tr>
<td>Height (in)</td>
<td>65.2 (24.4) 65.6 (2.6) n/a</td>
</tr>
<tr>
<td>Weight (lbs)</td>
<td>151.7 (27.2) 1531 (21.9) n/a</td>
</tr>
<tr>
<td>Functional Physical Function</td>
<td>50.3 (30.0) 970 (4.9) 2.7</td>
</tr>
<tr>
<td>Vitality</td>
<td>18.0 (21.1) 75.33 (10.6) 3.6</td>
</tr>
<tr>
<td>Mental Health</td>
<td>75.5 (12.1) 83.5 (8.4) 0.8</td>
</tr>
<tr>
<td>Bodily Pain</td>
<td>50.2 (22.6) 85.2 (16.9) 1.8</td>
</tr>
<tr>
<td>POMS Fatigue</td>
<td>18.8 (7.9) 3.6 (3.9) 2.2</td>
</tr>
<tr>
<td>POMS TMD</td>
<td>141.9 (30.9) 97.5 (16.9) 1.9</td>
</tr>
<tr>
<td>PEM</td>
<td>3.5 (1.4) n/a n/a</td>
</tr>
<tr>
<td>Unrefreshing Sleep</td>
<td>3.8 (0.9) n/a n/a</td>
</tr>
<tr>
<td>Muscle Pain</td>
<td>3.2 (0.9) n/a n/a</td>
</tr>
<tr>
<td>Joint Pain</td>
<td>2.8 (0.9) n/a n/a</td>
</tr>
<tr>
<td>Memory/Concentration</td>
<td>3.1 (1.1) n/a n/a</td>
</tr>
<tr>
<td>Headaches</td>
<td>2.7 (0.9) n/a n/a</td>
</tr>
<tr>
<td>Muscle Weakness</td>
<td>2.7 (1.3) n/a n/a</td>
</tr>
<tr>
<td>Swollen or Tender Lymph</td>
<td>1.5 (0.7) n/a n/a</td>
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<table>
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<tr>
<th>Table 2</th>
<th>Exercise testing data (Mean ± SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exercise Variable</td>
<td>ME/CFS (n = 15)</td>
</tr>
<tr>
<td>HR</td>
<td>127 (6)</td>
</tr>
<tr>
<td>VO2</td>
<td>13.2 (4.3)</td>
</tr>
<tr>
<td>RER</td>
<td>0.98 (0.20)</td>
</tr>
<tr>
<td>Watts</td>
<td>48.8 (22.3)</td>
</tr>
<tr>
<td>RPE (6-20)</td>
<td>13.3 (2.5)</td>
</tr>
<tr>
<td>Pain (0-10)</td>
<td>2.8 (1.6)</td>
</tr>
<tr>
<td>Lactate (Baseline)</td>
<td>2.2 (1.4)</td>
</tr>
<tr>
<td>Lactate (minute 12.5)</td>
<td>3.7 (1.1)</td>
</tr>
<tr>
<td>Lactate (Recovery)</td>
<td>3.1 (1.6)</td>
</tr>
</tbody>
</table>

HR = heart rate; VO2 = oxygen consumption; RER = respiratory exchange ratio; RPE = ratings of perceived exertion. These metabolic data represent average values collected continuously for the 25-min exercise bout. For lactate, baseline data were taken while comfortably seated on the cycle ergometer, minute 12.5 represents the midpoint of steady state exercise recovery represents minute 30 of exercise. Leg muscle pain and RPE data were obtained every five minutes during exercise and averaged across the 25 min of exercise.

ME/CFS significantly different from control (see results).
**Table 3**

Symptoms pre- and 24-h post-exercise (Mean ± SD).

