

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

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Abstract

The aim of this study was to explore the relationship between complex brain networks in people with Chronic Fatigue Syndrome (CFS) and neurocognitive impairment. Quantitative EEG (qEEG) recordings were taken from 14 people with CFS and 15 healthy controls (HCs) during an eye-closed resting condition. Exact low resolution electromagnetic tomography (eLORETA) was used to estimate cortical sources and perform a functional connectivity analysis. The graph theory approach was used to characterize network representations for each participant and derive the “small-worldness” index, a measure of the overall homeostatic balance between local and long-distance connectedness. Results showed that small-worldness for the delta band was significantly lower for patients with CFS compared to HCs. In addition, delta small-worldness was negatively associated with neurocognitive impairment scores on the DePaul Symptom Questionnaire (DSQ). Finally, delta small-worldness indicated a greater risk of complex brain network inefficiency for the CFS group. These results suggest that CFS pathology may be functionally disruptive to small-world networks. In turn, small-world characteristics might serve as a neurophysiological indicator for confirming a biological basis of cognitive symptoms, treatment outcome, and neurophysiological status of people with CFS.

Keywords: chronic fatigue syndrome; myalgic encephalomyelitis; qEEG; eLORETA; electrical neuroimaging; lagged coherence; functional connectivity; graph theory; complex networks; small-world

Citation: Zinn, M. A., Zinn, M. L., & Jason, L. A. (2017). Small-world network analysis of cortical connectivity in Chronic Fatigue Syndrome using quantitative EEG. *NeuroRegulation*, 4(3–4), 125–137. <http://dx.doi.org/10.15540/nr.4.3-4.125>

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Edited by: Rex L. Cannon, PhD, Knoxville Neurofeedback Group, Knoxville, Tennessee, USA

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Chronic fatigue syndrome (CFS) is a complex multi-system disease characterized by unexplained persistent or relapsing fatigue, post-exertional malaise, flu-like symptoms, and neurocognitive impairments not relieved by rest and worsened by physical or mental activity (Carruthers et al., 2003; Fukuda et al., 1994). Neurocognitive impairment is a hallmark symptom in CFS (Jason, Zinn, & Zinn, 2015) and one of the primary factors involved in the etiology of the condition (Johnson, DeLuca, & Natelson, 1996). 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). A meta-analysis found cognitive deficits in CFS pertaining to memory, attention, and information processing speed, particularly during sustained working memory tasks (Cockshell & Mathias, 2010). In addition, patients have 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) proposed that most memory deficits seen in patients are due to slower information processing rather than impairment in storage/retrieval mechanisms.

Functional MRI studies have observed that patients with CFS show signs of brain compensation in response to verbal working memory tasks (Cook, O'Connor, Lange, & Steffener, 2007; Lange et al., 2005). This suggests that dynamic reorganization of brain network topology in CFS with subsequent reductions in neural efficiency could be contributing to cognitive impairment indirectly. Thus, examining changes in overall brain information processing speed and neural efficiency factors in CFS may elucidate the relationship between cortical dysregulation and cognitive symptoms.

Knowledge of general principles of self-organization in real-world 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 (Sporns, 2013). In the past decade, graph theoretical analysis has been increasingly used in neuroscience as a framework for understanding how dynamic processes are involved in the emergence of cognition and behavior (Menon, 2012; Stam, 2014). This approach has a number of distinct advantages which allow researchers to: 1) quantify and model a wide range of varying network attributes, 2) characterize the balance of local and global trade-offs that operate within systems, 3) examine weakened elements of the system and compensatory dynamics responding to pathological processes, and 4) simultaneously account for relationships between all the network elements and a given cognitive function (Rubinov & Sporns, 2010). In this sense, the application of graph theoretical analysis can extend our understanding of the key aspects of brain function in patients with CFS.

