Spring 6-14-2019

Small-World Network Analysis of Cortical Connectivity in Chronic Fatigue Syndrome using EEG

Mark Alan Zinn
DePaul University, zinnmark2@gmail.com

Small-World Network Analysis of Cortical Connectivity in Chronic Fatigue Syndrome using EEG

A Thesis

Presented in

Partial Fulfillment of the

Requirements for the Degree of

Master of Arts

By

Mark Alan Zinn

June, 2017

Department of Psychology

College of Science and Health

DePaul University

Chicago, Illinois

Master's Thesis Committee

Leonard A. Jason, Ph.D.

Joseph A. Mikels, Ph.D.

Rex L. Cannon, Ph.D.

Table of Contents

List of Tables

List of Figures

Abstract

The primary aim of this thesis was to explore the relationship between electroencephalography (qEEG) and brain system dysregulation in people with Chronic Fatigue Syndrome (CFS). EEG recordings were taken from an archival dataset of 30 subjects, 15 people with CFS and 15 healthy controls (HCs), evaluated during an eye-closed resting state condition. Exact low resolution electromagnetic tomography (eLORETA) was applied to the qEEG data to estimate cortical sources and perform functional connectivity analysis assessing the strength of time-varying signals between all pairwise cortical regions of interest. To obtain a comprehensive view of local and global processing, eLORETA lagged coherence was computed on 84 regions of interest representing 42 Brodmann areas for the left and right hemispheres of the cortex, for the delta (1-3 Hz) and alpha-1 (8-10 Hz) and alpha-2 (10-12 Hz) frequency bands. Graph theory analysis of eLORETA coherence matrices for each participant was conducted to derive the "small-worldness" index, a measure of the optimal balance between the functional integration (global) and segregation (local) properties known to be present in brain networks. The data were also associated with the cognitive impairment composite score on the DePaul Symptom Questionnaire (DSQ), a patient-reported symptom outcome measure of frequency and severity of cognitive symptoms. Results showed that small-worldness for the delta band was significantly lower for patients with CFS compared to HCs. Small-worldness for delta, alpha-1, and alpha-2 were associated with higher cognitive composite scores on the DSQ. Finally, small-worldness in all 3 frequency bands correctly distinguished those with CFS from HCS with a classification rate of

nearly 87 percent. These preliminary findings suggest disease processes in CFS may be functionally disruptive to small-world characteristics, especially in the delta frequency band, resulting in cognitive impairments. In turn, these findings may help to confirm a biological basis for cognitive symptoms, providing clinically relevant diagnostic indicators, and characterizing the neurophysiological status of people with CFS.

Keywords: myalgic encephalomyelitis, chronic fatigue syndrome, quantitative EEG, eLORETA, EEG tomography, electrical neuroimaging, DePaul Symptom Questionnaire, lagged coherence, functional connectivity, graph theory, complex network analysis, small-world

“Small-World” Network Analysis of Cortical Connectivity in Chronic Fatigue Syndrome using EEG data

The brain is a global network comprised of many subnetworks with neural oscillations that characterize the coordinated activity between distributed brain regions underlying lie key aspects of neurocognitive performance in attention, perception, memory, language, and motor processing (van den Heuvel & Sporns, 2013; Wig, Schlaggar, & Petersen, 2011). As such, brain network analysis is important to exploring the relationship of intrinsic brain organization to cognitive symptoms of patients with chronic fatigue syndrome (CFS). CFS is a complex multi-system disease characterized by extreme fatigue, post-exertional malaise, flu-like symptoms, and neurocognitive impairment not relieved by rest and worsened by physical or mental activity (Fukuda et al., 1994). An estimated 1 million people in the United States suffer from CFS (Jason et al., 1999) with repercussions to society including annual direct and indirect cost of CFS to society was estimated to be over 18 billion dollars (Jason, Benton, Valentine, Johnson, & Torres-Harding, 2008). Furthermore, this illness has received national attention from a recent report by the Institute of Medicine (2015), documenting the many needs of patients with this illness.

CFS is similar to other neurological diseases where patients experience persistent cognitive impairments that are often characterized by an uneven symptom picture contributing to difficulty with diagnosis (Chaudhuri & Behan, 2004; Christodoulou et al., 1998). Though cognitive impairment is a core domain in CFS (Jason, Zinn, & Zinn, 2015), the factor or primary deficit responsible for

the etiology remains poorly understood and even controversial (Johnson, DeLuca, & Natelson, 1996; Twisk, 2014). The disparity between the severity of patient complaints and modest differences in neuropsychological test scores (Attree, Arroll, Dancey, Griffith, & Bansal, 2014) has done little to challenge notions that patients are exaggerating cognitive symptoms (Ocon, 2013), underperforming due to lack of effort (Goedendorp, Bleijenberg, & Knoop, 2014), or experiencing a manifestation of concomitant emotional and psychological factors (Fry & Martin, 1996; Mariman et al., 2013; Warren, Langenberg, & Clauw, 2013; White, 2010), environmental factors (Wearden & Appleby, 1997), or cultural reinforcement of persistent sickness behavior (Abbey & Garfinkel, 1991). In addition, the varying types of cognitive impairment reported by patients with CFS are underrepresented on traditional neuropsychological tests (DeLuca, 2005), who escape detection due to lack of test sensitivity and specificity (Koziol & Budding, 2009), inconsistencies (DeLuca, Genova, Capili, & Wylie, 2009), and the absence of systematic framework from which to interpret disparate findings. The guiding principles of this framework might include the following key points: 1) cognitive performance depends upon the integrity of globally integrated brain function; 2) functional adaptations are taking place such that compensation of the underlying deficit occurs via remaining intact connections; 3) since cognitive function arises from brain systems and not isolated regions, the development of multiple cognitive symptom disturbances from circumscribed cortical damage is actually the rule rather than the exception (Luria, 1980).

A meta-analysis of fifty neuropsychological studies including a total of 1,544 participants found cognitive deficits in CFS that broadly include problems with memory, attention, and reaction time severe enough to significantly impact daily functioning (Cockshell & Mathias, 2010). Approximately 90% of patients with CFS report having cognitive symptoms, anecdotally referred to in the clinic as "brain fog," profoundly affecting health and quality of life (Grafman et al., 1993; Hopkins & Jackson, 2006; Komaroff & Buchwald, 1991; Ocon, 2013). Brain fog may be defined as a perception and experience of mental fatigue that is associated with slowed cognitive processing and delayed reaction times, difficulty concentrating, absent mindedness, and derealization (Ocon, 2013). Affected domains include working memory and sustained attention (Capuron et al., 2006), verbal memory (Claypoole et al., 2007), visual episodic memory (Constant et al., 2011), word-finding, free memory recall (DeLuca, Johnson, Ellis, & Natelson, 1997), interference factors and capacity for learning (Michiels & Cluydts, 2001). Executive dysfunction has also been reported in patients with CFS (Marcel, Komaroff, Fagioli, Kornish, & Albert, 1996; Marshall, Forstot, Callies, Peterson, & Schenck, 1997; Smith, Behan, Bell, Millar, & Bakheit, 1993). Patients have also been shown to have slower reaction times in many studies (Busichio, Tiersky, Deluca, & Natelson, 2004; Constant et al., 2011; Majer et al., 2008; Thomas & Smith, 2009; Van Den Eede et al., 2011), particularly under conditions of increasing task complexity (Dobbs, Dobbs, & Kiss, 2001). Deluca, Johnson, and Natelson (1994) suggested that most memory deficits seen in patients are due to deficits in information processing speed rather than impairment to

storage/retrieval mechanisms. Thus, the assessment of changes to overall information processing speed and neural efficiency factors in CFS may provide understanding to cortical dysregulation associated with cognitive symptoms in CFS.

Neuroimaging Studies

Structural brain abnormalities. A primary aim of structural neuroimaging studies in CFS has been to find a physiological biomarker which could aid in clinical diagnosis, disease prognosis, and development of new treatments. Some MRI studies conducted in the early 1990s found a higher incidence of small punctate white matter lesions in the centrum semiovale for a subset of patients (Daugherty et al., 1991; Natelson, Cohen, Brassloff, & Lee, 1993; Schwartz, Garada, et al., 1994). However, white matter lesions were not confirmed by two studies that employed control groups with major depression (Cope, Pernet, Kendall, & David, 1995; Greco, Tannock, Brostoff, & Costa, 1997). Lange et al. (1999) found small white matter abnormalities mainly in the frontal lobe in a subset of 21 patients without psychiatric diagnosis. Together, the mixed nature of these results might be explained by heterogeneity within the patient samples and methodological differences between studies. Furthermore, these studies had problems with inter-rater reliability due to using human observers to assess and interpret MRI scans. Nonetheless, their findings offer support for disruption to global brain function; that is, small lesions to long-range axonal connections which might compromise brain function in extremely subtle

ways, thereby allowing patients to escape detection on neuropsychological tests of higher cortical function (Luria, 1980).

More recent MRI studies using voxel-based morphometric (VBM) statistical procedures have revealed structural brain abnormalities in patients with CFS. Okada, Tanaka, Kuratsune, Watanabe, and Sadato (2004) used VBM to show bi-lateral grey matter atrophy in the dorsolateral prefrontal cortex of 16 patients compared to 49 age-matched controls. Volume reductions in the right prefrontal cortex were negatively associated with a performance status score of fatigue severity. In another VBM study with 28 patients and 28 age-sex-education matched controls, a global reduction in grey matter was found inCFS and the decrease was associated with lower daily physical activity (de Lange et al., 2005). Puri et al. (2012) examined 26 patients and 26 age-gender matched controls and found both grey and white matter reductions in the occipital lobe as well as grey matter atrophy in the right angular gyrus and left parahippocampal gyrus. Using combined T1w and T2w MRI signal levels, Barnden et al. (2011) performed a series of voxel-based regression analyses against clinical data from 25 patients and 25 age-gender-matched controls and found that reduced white matter in the midbrain predicted increased fatigue duration, while grey matter atrophy in the brainstem was strongly associated with seated pulse pressure. This finding suggests that CFS might involve problems affecting the monoamine producing nuclei in the brainstem that play a key role in promoting arousal levels that are critical for the adaptive moderation of cognition, learning, and behavior (Saper, Fuller, Pedersen, Lu, & Scammell, 2010).

Functional abnormalities. Regarding functional characteristics in CFS, support for deficient metabolism in CFS has been found using single-photon emission computed tomography (SPECT) with reduced cerebral bloodflow in patients with CFS (Costa, Tannock, & Brostoff, 1995; Schwartz, Komaroff, et al., 1994). Using positron emission tomography (PET), Tirelli et al. (1998) demonstrated hypometabolism in the brainstem was a distinguishing factor between 18 non-depressed patients with CFS and 6 patients with major depression only. Similarly, hypometabolism was also found in the cingulate gyrus and orbitofrontal cortex of patients with CFS (Siessmeier et al., 2003) and it was globally lower in 9 out of 11 patients who underwent arterial spin labeling (ASL) neuroimaging (Biswal, Kunwar, & Natelson, 2011). However, discrepant results were obtained in a SPECT study involving a sample of 22 monozygotic twins which found no differences for twins with CFS compared to their healthy co-twins (Lewis et al., 2001).

Morris and Maes (2012) proposed a neuro-immune model for CFS that accounted for fatigue, post-exertional malaise, and cognitive symptoms. Their model proposed chronic activation of immune-inflammatory pathways in CFS as a pathological factor involved in suppressing brain function and producing fatigue, autonomic, and flu-like symptoms. Consistent with this model, Nakatomi et al. (2014) examined 14 patients and 14 health controls using PET and found widespread neuroinflammation in CFS that was associated with the severity of neuropsychological symptoms. Binding potential in the midbrain had the strongest statistics and was correlated with degree of cognitive impairment. Pain

scores were correlated with binding potential in the cingulate cortex and thalamus, and depression scores were likewise positively correlated with binding potential in the hippocampus. Thus, the findings of metabolic distress and immune-inflammatory brain pathology in CFS lend support to the approach of this thesis to investigate changes to vulnerable network elements involved in adaptive cortical connectivity reconfiguration and most sensitive to functional disruption.

Task-evoked studies using blood-oxygen-level-dependent functional MRI (BOLD fMRI) detected various functional differences in neural activity in CFS related to motor imagery (de Lange et al., 2004) and verbal working memory tasks (Lange et al., 2005), dependent upon increasing task load (Caseras et al., 2006) and fatigue inducing tasks (Caseras et al., 2008; Cook, O'Connor, Lange, & Steffener, 2007; Tanaka et al., 2006). Cook et al. (2007) observed significant relationships between brain abnormalities and self-reported physical function. Together with Lange et al. (2005), brain compensation was suggested by findings of more extensive activation of verbal memory networks in patients with CFS and dynamic reorganization with subsequent reductions in neural efficiency could be contributing to cognitive impairment indirectly. Overall, these studies have small sample sizes and the inconsistency of their findings create reliability and validity issues with concomitant diagnostic dilemmas for arriving at a clinical diagnosis of CFS.

Functional connectivity studies. Knowledge of general principles of self-organization in real-word systems has prompted a paradigm shift in neuroscience away from localization of brain responses toward a deeper understanding of brain

connectivity influences on information processing efficiency (O. Sporns, 2013). Unfortunately, neuroimaging studies using functional connectivity methods to investigate CFS have been lacking. Using arterial spin labeling neuroimaging, decreased connectivity was found by Gay et al. (2015) between the salience network and left the posterior cingulate. Similarly, Boissoneault et al. (2016) showed that patients had reduced connectivity within the salience network between the anterior cingulate and right insula. In an adolescent sample with CFS, Wortinger et al. (2016) reported decreased connectivity within the right posterior insula of the salience network was related to fatigue. Finally, Kim et al. (2015) found hyperconnectivity between the posterior and anterior cingulate in CFS and hyperconnectivity following network disruption is a common response to neurological disease transitional states (Hillary et al., 2015). Together, these studies are limited by their seed-based correlation approach which does not provide any connectivity information between each of the correlated regions (Wig et al., 2011). The approach of this thesis, however, accounts for aberrant connections within the systems comprising the whole cortex.

In a recent study with a sample of 9 patients with CFS compared to 9 healthy controls, Zinn, Zinn, and Jason (2016) used exact low resolution electromagnetic tomography (eLORETA) to assess functional connectivity between nodes of 3 fundamental neurocognitive networks based on Menon's triple network model of brain pathology (Menon, 2011). This model posits there are three primary large-scale brain networks that operate dynamically to regulate shifts in arousal, attention, and general access to cognitive abilities. The triple

network model includes the central executive network, salience network, and the default mode network and predicts that aberrant activity within any one these networks will significantly impact the other two networks resulting in pathological states. Using lagged phase synchronization as a connectivity measure (Pascual-Marqui, 2007a), this study found empirical evidence of hypoconnectivity in the delta and alpha frequency bands between nodes for all three networks in patients with CFS. In addition, patients had reduced alpha sources in the occipital lobe, parietal lobe, posterior temporal lobe, and posterior cingulate. These regions of the brain were shown by Hagmann et al. (2008) to contain the greatest packing density of highly connected, high "cost" hub regions which are more prone to metabolic failure (Crossley et al., 2014). The disruptions in delta and alpha band source activity as well as functional hypoconnectivity of networks in the triple-network model appear to underlie primary cognitive symptoms in CFS. This thesis represents an expansion of these preliminary findings, examining both functional connectivity and topological patterns within the entire cortex that are associated with brain disorder in CFS.

QEEG findings. Quantitative electroencephalography (qEEG) involves numeric analysis of local field potentials resulting from the summation of neuronal electrical activity that arises from the cell bodies and associated dendrites of large populations of synchronously active cortical pyramidal neurons (Niedermeyer & Lopez da Silva, 2005). The electrical currents are dependent on the integrity of the neural sodium/potassium and calcium ion pumps, reflecting metabolic activity and rendering qEEG a useful tool for quantifying and exploring

electrophysiological correlates of both normal and abnormal neurological function (Thatcher, 2016). The frequency, phase, and amplitude of band-limited EEG oscillations relates to the specific information processing taking place at different spatiotemporal scales at any given moment (Le Van Quyen, 2011). The high temporal resolution of qEEG on a millisecond timescale allows fine-grained detection of subtle differences in speed and efficiency within the relay of information flow via cooperative sequencing of oscillatory patterns and their phase differences (Buzsáki & Freeman, 2015; Steriade, 2005; Thatcher, North, & Biver, 2008).