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>ME/CFS Pre (n = 15)</th>
<th>ME/CFS Post (n = 15)</th>
<th>Control Pre (n = 15)</th>
<th>Control Post (n = 15)</th>
<th>Effect Size d ME/CFS compared to controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue</td>
<td>45.9 (27.3)</td>
<td>60.0 (28.9)</td>
<td>10.1 (11.0)</td>
<td>11.2 (16.7)</td>
<td>1.04</td>
</tr>
<tr>
<td>Muscle Pain</td>
<td>32.5 (26.0)</td>
<td>41.0 (28.8)</td>
<td>7.6 (7.8)</td>
<td>4.5 (11.6)</td>
<td>0.74</td>
</tr>
<tr>
<td>Joint Pain</td>
<td>31.0 (25.5)</td>
<td>33.9 (30.0)</td>
<td>5.7 (9.2)</td>
<td>3.4 (5.4)</td>
<td>0.32</td>
</tr>
<tr>
<td>Subjective Fever</td>
<td>6.5 (15.1)</td>
<td>7.5 (19.6)</td>
<td>0.1 (0.3)</td>
<td>0.1 (0.3)</td>
<td>0.26</td>
</tr>
<tr>
<td>Chills</td>
<td>7.7 (16.1)</td>
<td>11.3 (18.7)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0.61</td>
</tr>
<tr>
<td>Tender Lymph Nodes</td>
<td>11.2 (17.7)</td>
<td>16.7 (23.4)</td>
<td>0 (0)</td>
<td>0.2 (0.8)</td>
<td>0.82</td>
</tr>
<tr>
<td>Sore Throat</td>
<td>11.3 (19.8)</td>
<td>18.9 (26.9)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1.2</td>
</tr>
<tr>
<td>Headache</td>
<td>20.9 (26.2)</td>
<td>30.7 (27.5)</td>
<td>4.9 (12.6)</td>
<td>2.5 (5.8)</td>
<td>0.94</td>
</tr>
<tr>
<td>Memory</td>
<td>27.9 (26.8)</td>
<td>37.1 (32.5)</td>
<td>1.4 (3.2)</td>
<td>1.6 (3.6)</td>
<td>0.97</td>
</tr>
<tr>
<td>Concentration</td>
<td>28.7 (27.6)</td>
<td>42.4 (30.4)</td>
<td>3.4 (6.1)</td>
<td>3.1 (5.7)</td>
<td>1.1</td>
</tr>
<tr>
<td>POMS TMD</td>
<td>123.6 (21.8)</td>
<td>140.7 (38.4)</td>
<td>91.3 (9.8)</td>
<td>87.6 (9.7)</td>
<td>1.8</td>
</tr>
</tbody>
</table>

Effect size d estimates represent a comparison of pre- to post-exercise changes in symptoms for ME/CFS compared to control [(post – pre) – (post – pre)/(pooled standard deviation)].

**Fig. 1.** Total symptom changes for ME/CFS and control pre- to 24-h post-exercise. Total symptoms are based on the sum of 10 VAS ratings derived from 10 items contained in the CDC symptom inventory; see Table 3 for complete symptom list.

### 3.3. Post exertion malaise

Symptom changes from pre- to 24-h post-exercise for each item are listed in Table 3 and the total symptom burden based on the sum of 10 VAS ratings derived from 10 items contained in the CDC symptom inventory is illustrated in Fig. 1. As expected, there were large differences ($d \geq 0.8$) in self-reported symptoms between ME/CFS patients and controls. Twenty-four hours' post-exercise, ME/CFS patients reported large ($d \geq 0.8$) increases for the majority of symptoms compared to controls. For controls, symptom changes were uniformly small ($d \leq 0.3$) and often in the opposite direction (i.e. symptom improvement). When considering the sum of symptom changes measured (Fig. 1), ME/CFS patients reported significant increases compared to controls ($t = 3.25, p = 0.003$).

### 3.4. Mental fatigue and cognitive performance

For ratings of mental fatigue, there was a significant main effect for Time ($F = 20.2, p < 0.001$) and Group ($F = 86.3, p < 0.001$) and a significant Group by Time interaction ($F = 5.5, p = 0.005$). Both groups demonstrated increases in self-reported mental fatigue during the PASAT with the ME/CFS group reporting greater absolute levels and greater changes from pre- to post-exercise (See Fig. 2). ME/CFS participants reported significantly greater mental fatigue during both the finger tapping task ($F = 26.5, p < 0.001$) and the simple auditory monitoring task ($F = 24.2, p < 0.001$). For both finger tapping and auditory monitoring tasks there were also main effects for Time (Finger Tapping: $F = 8.4, p = 0.007$; Auditory Monitoring: $F = 24.3, p < 0.001$), but no Group by Time interactions ($p > 0.05$).