Complex networks are ubiquitous to the real world (e.g., social networks, airline routes, power grids, protein networks; Watts & Strogatz, 1998), and the brain itself is a complex network comprised of many subnetworks of distributed brain regions which instigate even the most basic behaviors (Deco, Jirsa, & Friston, 2012; Sepulcre, 2014; Stam, 2010). The coordinated activity within complex networks of the brain gives rise to fundamental aspects of neurocognitive domains involving attention, perception, memory, language, and motor processing (van den Heuvel & Sporns, 2013; Wig, Schlaggar, & Petersen, 2011). A homeostatic balance exists within complex brain networks between random neuronal growth processes and activity-dependent modification of those processes (Minati, Varotto, D'Incerti, Panzica, & Chan, 2013). This state of affairs can be explained in terms of parsimony; there is a continual drive in the system to

negotiate trade-offs to the costs involved in supporting and to create adaptively valuable functional connectivity (Bullmore & Sporns, 2012). The number of connections in the system is relegated by wiring cost (biological energy and materials), and there are evolutionary reasons for keeping the demand for long distance connections, which are more “expensive,” to a minimum (Stam, 2010). Peculiar trade-offs in the topological properties of complex brain networks can therefore serve as a marker for specific neurobiological adaptations to the CFS condition, modeling disease course and spread, aberrant plasticity, indexing overall information processing efficiency—all of which could aid clinical diagnosis of patients and even identify clinical subtypes (Crossley et al., 2014).

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 (Sporns & Honey, 2006). *Segregation* refers to the tendency of nearest neighbor elements to cluster together, whereas *integration* refers to the 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). The clustering coefficient and the characteristic path length constitute properties of the small-world network model. Taken together, they are an indicator of *small-worldness*, an index representing the suitable balance between functional integration and segregation of dynamic system organization (Humphries & Gurney, 2008; Stam, 2010; Thatcher, 2016; van Straaten & Stam, 2013).

Kim et al. (2015) demonstrated small-world abnormality in CFS using resting-state fMRI to examine 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 of information flow between any two nodes in the network. They also assessed *local efficiency*

which quantifies the fault tolerance of the network proportional to the clustering coefficient (Bassett & Bullmore, 2006). They found that global efficiency (integration) was lower in CFS compared to the HC group, while there were no differences in local efficiency (segregation). Increased demand for long distance connections in CFS suggests there is an added wiring expense for compensatory systems which negatively affects global efficiency of the network information processing. The degree of perturbation to small-world dynamics was linked to the amount of neurocognitive impairment in patients and brain processes found to be compromised reflected an underlying disturbance to small-world propensity. However, these investigators did not examine small-worldness, an overall indicator of optimal brain functioning and neural efficiency and neurocognitive impairment (e.g., memory, attention, slow thought, etc.) may represent a combination of pathology in the overall small-worldness measure with the concomitant overt behavioral changes in CFS.

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 & Lopes 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). Higher order cognitive processes appear to call upon even more temporal precision for sustained neuronal activity between neuronal populations (Nunez, Srinivasan, & Fields, 2015). 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). This is important given that 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 (Buzsáki, 2006; Sauseng & Klimesch, 2008; Steriade & Paré, 2006).

Tomographic EEG methods (electrical neuroimaging) use inverse methods to accurately map current source density in a three-dimensional brain volume, allowing the ability to visualize EEG abnormality in deeper brain structures (Grech et al., 2008; Thatcher, 2016). A growing number of studies are using electrical neuroimaging methods to elucidate information processing in the brain and small-world network organization in response to neurological conditions including 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). A comprehensive review on the role of electrical neuroimaging techniques for studying the brain in CFS can be found in Jason, Zinn, et al. (2015).

Using low resolution electromagnetic tomography (LORETA) to investigate 17 monozygotic twins with one twin with CFS vs. one healthy co-twin, Sherlin et al. (2007) showed that twins affected 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. Using eLORETA (where "e" stands for exact), Zinn et al. (2014) found significantly elevated delta sources in a widespread portion of the frontal lobe and limbic lobe as well as decreased beta sources in the parietal lobe bilaterally. 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 rhythmic alterations in these regions could be indicators of blunted emotional processing in CFS possibly related to reduced motivation and attentional difficulties. Interestingly, symptoms manifested by brain pathology within the medial prefrontal cortex, anterior cingulate, and orbitofrontal cortex are largely undetected by most traditional neuropsychological tests (Kozioł & Budding, 2009). Finally, using a Beamformer source analysis method, Flor-Henry, Lind, and Koles (2010) found sources that were globally reduced in the alpha and beta bands in those with CFS (delta band was not examined). Together, the various qEEG and tomographic EEG investigations mentioned here

demonstrate a relationship between EEG and CFS which lay the foundations for this study.