The reliability of qEEG has been consistently demonstrated in a series of studies on CFS. In a well-controlled study involving a sample of 632 patients, Duffy, McAnulty, McCreary, Cuchural, and Komaroff (2011) found that EEG coherence analysis between electrode sites could distinguish unmedicated patients with CFS from those with major depressive disorder with 90% accuracy. In a separate study, Billiot, Budzynski, and Andrasik (1997) found that patients had increased theta (5-7 Hz) during both conditions compared to age-matched healthy controls (HCs) using just a single electrode at Cz (central midline placement) during eyes-closed and serial sevens conditions. Zinn et al. (2014) measured peak alpha frequency in 50 patients with CFS and 50 healthy controls and reported significant effects in 58% of electrical potentials measured at the scalp surface. Peak alpha frequency is thought to be a measure of cognitive vigilance (Angelakis, Lubar, & Stathopoulou, 2004; Angelakis, Lubar, Stathopoulou, & Kounios, 2004) and the clinical emphasis on the qEEG interpretation of

widespread dysregulation of brain rhythms is placed on the impact to generalized brain activity rather than local or discrete brain regions. Peak alpha was computed within the alpha frequency band (8-12 Hz) based on each participant's EEG and this finding suggests that global changes in alpha may reflect the symptoms commonly associated with CFS including chronic low level of alertness (hypoarousal), impaired working memory and verbal episodic memory (Constant et al., 2011), impairments to attention, and reduced information processing speed (DeLuca et al., 1997).

Tomographic EEG methods (electrical neuroimaging) apply inverse methods to surface EEG recordings to map current sources in a 3-diminensional brain volume, allowing the ability to visualize abnormality in deeper brain structures (Thatcher, 2016). There are many inverse methods that can estimate the intracortical current sources to localize brain activity from the surface EEG signals, but low-resolution electromagnetic tomography (LORETA) has been demonstrated to be most accurate one (Grech et al., 2008). In a LORETA study conducted on 17 monozygotic pair twins, Sherlin et al. (2007) showed that affected twins with CFS had increased delta sources in the left uncus and parahippocampal gyrus, deeper structures of the limbic system. Sherlin et al. also found higher theta sources in the cingulate gyrus and right superior-frontal gyrus. According to the authors, rhythmic alterations in these regions could be indicators of blunted emotional processing in CFS possibly related to reduced motivation and attentional difficulties. Using eLORETA ("e" stands for exact), Zinn et al. (2014b) examined 50 patients with CFS and 50 healthy controls and patients had

significantly elevated delta sources in a widespread portion of the frontal lobe and limbic lobe as well as decreased beta activity in the parietal lobe bi-laterally. This suggests cortical hypoarousal in CFS consistent with the decreased PAF finding in their qEEG study. Higher delta sources were also associated with the reduced motivation scores on the Multidimensional Fatigue Inventory, a measure of fatigue severity commonly used in CFS studies. Increased delta in limbic structures is consistent with the findings of Sherlin et al. and symptoms manifested by brain pathology within the medial prefrontal cortex, anterior cingulate, and orbitofrontal cortex are largely undetected by most traditional neuropsychological tests (Koziol & Budding, 2009).

Using a different EEG tomographic method, Flor-Henry, Lind, and Koles (2010) performed a Beamformer source analysis on a sample of 61 women with CFS and 80 female healthy controls method which mainly showed sources that were globally reduced in the alpha and beta bands in those with CFS. Beamformer source density patterns were also effective in separating the two groups, with a retrospective classification rate of 72% while the subjects were at rest and an 83% in the alpha band during the verbal cognitive condition. During active cognitive conditions, the CFS group showed significantly greater source-current activity in the left frontal–temporal–parietal regions of the cortex, when compared to controls. Together, the various qEEG and tomographic EEG investigations mentioned here demonstrate a relationship between EEG and CFS which lay the foundations for this proposal.

EEG Coherence. Even the most basic cognitive processes depend on precise timing of phase relationships in the brain occurring through large populations of spontaneously synchronized neurons communicating among distributed brain regions (Buzsaki, 2006; Sauseng & Klimesch, 2008; Steriade & Pare, 2006). EEG coherence is a widely-used network measure which refers to consistency of phase differences in the time-series corresponding to different spatial locations (Lehmann, Faber, Gianotti, Kochi, & Pascual-Marqui, 2006; Pascual-Marqui, 2007a, 2007b). It is interpreted as an indicator of "connectivity" which quantifies the degree to which phase differences remain stable over time either between electrode sites, when measured at the scalp when using surface EEG (Buzsaki & Watson, 2012; Klimesch, Freunberger, Sauseng, & Gruber, 2008; Thatcher, 2016), or between two brain regions, in the case of tomography methods such as eLORETA (Pascual-Marqui et al., 2011). Furthermore, an advantage of eLORETA is that it uses *lagged* coherence, a specialized measure of functional connectivity that controls for physiological artifact by removing zero-lag contributions from volume conduction and spatial blurring effects (Pascual-Marqui, 2007a, 2007c). The magnitude of EEG coherence is sensitive to the number and strength of neuronal connections between brain ROIs. This measure is independent of the EEG amplitude, thus offering a more accurate depiction of brain function and making it more suitable for clinical applications (McAlaster, 1992; Pajevic, Basser, & Fields, 2014; van Baal, Boomsma, & de Geus, 2001). In this manner, EEG coherence is particularly viable to the study of CFS by providing a robust and clinically useful neocortical estimate of white matter

deficits (Nunez, Srinivasan, & Fields, 2014). Regions with higher coherence have increased phase consistency whereby phase differences are clustered very closely together over time. On the other hand, lower coherence means that the phase differences are fairly scattered or inconsistent over time, whereby the neurons become suppressed. This suggests a fundamental mechanism for selection of neurons: excitation is more likely to occur when phase differences are consistent and the firing threshold is lower, whereas suppression of those same neurons happens when their phase differences are inconsistent due to lack of entrainment or decoupling (Hughes et al., 2004).

Complex Networks and Graph Theory

The brain itself is a large complex network with functional interactions that can be reduced to graph representations of vertices (nodes) and connections between nodes (edges) (Sepulcre, 2014). Although cognitive processes appear to be seamless, they are the product of the complex interaction of cognitive functions required in everyday life, reflecting the attributes of complex networks found in the real world (e.g., social networks, airline routes, power grids, protein networks, etc.) (Watts & Strogatz, 1998). This approach carries a number of distinct advantages including: 1) being able to quantify, model, and visualize a wide range of varying network attributes; 2) providing a biologically meaningful framework for studying the balance of local and global trade-offs that operate within complex networks; 3) enabling better ways of describing dynamic self-organization from compensatory mechanisms responding to pathological processes and; 4) offering new ways of understanding the critical link between

brain connectivity and cognitive function. In this sense, the wealth of added information provided by graph theory can greatly extend the key aspects of brain activity related to basic and clinical research (Rubinov & Sporns, 2010).

In the past decade, graph theory analysis of complex brain networks has been extensively used in neuroscience as a framework for understanding how dynamical processes are involved in the emergence of cognition and behavior (Menon, 2012; Stam, 2014). It is necessary to differentiate complex network models, which represent the whole brain with hundreds of nodes, from other network models representing few regions of interest which coactivate to perform a specific function (e.g. default-mode network). Complex network analysis can be broadly divided into global, intermediate, and local levels (Lowe et al., 2016). Global analysis of whole-brain connectivity, the approach of this thesis, is used to describe the complete organization of functional coactivation patterns as they relate to neurological disease. Figure 1 illustrates the optimal balance of information processing between randomness and order governing the interactions within complex brain networks which instigate even the most basic behaviors (Deco, Jirsa, & Friston, 2012; Sepulcre, 2014; Stam, 2010). This shows the delicate relationship between random neuronal growth processes and activity dependent modification of random growth processes which is also highly sensitive to disease states (Minati, Varotto, D'Incerti, Panzica, & Chan, 2013). Bullmore and Sporns (2012) explain this state of affairs in terms of parsimony; there is a continual drive to minimize metabolic costs while supporting or creating adaptively valuable functional connectivity. Within this system, the brain is in a

continual process of negotiating these trade-offs. The number of connections in the system is relegated by wiring cost in terms of biological energy and materials needed and there are evolutionary adaptations in keeping long distance (more expensive) connections to a minimum (Stam, 2010). Peculiar trade-offs in system topological properties of segregation and integration can therefore serve as a marker for disruptions in the balance of optimal functioning that are highly sensitive to disease processes. Thus, the graph theory approach may specify neurobiological adaptions to the CFS condition, modeling disease course and spread, aberrant plasticity, indexing overall network processing efficiency, all of which could aid in clinical diagnosis of patients and perhaps even help identify clinical subtypes (Crossley et al., 2014).

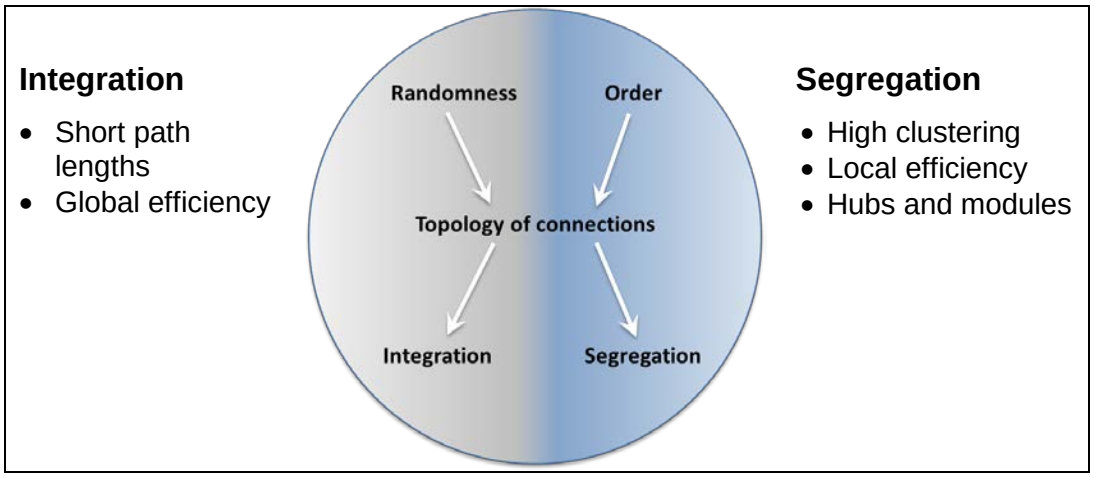


Figure 1. Schematic representation of optimal information processing in complex brain networks, a mixture between random and ordered components (Stam, 2010).

Small-World Networks. The "small-world" network model was introduced in a landmark study by Watts and Strogatz (1998) demonstrating for the first time that small-world properties exist in central nervous systems. The topology of small-world networks is characterized by high clustering

(segregation) and short path lengths (integration), representing a homeostatic balance between local and global processing in order to satisfy opposing demands which maximize processing speed at minimal neurobiological energy cost (Olaf Sporns & Honey, 2006). *Segregation* refers to the tendency of nearest neighbor elements to cluster together whereas *integration* refers to amount of interconnectedness and efficient information exchange within the entire network. The *clustering coefficient* is a measure of functional segregation or local connectedness whereas the *characteristic path length* is a measure of functional integration describing global, large-scale activity and coactivation of neuronal populations within the network (Telesford, Simpson, Burdette, Hayasaka, & Laurienti, 2011). Together, the clustering coefficient and the characteristic path length constitute properties of the small-world network model, an indicator of *small-worldness*, a marker of the homeostatic balance between randomness (chaos) and order (stability) of dynamic system organization (Humphries & Gurney, 2008; Stam, 2010; Thatcher, 2016; van Straaten & Stam, 2013).

Kim et al. (2015) were first to demonstrate small-world abnormality in CFS, using resting-state fMRI to examine small-world properties in a sample of 18 women with CFS and 18 age-matched female controls. They assessed *global efficiency*, the inverse of the mean shortest characteristic path length, relating to the functional efficiency which is vital to information flow between any two nodes in the network. Similarly they assessed *local efficiency* which quantifies the fault tolerance of the network proportional to the clustering coefficient (Bassett & Bullmore, 2006). Findings in that study revealed that global efficiency

(integration) was lower in CFS compared to the healthy control group, while there were no differences in local efficiency (segregation). By implication, disease-related reductions in long distance connections are occurring in CFS as a trade-off for wiring expense, suggesting that reduced global integration plays a role in decreased processing speed and higher-order cognitive dysfunction.

Rationale

This thesis examines the fundamental neurobiological relationships and adaptions could underlie cognitive symptoms in CFS. Information processing in the brain is strongly influenced by small-world relationships and a growing number of eLORETA graph theory studies have examined small-world network organization in patients with neurological disorders. These studies have found changes occurring to small-world network organization in response to epilepsy (Adebimpe, Aarabi, Bourel-Ponchel, Mahmoudzadeh, & Wallois, 2016; Vecchio, Miraglia, Curcio, Della Marca, et al., 2015), multiple sclerosis (Vecchio et al., 2017), and Alzheimer's disease (Hata et al., 2016; Vecchio, Miraglia, Curcio, Altavilla, et al., 2015; Vecchio et al., 2016). This was achieved using a whole-brain functional connectome approach, with 84 Brodmann areas representing the nodes for all cortical regions of interest; the degree of perturbation to small-world dynamics, imbalance of segregation/integration due to trade-offs associated with disease etiology, was linked to the amount of cognitive impairment in patients and brain processes that were found to be compromised reflected an underlying disturbance to small-world propensity. For example, Vecchio et al. (2016) performed a graph theory analysis with eLORETA combined with diffusion tract

imaging, and found that an overall reduction of hippocampal volume was associated with delta and alpha small-world characteristics, thereby demonstrating both structure and functional adaptations to memory performance in patients with cognitive decline (Vecchio et al., 2016). This thesis is informed by the functional part of their approach, using graph theory analysis of small-world characteristics with eLORETA connectivity data, to provide new insights into the linkage of brain organization with cognitive symptoms that are commonly associated with CFS (John, 2005; van Straaten & Stam, 2013).

The small-world network model posits that optimal brain function is best conceptualized with principles of local and global efficiency for understanding aberrations in brain connectivity. Cognitive dysfunction in CFS may be captured using this model whereby observed dysfunctional behavior is theorized as significantly altered eLORETA coherence between pairwise brain regions of interest (globally altered brain connectivity). As such, the observed association with behavioral scores on the DePaul Symptom Questionnaire (DSQ) for the symptoms of cognitive impairment (e.g. memory, attention, slow thought, etc.) will represent a combination of pathology in the underlying hypothesized small-world characteristics and the concomitant overt behavioral changes in CFS.

This thesis also builds upon the resting-state neuroscience literature by evaluating functional brain connectivity in CFS using resting-state EEG data collected during an eyes-closed condition. The resting-state now the predominant method used in neuroscience for a variety of reasons. The resting-state is an energetically costly condition and a major factor comprising ~80% of the brain’s

total energy budget involves spontaneous neuronal signaling processes. By contrast, the difference in signals induced by momentary environmental demands is relatively small in comparison to baseline resting activity, usually less than 5% (Raichle, 2011; Shulman, Rothman, Behar, & Hyder, 2004; Zhang & Raichle, 2010). In terms of the EEG, the electrical demands of neurons are more costly than blood oxygen and glucose, and cortical excitability is modulated by fluctuations in the delivery of glucose and adenosine triphosphate (ATP) energy to neurons (Raichle, 2011). The oscillatory processes of resting-state are indicative of the stable characteristics of intrinsic brain organization, defined as spontaneous interactions between network elements in the absence of a specific task state (Raichle, 2010). Ultimately, the resting-state represents the dynamic substrate of intrinsic oscillatory processes that are fundamental to information processing, even transcending levels of consciousness (Greicius et al., 2008). Given that intrinsic resting-state dynamics are sufficiently robust and correlate separately with task performance, it provides a highly flexible means to associate brain connectivity with scores on clinical behavioral measures or neuropsychological tests (Braun et al., 2012).

