Psychiatry Research: Neuroimaging 234 (2015) 292–297

Contents lists available at ScienceDirect

Psychiatry Research: Neuroimaging

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

Altered resting-state functional connectivity in women with chronic fatigue syndrome

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ARTICLE INFO

Article history:
Received 23 March 2015
Received in revised form
5 October 2015
Accepted 14 October 2015
Available online 23 October 2015

Keywords:
Chronic fatigue syndrome
Resting-state functional connectivity
Default mode network

ABSTRACT

The biological underpinnings of the psychological factors characterizing chronic fatigue syndrome (CFS) have not been extensively studied. Our aim was to evaluate alterations of resting-state functional connectivity in CFS patients. Participants comprised 18 women with CFS and 18 age-matched female healthy controls who were recruited from the local community. Structural and functional magnetic resonance images were acquired during a 6-min passive-viewing block scan. Posterior cingulate cortex seeded resting-state functional connectivity was evaluated, and correlation analyses of connectivity strength were performed. Graph theory analysis of 90 nodes of the brain was conducted to compare the global and local efficiency of connectivity networks in CFS patients with that in healthy controls. The posterior cingulate cortex in CFS patients showed increased resting-state functional connectivity with the dorsal and rostral anterior cingulate cortex. Connectivity strength of the posterior cingulate cortex to the dorsal anterior cingulate cortex significantly correlated with the Chalder Fatigue Scale score, while the Beck Depression Inventory (BDI) score was controlled. Connectivity strength to the rostral anterior cingulate cortex significantly correlated with the Chalder Fatigue Scale score. Global efficiency of the posterior cingulate cortex was significantly lower in CFS patients, while local efficiency showed no difference from findings in healthy controls. The findings suggest that CFS patients show inefficient increments in resting-state functional connectivity that are linked to the psychological factors observed in the syndrome.

1. Introduction

Chronic fatigue syndrome (CFS) is a syndrome characterized by severe, medically unexplained fatigue lasting longer than 6 months which affects quality of life and work productivity (Fukuda et al., 1994; Prins et al., 2006). Patients suffering from the syndrome not only complain of persistent physical fatigue, but they also exhibit various psychological symptoms, such as impaired cognitive functioning, increased rumination and focusing on fatigue sensation, and comorbid depression (Christley et al., 2013). Although CFS is often compared with depressive disorders because depression is frequently seen in CFS, the syndrome is distinguished from depressive disorders in that it has fewer problems with self-efficacy, guilt, suicidal ideation, and more attribution of symptoms to physical causes (Powell et al., 1990). These psychological factors have been known to not only predispose, precipitate, and perpetuate the syndrome (Knoop et al., 2010), but also be some of the core symptoms of CFS (Fukuda et al., 1994).

Several task-dependent functional neuroimaging studies in CFS have been carried out, many of which revealed that patients with CFS show different activation patterns from control subjects in terms of impaired cognitive functioning and fatigue perception. CFS patients showed lower performance on a verbal working memory task and required more extensive recruitment of brain regions associated with verbal working memory function, including prefrontal and parietal regions, supplementary motor cortex, premotor cortex and anterior cingulate, during the task (Lange et al., 2005). Another study using the n-back working memory task also revealed that abnormal activation of medial prefrontal regions, anterior cingulate gyrus and right inferior/medial temporal cortex was correlated with the task load (Caseras

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http://dx.doi.org/10.1016/j.pscychresns.2015.10.014

et al., 2006). Intensity of perceived fatigue after a challenging working memory task in CFS patients showed a significant positive correlation with the activation of brain regions including cerebellar, temporal, cingulate and frontal regions (Cook et al., 2007). Increased activation in the occipito-parietal cortex, posterior cingulate gyrus and parahippocampal gyrus, and decreased activation in the dorsolateral and dorsomedial prefrontal cortices during an fatigue-provoking task that mimicked real-life situations was found in CFS patients (Caseras et al., 2008). Findings of these previous studies suggest that altered neural activities and connectivity networks might be implicated in the etiology of CFS, especially regarding psychological factors such as cognitive impairment or perception of fatigue.

Studies of resting-state functional connectivity have gained increasing prominence since the introduction of the “default mode” of brain function (Raichle et al., 2001). Of the many resting-state functional connectivity networks explored, the default mode network (DMN) is one of the most studied due to its relationship with various psychiatric illnesses including major depressive disorder (MDD) (Anticevic et al., 2012; Menon, 2011). The DMN is a system of brain networks which is activated when individuals are left to think freely and, conversely, deactivated during attention-demanding task performance (Fox et al., 2005). The DMN comprises a set of brain regions showing intrinsic functional correlation in various neuroimaging modalities including positron emission tomography (PET), functional magnetic resonance image (fMRI), and local field potentials (LFPs) (Raichle, 2010).