Zinn, Zinn, and Jason (2016) performed eLORETA functional connectivity analysis in CFS to examine three 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. It includes the central executive network, salience network, and the default mode network and predicts that aberrant activity within any one of these networks will significantly impact the other two networks resulting in pathological states. Using lagged phase synchronization (Pascual-Marqui, 2007a), hypoconnectivity was found in the delta and alpha frequency bands between nodes for all three networks in the group with CFS in comparison to health controls. This finding is consistent with several functional connectivity studies using magnetic resonance which reported decreased connectivity involving key nodes of the salience network (Boissoneault et al., 2016; Gay et al., 2016; Wortinger et al., 2016). Disruptions to the salience network could underlie primary cognitive symptoms in CFS involving attention to internal/external events and adaptive engagement of systems responsible for processing of working memory and executive control. The above findings show that functional connectivity approaches including electrical neuroimaging methods are promising avenues for studying brain dysfunction in CFS.

The present study addressed the question of whether fundamental neurobiological relationships and adaptations could underlie cognitive symptoms in CFS. Our primary hypothesis was that patient networks would show deviations from normal in small-world network characteristics as measured by the small-worldness index, thus demonstrating a pathological imbalance affecting network efficiency and information processing due to the trade-offs associated with adaptive reconfiguration of network topology in CFS. Using graph theoretical analysis of small-world networks with eLORETA connectivity data was used for exploring the linkage of brain topology with cognitive impairments that are commonly associated with CFS (John, 2005; van Straaten & Stam, 2013). Secondly, changes in the small-worldness index were hypothesized to be associated with subjective levels of cognitive impairment due to maladaptive reconfigurations in network topology needed for supporting efficient brain processing in patients with CFS. Lastly, the

small-worldness index was tested as a way to look at risk in patients with CFS compared to HC participants. At the present time, there is no physiological marker that represents risk for neurocognitive impairment in patients with CFS. Having an accurate method for identifying risk of cognitive impairment in CFS would help establish the utility for this approach for identifying epidemiological factors relating to patient health.

Method

Participants

The participants in this investigation were 29 adults (14 individuals with CFS, 15 HCs) ranging in age from 20 to 80 years old and the mean age was 43.97 years ($SD = 20.32$). The effects of age were 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. This study was approved by the Institutional Review Board at DePaul University in Chicago.

Procedure

Eyes-closed, resting state EEG data for each participant was recorded for 5 min 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 k Ω . 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. The data collection apparatus involved Neuroguide qEEG signal processing software (Version 2.8.7, 2016) 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. During the EEG recording session, 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 set for high sensitivity at two standard deviations for immediate exclusion of EEG segments with eye movement, muscle, and drowsiness artifact; and 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. ICA/regression procedures intended to remove artifact actually produce distortion of phase relationships between channels by reconstructing the EEG time series. This methodological problem, which essentially invalidates the EEG data, has been empirically proven 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-sec EEG segments. Due to theoretical considerations, all analyses were limited to the delta (1–3 Hz), alpha-1 (8–10 Hz), and alpha-2 (10–12 Hz) frequency bands. Each frequency band provides an added layer of physiological significance to brain function.

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). 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 6 months on a 5-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). 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. The cognitive variable of this proposal was the aggregate average of nine items that fall under the neurocognitive dysfunction 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, absentmindedness or forgetfulness, and loss of depth perception (Jason, Sunnquist, et al., 2015).

Functional connectivity was analyzed using coherence, a measure of the consistency of phase differences in the time-series corresponding to different spatial locations (Lehmann, Faber, Gianotti, Kochi, & Pascual-Marqui, 2006; Pascual-Marqui, 2007a, 2007b). Coherence 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 (Buzsáki & Watson, 2012; Klimesch, Freunberger, Sauseng, & Gruber, 2008; Thatcher, 2016), or between two brain regions, in the case of eLORETA (Pascual-Marqui et al., 2011). 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). Functional connectivity analyses of coherence 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 three-dimensional cortical volume consisting of 6,239 voxels of unambiguous grey matter at 5 mm³ 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.

eLORETA lagged coherence was then calculated for all 84 ROIs for each participant, generating text files with output containing a separate weighted 84 x 84 coherence matrix for each frequency band. The coherence 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 coherence 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 1 illustrates the workflow for all the analyses that were implemented in this study.