Higher order cognitive processes appear to call upon even more temporal precision for sustained neuronal activity between neuronal populations (Nunez et al., 2014). Different frequency bands have different physiological significance. Delta activity is produced by cortico-cortical and thalamo-cortical networks (Steriade & McCarley, 2005) and is important for basic homeostatic processing, salience recognition, and language processes (Knyazev, 2012). Abnormal delta

oscillations have been observed in studies on Alzheimer's disease (Babiloni et al., 2013; Babiloni et al., 2006; Nishida et al., 2011). Delta activity during wakefulness has been associated with inflammatory diseases of the central nervous system (Westmoreland, 2005) and subsequent hypoarousal seen in the context of inflammatory conditions (Hegerl & Ulke, 2016). Abnormal delta small-world characteristics between regions that are more or less strongly connected could demonstrate a link between brain states, arousal, and efficiency, with decrements in information processing speed found in CFS (DeLuca, Johnson, & Natelson, 1993). Alpha oscillations are dominant during awake resting conditions, particularly in the posterior regions of the brain when the eyes are closed, modulated by dynamics within thalamo-cortical feedback loops. Strong alpha activity is associated with integration of information, working memory, and cortical inhibition (Klimesch, 2012). Alpha rhythms play a role in gating sensory information in order to enhance attention and perceptual performance; the strength of alpha connectivity was found to be correlated with level of perceptual threshold (Busch, Dubois, & VanRullen, 2009). This provides the basis for investigating delta and alpha frequency bands in association with cognitive symptoms in CFS.

Finally, the graph theory findings generated by this thesis could aid with patient diagnosis. Pathological brain states can be roughly divided into six categories: dementias, lesions, stroke, complications of surgical procedures, problems due to chronic medical conditions, or neurological diseases (e.g., multiple sclerosis). At the present time, however, these classifications fail to

include CFS within any diagnostic paradigm in medicine that represents the neurocognitive impairments for this illness.

Statement of Hypotheses

Hypothesis I. Patient networks are hypothesized to deviate from optimal small-world network characteristics of high clustering and short path lengths as measured by the small-worldness index. Deviations from small-worldness demonstrate the pathological imbalance between network efficiency and energy expenditure and quantifies the associated with trade-offs to adaptive reconfiguration of network topology in CFS.

Hypothesis II. Changes in the small-worldness index are expected to be associated with cognitive impairment, as measured by the composite score of cognitive symptoms on the DSQ. Reconfigurations that shift the balance of segregated and integrated processing demonstrate the role of network topology on influencing cognitive function in CFS. The strength of the beta weights in the regression model are expected to vary by frequency band. Illness duration will also be a predictor of the cognitive composite score to account for long-term changes with respect to illness duration. The importance of illness duration was underscored in a study by van Dellen et al. (2009) which reported the length of time patients had temporal lobe epilepsy was negatively correlated with the small-world network properties.

Hypothesis III. The small-worldness index will accurately classify and distinguish patients with CFS from healthy control participants, but the classification rate will vary by frequency band. Accurate classification of patients

will help establish the utility for this approach to aid in categorizing and developing diagnostic procedures for patients with CFS.

Method

Participants

EEG data was taken from an archival dataset (Zinn et al., 2016). The participants in this investigation were thirty adults (15 individuals with CFS, 15 healthy controls) ranging in age from 20 to 79 years and the mean age was 43.8 years (SD = 20.22). Age was statistically adjusted since the mean age between groups was significantly different and physiological aging is a significant factor within the EEG (Kirk, 2013; Rossini, Rossi, Babiloni, & Polich, 2007; Vysata et al., 2014). All participants visited the Center for Community Research at DePaul University to have their EEG recorded. The participants with CFS all met the Fukuda criteria (Fukuda et al., 1994) and they had been diagnosed with CFS by their physician. No participants were taking medications that would affect the EEG.

Procedure

Eyes-closed, resting state EEG data for each participant was recorded for 5 minutes from 19 electrode locations (Fp1, Fp2, F3, F4, F7, F8, Fz, C3, C4, Cz, P3, P4, Pz, T3, T4, T5, T6, O1, and O2) positioned on the scalp according to the international 10/20 system using standardized electrode caps (Jurcak, Tsuzuki, & Dan, 2007) with a linked-ears reference. During cap preparation, impedances for all electrode sites were measured and brought to within 5 kΩ. Once cap preparation was completed, participants were shown their raw EEG signals and

trained to minimize artifact by relaxing muscles in their forehead, jaws, and face to the best of their ability while they observed corresponding changes in the raw EEG. During the EEG measurement, each participant was seated upright in a comfortable chair in a room that was well-lit. Participants were given instructions to relax to the best of their ability while keeping their eyes closed until the recording session has ended. EEG data were acquired at a 256 Hz sampling rate and filtered offline between 1 and 40 Hz. Artifact removal procedures were as follows: 1) visual inspection and manual deletion of visible artifact by an EEG technician; 2) automated Z-score artifact removal using rejection algorithms built into Neuroguide (Applied Neuroscience, Largo, FL) set for high sensitivity at 2 standard deviations for immediate exclusion of EEG segments with eye movement, muscle, and drowsiness artifact; 3) second visual inspection and manual deletion of the artifact by an EEG technician. Since this study was directed toward understanding changes in phase relationships of the original time-series data, independent components analysis (ICA) was not performed to remove artifacts. The methodological problem of using ICA/regression procedures to remove artifact, including distortion of phase relationships between channels, has been empirically validated in several studies (Castellanos & Makarov, 2006; Kierkels, van Boxtel, & Vogten, 2006; Wallstrom, Kass, Miller, Cohn, & Fox, 2004). The EEG segments that were included for analysis showed greater than 95% split-half reliability and greater than 90% test–retest reliability coefficients instantaneously computed by Neuroguide and each record had a minimum total edit time of at least 1 minute. For each participant, the artifact-free data were then

fragmented into 2-second EEG segments with a 75% cosine taper window to minimize spectral leakage (Sterman & Kaiser, 2000).

Materials

All participants completed the DePaul Symptom Questionnaire (DSQ) (Jason, So, Brown, Sunnquist, & Evans, 2015) and data for the DSQ were collected and managed using the Research Electronic Data Capture (REDCap) hosted at DePaul University (Harris et al., 2009). REDCap is a secure, web-based application designed to support data capture for research studies, providing: 1) an intuitive interface for validated data entry; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for importing data from external sources. The DSQ is a self-report instrument that measures 54 symptoms related to criteria specified in the CDC criteria (Fukuda et al., 1994), the Canadian Criteria for ME/CFS (Carruthers et al., 2003), and the CFS International Consensus Criteria (Carruthers et al., 2011). For each symptom item, respondents are asked to separately rate the frequency and severity over the last six months on a five-point Likert scale (0 = none of the time, 1 = a little of the time, 2 = about half the time, 3 = most of the time, and 4 = all of the time). In addition, the DSQ contains items that gather information about demographics, relevant medical health history (including years since diagnosis), and social history. The DSQ has good test-retest reliability with Pearson's correlation coefficients above 0.70 and test-retest correlations for classified symptom categories (fatigue, post-exertional malaise, neurocognitive, and autonomic) at

0.80 or higher (Jason, So, et al., 2015). Results of factor analysis on the DSQ support at least three distinct symptom factors: 1) post-exertional malaise, 2) neurocognitive dysfunction, and 3) neuroendocrine/autonomic/immune dysfunction (Jason, Sunnquist, et al., 2015). Murdock et al. (2016), an independent group using the DSQ, found that it demonstrated excellent internal reliability and that among patient-reported symptom measures it optimally differentiated between patients and controls.

It is possible that most, if not all of these symptoms could be a byproduct of brain dysregulation. However, testing all of them would be beyond the scope of this proposal. Therefore, the cognitive variable of this proposal were limited to the average of nine items that fall under the cognitive impairment factor: problems remembering things, difficulty paying attention for a long period of time, difficulty with word finding or expressing thoughts, difficulty understanding things, only able to focus on one thing at a time, unable to focus vision attention, slowness of thought, absent-mindedness or forgetfulness, and loss of depth perception (see Appendix A) (Jason, Sunnquist, et al., 2015).

Apparatus

The data collection apparatus involved Neuroguide qEEG signal processing software (Applied Neuroscience, Largo, FL) together with the Brainmaster Discovery-24 (Bedford, OH) qEEG acquisition module, which allows up to 19-channels of EEG signals to be recorded simultaneously at 256 Hz.

Functional Connectivity Analysis

Functional connectivity analyses on the surface EEG data was conducted using the LORETA-KEY software package (Pascual-Marqui, 2015). This software is freely provided for download by the KEY Institute for Brain-Mind Research at http://www.uzh.ch/keyinst/loreta.htm. eLORETA is based on the stereotactic space provided by the Montreal Neurological Institute (MNI) template and offers a highly accurate estimate of the intracortical current source density within a 3-dimensional cortical volume consisting of 6,239 voxels of unambiguous grey matter at 5 mm^3 spatial resolution. Complete mathematical details of this inverse solution are provided in Pascual-Marqui et al. (2011). To obtain a topographic view of the whole cortex, coordinates were computed for 42 separate Brodmann areas (BAs: 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 13, 17, 18, 19 20, 21, 22, 23, 24, 25, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47) for the left and right hemispheres (84 total ROIs) using a single voxel to define each ROI centroid. Given that eLORETA has low spatial resolution based on the spatial smoothness assumption, the single center voxel is considered an accurate representation of activity within the ROI while minimizing the possibility of signal contamination from neighboring ROIs.

Due to theoretical considerations and the large amount of EEG data gathered, all analyses were limited to delta (1-3 Hz), alpha-1 (8-10 Hz), and alpha-2 (10-12 Hz) frequency bands. eLORETA lagged coherence was computed for all 84 ROIs for each participant, generating text files with output containing a separate weighted 84 x 84 adjacency-matrix (84 ROIs) for each frequency band.

The adjacency matrix contains the entire set of network connections whereby each cell has a value representing the magnitude of the statistical correlation (coherence) between any pair of nodes. In each adjacency-matrix, the table rows and columns represent the ROIs and the cell values represent the coherence magnitude of dependency between each pair of ROIs. Figure 2 illustrates the workflow for all the analyses that were implemented in this thesis.

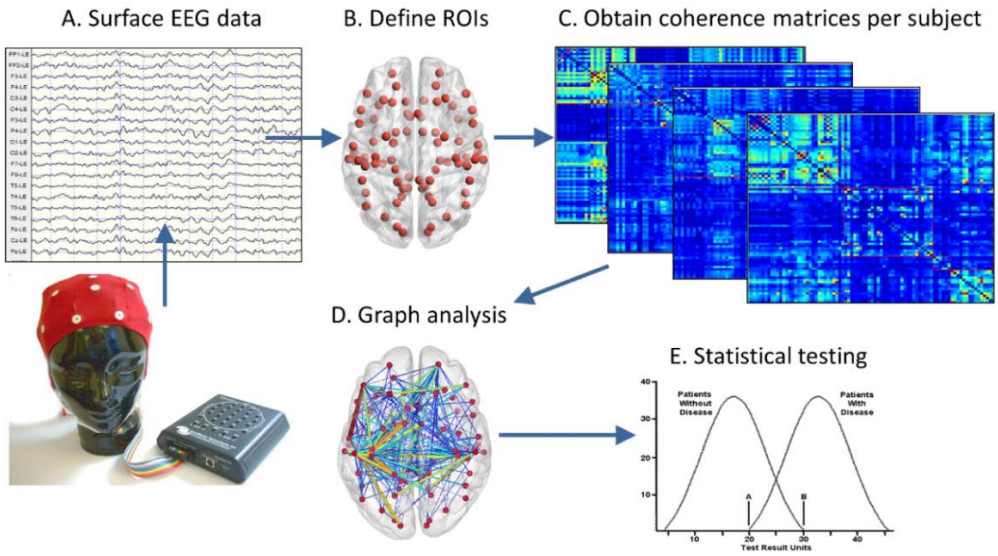


Figure 2. The workflow of all analyses in this thesis summarized as an overview.

Graph Theory Analysis

The adjacency matrix for each frequency band for each participant was subjected to graph theory analysis using the Matlab Brain Connectivity Toolbox (BCT) (Rubinov & Sporns, 2010). The BCT has functions that take into account the weighted undirected strength or magnitude of all the network connections. Descriptions and code for the mathematical functions in the BCT are freely available for download at https://sites.google.com/site/bctnet/. BCT functions were applied to each participant's network adjacency matrix to calculate small-

world characteristics. The weighted *clustering coefficient* around a given node varies from 0 to 1 and is quantified by the number of triangles formed by that node and its neighboring nodes. The weighted *characteristic path length*, defined as the average shortest weighted path between two given nodes using the sum of the individual weighted lengths. Path lengths with conversions based on values of the adjacency matrix were stored separately as a distance matrix with sequences of edges that connect nodes indirectly to form neural paths. The path length values in the distance matrix are not physical distances, but instead they represent the degree of topological separation between any two given nodes (Rubinov & Sporns, 2010). The Graphvar toolbox in Matlab (Kruschwitz, List, Waller, & Rubinov, 2015) was used to calculate *small-worldness*, which is the ratio between the clustering coefficient and characteristic path length compared to their values for equivalent randomly generated graphs (Humphries & Gurney, 2008). The *small-worldness index* variable was used in this study as an indicator of comparative complex network organization for each participant.

Statistical testing. The graph theory output that was produced using BCT functions in Matlab was subsequently exported to SPSS version 22 for conducting further statistical analyses. The archival dataset was already screened for outliers, missing data, skewness and kurtosis in meeting the assumptions for parametric statistics. Prior to analysis, continuous variables were tested for skewness and kurtosis and were log-transformed to meet the assumption of Gaussianity.

Results

Demographic and Clinical Characteristics

Demographic characteristics and clinical data for the subjects in this study is shown in Table 1.

Table 1

Demographic and Clinical Data

	15 People with ME	15 Healthy Controls	All 30 Participants
Age (years) Mean (*SD*)	56.46 (15.72)	31.13 (15.99)	43.8 (20.22)
Sex	12 Female 3 Male	11 Female 4 Male	23 Female 7 Male
Handedness	15 right 0 left	14 right 1 left	29 right 1 left
Education	1 Partial college 7 College 7 Graduate	2 Partial college 8 College 5 Graduate	3 Partial college 15 College 12 Graduate
Ethnicity	15 White	14 White 1 Latino	29 White 1 Latino
DSQ Cognitive Composite Score Mean (*SD*)	2.98 (.78)	1.25 (.30)	2.12 (.19)
Illness Duration Mean (*SD*)	17.2 (13.26)		

Data Processing

Data were drawn from random samples in the population and screened before and after entry into SPSS files (version 22) for outliers, missing data or odd data points. Assumptions associated with the *F* distribution (as well as the χ^2 distribution) were assessed across all continuous variables by study group through examination of histograms of the data, normality tests (Kolmogorov-Smirnov and Shapiro-Wilkes), examining skewness, then examining residuals using detrended normal Q-Q plots by study group to justify the mathematics in each statistical test. Minor violations of the normality assumption were found in the small-world

variables and in the illness duration measure; however, given that the *F*-test and the χ^2 tests are quite robust to departures from normality (Kirk, 2013; Tabachnick & Fidell, 2013) especially given equal n's across study groups, and that these variables were in the range of normality, they were used in the analysis without adjustment. One variable, the DSQ cognitive symptom composite (cognitive impairment) measure, was found to be non-normal so a logarithmic data transformation was performed to normalize that variable and to achieve normality of error effects (Kirk, 2013). All variables were then standardized to produce equal contributions to the analyses (Lemke & Wiersma, 1976). Age, potential confounder, was defined a priori based on Spearman's rho correlations of study variables (see Table 2) and entered into all analyses. For the MANOVA model, homogeneity of variances, homogeneity of regression slopes and homogeneity of variance / covariance matrices were checked and met in all variables across groups (Kirk, 2013; Tabachnick & Fidell, 2013). The linear regression homoscedasticity assumption was met. No multicollinearity or singularity was identified. Residuals were inspected for independence, linearity, normality and homoscedasticity. For logistic regression, the dependent variable was dichotomous with independent observations and the independent variables were linearly related to the logit of the dependent variable. Due to the heterogeneity of measurements, all variables in all analyses were standardized (Kirk, 2013). The results of the statistical tests are therefore considered to be a valid and accurate representation of the data in this study.

