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# Intrinsic Functional Hypoconnectivity in Core Neurocognitive Networks Suggests Central Nervous System Pathology in Patients with Myalgic Encephalomyelitis: A Pilot Study

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**Abstract** Exact low resolution electromagnetic tomography (eLORETA) was recorded from nineteen EEG channels in nine patients with myalgic encephalomyelitis (ME) and 9 healthy controls to assess current source density and functional connectivity, a physiological measure of similarity between pairs of distributed regions of interest, between groups. Current source density and functional connectivity were measured using eLORETA software. We found significantly decreased eLORETA source analysis oscillations in the occipital, parietal, posterior cingulate, and posterior temporal lobes in Alpha and Alpha-2. For connectivity analysis, we assessed functional connectivity within Menon triple network model of neuropathology. We found support for all three networks of the triple network model, namely the central executive network (CEN), salience network (SN), and the default mode network (DMN) indicating hypo-connectivity in the Delta, Alpha, and Alpha-2 frequency bands in patients with ME compared to controls. In addition to the current source density resting state dysfunction in the occipital, parietal, posterior temporal and posterior cingulate, the disrupted connectivity of the CEN, SN, and DMN appears to be involved in cognitive impairment for patients with ME. This research suggests that disruptions in these regions and networks could be a neurobiological feature of the disorder, representing underlying neural dysfunction.

**Keywords** eLORETA · Myalgic encephalomyelitis · Chronic fatigue syndrome · Lagged phase synchronization · Triple network model

## Introduction

According to current theories of brain function, cognitive abilities (Fuster 2009; Koziol and Budding 2009; Naglieri and Das 1997) are supported by functionally linked, correlated and spatially distributed neurophysiological events, sharing information in real time (Friston 2002; Hacker et al. 2013; Jann et al. 2012). Consistent with this view, within the past half-decade, hundreds of studies have demonstrated brain function is best understood through functional integration models showing the time-dependent patterns in neural activation of anatomically separated brain regions (Friston 2012; Menon 2012). These models contrast with traditional brain mapping procedures (functional segregation approach) utilizing regional cerebral activation changes to identify abnormalities (Fuster and Bressler 2012; Rabinovich et al. 2012a). As a result of a paradigm shift in neural assessment, methods used to evaluate the neurobiology of cognition currently measure the brain's intrinsic activity using multivariate functional connectivity approaches rather than relying on discrete brain regions to explain many aspects of neurobiology and cognition. To better understand this viewpoint, one has to go beyond classical information processing theory, seeing the brain as an information processing device, dependent upon multiple time series of continuous information flow to

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maintain steady-state homeostasis (Perlovsky 2012; Rabinovich et al. 2012a).

Myalgic encephalomyelitis (ME)[1] is a complicated disorder characterized by extreme fatigue not otherwise explained by an underlying medical condition. However, mild to moderate neurocognitive impairment (DSM-V), is present and often worsens after physical or mental activity, not improving with rest, rendering daily activities such as cooking meals, taking care of oneself, etc. difficult or impossible. Many with ME experience hyper-sensitivity to environmental events such as chemicals, noise or lights, and also experience persistent viral symptoms (sore throat, headache, nausea, etc.) (Jason et al. 2013). The most severe patients are bed-bound. Therefore, a crucial issue in the study of ME is to discover better methods to measure patient symptoms. Here, we focus on neurocognitive symptoms of the disorder (Jason et al. 2015).

Paradoxically, there is a considerable gap between current empirical findings which assess brain function using neuropsychological testing in ME, and patient self-reports (Cockshell and Mathias 2014; Hawk et al. 2006). Within neuroimaging literature, a similar situation exists whereby imaging studies have historically been conducted to examine the neurocognition in ME with only inconsistent and/or weak findings (DeLuca et al. 2009). For example, a recent meta-analysis of 50 studies covering 1544 patients with ME found that the neurocognitive deficits were only seen in memory, attention, and reduced responsiveness, failing to find support for many other symptoms and complaints routinely reported by patients. Typically, patients with ME describe symptomatology using constructs such as hypersensitivity to environmental events, deficits in motor functioning, selective and sustained attention, speech, planning, decision making, error correction, reading and speech comprehension, information processing speed, and visuospatial ability (Dickinson 1997; Jason et al. 2010a, b; Thomas and Smith 2009). The unfortunate outcome of the diverse findings discussed here have contributed to a wide schism in medicine and science regarding ME; that is, some believe that the absence of clear, consistent findings supports the hypothesis that ME is simply a form of somatization disorder with very little or no pathophysiology, while others believe that ME is a medical disorder whose etiology is not fully known (Lange et al. 1998, 2005; Tiersky et al. 1997; Twisk 2014). This confusion has in turn led to a debate about how to best investigate, classify, and treat ME (Twisk 2014). Another substantial literature indicates that neurocognitive deficits largely exist independently of ME (are not part of the illness) (Afari and Buchwald 2003; Claypoole et al. 2007; Constant et al. 2011; DeLuca et al. 1997; Sandman et al. 1993; Thomas and Smith 2009). Research indicates, however, that psychological antecedents, triggers, or mediators of ME may be present as in any medical problem. Several investigators have therefore shown that ME is not a primary psychological condition (Broderick et al. 2010; Hawk et al. 2006; Maes et al. 2012; Wilson et al. 2002) and though medical and/or psychological treatments may reduce symptomatology, they have never been shown to cure ME.

The use of quantitative electroencephalography (QEEG) to assess neurocognition in ME has a more consistent history. Known as the 'gold standard' measure of brain states (Thatcher 2012), it is a core assessment in polysomnography, epilepsy (Ropper and Samiuels 2014), as well as numerous disorders of cognition (Westmoreland 2005). In 1990, QEEG event-related potentials were used to assess the slowed speed of information processing in ME (Prasher et al. 1990). Since that time, a small but growing number of QEEG studies have been conducted, reporting oscillatory abnormalities (particularly delta and theta) and indications of homeostatic dysregulation in patients during wakefulness (Billiot et al. 1997; Decker et al. 2009; Flor-Henry et al. 2004; Hammond 2001; James and Folen 1996; Kishi et al. 2011; Le Bon et al. 2012; Sherlin et al. 2007; Siemionow et al. 2004; Van Hoof et al. 2007). In sum, QEEG and electrical neuroimaging may hold promise for use in evaluation of brain dysregulation in ME, especially since several authors now believe that the pathology of ME will be found at the cellular level (Broderick et al. 2010, 2011; Dinkel et al. 2002; Light et al. 2012; Wilson et al. 2002) and aberrant neural oscillations are a function of structural and functional abnormalities, often existing at the cellular level. It is therefore important to explore ME using QEEG methods as this distinctive modality will likely provide a more complete picture of neurocognitive symptoms associated with true physiological events.