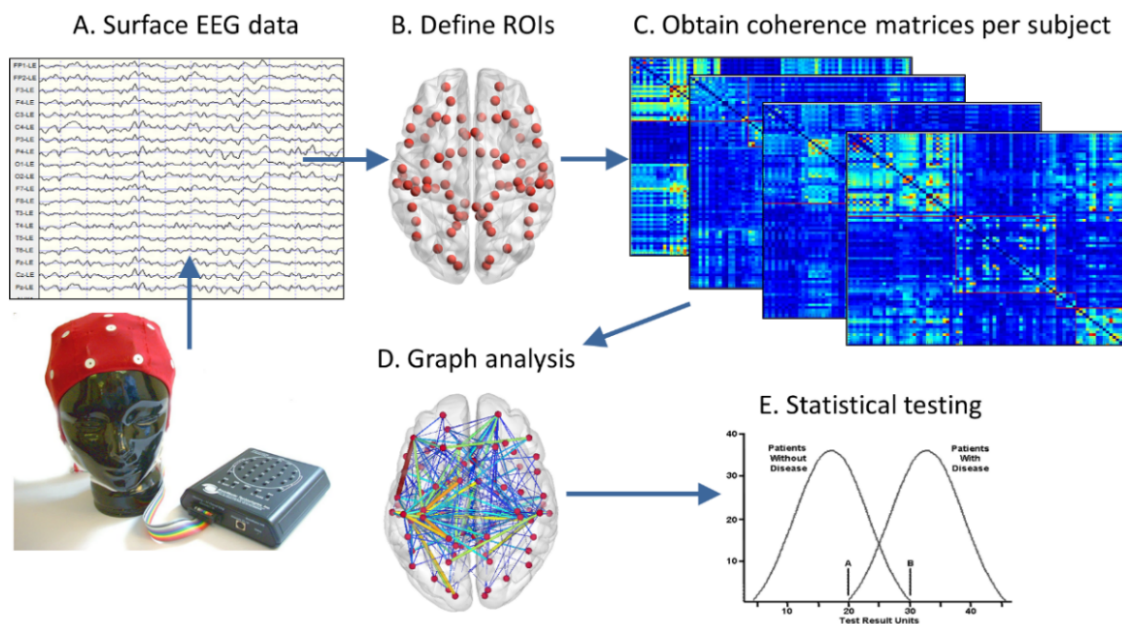


Figure 1. The workflow of all analyses in this thesis summarized as an overview.

Graph Theoretical Analysis

The coherence matrix for each frequency band for each participant was subjected to graph theoretical 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 coherence 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* is 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 coherence 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, & Walter, 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 (SW) was computed using $C_{sw} = (Cw/Cw_{rand})/(Lw/Lw_{rand})$ as a comparative marker of efficient brain functioning for each participant.

Statistical Analysis

The graph theory output that was produced using BCT functions in MATLAB was subsequently imported to SPSS version 23 for conducting further statistical analyses. The data were screened for outliers, missing data, skewness, and kurtosis in meeting the assumptions for parametric statistics.

Continuous variables were log-transformed to meet the assumption of Gaussianity.

Results

Demographic characteristics by study group and descriptives of key study variables are shown in Tables 1 and 2. Most patients with CFS were older than HCs and the potential confound of age was controlled for in all models. Given that some secondary outcomes were considered corresponding to the study hypotheses, this study is considered exploratory, and the *p* values considered descriptive. All data were evaluated with tests which were two-sided at the .05 level of significance.

Table 1
Demographic and Clinical Data.