Table 2
Correlations Among Key Study Variables

	Small-world delta	Small-world alpha-1	Small-world alpha-2	DSQ cognitive composite	Illness duration
Small-world delta	--				
Small-world alpha-1	.171	--			
Small-world alpha-2	.041	.095	--		
DSQ cognitive composite	-.407*	.125	-.266	--	
Illness duration	-.346	.230	-.245	.834**	--

* significant at $p < .05$ level
** significant at $p < .01$ level

The means and standard deviations of the small-world delta, alpha-1 and alpha-2 indices and their individual properties are shown in Tables 3 and 4. To evaluate hypothesis 1, Wilkes' Lambda tests and *F* tests from Analysis of Variance (MANCOVA, ANCOVA) models were performed to assess differences between the CFS and HC groups across a linear combination of the small-worldness indices for 3 frequency bands: delta, alpha-1 and alpha-2, adjusting for age. An overall statistically non-significant difference was found between the two groups (CFS vs.HCs), Wilks' $\Lambda = .788$, $F(3, 25) = 2.237$, $p = .109$, multivariate $\eta^2 = .212$, observed power = .499. However, the parameter coefficients for each variable distinguishing between the CFS and HC groups indicated that small-world delta contributed significantly to the overall MANCOVA, $\beta = 1.064$, $p = .023$, multivariate $\eta^2 = .177$ while both small world alpha-1 and small world alpha-2 failed to distinguish between study groups, $\beta = .340$, $p = .475$, multivariate $\eta^2 = .019$ for small-world alpha-1, and $\beta = .376$, $p = .439$, multivariate $\eta^2 = .022$ for small-world alpha-2. Post hoc univariate analyses were used to validate the small-worldness indices at each frequency band between the

CFS and HC groups using Bonferroni correction for multiple comparisons ($\alpha = 0.05/3 = 0.017$). The small-world delta comparison was significantly lower in the CFS group than HCs, $F(1,27) = 5.818$, $p = .023$, univariate $\eta^2 = .177$, observed power .643. For small-world alpha-1 and alpha-2, the comparison between the CFS and HC groups was not significant for either variable; small world-alpha-1, $F(1,27) = .524$, $p = .475$, univariate $\eta^2 = .019$, observed power = .108, or small world-alpha-2, $F(1,27) = .617$, $p = .439$, univariate $\eta^2 = .022$, observed power = .118 (Table 5).

Table 3

Means and Standard Deviations for Small-worldness Indices by Experimental Group

		Small-world delta	Small-world alpha-1	Small-world alpha-2
Group	*N*	*M (SD)*	*M (SD)*	*M (SD)*
HC	15	.878 (.049)	.785 (.07)	.83 (.051)
CFS	15	.829 (.062)	.794 (.732)	.801 (.078)

Table 4

Means and Standard Deviations for weighted Clustering Coefficients (Cw) and Characteristic Path Length (Lw) by Experimental Group

		Cw / Lw delta	Cw / Lw alpha-1	Cw / Lw alpha-2
Group	*n*	*M (SD)*	*M (SD)*	*M (SD)*
HC	15	.181 / 7.88 (.021 / .977)	.177 / .783 (.026 / .820)	.219 / 5.82 (.020 / .694)
CFS	15	.149 / 8.59 (.011 / .920)	.180 / .794 (.026 / 1.53)	.197 / 7.73 (.026 / 1.403)

Table 5

*Univariate Effects of Small-worldness on Experimental Group**

Source	Dependent variable	*df*	*F*	*p*	η^2	Observed Power
Exp. Group	Small world delta	1	5.818	.023	.177	.643
	Small world alpha-1	1	.524	.475	.019	.108
	Small world	1	.439	.022	.617	.118

	alpha-2	
Error	Small world delta, alpha-1, alpha-2	27

* Bonferroni adjusted

To examine cognitive impairment in patients with ME (hypothesis 2), hierarchical linear regression analyses were conducted to address whether small-worldness by frequency band (delta, alpha-1, alpha-2) predicted cognitive impairment and whether the addition of duration of illness to small-worldness and group membership increased the predictive power for cognitive impairment. Hierarchical regression analysis is typically used in model building to develop a subset of predictors that are useful in predicting the IVs and to eliminate those IVs which do not provide additional prediction to the IV's already present in the equation. The confounder of age was defined as a variable associated with the outcome variable only (cognitive impairment). Analysis was performed using SPSS regression and frequencies for evaluation of assumptions in all the models. Using a criterion of $p < .01$, Mahalanobis distance identified no outliers. There was no missing data and no suppressor variables were found, $N = 30$.

Model 1. Hierarchical regression was conducted to evaluate the effect of small-worldness in the delta band and illness duration on cognitive impairment. Beta weights and significance values for all models are presented in Table 6. The third model, which included small-world delta and illness duration (with age), explained the most variance in cognitive impairment, $R^2 = .788$, adjusted $R^2 = .754$, $F(3, 26) = 23.267$, $p < .001$. This indicates that nearly 79% of the variance in cognitive impairment was explained by this model. This is a strong effect size

according to Cohen (1988). The experimental group variable alone contributed significantly to the final model and small-world delta was approaching significance in models 1 and 2.

Table 6
Hierarchical Regression Analysis Summary Predicting Cognitive Composite Scores from Small-World Delta, Controlling for Age.

Variable	β	R^2	Adj. R^2	*SE*	ΔR^2
Model 1		.465	.426	.163	.074
Small-world delta	-.275				
Model 2		.528	.473	.156	.063
Small-world delta	-.252				
Illness duration	.358				
Model 3		.788	.754	.206	.26
Small-world delta	-.008				
Illness duration	.001				
Experimental group	.812*				

* $p < .001$

Model 2. A second hierarchical linear regression was conducted to investigate the effects of small-worldness alpha-1 and illness duration on cognitive impairment, controlling for age. Beta weights and significance values for all models are presented in Table 7. The third model, which included small-world alpha-1 and illness duration (with age), explained the most variance in cognitive impairment, $R^2 = .794$, adjusted $R^2 = .762$, $F(3, 26) = 24.162$, $p < .001$. This indicates that more than 79% of the variance in cognitive impairment was explained by this model. This is a strong effect size according to Cohen (1988). The experimental group variable alone contributed significantly to the final model.

Table 7
Hierarchical Regression Analysis Summary Predicting Cognitive Composite Scores from Small-World Alpha-1, Controlling for Age.

Variable	β	R^2	Adj. R^2	*SE*	ΔR^2
Model 1		.418	.375	.170	.027
Small-world alpha-1	-.171				

Model 2		.494	.436	.161	.075
Small-world alpha-1	-.173				
Illness duration	.391				
Model 3		.794	.762	.105	.301
Small-world alpha-1	-.083				
Illness duration	.009				
Experimental group	.799*				

* $p < .001$

Model 3. A third hierarchical linear regression was conducted to investigate the effects of small-worldness alpha-2 and illness duration on cognitive impairment, controlling for age. Beta weights and significance values for all models are presented in Table 8. The third model, which included small-world alpha-2 and illness duration (with age), explained the most variance in cognitive impairment, $R^2 = .797$, adjusted $R^2 = .764$, $F(3, 26) = 24.490$, $p < .001$. This indicates that nearly 80% of the variance in cognitive impairment was explained by this model. This is a strong effect size according to Cohen (1988). The experimental group alone contributed significantly to the final model.

Table 8
Hierarchical Regression Analysis Summary Predicting Cognitive Composite Scores from Small-World Alpha-2, Controlling for Age.

Variable	β	R^2	Adj. R^2	*SE*	ΔR^2
Model 1		.425	.383	.169	.034
Small-world alpha-2	-.06				
Model 2		.486	.427	.163	.061
Small-world alpha-2	-.145				
Illness duration	.356				
Model 3		.797	.764	.105	.311
Small-world alpha-2	-.095				
Illness duration	-.017				
Experimental group	.806*				

* $p < .001$

Hypothesis 3 assessed for whether small-worldness correctly distinguished between HCs and people with CFS. Hierarchical logistic regression models were

used to determine classification rates using predictor variables small-world delta, small-world alpha-1, and small-world alpha-2. All models were adjusted for the potential confounder of age. When all predictor variables were considered together, they significantly predicted whether or not a subject had CFS with 86.7% accuracy, $\chi^2 = 20.3$, $df = 4$, $p = .000$ (Table 9).

Table 9

Logistic Regression Classification

	Unadjusted		*Classification Accuracy*		*Age Adjusted*		*Classification Accuracy*	
Small-worldness	Sig. Test	*P*	%	*LL*	Sig. Test	*P*	%	*LL*
Small world delta	$\chi^2 = 5.446$, *df*= 1, *p* =.020		70	36.143	$\chi^2 = 18.731$, *df*= 2, *p* =.000		80.0	22.857
Small world alpha-1	$\chi^2 = 0.001$, *df*= 1, *p* =.977		50	41.588	$\chi^2 = 14.244$, *df*= 2, *p* =.001		83.3	26.937
Small world alpha-2	$\chi^2 = 0.009$, *df*= 1, *p* =.923		50	41.580	$\chi^2 = 14.238$, *df*= 2, *p* =.001		86.7	26.739
All 3 predictors	$\chi^2 = 3.575$, *df*= 1, *p* =.311		63	38.013	$\chi^2 = 20.300$, *df*= 4, *p* =.000		86.7	21.288

Discussion

This study demonstrated a significant association between small-world characteristics and cognitive symptoms reported in CFS. These findings of functional connectivity alterations underscore the importance of applying graph theory to connectome-scale analysis of network topology to detect subtle disruptions incurred by CFS sequelae. Cognitive impairment, as measured by the DSQ cognitive composite score, was negatively associated with small-worldness indices for the delta, alpha-1, and alpha-2 frequency bands currently under observation with a strong effect size. The group-level differences were also found, but only for small-worldness in the delta band. Finally, the small-worldness indices for all 3 frequency bands combined correctly distinguished nearly 87% of cases with CFS from HCs.

Small-world models of the brain systems highlight the balance between high clustering of local systems with short path lengths of global systems; these attributes are considered to be vital to the efficiency of information processing within neurocognitive networks (Menon, 2012; Rubinov & Sporns, 2010). This model emphasizes the morphological adaptations (e.g. changes to axonal diameter, white matter pathways, conduction velocities, and energy transport mechanisms, etc.) governed by trade-offs to components and compensation necessary for maintaining the multi-scale spatial-temporal patterns for which the brain operates. Differences in neural resource allocation in CFS were reported in three fMRI studies investigating compensatory responses to cognitive tasks (Caseras et al., 2006; Cook et al., 2007; Lange et al., 2005). The findings of this study explain these differences in terms of peculiarities to these trade-offs with subsequent weakness to small-worldness structure that could account for loss of cognitive function in people with CFS.

Secondarily, it was found that small-worldness in the delta band, over and above alpha-1 and alpha-2, accounted for the greatest amount of variance in cognitive composite scores for the hierarchical regression model equations. Delta is a slow oscillation that plays a key role in the dynamic coordination of large-scale cortical networks and modulation of faster rhythms through cross-frequency coupling (Buzsáki & Freeman, 2015). In the case of inflammatory disorders of the CNS, the most prominent change in large-scale network dynamics is the occurrence of cortical slowing (e.g. delta activity) during the waking state (Westmoreland, 2005). Furthermore, delta cortical slowing can result from a

decrease in the afferent drive due to white matter or subcortical lesions to deep midline areas (Gloor, Ball, & Schaul, 1977; Schaul, Gloor, & Gotman, 1981). Finding abnormal small-worldness in delta suggests there may be some similarities with Alzheimer's disease (Babiloni et al., 2013; Hata et al., 2016) and Parkinson's disease (Babiloni et al., 2011), where abnormal delta sources have been detected.

This is the first study to measure small-world properties in CFS in terms of the small-worldness index. Using resting-state fMRI data, Kim et al. (2015) found that functional integration (global efficiency) was decreased in CFS. Disruption to global efficiency in CFS suggests that, with fewer biologically "expensive" long distance connections, added burden is being placed on the system for satisfying opposing demands. The "costs" to chronically reduced functional integration may include: 1) a lowered ability to rapidly combine specialized information from distributed brain regions, 2) slowed information processing speed due to compensatory responses, and 3) generalized impairment to domains of cognitive function. However, this study found differences using the small-worldness index as a ratio of individual small-world properties (clustering and path lengths), suggesting that both global and local properties are salient in CFS depending on frequency band. This underscores the necessity for considering a combination of graph theory metrics for examination of CFS.

Limitations. There are some limitations in the present study to be addressed. The results of this study should be interpreted with caution due to small sample size. Although the present study describes significant deviations in

the reported small-worldness phenomena, neurological disorders are invariably associated with diffuse network changes. However, it was beyond the scope of this study to report the individual nodes, hub, and modules that may be involved in suboptimal information processing efficiency and prone to failure in CFS. Although the outcome of brain function following individual hub failure would likely go beyond discrete local regions, future research could explore a more comprehensive inspection of hub strength, distribution, and participation within modular structures to identify ROIs that serve as potential targets for treatment. As another limitation of this study, the examination of small-world differences was kept within the delta, apha-1, and alpha-2 frequency bands. Frequency-dependent changes to cortical arrangements occurring in other frequency bands (e.g. theta, beta) should also be explored. Finally, there was less than 100% accuracy of the eLORETA coherence based classification function. This finding could reflect a deficiency in the diagnostic criteria for CFS, a deficiency in the coherence-based measure itself, a problem with the way the ROIs were defined, and/or unexplored levels of complex network analysis using other graph theory metrics. Functional connectivity EEG markers associated with cognitive impairment and differential classification should be verified in future studies in CFS.

Conclusions

The present findings support the concept that small-worldness is altered in CFS. This has important implications for this field of study. For example, system dependent coupling of oscillations has fundamental importance to CNS function

and may be strongly influenced by delays in conduction velocity and myelin plasticity. Changes to white matter have been reported in CFS (Puri et al., 2012), also associated with clinical measures and illness duration (Barnden et al., 2011), and a severity-dependent increase in myelination has also been found (Barnden, Crouch, Kwiatek, Burnet, & Del Fante, 2015). Disruption to white matter could explain the relationship between abnormal eLORETA coherence patterns over large-scale complex systems in CFS. Furthermore, revealing the linkage between cognitive symptoms, illness duration, and small-worldness demonstrates the fundamental importance of timing, stability, and adaptation of complex systems to CFS which could be related to findings of widespread neuroinflammation in patients (Kuratsune, Nakatomi, Mizuno, & Watanabe, 2014; Nakatomi et al., 2014). Understanding the network dynamics of CFS in terms of eLORETA coherence is an important way of comprehending compensatory mechanisms and could serve as a practical tool for investigating large-scale loss of cognitive function related to adaptive re-configuration of brain networks. This study therefore demonstrates a need for future research into the activity-dependent modifications of brain connectivity in CFS with disruption to neurocognitive processes.

References

Abbey, S. E., & Garfinkel, P. E. (1991). Neurasthenia and chronic fatigue syndrome: the role of culture in the making of a diagnosis. *American Journal of Psychiatry, 148*(12), 1638-1646.