Another advantage of QEEG over fMRI, PET, SPECT, MRI, CT and similar methods is that EEG measures directly assess neuronal activity at a high time-resolution (at the millisecond level), thereby detecting subtle time differences in neuronal communication through examination of oscillatory patterns generated by cortical and subcortical regions (Buzsaki 2006; Steriade 2005; Thatcher 2012). This is a distinct advantage given today's neural assessment models that emphasize the perpetual dynamic nature of the brain and how neuropsychiatric issues can, and often do, stem from dysregulated dynamic systems. The electroencephalograph is able to detect functional changes even in situations when MRI detects no or few structural problems. Exact low resolution electromagnetic tomography (eLORETA) is a linear, discrete, three-

[1] For the sake of clarity, throughout this article we will use ME even though a number of studies use Chronic Fatigue Syndrome (CFS) to describe their patient samples.

dimensional weighted minimal norm inverse solution and the latest iteration in a family of well-established EEG inverse methods (Pascual-Marqui 2002; Pascual-Marqui et al. 1994, 2011a). eLORETA has the advantage of allowing a non-invasive study of intra-cortical interactions with accurate spatial resolution that is similar to fMRI even after spatial filtering which is commonly applied, to increase the signal-to-noise ratio of the hemodynamic signal (Poldrack et al. 2012). Lagged phase synchronization, one measure of information transfer between two brain regions, is a real-time animation of the information transfer that links patients' symptoms and complaints to functional systems in the brain. Here, we used this technology to assess the hypothesized functional system dysregulation in the brains of patients with ME.

### Triple Network Model of Brain Pathology

Functional connectivity approaches have ushered in a substantial paradigm shift in the study of cognitive impairment (Menon 2011). These approaches aid in the understanding of how functionally connected systems produce pathology through alterations in connectivity patterns or brain dynamics (de Pasquale et al. 2012; Sporns 2013). However, brain networks do not operate in isolation. The Menon Triple Network model of brain pathology (Greicius et al. 2008, 2009; Menon 2011, 2012; Supekar and Menon 2012) offers such a system to assess cognitive dysfunction in a variety of neurocognitive disorders (Menon 2012; Rabinovich et al. 2012b). It hypothesizes that there are three primary networks which operate synergistically to regulate shifts in arousal, attention, and general access to cognitive abilities (Menon 2012; Raichle 2010; Uddin et al. 2011). Predictions from the model include that dysregulation in one of the three core networks will significantly impact the other two networks, producing dysregulation of, and symptoms in, all three networks. The complex symptom structures of these networks will then vary according to their source (environmental events, internal states, genetics), and can yield a number of levels of prominence by time and individual.

For example, in a healthy brain, the central executive network (CEN) and the salience network (SN) activity increases as a function of cognitive and affective processing (Uddin et al. 2013) while the Default Mode Network (DMN) decreases activity during the same processing; the opposite occurs during activation of the DMN activity (Greicius and Menon 2004; Supekar and Menon 2012). According to the model, when all three networks display deficient context-dependent engagement and/or disengagement signaling, they create imbalances leading to neuropsychological symptomology produced by deficits SN, DMN, and CEN activation and coactivation (Chand and Dhamala 2015; Chiong et al. 2013; George and Pearce 2012).

The anterior insula (AI), a crucial hub in brain networks (Laird et al. 2011; Seo and Choo 2015) has been shown to produce patterns of structural and functional changes during cognitive impairment (Bora et al. 2010; Nickl-Jockschat et al. 2012). The anterior insula is in the SN, which is primarily made up of the dorsal anterior cingulate and anterior insula cortices (Laird et al. 2011; Thatcher 2012) playing a key role in sorting out relevant stimuli, both external and internal (Haase et al. 2016; Nguyen et al. 2016; Romero-Grimaldi et al. 2015); this switching mechanism, between all three networks, aids in focused attention to environmental events, allowing the stimuli to be interpreted with increased importance (Hu et al. 2015; Makovac et al. 2016; Qin et al. 2015; Sridharan et al. 2008). In pathological states, the SN not only is impaired in its ability to sufficiently switch between the CEN and the DMN, but it inappropriately assigns importance to inconsequential events or too little importance to significant events, both internal and external (Greicius et al. 2009) thereby producing deregulated signals of pain, anxiety, and/or other negative states (Yang et al. 2012).

The CEN includes the dorsolateral prefrontal cortex and the posterior parietal cortex (Menon 2012; Sridharan et al. 2008). Its key roles include maintenance of working memory, goal-directed behavior, judgment and decision-making, activating during executive functioning, then deactivating during the self-referential thought including autobiographical episodic memory and mentation of the DMN (Kim et al. 2016; Varela 2014). The DMN, the most studied network, characterizes basic neural activity which negotiates self-referential thought, mentation, and introspection (McCormick et al. 2013), decreasing activity with task demands (Bonnelle et al. 2011, 2012). The DMN is metabolically 'expensive,' involving a high number of brain regions, and is implicated independently in a number of neurocognitive disorders (Bonnelle et al. 2011, 2012; Crone et al. 2011; Damoiseaux et al. 2006, 2008). Deficits in this process may play a substantial role in neurocognitive disorders (Menon 2011; Putcha et al. 2015), creating phenotypic deficits in executive functioning (memory, information processing speed, learning capability, etc.) as well as the ability to self-reflect and process personal information (Menon 2012).

The CEN is engaged during external cognitive tasks (e.g. planning, attention, adaptive cognitive processes to meet environmental demands) (Varela 2014) and is negatively correlated with DMN activity (Putcha et al. 2015). The SN is involved in awareness of body states (Chiong et al. 2013; Menon and Uddin 2010) and in switching states between the DMN and CEN (Daniels et al. 2010). Taken

together, in neurocognitive disorders, the 3 networks presented here, display deficits in access, commitment, and separation of resources (Greicius et al. 2003, 2004; Greicius and Menon 2004).

The purpose of the present study was therefore to first examine the differences in cortical source density between patients with ME and healthy controls, then using the same individuals, assess lagged phase synchronization (or phase lock) in the same individuals, within the Menon Triple Network model. We hypothesized that abnormal neural function would be evidenced by dysregulated rhythms in the delta, theta and/or alpha frequency bands. Based on previous work finding dysregulation in these bands using source localization methods (Canuet et al. 2011; Flor-Henry et al. 2010; Lehmann et al. 2012; Sherlin et al. 2007). Given its high sensitivity and specificity with precise localization, eLORETA (Pascual-Marqui et al. 2011a) was chosen to extract the most clinically relevant information from the QEEG data. eLORETA lagged phase synchronization was used to assess functional connectivity within the triple network model, due to previous observations of slowed phase lock duration in this population (Zinn et al. 2016). We also sought to determine whether the eLORETA lagged phase synchronization may be a viable tool in the study of ME in clinical applications to aid in the diagnosis and treatment planning.

## Method

### Participants

Eighteen adults were included in this study (9 individuals with ME, 9 healthy controls) ranging in age from 23 to 79 years and the mean age was 42.4 years ($SD = 20.5$). There were 3 males and 15 females, 17 participants were right handed, and all participants were Caucasian. All participants visited the DePaul University Center for Community Psychology Research. The ME group met the Canadian Clinical Criteria (Carruthers et al. 2003) and had been diagnosed with ME (some physicians used the term CFS). No participants were taking medications that would affect the EEG.