Cognitive performance data for the PASAT are illustrated in Fig. 3. There was a significant Group by Time Interaction ($F = 8.4, p = 0.007$), but non-significant main effects for Group ($p > 0.05$) and Performance ($p > 0.05$). Cognitive performance generally improved for controls both during scanning and from pre- to post-exercise. The opposite occurred for ME/CFS with a worsening of performance (i.e. greater errors) across blocks during scanning, as well as from pre- to post-exercise. There were no significant main effects or interactions for the simple auditory monitoring task with both groups demonstrating near perfect performance both pre- (14.9/15 ME/CFS; 14.9/15 control) and post-exercise (14.7/15 ME/CFS; 14.9/15 control).

### 3.5. Brain responses to fatiguing and Non-Fatiguing tasks

Whole brain responses for both ME/CFS and control groups in response to finger tapping, auditory monitoring and the PASAT are illustrated in Supplementary Figs. 1, 2 and 3. Data presented here are limited to our spatial hypotheses and are based on the a priori chosen regions of interest described in the Materials and Methods section.

### 3.6. Finger tapping

There were no significant differences in brain responses to finger tapping between patients and controls either pre- or post-exercise ($p > 0.05$). Further, there were no within group changes in brain responses to finger tapping from pre- to post-exercise for either ME/CFS patients or controls ($p > 0.05$). No significant relationships between symptoms and brain responses during finger tapping were observed for either ME/CFS patients or controls ($p > 0.05$). Brain responses to the finger-tapping task for ME/CFS patients and controls are illustrated in Supplementary Fig. 2 and listed in Supplementary Table 1.

### 3.7. Auditory monitoring

Prior to exercise, controls exhibited significantly greater activity in the posterior cingulate (177 voxels) and inferior parietal (122 voxels) cortices during the simple auditory monitoring task compared to ME/CFS patients ($p < 0.05_{corrected}$). There were no significant group differences post-exercise ($p > 0.05$). Compared to their...
pre-exercise brain response, ME/CFS patients exhibited less activity in the right inferior parietal cortex (175 voxels) post-exercise. Controls exhibited significantly less activity in clusters encompassing the right superior temporal lobe and right inferior frontal gyrus (462 voxels), left superior temporal gyrus (106 voxels), and bilateral inferior parietal cortices (right = 403 voxels; left = 288 voxels) post-exercise compared to pre-exercise ($p < 0.05_{\text{corrected}}$).

For ME/CFS patients, VAS ratings of “difficulty concentrating” post-exercise were significantly and positively related to activity in the left inferior parietal cortex (215 voxels; $p < 0.05_{\text{corrected}}$). There were no significant correlations between symptoms and brain responses during auditory monitoring for controls. Brain responses to the auditory monitoring task for ME/CFS and controls are illustrated in Supplementary Fig. 3 and listed in Supplementary Table 2. Within-group brain changes from pre- to post-exercise for auditory monitoring are illustrated in Supplementary Fig. 5.

3.8. Paced auditory Serial addition task (PASAT)

Baseline (scan #1) brain responses to the PASAT for ME/CFS patients and controls are illustrated in Fig. 4, and listed in Table 4. Both groups demonstrated significant activity across several cognition-relevant brain regions including the thalamus and the inferior parietal, superior parietal, superior temporal, medial frontal, inferior frontal and cingulate cortices. Within-group comparisons of brain activity during the PASAT from pre- and 24-h post-exercise are illustrated in Fig. 5. ME/CFS patients demonstrated greater activity bilaterally in the inferior and superior parietal cortices ($p < 0.05_{\text{corrected}}$). Due to the within-group nature of this comparison and because fatigue changed from pre- to post-exercise for the ME/CFS participants, we entered fatigue as a covariate to determine the effect of the pre- to post-exercise differences. These differences were eliminated when controlling for self-reported fatigue (VAS) ($p > 0.05_{\text{corrected}}$). Controls demonstrated the opposite response with widespread
decreases in brain activity from pre- to post-exercise within the inferior and superior parietal cortices (bilateral), the right supramarginal gyrus, left superior temporal gyrus, medial frontal gyri and the right inferior frontal gyrus. Controlling for fatigue (VAS) did not substantially change the observed differences.