Adebimpe, A., Aarabi, A., Bourel-Ponchel, E., Mahmoudzadeh, M., & Wallois, F. (2016). EEG Resting State Functional Connectivity Analysis in Children with Benign Epilepsy with Centrotemporal Spikes. *Frontiers in Neuroscience, 10*, 143. doi:10.3389/fnins.2016.00143

Angelakis, E., Lubar, J. F., & Stathopoulou, S. (2004). Electroencephalographic peak alpha frequency correlates of cognitive traits. *Neuroscience Letters, 371*(1), 60-63. doi:10.1016/j.neulet.2004.08.041

Angelakis, E., Lubar, J. F., Stathopoulou, S., & Kounios, J. (2004). Peak alpha frequency: An electroencephalographic measure of cognitive preparedness. *Clinical Neurophysiology, 115*(4), 887-897. doi:10.1016/j.clinph.2003.11.034

Attree, E. A., Arroll, M. A., Dancey, C. P., Griffith, C., & Bansal, A. S. (2014). Psychosocial factors involved in memory and cognitive failures in people with myalgic encephalomyelitis/chronic fatigue syndrome. *Psychology Research and Behavior Management, 7*, 67-76. doi:10.2147/prbm.s50645

Babiloni, C., Carducci, F., Lizio, R., Vecchio, F., Baglieri, A., Bernardini, S., . . . Frisoni, G. B. (2013). Resting state cortical electroencephalographic rhythms are related to gray matter volume in subjects with mild cognitive

impairment and Alzheimer's disease. *Human Brain Mapping, 34*(6), 1427-1446. doi:10.1002/hbm.22005

Babiloni, C., De Pandis, M. F., Vecchio, F., Buffo, P., Sorpresi, F., Frisoni, G. B., & Rossini, P. M. (2011). Cortical sources of resting state electroencephalographic rhythms in Parkinson's disease related dementia and Alzheimer's disease. *Clinical neurophysiology : official journal of the International Federation of Clinical Neurophysiology, 122*(12), 2355-2364. doi:10.1016/j.clinph.2011.03.029

Babiloni, C., Frisoni, G., Steriade, M., Bresciani, L., Binetti, G., Del Percio, C., . . . Rossini, P. M. (2006). Frontal white matter volume and delta EEG sources negatively correlate in awake subjects with mild cognitive impairment and Alzheimer's disease. *Clinical Neurophysiology, 117*(5), 1113-1129. doi:10.1016/j.clinph.2006.01.020

Barnden, L. R., Crouch, B., Kwiatek, R., Burnet, R., & Del Fante, P. (2015). Evidence in chronic fatigue syndrome for severity-dependent upregulation of prefrontal myelination that is independent of anxiety and depression. *NMR in biomedicine, 28*(3), 404-413. doi:10.1002/nbm.3261

Barnden, L. R., Crouch, B., Kwiatek, R., Burnet, R., Mernone, A., Chryssidis, S., . . . Del Fante, P. (2011). A brain MRI study of chronic fatigue syndrome: Evidence of brainstem dysfunction and altered homeostasis. *NMR in Biomedicine, 24*(10), 1302-1312. doi:10.1002/nbm.1692

Bassett, D. S., & Bullmore, E. (2006). Small-world brain networks. *Neuroscientist, 12*(6), 512-523. doi:10.1177/1073858406293182

Billiot, K. M., Budzynski, T. H., & Andrasik, F. (1997). EEG Patterns and CFS. *Journal of Neurotherapy, 2-2*(4).

Biswal, B., Kunwar, P., & Natelson, B. H. (2011). Cerebral blood flow is reduced in chronic fatigue syndrome as assessed by arterial spin labeling. *Journal of the Neurological Sciences, 301*(1-2), 9-11. doi:10.1016/j.jns.2010.11.018

Boissoneault, J., Letzen, J., Lai, S., O'Shea, A., Craggs, J., Robinson, M. E., & Staud, R. (2016). Abnormal resting state functional connectivity in patients with chronic fatigue syndrome: An arterial spin-labeling fMRI study. *Magnetic Resonance Imaging, 34*(4), 603-608. doi:10.1016/j.mri.2015.12.008

Braun, U., Plichta, M. M., Esslinger, C., Sauer, C., Haddad, L., Grimm, O., . . . Meyer-Lindenberg, A. (2012). Test-retest reliability of resting-state connectivity network characteristics using fMRI and graph theoretical measures. *NeuroImage, 59*(2), 1404-1412. doi:10.1016/j.neuroimage.2011.08.044

Bullmore, E., & Sporns, O. (2012). The economy of brain network organization. *Nature Reviews. Neuroscience, 13*(5), 336-349. doi:10.1038/nrn3214

Busch, N. A., Dubois, J., & VanRullen, R. (2009). The phase of ongoing EEG oscillations predicts visual perception. *Journal of Neuroscience, 29*(24), 7869-7876. doi:10.1523/jneurosci.0113-09.2009

Busichio, K., Tiersky, L. A., Deluca, J., & Natelson, B. H. (2004). Neuropsychological deficits in patients with chronic fatigue syndrome.

Journal of the International Neuropsychological Society, 10(2), 278-285. doi:10.1017/s1355617704102178

Buzsaki, G. (2006). *Rhythms of the Brain*: Oxford University Press.

Buzsáki, G., & Freeman, W. (2015). Editorial overview: Brain rhythms and dynamic coordination. *Current Opinion in Neurobiology, 31*, v-ix. doi:10.1016/j.conb.2015.01.016

Buzsaki, G., & Watson, B. O. (2012). Brain rhythms and neural syntax: Implications for efficient coding of cognitive content and neuropsychiatric disease. *Dialogues in Clinical Neuroscience, 14*(4), 345-367. Retrieved from http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3553572/pdf/DialoguesClinNeurosci-14-345.pdf

Capuron, L., Welberg, L., Heim, C., Wagner, D., Solomon, L., Papanicolaou, D. A., . . . Reeves, W. C. (2006). Cognitive dysfunction relates to subjective report of mental fatigue in patients with chronic fatigue syndrome. *Neuropsychopharmacology, 31*(8), 1777-1784. doi:10.1038/sj.npp.1301005

Carruthers, B. M., Jain, A. K., de Meirleir, K., Peterson, D. L., Klimas, N. G., Lerner, A. M., . . . Van de Sande, M. I. (2003). Myalgic encephalomyelitits/chronic fatigue syndrome: Clinical working case definition, diagnostic, and treatment protocols *Journal of Chronic Fatigue Syndrome, 11*(1).

Carruthers, B. M., van de Sande, M. I., De Meirleir, K. L., Klimas, N. G., Broderick, G., Mitchell, T., . . . Stevens, S. (2011). Myalgic Encephalomyelitis: International Consensus Criteria. *Journal of Internal Medicine* doi:10.1111/j.1365- 2796.2011.02428.x

Caseras, X., Mataix-Cols, D., Giampietro, V., Rimes, K. A., Brammer, M., Zelaya, F., . . . Godfrey, E. L. (2006). Probing the working memory system in chronic fatigue syndrome: A functional magnetic resonance imaging study using the n-back task. *Psychosomatic Medicine, 68*(6), 947-955. doi:10.1097/01.psy.0000242770.50979.5f

Caseras, X., Mataix-Cols, D., Rimes, K. A., Giampietro, V., Brammer, M., Zelaya, F., . . . Godfrey, E. (2008). The neural correlates of fatigue: an exploratory imaginal fatigue provocation study in chronic fatigue syndrome. *Psychological Medicine, 38*(7), 941-951. doi:10.1017/s0033291708003450

Castellanos, N. P., & Makarov, V. A. (2006). Recovering EEG brain signals: artifact suppression with wavelet enhanced independent component analysis. *Journal of neuroscience methods, 158*(2), 300-312. doi:10.1016/j.jneumeth.2006.05.033

Chaudhuri, A., & Behan, P. O. (2004). Fatigue in neurological disorders. *The Lancet, 363*(9413), 978-988. doi:10.1016/S0140-6736(04)15794-2

Christodoulou, C., DeLuca, J., Lange, G., Johnson, S. K., Sisto, S. A., Korn, L., & Natelson, B. H. (1998). Relation between neuropsychological impairment and functional disability in patients with chronic fatigue syndrome.

Journal of Neurology, Neurosurgery, and Psychiatry, *64*(4), 431-434. Retrieved from http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2170049/pdf/v064p00431.pdf

Claypoole, K. H., Noonan, C., Mahurin, R. K., Goldberg, J., Erickson, T., & Buchwald, D. (2007). A twin study of cognitive function in chronic fatigue syndrome: the effects of sudden illness onset. *Neuropsychology, 21*(4), 507-513. doi:10.1037/0894-4105.21.4.507

Cockshell, S. J., & Mathias, J. L. (2010). Cognitive functioning in chronic fatigue syndrome: A meta-analysis. *Psychological medicine, 40*(8), 1253-1267. doi:10.1017/s0033291709992054

Constant, E. L., Adam, S., Gillain, B., Lambert, M., Masquelier, E., & Seron, X. (2011). Cognitive deficits in patients with chronic fatigue syndrome compared to those with major depressive disorder and healthy controls. *Clinical Neurology and Neurosurgery, 113*(4), 295-302. doi:10.1016/j.clineuro.2010.12.002

Cook, D. B., O'Connor, P. J., Lange, G., & Steffener, J. (2007). Functional neuroimaging correlates of mental fatigue induced by cognition among chronic fatigue syndrome patients and controls. *Neuroimage, 36*(1), 108-122. doi:10.1016/j.neuroimage.2007.02.033

Cope, H., Pernet, A., Kendall, B., & David, A. (1995). Cognitive functioning and magnetic resonance imaging in chronic fatigue. *British Journal of*

Psychiatry, 167(1), 86-94. Retrieved from http://bjp.rcpsych.org.laneproxy.stanford.edu/content/167/1/86.full.pdf

Costa, D. C., Tannock, C., & Brostoff, J. (1995). Brainstem perfusion is impaired in chronic fatigue syndrome. *QJM, 88*(11), 767-773.

Crossley, N. A., Mechelli, A., Scott, J., Carletti, F., Fox, P. T., McGuire, P., & Bullmore, E. T. (2014). The hubs of the human connectome are generally implicated in the anatomy of brain disorders. *Brain, 137*(Pt 8), 2382-2395. doi:10.1093/brain/awu132

Daugherty, S. A., Henry, B. E., Peterson, D. L., Swarts, R. L., Bastien, S., & Thomas, R. S. (1991). Chronic fatigue syndrome in northern Nevada. *Reviews of Infectious Diseases, 13 Suppl 1*, S39-44.

de Lange, F. P., Kalkman, J. S., Bleijenberg, G., Hagoort, P., van der Meer J. W. M., & Toni, I. (2005). Gray matter volume reduction in the chronic fatigue syndrome. *Neuroimage, 26*, 777-781.

de Lange, F. P., Kalkman, J. S., Bleijenberg, G., Hagoort, P., van der Werf, S. P., van der Meer, J. W., & Toni, I. (2004). Neural correlates of the chronic fatigue syndrome: An fMRI study. *Brain, 127*(Pt 9), 1948-1957. doi:10.1093/brain/awh225

Deco, G., Jirsa, V., & Friston, K. J. (2012). The dynamical structural basis of brain activity. In M. I. Rabinovich, K. Friston, & P. Varona (Eds.), *Principles of Brain Dynamics: Global State Interactions* (pp. 1-23). Cambridge, MA: MIT Press.

DeLuca, J. (2005). *Fatigue as a Window to the Brain* (J. DeLuca Ed.). Cambridge, MA: The MIT Press.

DeLuca, J., Genova, H. M., Capili, E. J., & Wylie, G. R. (2009). Functional neuroimaging of fatigue. *Physical Medicine and Rehabilitation Clinics of North America, 20*(2), 325-337. doi:10.1016/j.pmr.2008.12.007

DeLuca, J., Johnson, S. K., Ellis, S. P., & Natelson, B. H. (1997). Cognitive functioning is impaired in patients with chronic fatigue syndrome devoid of psychiatric disease. *Journal of Neurology, Neurosurgery, and Psychiatry, 62*(2), 151-155. Retrieved from http://www.ncbi.nlm.nih.gov/pmc/articles/PMC486726/pdf/jnnpsyc00002-0043.pdf

DeLuca, J., Johnson, S. K., & Natelson, B. H. (1993). Information processing efficiency in chronic fatigue syndrome and multiple sclerosis. *Archives of neurology, 50*(3), 301-304. Retrieved from http://archneur.jamanetwork.com/article.aspx?articleid=592247

Deluca, J., Johnson, S. K., & Natelson, B. H. (1994). Neuropsychiatric status of patients with chronic fatigue syndrome: An overview. *Toxicology and industrial health, 10*(4-5), 513-522.

Dobbs, B. M., Dobbs, A. R., & Kiss, I. (2001). Working memory deficits associated with chronic fatigue syndrome. *Journal of the International Neuropsychological Society, 7*(3), 285-293.

Duffy, F. H., McAnulty, G. B., McCreary, M. C., Cuchural, G. J., & Komaroff, A. L. (2011). EEG spectral coherence data distinguish chronic fatigue

syndrome patients from healthy controls and depressed patients: A case control study. *BMC neurology, 11*, 82. doi:10.1186/1471-2377-11-82

Flor-Henry, P., Lind, J. C., & Koles, Z. J. (2010). EEG source analysis of chronic fatigue syndrome. *Psychiatry research, 181*(2), 155-164. doi:10.1016/j.pscychresns.2009.10.007

Fry, A. M., & Martin, M. (1996). Fatigue in the chronic fatigue syndrome: a cognitive phenomenon? *Journal of Psychosomatic Research, 41*(5), 415-426. Retrieved from http://ac.els-cdn.com/S0022399996001900/1-s2.0-S0022399996001900-main.pdf?_tid=843c680c-cee5-11e2-a7b1-00000aab0f6c&acdnat=1370549773_fcc0dd1da1152ba9446897c550548fa5

Fukuda, K., Straus, S. E., Hickie, I., Sharpe, M. C., Dobbins, J. G., & Komaroff, A. (1994). The chronic fatigue syndrome: A comprehensive approach to its definition and study. *Annals of internal medicine, 121*(12), 953-959.

Gay, C., Robinson, M. E., Lai, S., O'Shea, A., Craggs, J., Price, D. D., & Staud, R. (2015). Abnormal Resting-State Functional Connectivity in Patients with Chronic Fatigue Syndrome: Results of Seed and Data-Driven Analyses. *Brain Connectivity*. doi:10.1089/brain.2015.0366

Gloor, P., Ball, G., & Schaul, N. (1977). Brain lesions that produce delta waves in the EEG. *Neurology*, *27*(4), 326-333.

Goedendorp, M. M., Bleijenberg, G., & Knoop, H. (2014). Response to 'Underperformance of myalgic encephalomyelitis (ME)/chronic fatigue syndrome (CFS) patients at neurocognitive tests should be assessed

objectively'. *Journal of Psychosomatic Research, 76*(4), 340. doi:10.1016/j.jpsychores.2013.12.006

Grafman, J., Schwartz, V., Dale, J. K., Scheffers, M., Houser, C., & Straus, S. E. (1993). Analysis of neuropsychological functioning in patients with chronic fatigue syndrome. *Journal of neurology, neurosurgery, and psychiatry, 56*(6), 684-689.

Grech, R., Cassar, T., Muscat, J., Camilleri, K. P., Fabri, S. G., Zervakis, M., . . . Vanrumste, B. (2008). Review on solving the inverse problem in EEG source analysis. *Journal of neuroengineering and rehabilitation, 5*, 25. doi:10.1186/1743-0003-5-25

Greco, A., Tannock, C., Brostoff, J., & Costa, D. C. (1997). Brain MR in chronic fatigue syndrome. *American Journal of Neuroradiology, 18*(7), 1265-1269. Retrieved from http://www.ajnr.org.laneproxy.stanford.edu/content/18/7/1265.full.pdf

Greicius, M. D., Kiviniemi, V., Tervonen, O., Vainionpaa, V., Alahuhta, S., Reiss, A. L., & Menon, V. (2008). Persistent default-mode network connectivity during light sedation. *Human brain mapping, 29*(7), 839-847. doi:10.1002/hbm.20537

Hagmann, P., Cammoun, L., Gigandet, X., Meuli, R., Honey, C. J., Wedeen, V. J., & Sporns, O. (2008). Mapping the structural core of human cerebral cortex. *PLoS Biology, 6*(7), e159. doi:10.1371/journal.pbio.0060159

Harris, P. A., Taylor, R., Thielke, R., Payne, J., Gonzalez, N., & Conde, J. G. (2009). Research electronic data capture (REDCap)--A metadata-driven

methodology and workflow process for providing translational research informatics support. *Journal of Biomedical Informatics, 42*(2), 377-381. doi:10.1016/j.jbi.2008.08.010

Hata, M., Kazui, H., Tanaka, T., Ishii, R., Canuet, L., Pascual-Marqui, R. D., . . . Takeda, M. (2016). Functional connectivity assessed by resting state EEG correlates with cognitive decline of Alzheimer's disease: An eLORETA study. *Clinical Neurophysiology, 127*(2), 1269-1278. doi:10.1016/j.clinph.2015.10.030

Hegerl, U., & Ulke, C. (2016). Fatigue with up- vs downregulated brain arousal should not be confused. *Progress in Brain Research, 229*, 239-254. doi:10.1016/bs.pbr.2016.06.001

Hillary, F. G., Roman, C. A., Venkatesan, U., Rajtmajer, S. M., Bajo, R., & Castellanos, N. D. (2015). Hyperconnectivity is a fundamental response to neurological disruption. *Neuropsychology, 29*(1), 59-75. doi:10.1037/neu0000110

Hopkins, R. O., & Jackson, J. C. (2006). Long-term neurocognitive function after critical illness. *Chest, 130*(3), 869-878. doi:10.1378/chest.130.3.869

Hughes, S. W., Lorincz, M., Cope, D. W., Blethyn, K. L., Kekesi, K. A., Parri, H. R., . . . Crunelli, V. (2004). Synchronized oscillations at alpha and theta frequencies in the lateral geniculate nucleus. *Neuron, 42*(2), 253-268. Retrieved from http://ac.els-cdn.com/S0896627304001916/1-s2.0-S0896627304001916-main.pdf?_tid=4cd473e8-70fd-11e5-8a16-

00000aacb35e&acdnat=1444667072_fa174693c0292509411c0d5ff7241c06

Humphries, M. D., & Gurney, K. (2008). Network 'small-world-ness': a quantitative method for determining canonical network equivalence. *PloS one, 3*(4), e0002051. doi:10.1371/journal.pone.0002051

Institute of Medicine. (2015). *Beyond Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: Redefining an Illness*. Washington (DC): National Academies Press

Jason, L. A., Benton, M. C., Valentine, L., Johnson, A., & Torres-Harding, S. (2008). The economic impact of ME/CFS: individual and societal costs. *Dynamic medicine : DM, 7*, 6. doi:10.1186/1476-5918-7-6

Jason, L. A., Richman, J. A., Rademaker, A. W., Jordan, K. M., Plioplys, A. V., Taylor, R. R., . . . Plioplys, S. (1999). A community-based study of chronic fatigue syndrome. *Archives of internal medicine, 159*(18), 2129-2137. Retrieved from http://archinte.jamanetwork.com/data/Journals/INTEMED/11951/ioi90161.pdf

Jason, L. A., So, S., Brown, A., Sunnquist, M., & Evans, M. (2015). Test-retest reliability of the DePaul Symptom Questionnaire. *Fatigue Biomedicine Health & Behavior, 3*(1), 16-32.