### Materials and Procedure

Eyes-closed, resting state EEG was recorded for 5 min using the Discovery 19-channel acquisition amplifier (BrainMaster Technologies, Bedford, Ohio) with Neuroguide (Applied Neuroscience, Inc.) software (version 2.8.5) from 19 scalp electrode locations (Fp1, F3, F4, F7, F8, Fz, C3, C4, Cz, P3, P4, Pz, T3, T4, T5, T6, O1, O2) positioned according to the international 10/20 system using standardized electrode caps (Jurcak et al. 2007) employing passive electrodes for the linked ears references (2). During electrode preparation, impedances for all sites were maintained below 5 kΩ. Participants were 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. Each participant was seated upright in a comfortable chair in a well-lit room. Participants were given instructions to "relax to the best of your ability while keeping your 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. Deartifacting was conducted as follows: first, by visually inspecting and manually editing to remove any visible artifact. Then, using Neuroguide automated Z-score artifact rejection algorithms, set for high sensitivity as well as amplitude selection set at 2 standard deviations for immediate exclusion of EEG segments, eye movement, muscle, and drowsiness artifact were eliminated. Third, a second visual inspection and manual removal of the artifact was done by the EEG technician. Since this study was directed toward understanding changes in phase relationships of the original time-series data, independent components analysis was not used. The methodological problem of distorting time and phase relations present in the original time series from using ICA/Regression procedures has been empirically validated in several studies (Castellanos and Makarov 2006; Kierkels et al. 2006; Wallstrom et al. 2004). Only epochs with >95 % split-half reliability and >90 % test–retest reliability coefficients computed by Neuroguide with total measurement for at least 1 min were subjected to the analysis. Split-half reliability is the ratio of variance between the even and odd seconds of the time series of selected digital EEG. Test–retest reliability is the ratio of variance between the first half versus the second half of the selected EEG segments (Thatcher 2012). For each participant, artifact-free data were then exported to text files containing 2-s EEG segments with a 75 % cosine taper window to minimize leakage (Sterman and Kaiser 2000). Further procedures were performed on the exported surface EEG data using LORETA-KEY software (R. Pascual-Marqui 2015) as freely provided by the Key Institute for Brain-Mind Research, University Hospital of Psychiatry, Zurich at http://www.uzh.ch/keyinst/loreta.htm.

#### *eLORETA Source Localization*

Eyes-closed resting EEG data were analyzed using eLORETA to compute the 3-dimensional distribution of intracortical brain electrical activity (Pascual-Marqui 2007; Pascual-Marqui et al. 2011b). The eLORETA inverse solution has zero localization error under ideal, noise-free

conditions and the solution space has a volume of 6239 voxels at 5 $mm^3$ spatial resolution. Computations of cortical current source density are restricted to unambiguous cortical grey matter (Mazziotta 2001) using Montreal Neurological Institute (MNI) coordinates for the significantly active regions of interest with neuroanatomical labels and Brodmann areas based on "corrected" Talairach coordinates (Lancaster et al. 2000; Talairach and Tournoux 1988). Implementation is based on a 3-shell spherical head model and EEG electrode coordinates derived from spherical and realistic Talairach head geometry (Towle et al. 1993). A detailed report of this inverse solution, together with the proof of its exact zero-error localization property, can be found in an article by Grech et al. (2008). eLORETA functional images of current source density was computed from 1 to 40 Hz for the following nine frequency bands: delta (1–3 Hz), theta (4–7 Hz), alpha-1 (8–10 Hz), alpha-2 (10–12 Hz), alpha (8–12 Hz), beta-1(13–18 Hz), beta-2 (19–21 Hz), beta-3 (22–30 Hz) and gamma (30–40 Hz).

*Functional Connectivity Analysis*

Cortical regions of interest (ROIs) within each of the core neurocognitive networks were defined a priori, chosen on the basis of previously published research on resting-state networks (Raichle 2011) derived from BOLD fMRI signals (coordinates shown in Tables 1, 2, 3). All connectivity analyses were conducted within the ROI's specific to the network being analyzed. Each ROI under investigation was assigned one 5-$mm^3$ voxel and all of its nearest adjacent voxels (5 × 5 voxels/15 × 15 $mm^3$ maximum) to represent each corresponding Brodmann area. To conduct the functional connectivity analysis, we used eLORETA to evaluate group differences in lagged phase synchronization for all nine frequency bands between each of the 6 pairs of ROIs within the SN (135 connections), 6 pairs of ROI's within the CEN (135 connections), and within 7 pairs of ROI's in the DMN (189 connections), for each of the nine frequency bands (total ROIs X 9 = n connections). We chose lagged phase synchronization to assess the functional similarity in the multivariate time series of signaling between all pairs of regions of interest within each network. Lagged phase synchronization measures the nonlinear dependence between two signals in the frequency domain while correcting for the instantaneous zero-lag component to remove artifact. This phase synchrony correction is necessary to exclude contamination due to non-physiological effects, and physics artifact from low spatial resolution and volume conduction. Therefore, lagged phase synchronization is considered to be an index of true physiological functional connectivity information (Pascual-Marqui et al. 2011b). Lagged phase synchronization was calculated for each participant from 1 to 40 Hz in the following nine frequency bands: delta (1–3 Hz), theta (4–7 Hz), alpha-1 (8–10 Hz), alpha-2 (10–12 Hz), alpha (8–12 Hz), beta-1(13–18 Hz), beta-2 (19–21 Hz), beta-3 (22–30 Hz) and gamma (30–40 Hz) for each network. This produced a text output file for each person with a correlation matrix showing columns equal to the number of ROIs, and rows equal to the number of time frames.

*eLORETA Statistics and Multiple Comparison Corrections*

The eLORETA software package was used to evaluate group differences in current source density in cortical source localization between groups within each frequency band. To create three-dimensional statistical images for all nine frequency bands, we conducted voxel-by-voxel independent sample *F*-ratio-tests to evaluate the differences, based on eLORETA log-transformed current source density power. To control for potential global experimental effects, a subject-wise normalization was performed to scale the data for each subject by dividing the value of every single voxel by the total power of all voxels of each image. Source voxels with significant differences were then identified using a nonparametric permutation/randomization procedure (Fisher 1971), with a threshold set at the 0.05 probability level. To control for Type 1 error, we applied a statistical non-parametric mapping (SnPM) procedure to estimate the empirical probability distribution and find the "maximal-statistic" at the 95th percentile under the null hypothesis. SnPM has been shown elsewhere to be effective in controlling the Type I error in neuroimaging studies (particularly when evaluating electrophysiological data) without the need to rely on Gaussianity (Holmes et al. 1996; Nichols and Holmes 2002). Another

**Table 1** eLORETA coordinates used for default mode network regions of interest (adapted from Raichle 2011)

| Orientation | Brodmann area | X, Y, Z coordinates[a] | Neuroanatomical label |
|---|---|---|---|
| Left medial | 23 | 0, −52, 27 | Posterior cingulate |
| Left | 9 | −1, 54, 27 | Medial frontal gyrus |
| Left | 39 | −46, −66, 30 | Left angular gyrus |
| Right | 39 | 49, −63, 33 | Right angular gyrus |
| Left | 21 | −61, −24, −9 | Middle temporal gyrus |
| Right | 21 | 58, −24, −9 | Middle temporal gyrus |

[a] x,y,z coordinates provided in MNI space. Neuroanatomical labels taken from eLORETA

**Table 2** eLORETA coordinates used for central executive network regions of interest (adapted from Raichle 2011)

| Orientation | Brodmann area | X, Y, Z coordinates[a] | Neuroanatomical label |
|---|---|---|---|
| Left medial | 8 | 0, 24, 46 | Medial frontal gyrus |
| Left | 8 | −33, 22, 53 | Superior frontal gyrus |
| Left | 10 | −44, 45, 0 | Inferior frontal gyrus |
| Right | 10 | 44, 45, 0 | Inferior frontal gyrus |
| Left | 40 | −50, −51, 45 | Inferior parietal lobule |
| Right | 40 | 50, −51, 45 | Inferior parietal lobule |

[a] x,y,z coordinates provided in MNI space. Neuroanatomical labels taken from eLORETA