Group comparisons of brain activity during the PASAT pre- and 24-h post-exercise are illustrated in Fig. 6. Pre-exercise (6a) controls demonstrated greater activity in the left inferior parietal, superior parietal and supramarginal gyrus (215 voxels; p < 0.05corrected). Post-exercise (6b & 6c), ME/CFS patients exhibited greater brain responses during the PASAT in the mid and anterior cingulate cortices and the right inferior frontal cortex. As illustrated in Fig. 6d-f, there was also a significant Group X Time interaction with ME/CFS patients exhibiting greater changes in brain activity from pre- to post-exercise compared to controls bilaterally for the inferior and superior parietal cortices, as well as the cingulate cortex.

3.9. Relationships between PASAT brain responses and symptoms of PEM

Self-reported fatigue (POMS) following exercise was significantly and positively related to brain responses in the right inferior parietal and superior temporal cortices for ME/CFS patients (184 voxels; p < 0.05corrected – See Fig. 7). In addition, self-reported muscle pain post-exercise was positively and significantly related to activity within the left inferior frontal cortex (102 voxels; p < 0.05corrected). For controls, self-reported fatigue was significantly and negatively related to activity within the right inferior parietal cortex (120 voxels; p < 0.05corrected) and this relationship was significant different than that observed in the ME/CFS group. No other significant relationships were found for the subscales of the POMS or other CDC VAS ratings.

We also examined the relationship between total errors on the PASAT and brain activity. For ME/CFS patients, errors were significantly and negatively related to activity within the left inferior parietal cortex (369 voxels; p < 0.05corrected), as well as, bilateral superior temporal cortices (left: 156 voxels, right: 124 voxels; p < 0.05corrected). For controls, errors were significantly and positively associated with activity within the mid- and posterior cingulate cortices (167 voxels; p < 0.05corrected).

Exploratory analysis of the relationships between metabolic and behavioral data during exercise and brain responses to the PASAT post-exercise did not reveal any significant correlations for the ME/CFS group. For controls, there was a significant positive

![Brain responses during the PASAT (Baseline) for ME/CFS and controls. Statistical maps were thresholded at a voxelwise p-value of 0.01 and applied a cluster-size threshold of 101 voxels (7101 mm³), corresponding to a cluster-wise alpha of 0.05 as determined by AFNI’s 3dClustSim.](image)
relationship between heart rate and brain activity during the PASAT in a large cluster encompassing the anterior and mid-cingulate cortices. Considering that activity in this brain region was below baseline during the PASAT, this relationship should be interpreted as those individuals with the greatest heart rate during exercise (i.e. the least fit) showed the smallest reduction in cingulate BOLD responses during the PASAT compared to baseline. This is illustrated in Supplemental Fig. 7.

4. Discussion

We sought to examine the neural consequences of acute exercise in ME/CFS using functional neuroimaging methods – determining brain responses to both fatiguing and non-fatiguing cognitive and motor tasks. Our results demonstrated that for ME/CFS patients acute exercise exacerbated numerous symptoms, impaired cognitive performance and affected brain function. These
converging results, linking behaviors associated with PEM to brain function, illustrate some of the potential detrimental effects of PEM and provide additional support for central nervous system dysregulation in the pathophysiology of ME/CFS.

Our previous work demonstrated that mental fatigue was significantly associated with brain responses to fatiguing cognition in both ME/CFS patients and healthy controls (Cook et al., 2007). However, brain responses to non-fatiguing tasks (finger tapping & simple auditory monitoring) were not significantly related to mental fatigue for either group. Moreover, ME/CFS patients exhibited greater brain responses during the fatiguing cognitive task but not the non-fatiguing task. These results suggested that the experience of fatigue affected neural processing during cognition for both patients and controls, with ME/CFS patients showing increased neural responses. In general, these findings were consistent with results from other groups studying ME/CFS (De Lange et al., 2004; Miller et al., 2014; Gay et al., 2016), multiple sclerosis (DeLuca et al., 2008; Tartaglia et al., 2008; Genova et al., 2009; Huolman et al., 2011) and traumatic brain injury (Kohl et al., 2009) – all demonstrating detrimental effects of fatigue on neural processing during cognition. The present investigation extends this work by stressing the cardiopulmonary and neural systems via acute exercise and determining the resultant effects on symptoms, cognitive performance and brain function.