Jason, L. A., Sunnquist, M., Brown, A., Furst, J., Cid, M., Farietta, J., . . . Strand, E. B. (2015). Factor analysis of the DePaul Symptom Questionnaire:

Identifying core domains. *Journal of Neurology and Neurobiology, 1*(4). doi:10.16966/2379-7150.114

Jason, L. A., Zinn, M. L., & Zinn, M. A. (2015). Myalgic encephalomyelitis: symptoms and biomarkers. *Current Neuropharmacology, 13*(5), 701-734.

John, E. R. (2005). From synchronous neuronal discharges to subjective awareness? In S. Laureys (Ed.), *Progress in Brain Research* (Vol. 150): Elsevier.

Johnson, S. K., DeLuca, J., & Natelson, B. H. (1996). Assessing somatization disorder in the chronic fatigue syndrome. *Psychosomatic Medicine, 58*(1), 50-57.

Jurcak, V., Tsuzuki, D., & Dan, I. (2007). 10/20, 10/10, and 10/5 systems revisited: their validity as relative head-surface-based positioning systems. *NeuroImage, 34*(4), 1600-1611. doi:10.1016/j.neuroimage.2006.09.024

Kierkels, J. J., van Boxtel, G. J., & Vogten, L. L. (2006). A model-based objective evaluation of eye movement correction in EEG recordings. *IEEE transactions on bio-medical engineering, 53*(2), 246-253. doi:10.1109/tbme.2005.862533

Kim, B. H., Namkoong, K., Kim, J. J., Lee, S., Yoon, K. J., Choi, M., & Jung, Y. C. (2015). Altered resting-state functional connectivity in women with chronic fatigue syndrome. *Psychiatry Research, 234*(3), 292-297. doi:10.1016/j.pscychresns.2015.10.014

Kirk, R. E. (2013). *Experimental design: Procedures for the behavioral sciences* (4th ed.). Los Angeles: Sage.

Klimesch, W. (2012). alpha-band oscillations, attention, and controlled access to stored information. *Trends in cognitive sciences, 16*(12), 606-617. doi:10.1016/j.tics.2012.10.007

Klimesch, W., Freunberger, R., Sauseng, P., & Gruber, W. (2008). A short review of slow phase synchronization and memory: evidence for control processes in different memory systems? *Brain research, 1235*, 31-44. doi:10.1016/j.brainres.2008.06.049

Knyazev, G. G. (2012). EEG delta oscillations as a correlate of basic homeostatic and motivational processes. *Neuroscience and biobehavioral reviews, 36*(1), 677-695. doi:10.1016/j.neubiorev.2011.10.002

Komaroff, A. L., & Buchwald, D. (1991). Symptoms and signs of chronic fatigue syndrome. *Reviews of Infectious Diseases, 13 Suppl 1,* S8-11.

Koziol, L. F., & Budding, D. E. (2009). *Subcortical Structures and Cognition: Implications for Neuropsychological Assessment.* New York: Springer.

Kuratsune, H., Nakatomi, Y., Mizuno, K., & Watanabe, Y. (2014). *Neuroinflammation in patients with ME: a positron emission topography study.* Paper presented at the 11th Biennial International Association of CFS/ME Conference, San Francisco, Ca.

Lange, G., DeLuca, J., Maldjian, J. A., Lee, H., Tiersky, L. A., & Natelson, B. H. (1999). Brain MRI abnormalities exist in a subset of patients with chronic fatigue syndrome. *Journal of the Neurological Sciences, 171*(1), 3-7.

Lange, G., Steffener, J., Cook, D. B., Bly, B. M., Christodoulou, C., Liu, W. C., . . . Natelson, B. H. (2005). Objective evidence of cognitive complaints in

Chronic Fatigue Syndrome: A BOLD fMRI study of verbal working memory. *Neuroimage, 26*(2), 513-524. doi:10.1016/j.neuroimage.2005.02.011

Le Van Quyen, M. (2011). The brainweb of cross-scale interactions. *New Ideas in Psychology*, *29*(2), 57-63. doi:10.1016/j.newideapsych.2010.11.001

Lehmann, D., Faber, P. L., Gianotti, L. R., Kochi, K., & Pascual-Marqui, R. D. (2006). Coherence and phase locking in the scalp EEG and between LORETA model sources, and microstates as putative mechanisms of brain temporo-spatial functional organization. *Journal of Physiology, Paris, 99*(1), 29-36. doi:10.1016/j.jphysparis.2005.06.005

Lewis, D. H., Mayberg, H. S., Fischer, M. E., Goldberg, J., Ashton, S., Graham, M. M., & Buchwald, D. (2001). Monozygotic twins discordant for chronic fatigue syndrome: regional cerebral blood flow SPECT. *Radiology, 219*(3), 766-773. doi:10.1148/radiology.219.3.r01jn18766

Lowe, M. J., Sakaie, K. E., Beall, E. B., Calhoun, V. D., Bridwell, D. A., Rubinov, M., & Rao, S. M. (2016). Modern Methods for Interrogating the Human Connectome. *Journal of the International Neuropsychological Society, 22*(2), 105-119. doi:10.1017/s1355617716000060

Luria, A. R. (1980). *Higher cortical functions in man.* (2nd ed.). New York: Basic Books Publishers.

Majer, M., Welberg, L. A., Capuron, L., Miller, A. H., Pagnoni, G., & Reeves, W. C. (2008). Neuropsychological performance in persons with chronic

fatigue syndrome: results from a population-based study. *Psychosomatic medicine, 70*(7), 829-836. doi:10.1097/PSY.0b013e31817b9793

Marcel, B., Komaroff, A. L., Fagioli, L. R., Kornish, R. J., 2nd, & Albert, M. S. (1996). Cognitive deficits in patients with chronic fatigue syndrome. *Biological Psychiatry, 40*(6), 535-541.

Mariman, A., Delesie, L., Tobback, E., Hanoulle, I., Sermijn, E., Vermeir, P., . . . Vogelaers, D. (2013). Undiagnosed and comorbid disorders in patients with presumed chronic fatigue syndrome. *Journal of Psychosomatic Research, 75*(5), 491-496. doi:10.1016/j.jpsychores.2013.07.010

Marshall, P. S., Forstot, M., Callies, A., Peterson, P. K., & Schenck, C. H. (1997). Cognitive slowing and working memory difficulties in chronic fatigue syndrome. *Psychosomatic Medicine, 59*(1), 58-66.

McAlaster, R. (1992). Postnatal cerebral maturation in Down's syndrome children: A developmental EEG coherence study. *International Journal of Neuroscience, 65*(1-4), 221-237.

Menon, V. (2011). Large-scale brain networks and psychopathology: a unifying triple network model. *Trends in cognitive sciences, 15*(10), 483-506. doi:10.1016/j.tics.2011.08.003

Menon, V. (2012). Functional connectivity, neurocognitive networks, and brain dynamics. In M. I. Rabinovich, K. J. Friston, & P. Varona (Eds.), *Principles of Brain Dynamics: Global State Interactions* (pp. 27-47). Cambridge, MA: MIT Press.

Michiels, V., & Cluydts, R. (2001). Neuropsychological functioning in chronic fatigue syndrome: a review. *Acta Psychiatrica Scandinavica, 103*(2), 84-93. Retrieved from http://onlinelibrary.wiley.com.laneproxy.stanford.edu/store/10.1034/j.1600-0447.2001.00017.x/asset/j.1600-0447.2001.00017.x.pdf?v=1&t=hhmcyyvy&s=c8a16699b4c232e66285917e35d092c09b6aa919

Minati, L., Varotto, G., D'Incerti, L., Panzica, F., & Chan, D. (2013). From brain topography to brain topology: Relevance of graph theory to functional neuroscience. *Neuroreport, 24*(10), 536-543. doi:10.1097/WNR.0b013e3283621234

Morris, G., & Maes, M. (2012). A neuro-immune model of Myalgic Encephalomyelitis/Chronic fatigue syndrome. *Metabolic brain disease.* doi:10.1007/s11011-012-9324-8

Murdock, K. W., Wang, X. S., Shi, Q., Cleeland, C. S., Fagundes, C. P., & Vernon, S. D. (2016). The utility of patient-reported outcome measures among patients with myalgic encephalomyelitis/chronic fatigue syndrome. *Quality of Life Research*. doi:10.1007/s11136-016-1406-3

Nakatomi, Y., Mizuno, K., Ishii, R., Wada, Y., Tanaka, M., Tazawa, S., . . . Watanabe, Y. (2014). Neuroinflammation in patients with Chronic Fatigue Syndrome/Myalgic Encephalomyelitis: An 11C-(R)-PK11195 PET study. *Journal of Nuclear Medicine, 55*(6), 945-950. Retrieved from http://jnm.snmjournals.org/content/55/6/945.full.pdf

Natelson, B. H., Cohen, J. M., Brassloff, I., & Lee, H. J. (1993). A controlled study of brain magnetic resonance imaging in patients with the chronic fatigue syndrome. *Journal of the Neurological Sciences, 120*(2), 213-217.

Niedermeyer, E., & Lopez da Silva, F. (2005). *Electroencephalography: Basic principles, clinical applications and related fields* (5th ed. ed.). Philadelphia: Lippincott Williams and Wilkins.

Nishida, K., Yoshimura, M., Isotani, T., Yoshida, T., Kitaura, Y., Saito, A., . . . Kinoshita, T. (2011). Differences in quantitative EEG between frontotemporal dementia and Alzheimer's disease as revealed by LORETA. *Clinical Neurophysiology, 122*(9), 1718-1725. doi:10.1016/j.clinph.2011.02.011

Nunez, P. L., Srinivasan, R., & Fields, R. D. (2014). EEG functional connectivity, axon delays and white matter disease. *Clinical Neurophysiology*(0). doi:10.1016/j.clinph.2014.04.003

Ocon, A. J. (2013). Caught in the thickness of brain fog: Exploring the cognitive symptoms of chronic fatigue syndrome. *Frontiers in Physiology, 4*, 63. doi:10.3389/fphys.2013.00063

Okada, T., Tanaka, M., Kuratsune, H., Watanabe, Y., & Sadato, N. (2004). Mechanisms underlying fatigue: a voxel-based morphometric study of chronic fatigue syndrome. *BMC Neurology, 4*(1), 14. doi:10.1186/1471-2377-4-14

Pajevic, S., Basser, P. J., & Fields, R. D. (2014). Role of myelin plasticity in oscillations and synchrony of neuronal activity. *Neuroscience, 276,* 135-147. doi:10.1016/j.neuroscience.2013.11.007

Pascual-Marqui, R. D. (2007a). *Coherence and phase synchronization: Generalization to pairs of multivariate time series, and removal of zero-lag contribution* (arXiv:0706.1776v3 [stat.ME]). Retrieved from http://arxiv.org/pdf/0706.1776

Pascual-Marqui, R. D. (2007b). *Discrete, 3D distributed linear imaging methods of electric neuronal activity. Part 1: Exact, zero error localization* (arXiv:0710.3341 [math-ph]). Retrieved from https://arxiv.org/ftp/arxiv/papers/0710/0710.3341.pdf

Pascual-Marqui, R. D. (2007c). *Instantaneous and lagged measurements of linear and nonlinear dependence between groups of multivariate time series: Frequency decomposition* (arXiv:0711.1455[stat.ME]). Retrieved from https://arxiv.org/pdf/0711.1455v1

Pascual-Marqui, R. D. (2015). LORETA-KEY software (Version 2015-12-22). Zurich, Switzerland: KEY Institute for Brain-Mind Research. Retrieved from http://www.uzh.ch/keyinst/loreta.htm

Pascual-Marqui, R. D., Lehmann, D., Koukkou, M., Kochi, K., Anderer, P., Saletu, B., . . . Kinoshita, T. (2011). Assessing interactions in the brain with exact low-resolution electromagnetic tomography. *Philosophical transactions. Series A, Mathematical, physical, and engineering sciences, 369*(1952), 3768-3784. doi:10.1098/rsta.2011.0081

Puri, B. K., Jakeman, P. M., Agour, M., Gunatilake, K. D., Fernando, K. A., Gurusinghe, A. I., . . . Gishen, P. (2012). Regional grey and white matter volumetric changes in myalgic encephalomyelitis (chronic fatigue syndrome): A voxel-based morphometry 3 T MRI study. *British Journal of Radiology, 85*(1015), e270-273. doi:10.1259/bjr/93889091

Raichle, M. E. (2010). Two views of brain function. *Trends in Cognitive Sciences, 14*(4), 180-190. doi:10.1016/j.tics.2010.01.008

Raichle, M. E. (2011). The restless brain. *Brain Connectivity, 1*(1), 3-12. doi:10.1089/brain.2011.0019

Rossini, P. M., Rossi, S., Babiloni, C., & Polich, J. (2007). Clinical neurophysiology of aging brain: From normal aging to neurodegeneration. *Progress in Neurobiology, 83*(6), 375-400. doi:10.1016/j.pneurobio.2007.07.010

Rubinov, M., & Sporns, O. (2010). Complex network measures of brain connectivity: Uses and interpretations. *Neuroimage, 52*(3), 1059-1069. doi:10.1016/j.neuroimage.2009.10.003

Saper, C. B., Fuller, P. M., Pedersen, N. P., Lu, J., & Scammell, T. E. (2010). Sleep state switching. *Neuron, 68*(6), 1023-1042. doi:10.1016/j.neuron.2010.11.032

Sauseng, P., & Klimesch, W. (2008). What does phase information of oscillatory brain activity tell us about cognitive processes? *Neuroscience and biobehavioral reviews, 32*(5), 1001-1013. doi:10.1016/j.neubiorev.2008.03.014

Schaul, N., Gloor, P., & Gotman, J. (1981). The EEG in deep midline lesions. *Neurology, 31*(2), 157-167.