**Table 3** eLORETA coordinates used for salience network regions of interest (adapted from Raichle 2011)

| Orientation | Brodmann area | X, Y, Z coordinates[a] | Neuroanatomical label |
|---|---|---|---|
| Left medial | 32 | 0, 21, 36 | Cingulate gyrus |
| Left | 10 | −35, 45, 30 | Middle frontal gyrus |
| Right | 10 | 32, 45, 30 | Middle frontal gyrus |
| Left | 13 | −41, 3, 6 | Insula |
| Right | 13 | 41, 3, 6 | Insula |
| Left | 40 | −62, −45, 30 | Supramarginal gyrus |
| Right | 40 | 62, −45, 30 | Supramarginal gyrus |

[a] x,y,z coordinates provided in MNI space. Neuroanatomical labels taken from eLORETA

advantage of permutation strategies is that they can be applied to any statistic (t-tests, r values, *F*-ratios) to find its critical probability value under the null hypothesis. In our study, we utilized eLORETA software to compute 5000 data randomizations to create an approximate permutation distribution needed to determine the critical threshold value at the $p = 0.05$ alpha level for the observed *log* of *F*-ratio statistic to correct for Type 1 error across all voxels and for all frequencies. The initial procedure described here, the use of SnPM for creating eLORETA single-voxel statistical images, has been confirmed in studies (Anderer et al. 1998; Pascual-Marqui et al. 1999). The value for the critical threshold is then entered into the "scale-max" parameter of the LORETA viewer for showing the comparative analysis with positive/negative color coded significant statistical values pertaining to the "surviving" voxels (those rejecting the omnibus null hypothesis). SnPM procedures in eLORETA also perform exceedance proportion tests to for determining the critical probability thresholds for supra-threshold voxels based on spatial extent for cluster-based inference (cluster statistics). This approach yields greater sensitivity over the singe-voxel test while trading off specificity.

For the functional connectivity analysis, eLORETA performed using an independent sample t-tests for generating t-statistic values of brain connectivity. The ROI's for each network can be seen in Tables 1, 2, and 3. As mentioned above, we applied the same permutation/randomization strategy (SnPM) with 5000 randomizations to find the critical probability thresholds at significant alpha levels and correct for Type 1 error.

## Results

### Source Analysis Using eLORETA

To capture the spatial extent of cortical source activations, statistical images were assessed for cluster-wise significance (Nichols and Holmes 2002). Independent groups t-tests were performed to compare group differences in all 6239 cortical grey matter voxels within the entire eLORETA solution space. Deviant current source density values were found in alpha (ME: 0.065, HC: 0.429) and alpha-2 bands (ME: 0.075, HC: 0.305), (log-*F*-ratio threshold $= -1.65$, $p = 0.033$, two-tailed, corrected) in the bilateral parietal, occipital and posterior temporal lobes (Figs. 1, 2). No other significant differences or significant relationships in source localization were found between the patient and control groups in the above analyses with respect to the delta, theta, beta or gamma frequency bands as defined in this study.

### Functional Connectivity Analysis Using eLORETA

In the assessment of the triple network model, functional connectivity in patients with ME compared with healthy controls showed significantly decreased lagged phase synchronization for Delta, Alpha, and Alpha-2 in most cortical regions: DMN (threshold: $t = -1.84$; $p = 0.021$, one-tailed, corrected), the SN (threshold: $t = -1.9$; $p = 0.037$, one-tailed, corrected), and the CEN (threshold: $t = -1.36$; $p = 0.024$, one-tailed, corrected) (Figs. 3, 4, 5, 6, 7, 8). One-tailed tests were chosen a priori due to

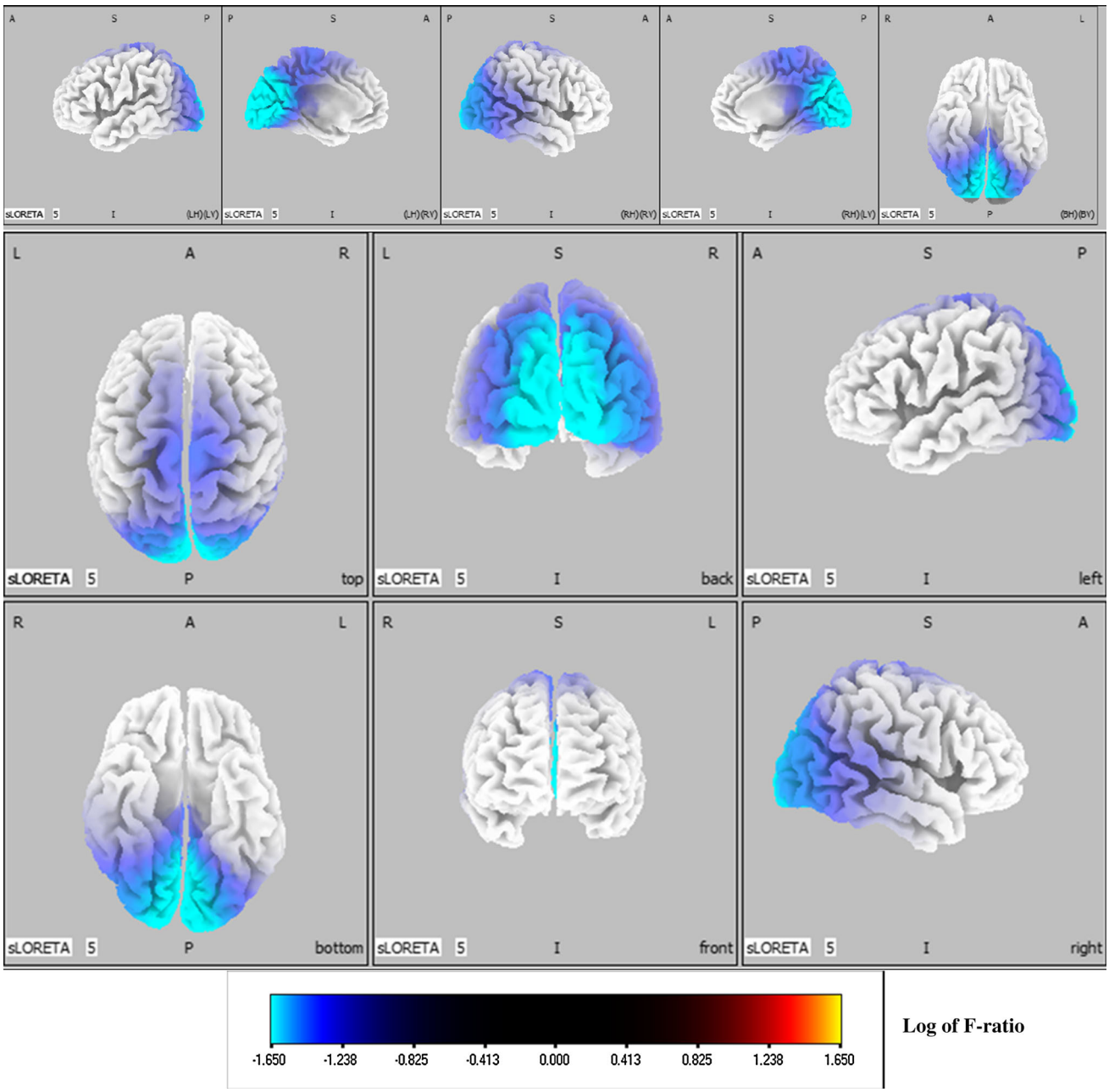


**Fig. 1** eLORETA source current density in Alpha 8–12 Hz in ME patients compared to healthy controls

evidence of cortical hypofunction found in our source analysis in addition to our prior investigations (Zinn et al. 2014a, b).