4.1. Brain regions associated with PEM

The primary brain regions that distinguished brain responses between ME/CFS and controls and that were sensitive to acute
exercise and symptoms of PEM were the inferior frontal, parietal and cingulate cortices. These regions are critical for efficient cognitive processing involving processes associated with attention, error detection, and cognitive control/central executive functions (Bush et al., 2000; Cabeza and Nyberg, 2000; Shackman et al., 2011; D’Esposito and Postle, 2015). In general, ME/CFS patients demonstrated augmented neural responses in these regions following acute exercise and these brain responses were significantly associated with symptoms of PEM.

The frontal cortices have been characterized as the central executive exerting top-down control of cognitive function (D’Esposito and Postle, 2015). Specifically, the inferior frontal cortex has been implicated in inhibitory control and task-switching functions, with damage to these regions interfering with the efficiency of these processes (Aron et al., 2014). Our results suggest that PEM negatively affects executive function in ME/CFS with greater errors during the PASAT as a consequence. The significant and positive relationship with self-reported muscle pain suggests that those ME/CFS patients with the most pain symptoms required greater recruitment of executive control processes to perform the PASAT or that muscle pain interfered with the top-down control during performance of a demanding cognitive task.

The cingulate cortex is critically involved in cognition, pain and emotion signifying its functional overlap among these distinct yet related behaviors (Cabeza and Nyberg, 2000; Shackman et al., 2011; Shenhav et al., 2013). For cognitive performance, the cingulate cortices are functionally involved in filtering of information, interference, increased memory loads and monitoring task performance (MacDonald et al., 2000; Habeck et al., 2005). We observed increased activity in the anterior cingulate cortex of ME/CFS patients during the PASAT from pre- to post-exercise and compared to healthy controls. However, activity within the cingulate cortex was not significantly associated with symptoms or task performance. It is possible that PEM challenged the patient’s ability to filter information during the PASAT, thereby requiring greater reliance on the cingulate. Augmented cingulate activity may also reflect greater monitoring of symptoms during cognitive performance (Vogt and Laureys, 2005). Previous neuroimaging studies of fatigue have reported significant relationships between self-reported fatigue and cingulate cortex activity (Lange et al., 2005; Cook et al., 2007; Tartaglia et al., 2008; Kohl et al., 2009). Tartaglia and colleagues (Tartaglia et al., 2008) reported that MS patients exhibited augmented brain responses to a “mentally fatiguing” PASAT task in several brain regions, including the anterior cingulate, compared to controls. Importantly, they tested the influence of the PASAT task on subsequent brain responses to a motor task (finger tapping) and found increased activity in bilateral cingulate cortex (among other regions) compared to the pre-PASAT motor responses.

A common thread among cognition studies of fatiguing illnesses is the involvement of the inferior and superior parietal cortices and the relationships with self-reported fatigue (Lange et al., 2005; Cook et al., 2007; DeLuca et al., 2008; Tartaglia et al., 2008; Kohl et al., 2009; Enström et al., 2013). The parietal regions integrate incoming sensory information from multiple systems (e.g., auditory, visual, tactile) and have well-established functional connections with the frontal lobe (Andersen et al., 1990; Friedman and Goldman-Rakic, 1994). As such they have been referred to as the “posterior attention system” and are integrally involved in cognitive tasks requiring sustained attention such as the PASAT (Posner, 1990; Cabeza and Nyberg, 2000). We previously demonstrated that activity in these regions was negatively associated with the perception of mental fatigue and hypothesized that as tasks become more fatiguing, the ability to attend to the task becomes compromised (Cook et al., 2007). Those analyses only included baseline testing and combined ME/CFS patients and controls. Thus, symptom exacerbation and differential relationships between ME/CFS patients and controls were not explored. Results from the present study support and extend this finding by demonstrating negative relationships between self-reported fatigue and inferior parietal activity for controls, consistent with our previous work, and essentially no effect of acute exercise. For ME/CFS patients, activity in the parietal regions was positively related to self-reported fatigue and difficulty concentrating, but only post exercise when symptoms were exacerbated. Moreover, general patterns of parietal activity during cognitive tasks at rest and 24 h following exercise differed in ME/CFS as compared with controls suggesting that activity in this set of regions may help to distinguish brain responses in ME/CFS.