Schwartz, R. B., Garada, B. M., Komaroff, A. L., Tice, H. M., Gleit, M., Jolesz, F. A., & Holman, B. L. (1994). Detection of intracranial abnormalities in patients with chronic fatigue syndrome: comparison of MR imaging and SPECT. *AJR. American journal of roentgenology, 162*(4), 935-941. doi:10.2214/ajr.162.4.8141020

Schwartz, R. B., Komaroff, A. L., Garada, B. M., Gleit, M., Doolittle, T. H., Bates, D. W., . . . Holman, B. L. (1994). SPECT imaging of the brain: comparison of findings in patients with chronic fatigue syndrome, AIDS dementia complex, and major unipolar depression. *American Journal of Roentgenology, 162*(4), 943-951. doi:10.2214/ajr.162.4.8141022

Sepulcre, J. (2014). Functional Streams and Cortical Integration in the Human Brain. *The Neuroscientist, 20*(5), 499-508. doi:10.1177/1073858414531657

Sherlin, L., Budzynski, T., Kogan Budzynski, H., Congedo, M., Fischer, M. E., & Buchwald, D. (2007). Low-resolution electromagnetic brain tomography (LORETA) of monozygotic twins discordant for chronic fatigue syndrome. *NeuroImage, 34*(4), 1438-1442. doi:10.1016/j.neuroimage.2006.11.007

Shulman, R. G., Rothman, D. L., Behar, K. L., & Hyder, F. (2004). Energetic basis of brain activity: implications for neuroimaging. *Trends in neurosciences, 27*(8), 489-495. doi:10.1016/j.tins.2004.06.005

Siessmeier, T., Nix, W. A., Hardt, J., Schreckenberger, M., Egle, U. T., & Bartenstein, P. (2003). Observer independent analysis of cerebral glucose metabolism in patients with chronic fatigue syndrome. *Journal of Neurology, Neurosurgery, and Psychiatry, 74*(7), 922-928. Retrieved from http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1738575/pdf/v074p00922.pdf

Smith, A. P., Behan, P. O., Bell, W., Millar, K., & Bakheit, M. (1993). Behavioural problems associated with the chronic fatigue syndrome. *British Journal of Psychology, 84 (Pt 3)*, 411-423.

Sporns, O. (2013). Structure and function of complex brain networks. *Dialogues in clinical neuroscience, 15*(3), 247-262. Retrieved from http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3811098/pdf/DialoguesClinNeurosci-15-247.pdf

Sporns, O., & Honey, C. J. (2006). Small worlds inside big brains. *Proceedings of the National Academy of Sciences, 103*(51), 19219-19220. doi:10.1073/pnas.0609523103

Stam, C. J. (2010). Characterization of anatomical and functional connectivity in the brain: a complex networks perspective. *International Journal of Psychophysiology, 77*(3), 186-194. doi:10.1016/j.ijpsycho.2010.06.024

Stam, C. J. (2014). Modern network science of neurological disorders. *Nature Reviews. Neuroscience, 15*(10), 683-695. doi:10.1038/nrn3801

Steriade, M. (2005). Cellular substrates of brain rhythms. In E. Niedermeyer & F. H. Lopes de Silva (Eds.), *Electroencephalography: Basic principles, clinical applications and related fields* (pp. 31-83). New York: Lippincott Williams & Wilkins.

Steriade, M., & McCarley, R. W. (2005). *Brain control of wakefulness and sleep*. New York: Springer.

Steriade, M., & Pare, D. (2006). *Gating in cerebral networks*. Cambridge: Cambridge University Press.

Sterman, M. B., & Kaiser, D. A. (2000). Automatic artifact detection, overlapping windows, and state transitions. *Jounal of Neurotherapy*, *4*(3), 85-92.

Tanaka, M., Sadato, N., Okada, T., Mizuno, K., Sasabe, T., Tanabe, H. C., . . . Watanabe, Y. (2006). Reduced responsiveness is an essential feature of chronic fatigue syndrome: A fMRI study. *BMC Neurology*, *6*, 9. doi:10.1186/1471-2377-6-9

Telesford, Q. K., Simpson, S. L., Burdette, J. H., Hayasaka, S., & Laurienti, P. J. (2011). The brain as a complex system: using network science as a tool for understanding the brain. *Brain connectivity*, *1*(4), 295-308. doi:10.1089/brain.2011.0055

Thatcher, R. W. (2016). *Handbook of Quantitattive Electroencephalography and EEG Biofeedback*. St. Petersburg, FLA: ANI Publishing.

Thatcher, R. W., North, D. M., & Biver, C. J. (2008). Intelligence and EEG phase reset: a two compartmental model of phase shift and lock. *NeuroImage*, *42*(4), 1639-1653. doi:10.1016/j.neuroimage.2008.06.009

Thomas, M., & Smith, A. (2009). An investigation into the cognitive deficits associated with chronic fatigue syndrome. *The Open Neurology Journal, 3*, 13-23. doi:10.2174/1874205x00903010013

Tirelli, U., Chierichetti, F., Tavio, M., Simonelli, C., Bianchin, G., Zanco, P., & Ferlin, G. (1998). Brain positron emission tomography (PET) in chronic fatigue syndrome: preliminary data. *American Journal of Medicine, 105*(3A), 54S-58S.

Twisk, F. N. (2014). Underperformance of myalgic encephalomyelitis (ME)/chronic fatigue syndrome (CFS) patients at neurocognitive tests should be assessed objectively without an a priori judgment about the etiology. *Journal of Psychosomatic Research, 76*(4), 339. doi:10.1016/j.jpsychores.2013.10.016

van Baal, G. C., Boomsma, D. I., & de Geus, E. J. (2001). Longitudinal genetic analysis of EEG coherence in young twins. *Behavior genetics, 31*(6), 637-651.

van Dellen, E., Douw, L., Baayen, J. C., Heimans, J. J., Ponten, S. C., Vandertop, W. P., . . . Reijneveld, J. C. (2009). Long-term effects of temporal lobe epilepsy on local neural networks: a graph theoretical analysis of corticography recordings. *PloS one, 4*(11), e8081. doi:10.1371/journal.pone.0008081

Van Den Eede, F., Moorkens, G., Hulstijn, W., Maas, Y., Schrijvers, D., Stevens, S. R., . . . Sabbe, B. G. (2011). Psychomotor function and response

inhibition in chronic fatigue syndrome. *Psychiatry research, 186*(2-3), 367-372. doi:10.1016/j.psychres.2010.07.022

van den Heuvel, M. P., & Sporns, O. (2013). An anatomical substrate for integration among functional networks in human cortex. *The Journal of Neuroscience, 33*(36), 14489-14500. doi:10.1523/jneurosci.2128-13.2013

van Straaten, E. C., & Stam, C. J. (2013). Structure out of chaos: Functional brain network analysis with EEG, MEG, and functional MRI. *European Neuropsychopharmacology, 23*(1), 7-18. doi:10.1016/j.euroneuro.2012.10.010

Vecchio, F., Miraglia, F., Curcio, G., Altavilla, R., Scrascia, F., Giambattistelli, F., . . . Rossini, P. M. (2015). Cortical brain connectivity evaluated by graph theory in dementia: A correlation study between functional and structural data. *Journal of Alzheimer's Disease, 45*(3), 745-756. doi:10.3233/jad-142484

Vecchio, F., Miraglia, F., Curcio, G., Della Marca, G., Vollono, C., Mazzucchi, E., . . . Rossini, P. M. (2015). Cortical connectivity in fronto-temporal focal epilepsy from EEG analysis: A study via graph theory. *Clinical Neurophysiology, 126*(6), 1108-1116. doi:10.1016/j.clinph.2014.09.019

Vecchio, F., Miraglia, F., Porcaro, C., Cottone, C., Cancelli, A., Rossini, P. M., & Tecchio, F. (2017). Electroencephalography-Derived Sensory and Motor Network Topology in Multiple Sclerosis Fatigue. *Neurorehabilitation and Neural Repair, 31*(1), 56-64. doi:10.1177/1545968316656055

Vecchio, F., Miraglia, F., Quaranta, D., Granata, G., Romanello, R., Marra, C., . . . Rossini, P. M. (2016). Cortical connectivity and memory performance in cognitive decline: A study via graph theory from EEG data. *Neuroscience, 316*, 143-150. doi:10.1016/j.neuroscience.2015.12.036

Vysata, O., Kukal, J., Prochazka, A., Pazdera, L., Simko, J., & Valis, M. (2014). Age-related changes in EEG coherence. *Neurologia i Neurochirurgia Polska, 48*(1), 35-38. doi:10.1016/j.pjnns.2013.09.001

Wallstrom, G. L., Kass, R. E., Miller, A., Cohn, J. F., & Fox, N. A. (2004). Automatic correction of ocular artifacts in the EEG: A comparison of regression-based and component-based methods. *International Journal of Psychophysiology, 53*(2), 105-119. doi:10.1016/j.ijpsycho.2004.03.007

Warren, J. W., Langenberg, P., & Clauw, D. J. (2013). The number of existing functional somatic syndromes (FSSs) is an important risk factor for new, different FSSs. *Journal of Psychosomatic Research, 74*(1), 12-17. doi:10.1016/j.jpsychores.2012.09.002

Watts, D. J., & Strogatz, S. H. (1998). Collective dynamics of "small-world" networks. *Nature, 393*(6684), 440-442. Retrieved from http://dx.doi.org/10.1038/30918

Wearden, A., & Appleby, L. (1997). Cognitive performance and complaints of cognitive impairment in chronic fatigue syndrome (CFS). *Psychological Medicine, 27*(1), 81-90.

Westmoreland, B. (2005). The EEG in Cerebral Inflammatory Processes. In E. Niedermeyer & F. Lopez da Silva (Eds.), *Electroencephalography: Basic*

principles, clinical applications and related fields (5th ed. ed., pp. 323-337). Philadelphia: Lippincott Williams and Wilkins.

White, P. D. (2010). Chronic fatigue syndrome: Is it one discrete syndrome or many? Implications for the "one vs. many" functional somatic syndromes debate. *Journal of psychosomatic research, 68*(5), 455-459. doi:10.1016/j.jpsychores.2010.01.008

Wig, G. S., Schlaggar, B. L., & Petersen, S. E. (2011). Concepts and principles in the analysis of brain networks. *Annals of the New York Academy of Sciences, 1224*, 126-146. doi:10.1111/j.1749-6632.2010.05947.x

Wortinger, L. A., Endestad, T., Melinder, A. M., Oie, M. G., Sevenius, A., & Bruun Wyller, V. (2016). Aberrant Resting-State Functional Connectivity in the Salience Network of Adolescent Chronic Fatigue Syndrome. *PLoS One, 11*(7), e0159351. doi:10.1371/journal.pone.0159351

Zhang, D., & Raichle, M. E. (2010). Disease and the brain's dark energy. *Nature Reviews. Neurology, 6*(1), 15-28. doi:10.1038/nrneurol.2009.198

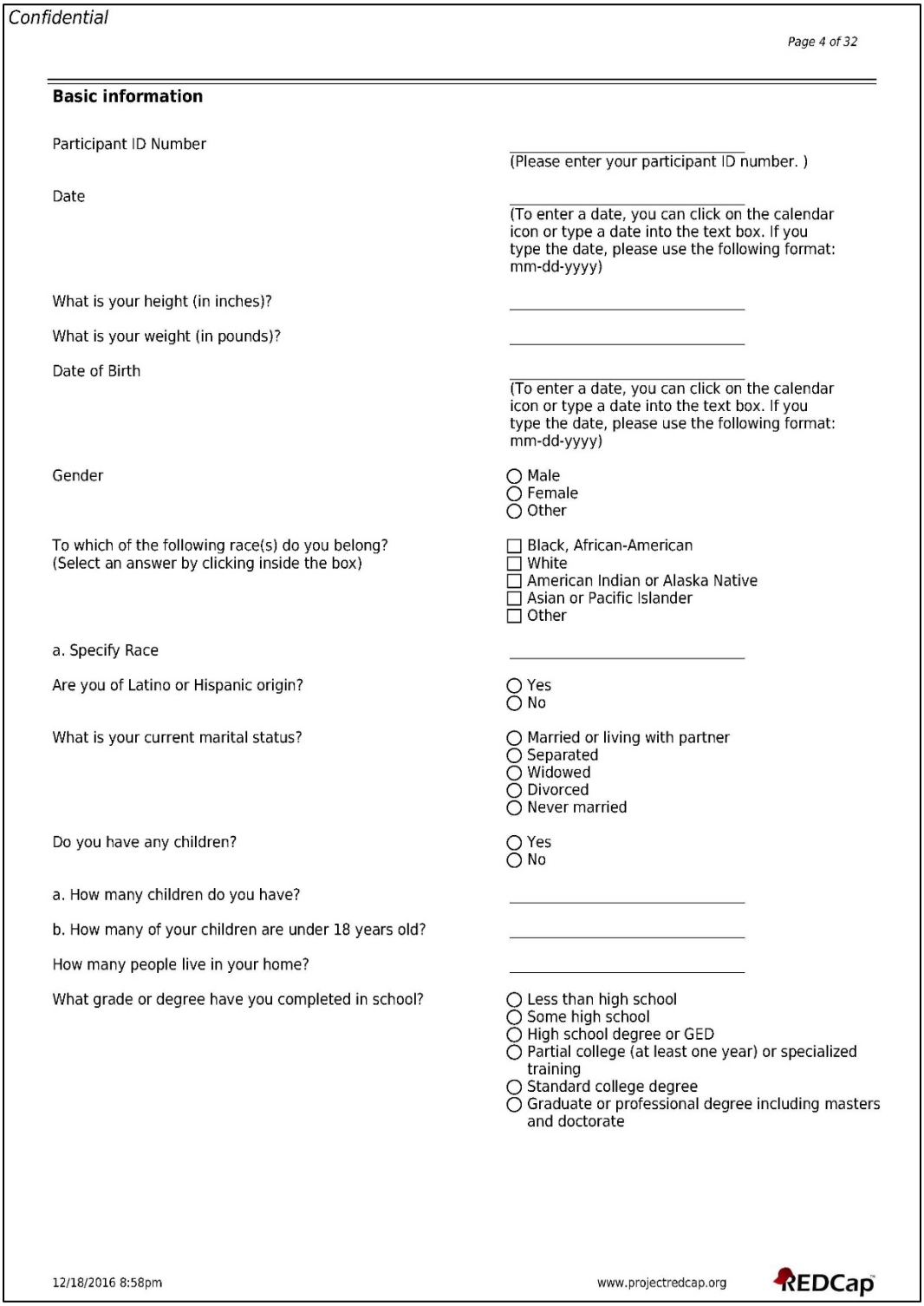
Zinn, M. L., Zinn, M. A., & Jason, L. A. (2016). Intrinsic Functional Hypoconnectivity in Core Neurocognitive Networks Suggests Central Nervous System Pathology in Patients with Myalgic Encephalomyelitis: A Pilot Study. *Applied Psychophysiology and Biofeedback, 41*(3), 283-300. doi:10.1007/s10484-016-9331-3

Zinn, M. L., Zinn, M. A., Norris, J. L., Valencia, I., Montoya, J. G., & Maldonado, J. R. (2014, March). *EEG Peak Alpha Frequency Correlates in Chronic Fatigue Syndrome: A Case-Control Observational Study*.

Paper presented at the IACFS/ME 2014 Biennial Conference, San Francisco, CA, USA.

Appendix A: DePaul Symptom Questionnaire

Please note, this is only the portion of the DSQ that will be used in this proposed study. The entire DSQ, in can be viewed online with the following URL: https://redcap.is.depaul.edu/surveys/?s=73A9C7HYPD



Confidential

Page 4 of 32

Basic information

Participant ID Number
_____
(Please enter your participant ID number.)

Date
_____
(To enter a date, you can click on the calendar icon or type a date into the text box. If you type the date, please use the following format: mm-dd-yyyy)

What is your height (in inches)?
_____

What is your weight (in pounds)?
_____

Date of Birth
_____
(To enter a date, you can click on the calendar icon or type a date into the text box. If you type the date, please use the following format: mm-dd-yyyy)

Gender
- ○ Male
- ○ Female
- ○ Other

To which of the following race(s) do you belong? (Select an answer by clicking inside the box)
- ☐ Black, African-American
- ☐ White
- ☐ American Indian or Alaska Native
- ☐ Asian or Pacific Islander
- ☐ Other

a. Specify Race
_____

Are you of Latino or Hispanic origin?
- ○ Yes
- ○ No

What is your current marital status?
- ○ Married or living with partner
- ○ Separated
- ○ Widowed
- ○ Divorced
- ○ Never married

Do you have any children?
- ○ Yes
- ○ No

a. How many children do you have?
_____

b. How many of your children are under 18 years old?
_____

How many people live in your home?
_____

What grade or degree have you completed in school?
- ○ Less than high school
- ○ Some high school
- ○ High school degree or GED
- ○ Partial college (at least one year) or specialized training
- ○ Standard college degree
- ○ Graduate or professional degree including masters and doctorate

12/18/2016 8:58pm www.projectredcap.org REDCap

Confidential

What is your current work status? (Check all that apply)

- ☐ On disability
- ☐ Student
- ☐ Homemaker
- ☐ Retired
- ☐ Unemployed
- ☐ Working part-time
- ☐ Working full-time

a. If you are on disability, for what condition do you receive disability compensation? (Please Specify) _____

What is your current occupation? _____

a. If you are currently not working, what was your most recent occupation? _____

Confidential

Page 6 of 32

For the following questions (13-66), we would like to know how often you have had each symptom and how much each symptom has bothered you over the last 6 months. For each symptom please select one number for frequency and one number for severity.