Graph theory involves the topological relationship between points of interests, called nodes, and is frequently applied to analyze various kinds of networks, including structural and functional connectivity of brain networks (Stam and Reijneveld, 2007). The connection of two nodes in a graph is defined as an edge. Efficiency is a measure of a graph representing how easily two nodes can get connected to each other without having to pass through other nodes. Global efficiency is defined as average overall pairwise efficiencies, when efficiency is inverse of the shortest distance between two nodes. Local efficiency is the mean of the efficiencies of subgraphs of neighboring nodes from a specific node (Stam and Reijneveld, 2007). Among network models in graph theory, “small-world” is a term depicting a network with several clusters of densely connected nodes, and small numbers of connections involved in maintaining connections between these clusters (Watts and Strogatz, 1998). A network with small-world attributes has advantages over a random network in maximizing the efficiency of a graph while minimizing its cost, which is the probability of connection between two nodes. Structural and functional networks of the brain are thought to be composed of this small-world attribute to maintain maximal efficiency of the neural connectome (Sporns and Honey, 2006; Achard and Bullmore, 2007).

To date, resting-state functional neuroimaging studies examining psychological characteristics of CFS have been lacking. Since the posterior cingulate cortex (PCC) has consistently been shown to be the main hub of the DMN in previous studies, we selected the PCC as the “seed” node based on the hypothesis that alterations in DMN in CFS will be similar to, but distinguishable from, MDD. In this article, we will first focus on resting-state fMRI findings in CFS patients compared with healthy controls to document the quantitative correlation of psychological factors with aberrant functional connectivity. Then we will qualitatively analyze the network applying graph-theoretical analysis.

2. Methods

2.1. Participants

The study participants consisted of 18 women with CFS (mean age = 43.9 years, SD = 4.8.) and 18 age-matched female healthy controls. All were recruited from the local community through flyers, announcements, or word-of-mouth. All participants initially underwent clinical interviews to exclude those with other psychiatric illnesses. Participants were then administered structured interviews by a clinical research psychologist to assess functional status and symptoms. The CFS subjects met the revised diagnostic criteria for CFS proposed by the Centers for Disease Control and Prevention (Fukuda et al., 1994; Reeves et al., 2005). We excluded those with current or past psychiatric disorders, traumatic brain injury, neurological illness, relevant visual defects or any radiological contraindications for MRI scanning. All participants were right-handed. This study was carried out under the guidelines for the use of human participants established by the Institutional Review Board at Severance Mental Health Hospital, Yonsei University. Following a complete description of the scope of the study to all participants, written informed consent was obtained.

2.2. Psychometric self-report scales

Participants have completed psychometric self-reports, including the Chalder Fatigue Scale (Chalder et al., 1993), Beck Depression Inventory (BDI), Beck Anxiety Inventory (BAI) and Psychological General Well-Being Index (PGWBI), to assess the subjective feelings and severity of chronic fatigue symptoms.

2.3. Image acquisition and preprocessing

MR imaging was conducted on a 3T Siemens Magnetom MRI scanner (Siemens AG, Erlangen, Germany) equipped with an eight-channel head coil. Whole-brain fMRI data were acquired with a T2*-weighted gradient echo planar pulse sequence (echo time = 30 ms, repetition time = 2200 ms, flip angle = 90°, field of view = 240 mm, matrix = 64×64, slice thickness = 4 mm) during a 6-min passive-viewing block scan. Subjects were instructed to fixate on a white cross-hair in the center of a black background screen, and to refrain from any cognitive, lingual, or motor tasks as much as possible. High resolution anatomical images were acquired with a T1 weighted spoiled gradient-echo sequence (TE = 2.19 ms; TR = 1780 ms, flip angle = 9°, field of view = 256 mm, matrix = 256×256. slice thickness = 1 mm) to serve as an anatomical template for the fMRI data.

Spatial preprocessing and statistical analysis of functional images were performed using SPM8 (Wellcome Trust Centre for Neuroimaging; http://www.fil.ion.ucl.ac.uk/spm). The first seven points in the times series data were discarded to eliminate signal decay. Motion artifacts were assessed in individual subjects by visual inspection to confirm that the maximum head motion in each axis was less than 3 mm, without any abrupt head motion. Functional images were realigned and registered to structural images for each subject. The anatomical volume was then segmented into gray matter, white matter, and cerebrospinal fluid. The gray matter image was used to determine the parameters of normalization applied to the gray matter template. The spatial parameters were then applied to the realigned and unwarped functional volumes, which were then resampled to voxels of $2 \times 2 \times 2$ mm^3 and smoothed with an 8-mm full-width at half-maximum Gaussian kernel.