4.2. Task difficulty and exercise interactions

Consistent with our previous work (Lange et al., 2005; Cook et al., 2007), group differences and changes from pre- to post-exercise appeared to follow a pattern of task difficulty. For the finger tapping task, no significant group differences were observed and no changes occurred for either group from pre- to post-exercise. For the auditory monitoring task, there were small group differences at baseline with controls showing greater activity in posterior cingulate and inferior parietal regions, but no group differences were observed post-exercise. The most robust group differences occurred during the more challenging PASAT task – transitioning from pre- to post-exercise. For this task, ME/CFS patients showed greater activity in several brain regions including the inferior and superior parietal cortices, the supramarginal gyrus, cingulate cortex and the inferior frontal and superior temporal cortices.

An important aspect of this study is that brain responses in ME/CFS patients were significantly related to symptoms of PEM – including fatigue, pain and difficulty concentrating. For self-reported fatigue, significant relationships were observed within temporal and parietal regions with significant differences between ME/CFS and controls within the right inferior parietal cortex – further implicating this brain region as important for integrating sensory and cognitive processes during symptom exacerbation. The presence of brain and behavior relationships is critical for accurate interpretation of functional brain data. When present, these relationships provide objective (brain activity) evidence in support of the subjective (self-report) experience. Our data suggest that PEM affects multiple neural processes, particularly those involved when performing more challenging cognitive tasks.

One of the more striking findings was the magnitude of the reduction in brain responses during the PASAT for the controls from pre- to post-exercise. White and colleagues Reductions in brain responses occurred within multiple regions including parietal, temporal and frontal cortices and suggest that the controls required less neural resources to quickly and accurately perform the serial addition task. ME/CFS patients did not demonstrate any significant reductions in brain responses during the PASAT and instead showed significant increases in both inferior and superior parietal cortices post-exercise. These results provide objective evidence that for ME/CFS, PEM affects cognition, having widespread effects on brain regions associated attention, working memory and executive function. The pre- to post-exercise reductions in brain activity for controls were also associated with improved cognitive performance (i.e. reduced errors), which may reflect further practice effects or greater comfort within the neuroimaging environment. Because ME/CFS patients responded opposite to controls, having greater brain activity, reduced cognitive performance and increased symptoms post-exercise, these results emphasize the strong negative impact that PEM can have on the central nervous system.
4.3. Exercise and cognition

In general, exercise training and physical activity behaviors are associated with improvements in brain health and cognitive performance in healthy adults and the elderly (Colcombe and Kramer, 2003; Hillman et al., 2008; Dougherty et al., 2016). The influence of acute exercise on cognitive performance is less clear, but in general reaction times tend to decrease and performance increases following acute exercise (Lambourne and Tomporowski, 2010; Chang et al., 2012). In ME/CFS, cognitive difficulties are most consistently reported for the domains of information processing speed and tasks that challenge executive function (Cockshead and Mathias, 2010; Jason et al., 2013b). To date, the influence of acute exercise on cognitive performance in ME/CFS is equivocal (Blackwood et al., 1998; LaManca et al., 1998; Claypoole et al., 2001; Cook et al., 2005). Moreover, much of the neuroimaging literature examining the relationship between cognitive performance and fatigue has not demonstrated consistent changes in behavioral performance (Genova et al., 2013). In the present study, group differences in the pattern of cognitive performance were clear. ME/CFS patients showed increasing errors as a function of both within-in task performance (i.e. increasing errors with time-on-task) and as a function of acute exercise (i.e. greater errors 24 h post-exercise). Controls showed significantly different and characteristically opposite responses that were reflective of the neuroimaging data. In general, controls improved as a function of time-on-task and continued to improve 24 h post-exercise. Physiologically, this was represented by reduced brain activity among multiple cognitively-relevant brain regions following exercise.