## Discussion

In the present study, we applied two new methodological approaches to investigate resting-state neurological differences in people with ME compared to healthy controls (source analysis and functional connectivity analysis). First, abnormalities in current source densities were found with our patient group, displaying decreased alpha and alpha-2 current sources primarily in the bi-lateral parieto-occipital region (Figs. 1, 2). Alpha rhythm, the dominant oscillation in the human brain, is especially prominent in the posterior regions, representing a distinctive feature of the normal brain in the waking resting state. The alpha rhythm has been shown to modulate inhibition, timing, attention, memory processes including consolidation, detection of irrelevant stimuli, and information processing speed (Capotosto et al. 2009; Ishii et al. 2010; Klimesch

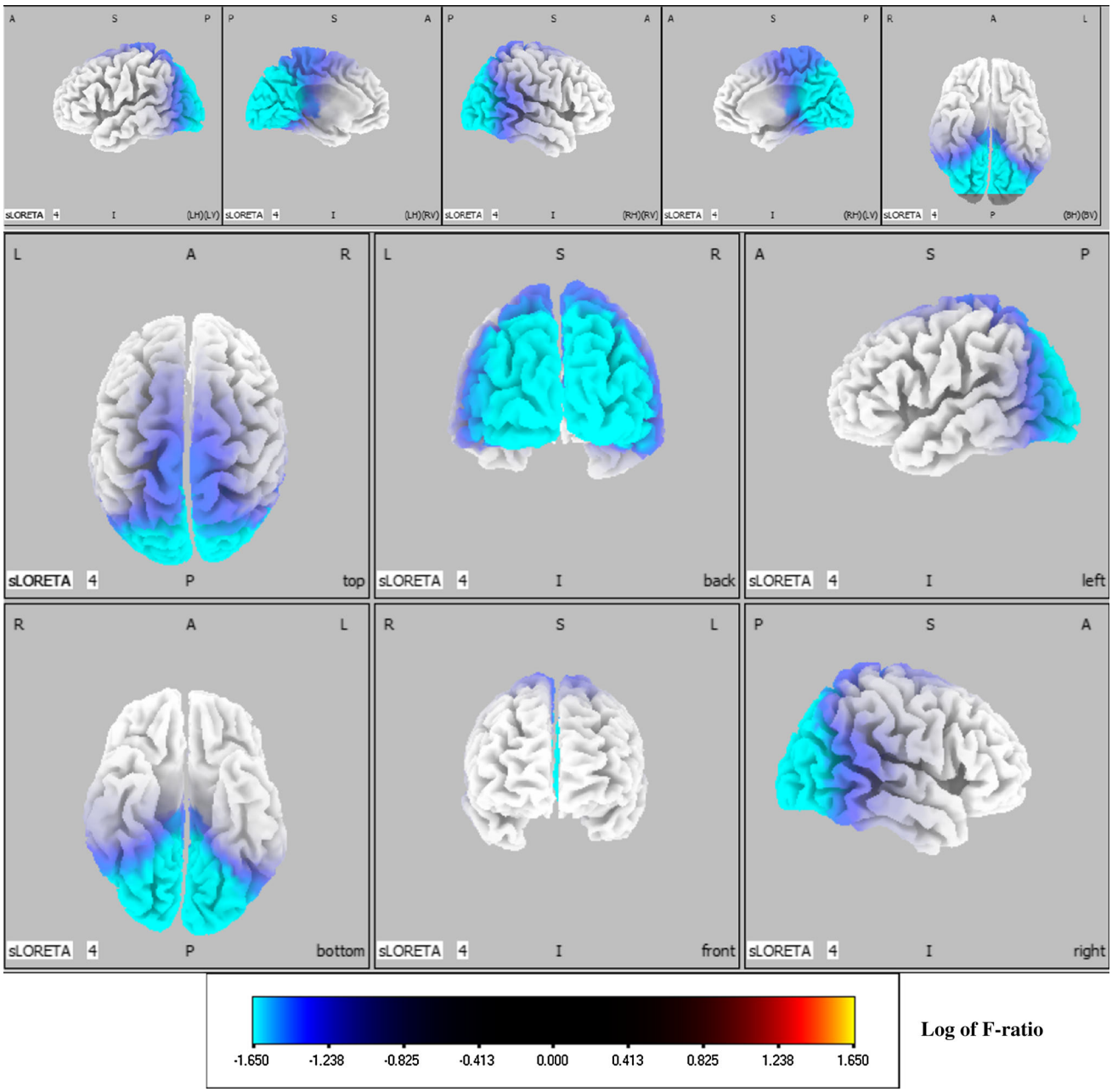


**Fig. 2** eLORETA source current density in Alpha 2, 10–12 Hz in ME patients compared to healthy controls

1996, 1997, 1999; Klimesch et al. 1997, 2010; Schabus et al. 2011). Abnormalities in alpha are typically seen in the parietal-occipital regions which can represent signs of cerebral dysfunction in neurocognitive disorders (Babiloni et al. 2014). Many of these symptoms corroborate those commonly reported by patients with ME, especially the slowed information processing speed.

The alpha frequency band is currently regarded as important in cognitive function due its strong correlation with general cognitive abilities. Alpha activity matures in early adolescence (Simkin et al. 2014; Thatcher et al. 2008), declines in old age (Klimesch 2012) and is a reliable predictor of many aspects of memory (Angelakis et al. 2004; Vogt et al. 1998). The alpha frequency band has reliably demonstrated predictive power of individual differences in a large number of studies involving cognitive and perceptual processes (Osaka 1984; Osaka et al. 1999), including visual encoding (Klimesch et al. 2011), response selection (Klimesch et al. 2011) and motor preparation (Holz et al. 2008; Sauseng et al. 2009). Taken together, studies such as these find a strong positive relationship between the alpha frequency and executive functioning. For example, Klimesch