Confidential

Page 11 of 32

Problems remembering things

Frequency: Throughout the past 6 months, how often have you had problems remembering things?
- ◯ 0 = none of the time
- ◯ 1 = a little of the time
- ◯ 2 = about half the time
- ◯ 3 = most of the time
- ◯ 4 = all of the time

Severity: Throughout the past 6 months, how much have problems remembering things bothered you?
- ◯ 0 = symptom not present
- ◯ 1 = mild
- ◯ 2 = moderate
- ◯ 3 = severe
- ◯ 4 = very severe

Difficulty paying attention for a long period of time

Frequency: Throughout the past 6 months, how often have you had difficulty paying attention for a long period of time?
- ◯ 0 = none of the time
- ◯ 1 = a little of the time
- ◯ 2 = about half the time
- ◯ 3 = most of the time
- ◯ 4 = all of the time

Severity: Throughout the past 6 months, how much has difficulty paying attention for a long period of time bothered you?
- ◯ 0 = symptom not present
- ◯ 1 = mild
- ◯ 2 = moderate
- ◯ 3 = severe
- ◯ 4 = very severe

Difficulty finding the right word to say or expressing thoughts

Frequency: Throughout the past 6 months, how often have you had difficulty finding the right word to say or expressing thoughts?
- ◯ 0 = none of the time
- ◯ 1 = a little of the time
- ◯ 2 = about half the time
- ◯ 3 = most of the time
- ◯ 4 = all of the time

Severity: Throughout the past 6 months, how much has difficulty finding the right word to say or expressing thoughts bothered you?
- ◯ 0 = symptom not present
- ◯ 1 = mild
- ◯ 2 = moderate
- ◯ 3 = severe
- ◯ 4 = very severe

Difficulty understanding things

Frequency: Throughout the past 6 months, how often have you had difficulty understanding things?
- ◯ 0 = none of the time
- ◯ 1 = a little of the time
- ◯ 2 = about half the time
- ◯ 3 = most of the time
- ◯ 4 = all of the time

Severity: Throughout the past 6 months, how much has difficulty understanding things bothered you?
- ◯ 0 = symptom not present
- ◯ 1 = mild
- ◯ 2 = moderate
- ◯ 3 = severe
- ◯ 4 = very severe

Only able to focus on one thing at a time

Frequency: Throughout the past 6 months, how often have you only been able to focus on one thing at a time?
- ◯ 0 = none of the time
- ◯ 1 = a little of the time
- ◯ 2 = about half the time
- ◯ 3 = most of the time
- ◯ 4 = all of the time

Confidential

Severity: Throughout the past 6 months, how much has only being able to focus on one thing at a time bothered you?

- ◯ 0 = symptom not present
- ◯ 1 = mild
- ◯ 2 = moderate
- ◯ 3 = severe
- ◯ 4 = very severe

Unable to focus vision and/or attention

Frequency: Throughout the past 6 months, how often have you been unable to focus vision and/or attention?

- ◯ 0 = none of the time
- ◯ 1 = a little of the time
- ◯ 2 = about half the time
- ◯ 3 = most of the time
- ◯ 4 = all of the time

Severity: Throughout the past 6 months, how much has being unable to focus vision and/or attention bothered you?

- ◯ 0 = symptom not present
- ◯ 1 = mild
- ◯ 2 = moderate
- ◯ 3 = severe
- ◯ 4 = very severe

Loss of depth perception

Frequency: Throughout the past 6 months, how often have you had loss of depth perception?

- ◯ 0 = none of the time
- ◯ 1 = a little of the time
- ◯ 2 = about half the time
- ◯ 3 = most of the time
- ◯ 4 = all of the time

Severity: Throughout the past 6 months, how much has loss of depth perception bothered you?

- ◯ 0 = symptom not present
- ◯ 1 = mild
- ◯ 2 = moderate
- ◯ 3 = severe
- ◯ 4 = very severe

Slowness of thought

Frequency: Throughout the past 6 months, how often have you had slowness of thought?

- ◯ 0 = none of the time
- ◯ 1 = a little of the time
- ◯ 2 = about half the time
- ◯ 3 = most of the time
- ◯ 4 = all of the time

Severity: Throughout the past 6 months, how much has slowness of thought bothered you?

- ◯ 0 = symptom not present
- ◯ 1 = mild
- ◯ 2 = moderate
- ◯ 3 = severe
- ◯ 4 = very severe

Absent-mindedness or forgetfulness

Frequency: Throughout the past 6 months, how often have you had absent-mindedness or forgetfulness?

- ◯ 0 = none of the time
- ◯ 1 = a little of the time
- ◯ 2 = about half the time
- ◯ 3 = most of the time
- ◯ 4 = all of the time

Severity: Throughout the past 6 months, how much has absent-mindedness or forgetfulness bothered you?

- ◯ 0 = symptom not present
- ◯ 1 = mild
- ◯ 2 = moderate
- ◯ 3 = severe
- ◯ 4 = very severe

Bladder problems

Appendix B: Brain Connectivity Toolbox Function Code

Clustering Coefficient

```
function C=clustering_coef_wu(W)
%CLUSTERING_COEF_WU     Clustering coefficient
%
%   ClustCoef = clustering_coef_wu(W);
%
%   The weighted clustering coefficient is the average "intensity"
%   (geometric mean) of all triangles associated with each node.
%
%   Input:      W,      weighted undirected connection matrix
%                       (all weights must be between 0 and 1)
%
%   Output:     C,      clustering coefficient vector
%
%   Note:   All weights must be between 0 and 1.
%           This may be achieved using the weight_conversion.m function,
%           W_nrm = weight_conversion(W, 'normalize');
%
%   Reference: Onnela et al. (2005) Phys Rev E 71:065103
%
%
%   Mika Rubinov, UNSW/U Cambridge, 2007-2015

%   Modification history:
%   2007: original
%   2015: expanded documentation

K=sum(W~=0,2);
cyc3=diag((W.^(1/3))^3);
K(cyc3==0)=inf;             %if no 3-cycles exist, make C=0 (via K=inf)
C=cyc3./(K.*(K-1));         %clustering coefficient
```

Characteristic Path Length

```
function  [lambda,efficiency,ecc,radius,diameter] = charpath(D)
%CHARPATH       Characteristic path length, global efficiency and
% related statistics
%
%   lambda = charpath(D);
%   [lambda,efficiency] = charpath(D);
%   [lambda,ecc,radius,diameter] = charpath(D);
%
%   The characteristic path length is the average shortest path length in
%   the network. The global efficiency is the average inverse shortest
%   path length in the network.
%
%   Input:      D,              distance matrix
%
%   Outputs:    lambda,         characteristic path length
%               efficiency,     global efficiency
%               ecc,            eccentricity (for each vertex)
%               radius,         radius of graph
%               diameter,       diameter of graph
%
%   Notes:
%       The input distance matrix may be obtained with any of the
%   distance functions, e.g. distance_bin, distance_wei.
```

```
%       Characteristic path length is calculated as the global mean of
%   the distance matrix D, excludings any 'Infs' but including distances
%   on the main diagonal.
%
%
%   Olaf Sporns, Indiana University, 2002/2007/2008

% Modification, 2010 (Mika Rubinov): incorporation of global efficiency

% Mean of finite entries of D(G)
lambda = sum(sum(D(D~=Inf)))/length(nonzeros(D~=Inf));

% Eccentricity for each vertex (note: ignore 'Inf')
ecc = max(D.*(D~=Inf),[],2);

% Radius of graph
radius = min(ecc);  % but what about zeros?

% Diameter of graph
diameter = max(ecc);

% Efficiency: mean of inverse entries of D(G)
n = size(D,1);
D = 1./D;                           %invert distance
D(1:n+1:end) = 0;                   %set diagonal to 0
efficiency = sum(D(:))/(n*(n-1));   %compute global efficiency
```

Compute Distance Matrix

```
function [D B]=distance_wei(G)
%DISTANCE_WEI       Distance matrix
%
%   D = distance_wei(L);
%   [D B] = distance_wei(L);
%
%   The distance matrix contains lengths of shortest paths between all
%   pairs of nodes. An entry (u,v) represents the length of shortest path
%   from node u to node v. The average shortest path length is the
%   characteristic path length of the network.
%
%   Input:      L,      Directed/undirected connection-length matrix.
%
%   Output:     D,      distance (shortest weighted path) matrix
%               B,      number of edges in shortest weighted path matrix
%
%   Notes:
%       The input matrix must be a connection-length matrix, typically
%   obtained via a mapping from weight to length. For instance, in a
%   weighted correlation network higher correlations are more naturally
%   interpreted as shorter distances and the input matrix should
%   consequently be some inverse of the connectivity matrix.
%       The number of edges in shortest weighted paths may in general
%   exceed the number of edges in shortest binary paths (i.e. shortest
%   paths computed on the binarized connectivity matrix), because
shortest
%   weighted paths have the minimal weighted distance, but not
necessarily
%   the minimal number of edges.
%       Lengths between disconnected nodes are set to Inf.
%       Lengths on the main diagonal are set to 0.
%
```

```
%   Algorithm: Dijkstra's algorithm.
%
%
%   Mika Rubinov, UNSW/U Cambridge, 2007-2012.
%   Rick Betzel and Andrea Avena, IU, 2012

%Modification history
%2007: original
%2009-08-04: min() function vectorized
%2012 added number of edges in shortest path as additional output

n=length(G);
D=zeros(n); D(~eye(n))=inf;                 %distance matrix
B=zeros(n);                                 %number of edges matrix

for u=1:n
    S=true(1,n);                            %distance permanence (true is
temporary)
    G1=G;
    V=u;
    while 1
        S(V)=0;                             %distance u->V is now
permanent
        G1(:,V)=0;                          %no in-edges as already
shortest
        for v=V
            W=find(G1(v,:));                %neighbours of shortest nodes
            [d wi]=min([D(u,W);D(u,v)+G1(v,W)]);
            D(u,W)=d;                       %smallest of old/new path
lengths
            ind=W(wi==2);                   %indices of lengthened paths
            B(u,ind)=B(u,v)+1;              %increment no. of edges in
lengthened paths
        end

        minD=min(D(u,S));
        if isempty(minD)||isinf(minD),      %isempty: all nodes reached;
            break,                          %isinf: some nodes cannot be
reached
        end;

        V=find(D(u,:)==minD);
    end
end
```

Weight Conversion and Scaling

```
function W = weight_conversion(W, wcm)
% WEIGHT_CONVERSION    Conversion of weights in input matrix
%
%   W_bin = weight_conversion(W, 'binarize');
%   W_nrm = weight_conversion(W, 'normalize');
%   L = weight_conversion(W, 'lengths');
%
%   This function may either binarize an input weighted connection
matrix,
%   normalize an input weighted connection matrix or convert an input
%   weighted connection matrix to a weighted connection-length matrix.
%
```

```
%       Binarization converts all present connection weights to 1.
%
%       Normalization scales all weight magnitudes to the range [0,1] and
%   should be done prior to computing some weighted measures, such as the
%   weighted clustering coefficient.
%
%       Conversion of connection weights to connection lengths is needed
%   prior to computation of weighted distance-based measures, such as
%   distance and betweenness centrality. In a weighted connection
network,
%   higher weights are naturally interpreted as shorter lengths. The
%   connection-lengths matrix here is defined as the inverse of the
%   connection-weights matrix.
%
%   Inputs: W           weighted connectivity matrix
%           wcm         weight-conversion command - possible values:
%                           'binarize'      binarize weights
%                           'normalize'     normalize weights
%                           'lengths'       convert weights to lengths
%
%   Output: W_          connectivity matrix with converted weights
%
%
%   Mika Rubinov, U Cambridge, 2012

%   Modification History:
%   Sep 2012: Original

switch wcm
    case 'binarize'
        W=double(W~=0);         %binarize
    case 'normalize'
        W=W./max(abs(W(:)));    %scale by maximal weight
    case 'lengths'
        E=find(W);
        W(E)=1./W(E);           %invert weights
    otherwise
        error('Unknown weight-conversion command.')
end
```

Appendix C: Glossary

Term	Definition
Adjacency matrix	A table used for graph analysis of a network where each cell has a value representing the link status for each node pair. For functional connectivity, this value can be a binary number indicating whether a connection exists, or a weighted number, representing the magnitude of the statistical correlation two given nodes.
Amplitude	Measure of the size or strength of a wave cycle which is strongly influenced by the number of synchronously firing neurons.
Complex networks	Real-life networks which exhibit properties of intrinsic organization with different hierarchical clusters of nodes, hubs, and modules. Examples include social networks, the internet, airline traffic routes, protein networks, and brain networks.
Brain oscillations	Refers to simultaneous rhythmic waveform patterns being generated by synchronized populations of excitatory pyramidal neurons. Brain rhythms are thought to be a natural timing mechanism for information processing within and between brain regions
Coherence	Measures the stability or strength of phase or phase/amplitude coupling in a time series between two sites or two brain regions at a given frequency, expressed as a squared correlation co-efficient (from 0 to 1). Higher coherence values that are closer to 1 show the phase differences have less variability and higher consistency.
Current source density	Refers to the amount of undifferentiated electric current being generated by an active cluster of pyramidal neurons within a given voxel unit.
Degree	The number of nearest neighbors to which a given node is connected.
eLORETA	Stands for exact low resolution brain electromagnetic tomography. “Exact” refers to this method’s zero-error localization capability to test-point sources even under the presence of structured noise. It can be applied to surface EEG signals to estimate the distribution of current source density for a brain volume consisting of 6,239 voxels of cortical grey matter. Brain maps generated reveal a 3-dimensional distribution of intracortical activity throughout the cortex at spatial resolution within 5 mm^3.

Frequency band	A portion of the frequency spectrum as a way of characterizing oscillations recorded in the raw EEG in the time domain. There is a direct mathematical relationship between the time domain and the frequency spectrum. Computers are used to instantaneously transform the oscillations into frequencies which traditionally divided into bandwidths according to an ascending order: delta (1-4 Hz), theta (4-7 Hz), alpha (8-12 Hz), beta (13-30 Hz), gamma (>30 Hz). Further subdivisions and different bandwidth specifications within the frequency spectrum are increasingly common.
Functional Connectivity	The time-based temporal correlations of synchronized activity between distributed regions of activated brain networks during the awake resting-state or when performing a particular cognitive task.
Graph Theory	A branch of mathematics that deals with the process of modeling the topology of networks to describe a dynamic complex system of interactions based upon elements (nodes) and the connections between nodes (edges).
Hubs	Highly centralized regions that link distinct nodes or modules facilitating a high degree of functional connectivity over a network. **Provincial hubs** link regions which are highly connected nodes within a given module whereas **connector hubs** join two or more modules together.
Modules	Clusters of nodes with high a density of nearest neighbors and high degree hubs, also referred to as neighborhoods and communities.
Phase	Refers to the time-varying characteristics (e.g. phase angle, amplitude) and the position within a given rhythmic cycle of an oscillating wave pattern, frequently measured in degrees (0-360°).
Phase difference	Describes the time delay or advancement components or offset between two or more signals. When the phase differences are significant, they imply significant changes within a network are not due to physiological artifact (e.g., volume conduction).
Small-world network	A term used to describe the optimal balance between differentiation and integration, local and global connectivity, in complex real-life networks including central nervous systems. The topology of small-world networks is characterized by high clustering (segregation) and short path lengths (integration), representing a trade-off in local and global processing in order to satisfy opposing demands which maximize processing speed at minimal neurobiological energy cost.