4.4. Exercise, PEM and neuroimaging

Two recent studies by Rayhan and colleagues (Rayhan et al., 2013a; Rayhan et al., 2013b) are particularly germane to our project and highlight the potential for brain imaging methods in the study of PEM. Testing Veterans with Gulf War Illness (GWI) prior to and one-hour following two maximal exercise tests, these investigators reported neural augmentation during a working memory task in a subgroup of Veterans characterized as the “Stress Test Occurring Phantom Perception (STOPP) phenotype” and a failure to activate the working memory system in a subgroup of Veterans characterized as the “Stress Test Associated Reversible Tachycardia (START) phenotype” (Rayhan et al., 2013b). Similarly, this same group (Rayhan et al., 2013a) reported differential brain lactate responses in the prefrontal lobe pre-exercise in subgroups of Veterans with GWI. One subgroup characterized as “decreaseers” based on a worsening of working memory performance post-exercise showed greater prefrontal lactate levels at baseline compared to the subgroup showing improved working memory performance post-exercise – labeled as “increaseers”. Our study, although different methodologically (e.g. submaximal exercise, testing 24 h post exercise, ME/CFS vs GWI), compliments this research. Future research among ME/CFS subgroups, either based on symptom presentation, illness onset or pathophysiology, will be important towards determining for whom PEM is most debilitating and perhaps help guide future treatment approaches. It is also important to emphasize that this study is not an exercise training trial and any extrapolation from a single bout of exercise to the chronic exercise training literature should be done with caution. The results do suggest caution for patients attempting to increase their exercise training intensity and modes.

5. Conclusions

This study adds to the growing body of research implicating the central nervous system, particularly abnormalities of brain structure and function, in the pathophysiology of ME/CFS (Nijs et al., 2012). Although the genesis of the illness cannot be determined due to the cross-sectional nature of the current body of research, studies demonstrating altered resting state function (Boissonneault et al., 2016; Gay et al., 2016), reduced basal ganglia responsiveness (Miller et al., 2014), increased neural processing during cognition (Lange et al., 2005), altered brain levels of lactate and n-acetyl aspartate (Murrough et al., 2010), enhanced neuroinflammation (Nakatomi et al., 2014) and altered metabolism (Naviaux et al., 2016), combined with earlier research showing reduced brain blood flow, increased white matter lesion burden (Lange et al., 1999; Cook et al., 2001) and reduced gray and white matter training is efficacious and for whom exercise training is contraindicated requires more research.

Results from this study should be considered with respect to potential interactions between the central nervous system and other systems implicated in the pathophysiology of ME/CFS. Principle among these are the immune, neuroendocrine and autonomic nervous systems. From a central nervous system injury perspective, neural inflammation or the activation of inflammasomes and other inflammatory processes can lead to a vicious cycle or as Gerywn and Maes describe as a “self-sustaining feed forward mechanism” of illness maintenance (de Rivera Vaccari et al., 2014; Morris and Maes, 2014). The neuroendocrine system has long been hypothesized as being involved in the genesis and maintenance of ME/CFS (Demitrack, 1998) and altered neuroendocrine responses to exercise have been observed by some (Racciatti et al., 2001), but not others (Ottenweller et al., 2001). Like the neuroendocrine system, the autonomic nervous system has been explored extensively in ME/CFS and a recent meta-analysis reported “good evidence” for higher heart rate and reduced blood pressure responses during head-up tilt (Cauwenbergh et al., 2014). It was also suggested that autonomic reactivity may be a useful future diagnostic tool. To date, the interactions among these linked systems has not been systematically evaluated for ME/CFS in general nor specifically for PEM. Future research examining how these biological systems respond to exercise, interact and predict symptoms of PEM will be necessary to further understand the mechanisms of symptom generation and maintenance in ME/CFS and will provide critical steps towards understanding the heterogeneity and pathophysiology of the disease.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bbi.2017.02.009.

References