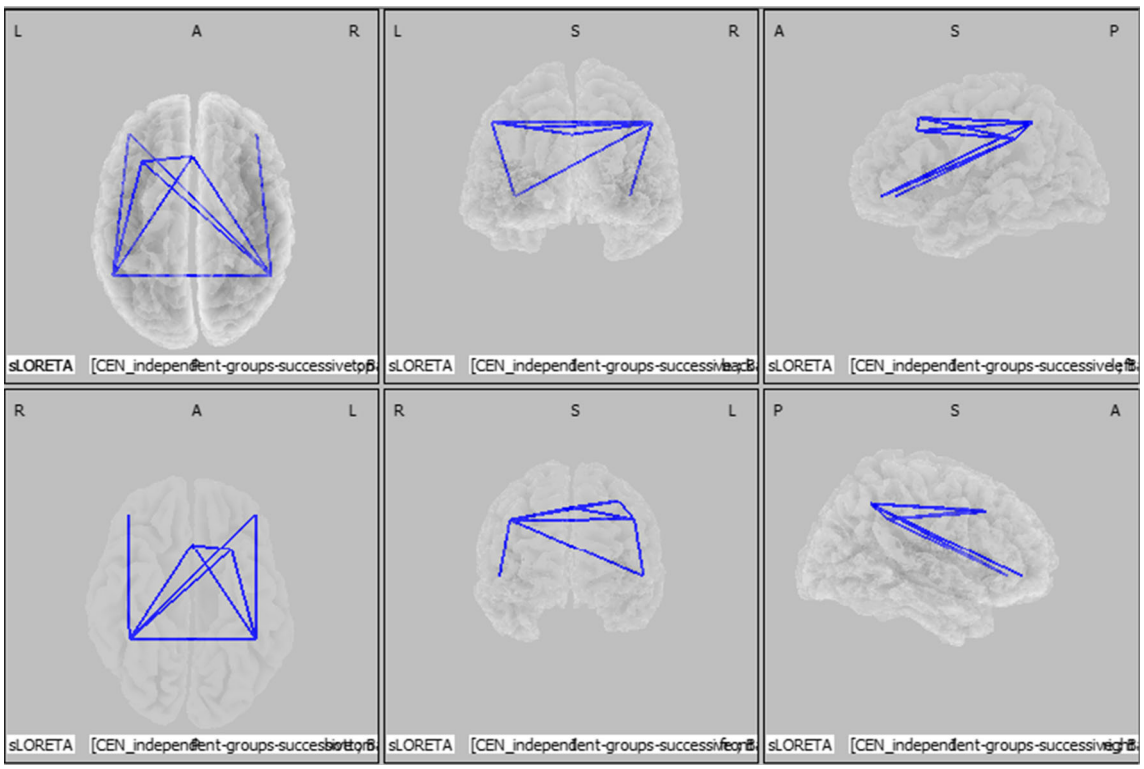


**Fig. 3** CEN high Alpha 2 (10–12 Hz). eLORETA wire diagram indicating cortical regions with significantly decreased alpha 2 lagged phase synchronization in patients with Myalgic Encephalomyelitis compared to healthy controls

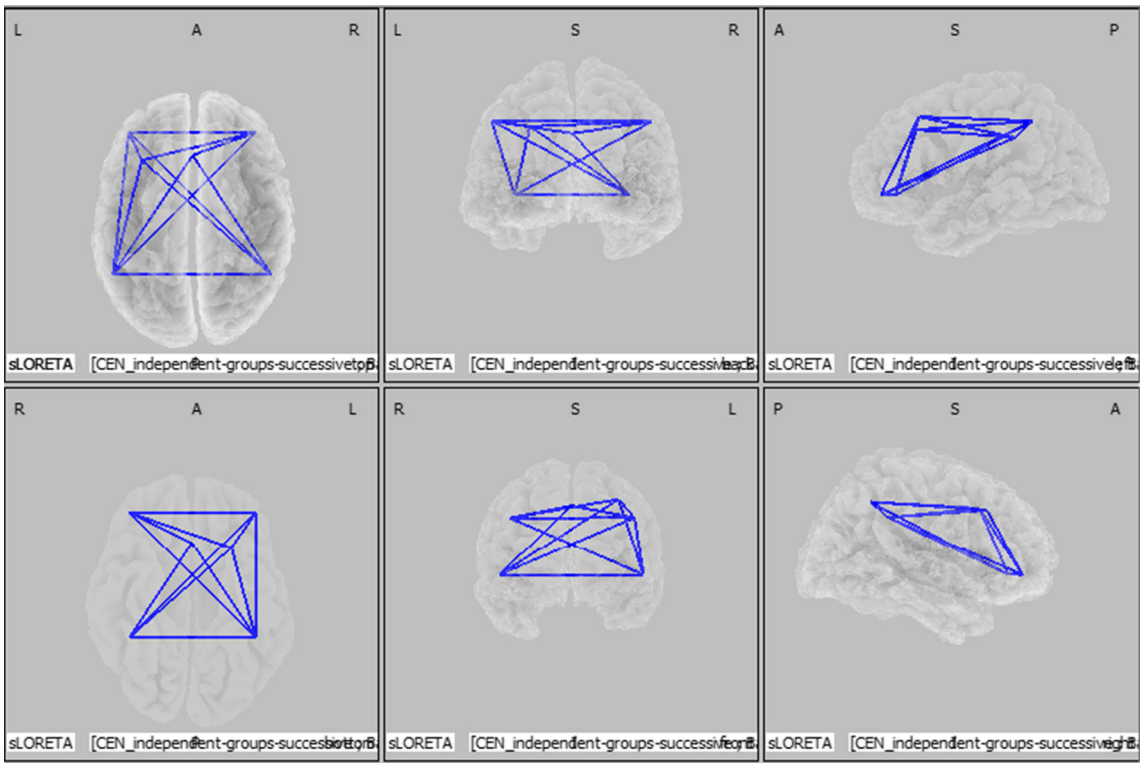


**Fig. 4** CEN delta (1–3 Hz). eLORETA wire diagram indicating cortical regions with significantly decreased delta lagged phase synchronization in patients with Myalgic Encephalomyelitis compared to healthy controls

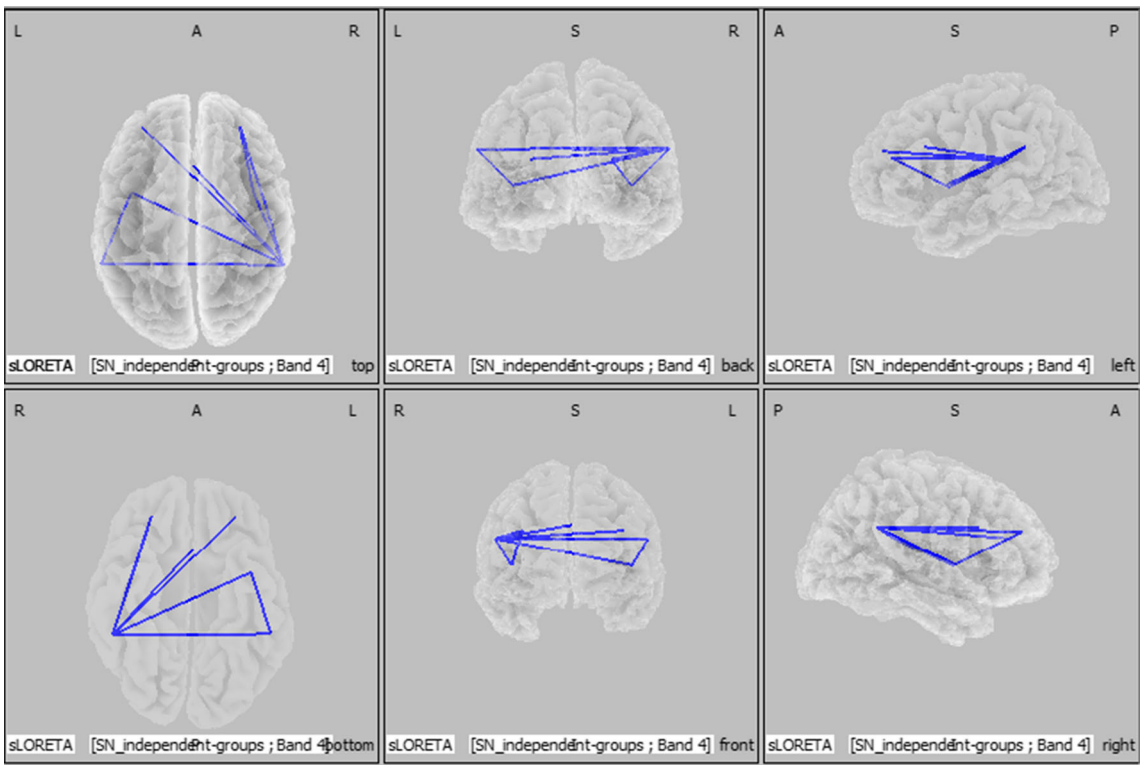


**Fig. 5** SN high Alpha 2 (10–12 Hz). eLORETA wire diagram indicating cortical regions with significantly decreased alpha 2 lagged phase synchronization in patients with Myalgic Encephalomyelitis compared to healthy controls