	14 CFS	15 HCs	All 29 Participants
Age (years)* Mean (SD)	57.71 (15.15)	31.13 (15.63)	43.97 (20.32)
Sex	11 Female 3 Male	11 Female 4 Male	22 Female 7 Male
Handedness	14 Right 0 Left	14 Right 1 Left	28 Right 1 Left
Education	1 Partial college 6 College 7 Graduate	2 Partial college 8 College 5 Graduate	3 Partial college 14 College 12 Graduate
Ethnicity	14 White	14 White 1 Latino	28 White 1 Latino
DSQ Cognitive Composite score* Mean (SD)	2.87 (.10)	1.25 (.04)	2.03 (.10)

* $p < .01$

Table 2
Means and Confidence Intervals for Small-worldness Indices by Experimental Group.

Group	N	Small-world delta	Small-world alpha-1	Small-world alpha-2
		M (CI)	M (CI)	M (CI)
HC	15	.89 (.85–.92)	.79 (.76–.83)	.84 (.80–.88)
CFS	14	.82 (.78–.85)	.78 (.74–.82)	.79 (.76–.82)

The primary outcome of interest was to determine whether small-world network values deviate from normal in a sample of patients with CFS. Analysis of

Variance (ANOVA) was conducted to assess whether networks of patients with CFS deviated significantly from those of HCs, adjusting for age. We first identified statistically significant ANOVA values in an overall test, $F(2, 80) = 4.915, p = .029$, which indicated a significantly lower small-worldness index z-value for patients with CFS ($M = -.181, SD = 1.047$) than HCs ($M = .164, SD = .950$). To identify the differences between small-worldness within each frequency band in this study, follow-up tests were conducted with the Bonferroni correction for multiple comparisons. These estimates identified SW delta as statistically different between patients with CFS and HCs, $p = .014$; however, the SW alpha-1 and

SW alpha-2 were not significant between both groups ($p = .622$ for alpha-1; $p = .099$ for alpha-2; Figure 2). Within the HC group, a significant difference was found between SW delta and SW alpha-1 ($p = .001$), but not between SW delta and SW alpha-2 ($p = .177$). Within the CFS group, however, there was no significant difference between any SW frequency bands ($p = .355$).

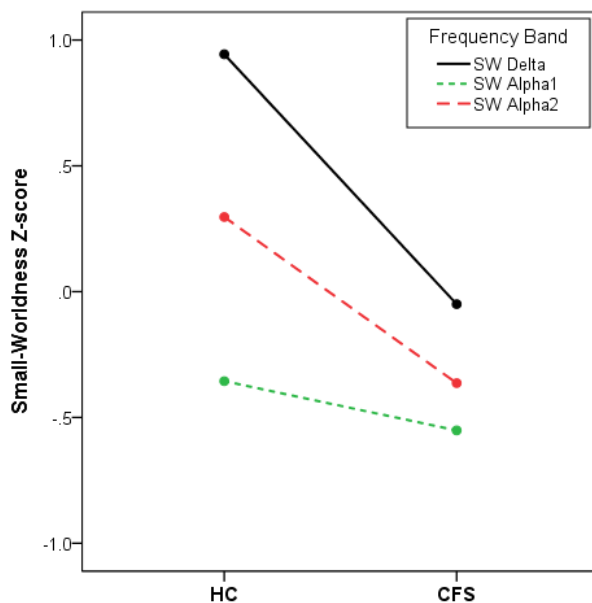


Figure 2. Small-worldness results of group comparisons by frequency band. The CFS group was 1 SD lower than the HC group for SW delta ($p = .014$).

Next, hierarchical regression techniques were used to determine the linear relationship of small-world network organization (measured by SW delta, SW alpha-1, and SW alpha-2 combined) with neurocognitive impairment. Two models were fit for estimating this relationship, age-adjusted, and found that small-worldness significantly predicted the neurocognitive impairment scores, $F(2, 84) = 53.482$, $p = .000$, adjusted $R^2 = .550$ for model 1 and $F(2, 83) = 122.546$, $p = .000$, adjusted $R^2 = .809$. These strong effect sizes suggest that deviations from small-worldness affect neurocognitive impairment. For model 2 in particular, 80.9% of neurocognitive impairment was predicted by the combination of small-worldness, experimental group, and age (Figure 3).