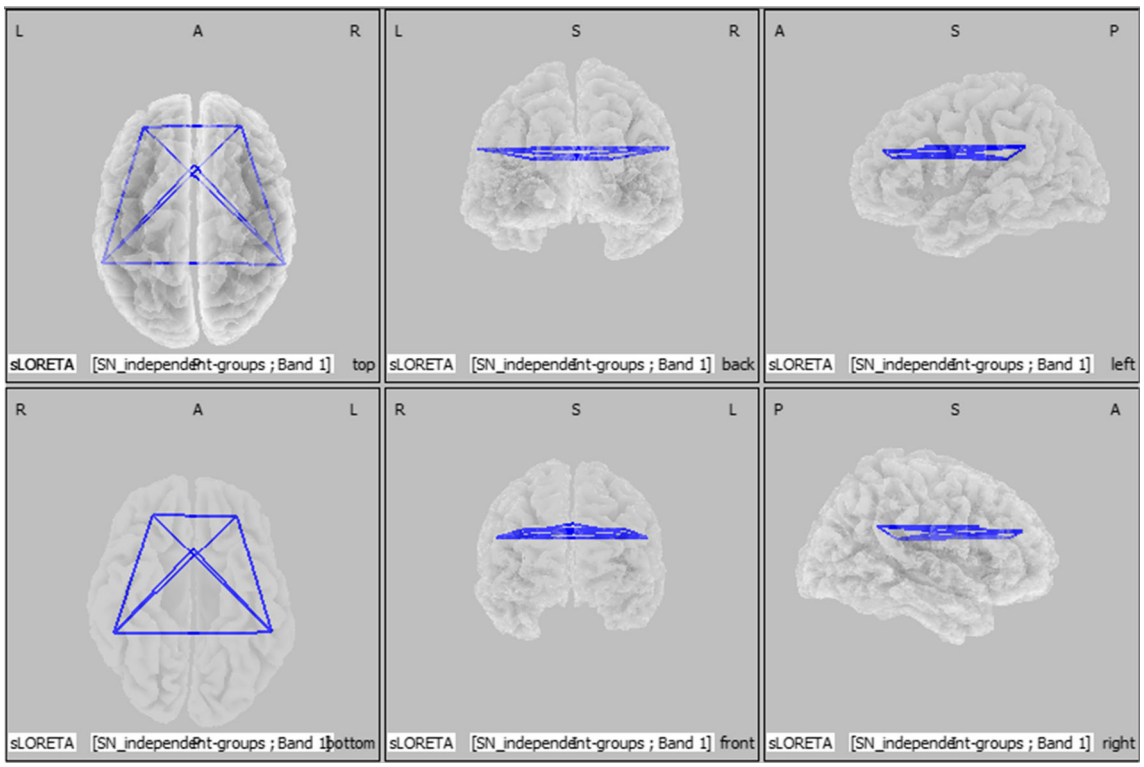


**Fig. 6** SN Delta (1–3 Hz). eLORETA wire diagram indicating cortical regions with significantly decreased delta lagged phase synchronization in patients with Myalgic Encephalomyelitis compared to healthy controls

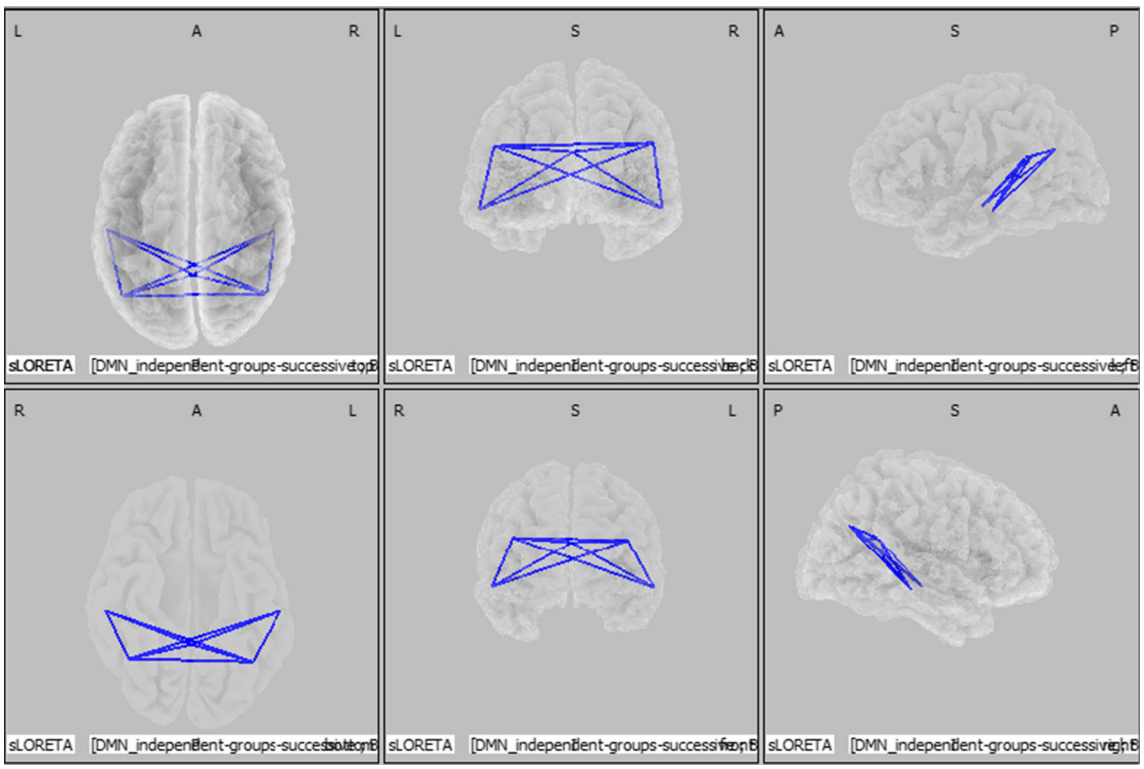


**Fig. 7** DMN high Alpha 2 (10–12 Hz). eLORETA wire diagram indicating cortical regions with significantly decreased alpha 2 lagged phase synchronization in patients with Myalgic Encephalomyelitis compared to healthy controls