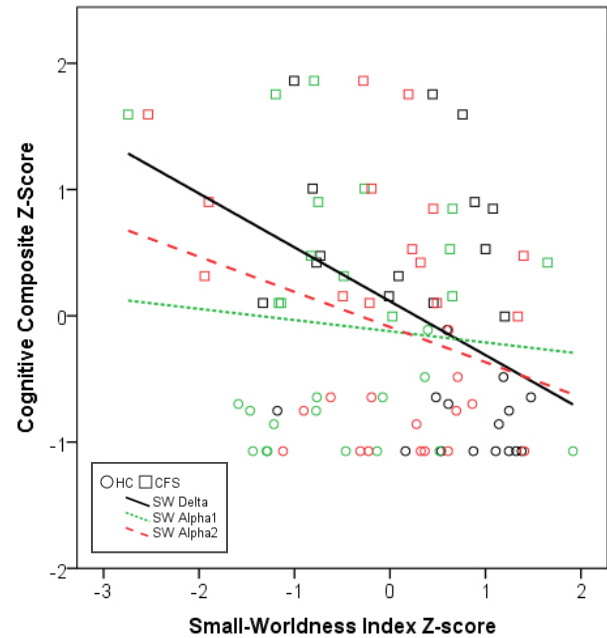


Figure 3. Small-worldness results of regression analysis by frequency band.

Our third outcome of interest was the development of prediction models to estimate odds ratios and 95% CIs for patients with CFS in SW delta, SW alpha-1, and SW alpha-2. Fixed-effects multinomial logistic regression allowed us to appropriately model the relationship between group membership and small-world effects at each frequency band. All models were adjusted for the potential confounder of age. To estimate differences between patients with CFS in our study cohort, the deviated small-world values (small-worldness index variable) in the fixed-effects logistic regression model were associated with increased risk in CFS of SW delta (OR 1.425; 95% CI: 0.500–3.75) but not for SW alpha-1 (OR 0.702; 95% CI: 0.310–1.590) or SW alpha-2 (OR 0.786; 95% CI: 0.386–1.601). According to this data set, the group with CFS was 1.425 times as likely to have deviations from normal in small-worldness in the delta frequency band but not in the alpha-1 or alpha-2 band. The overall regression model was significant at $p = .05$.

Discussion

To our knowledge, this is the first study to evaluate an association between small-world characteristics and cognitive symptoms reported in CFS. These findings of functional connectivity alterations suggest the importance of applying graph theory to connectome-scale analysis of network topology to detect subtle disruptions incurred by CFS sequelae.

Neurocognitive impairment, as measured by the DSQ cognitive composite score, was negatively associated with small-worldness index for the delta band under observation. Group-level differences were also found, but only for small-worldness in the delta band. Finally, the risk of having small-worldness deviations in the delta band is increasingly greater in CFS.

Small-world models of the brain systems explore 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 in axonal diameter, white matter pathways, conduction velocities, and energy transport mechanisms) governed by trade-offs within components and compensation necessary for maintaining the multiscale 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 our 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 accounted for the greatest amount of variance in cognitive composite scores for the hierarchical regression model equation. 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 between CFS and Alzheimer's disease (Babiloni et al., 2013; Hata et al., 2016), multiple sclerosis (Babiloni 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 and disruption to global efficiency 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 in CFS 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) a generalized impairment to domains of cognitive function. However, our study found differences using the small-worldness index as a ratio of individual small-world properties (clustering and path lengths), a measure of both global and local properties which are salient in CFS depending on frequency band. This underscores the need for considering a combination of graph theory metrics for a more comprehensive examination of CFS.

There are some limitations in the present study. The results of this study should be interpreted with caution due to small sample size. Although significant deviations in the reported small-worldness phenomena were found in people with CFS, 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, alpha-1, and alpha-2 frequency bands. Frequency-dependent changes to cortical arrangements occurring in other frequency bands (e.g., theta, beta) could also be explored. Finally, insignificant findings in alpha-1 and alpha-2 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 neurocognitive impairment and small-worldness

in different frequency bands should be verified in future studies.

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 (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, the linkage between cognitive symptoms and small-worldness demonstrates the fundamental importance of timing, stability, and adaptation of complex systems to CFS which could be related to findings of neuroinflammation in patients (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 reconfiguration of brain networks. There is a need for future research that models the activity-dependent modifications of brain connectivity in CFS with disruption to neurocognitive processes.

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Received: August 18, 2017

Accepted: August 30, 2017

Published: December 8, 2017