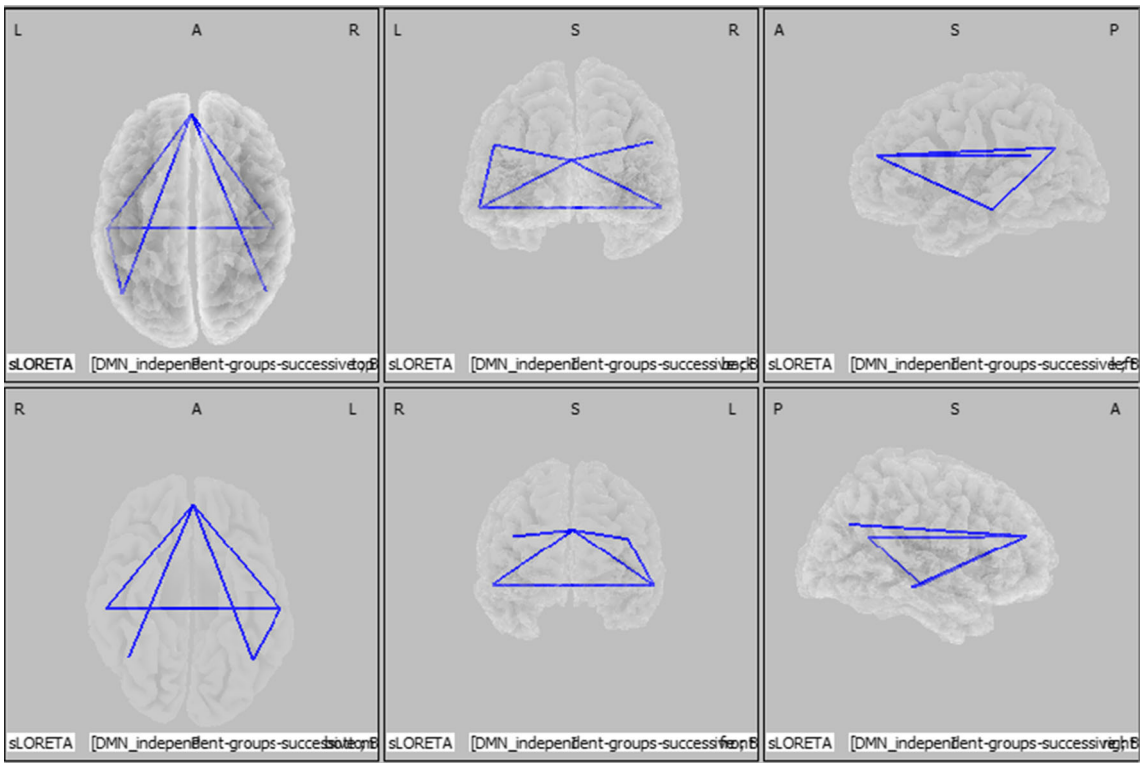


**Fig. 8** DMN Delta (1–3 Hz). eLORETA wire diagram indicating cortical regions with significantly decreased delta lagged phase synchronization in patients with Myalgic Encephalomyelitis compared to healthy controls

et al. (1993) characterized alpha phase synchronization as a control process that organizes top-down modulation of working memory and attention as well as access to long-term memory. Other authors find relationships between human memory, alpha amplitude and network dynamics (Hughes and John 1999). The effects of modulation of cognition within the alpha band are strong regardless of the nature or direction of the cognitive domain assessed. Our source density finding showing reduced alpha reflects the types of cognitive impairment that it is associated with (e.g. memory, attention, concentration, information processing speed). Furthermore, alpha rhythms are known to have involvement in ME (Billiot et al. 1997).

Specific locations of the reduced alpha band activity included the cuneus region, precuneus, lingual gyrus, posterior cingulate, parahippocampal gyrus, fusiform gyrus, superior parietal lobule, premotor and primary motor areas (precentral gyrus), middle temporal gyrus, inferior temporal gyrus, and angular gyrus. Taken together, abnormal delta and alpha-2 rhythms in occipital, parietal, temporal, and limbic regions provide objective evidence for ME neurocognitive symptoms with disruption to the perception–action cycle (Fuster 2009) and associated sensorimotor deficits.

Sherlin et al. (2007) found increased delta in the left uncus, left parahippocampal gyrus, and increased theta in the cingulate gyrus and right superior frontal gyrus, and in 2014, Zinn et al. found increased delta in over 50 % of the frontal-limbic regions in the superior frontal gyrus, entire cingulate gyrus, medial frontal gyrus, orbito-frontal cortex, middle frontal gyrus, insula, superior temporal gyrus and in the rectal gyrus. Our overall findings extended previous ME neuroimaging research by providing a more complete analysis of neurocognitive deficits. First, alpha, alpha 1, and alpha-2 current source density was deviant from normal in patients with ME involving the entire occipital lobe, extending into portions of the parietal, temporal and limbic lobe (Figs. 1, 2). The divergent results most likely indicate severity levels of disease and individual differences in brain pathology.

Second, there was significantly reduced lagged phase synchronization in the DMN, the SN and the CEN in delta and alpha bands, supporting the triple network model. Evidence of psychomotor slowing in ME was found by Van Den Eede et al. (2011) who demonstrated delayed reaction time and movement time in patients with ME, a confirmation of earlier ME studies showing psychomotor slowing, persistent motor impairment, and impaired cortical motor area excitability in patients (Gaudino et al. 1997; Majer et al. 2008; Prasher et al. 1990). Taken together, these studies support our finding of hypoconnectivity in lagged phase synchronization in all three networks of the Menon triple network model in the occipital, parietal, posterior cingulate, and posterior temporal lobes. Functional connectivity disruptions between nodes and hubs of all three networks in the triple network model reveal the presence of decreased phase lag synchronization affecting the delta and alpha bands. This is consistent with other neuropsychological studies finding significantly decreased delta band connectivity using both linear (coherence) (Burroughs et al. 2014) and nonlinear (phase lag synchronization) measures (Bosma et al. 2009; Cooray et al. 2011; Zeng et al. 2015). Decreased functional connectivity within the SN, DMN and CEN could indicate a biomarker if commonly found in patients with ME. Finding support for the triple network model has far-reaching implications for ME, given that it may explain many of the symptoms reported by patients. Some of those symptoms include the feelings of derealization (brain fog) commonly experienced in the disease. Other implications include issues in complex spatial patterns, deductive reasoning, mental navigation, visual rotation and similar spatial issues. ME patients are known for their inability to drive a car, and often become lost even in their own neighborhood. Hypoactive mental states interrupt consciousness, sleep and can bring on vegetative states, underpinning changes in behavior and general self- and other-awareness (Ramos Reis et al. 2013).

These combined findings present support for inefficient allocation of resources dependent on three factors: (1) that the incomplete switching between the DMN and CEN were likely present (but not directly measured). Recent studies have observed the fluctuations in activation of all networks, including the SN in both task-based and task-free states. For example, in normal, healthy individuals, switching occurs whenever the task performance occurs and is correlated with the CEN. However, during pathological states, the switching effect is compromised, creating significant group differences between engagement and disengagement of the CEN (Daniels et al. 2010). In this manner, aberrant switching would prevent optimal cognitive states in our sample. (2) We found weakened coupling within the SN suggests hypersensitivity within many domains, another facet of ME symptom presentation. Though we did not measure hypersensitivity, it is an exceedingly common complaint of patients with ME. (3) Due to aberrant SN switching and weakened connectivity, the DMN would likely never be fully active, resulting in patients having considerable trouble engaging in self-reflection and mentation, thereby interrupting normal brain dynamics within moving time windows. We believe this may contribute to "brain fog," slowed information processing speed and possibly deregulation in other aspects of cognitive function. Overall, these deficits would be seen as cognitive decline.

## Limitations

Although the present findings taken from eLORETA neuroimaging method reveal dysregulation in the alpha band, as well as support for the triple network model, we acknowledge limitations of this study. First the eLORETA neuroimaging method can only examine cortical areas but does not look at subcortical structures such as the hypothalamus, thalamus, amygdala, hippocampus, basal ganglia, cerebellum, and brainstem. However, cortical pathology within brain circuits indirectly implicates these subcortical structures by inference. For this pilot study, results should be cautiously interpreted because of the relatively small sample size. Future studies should include larger sample sizes with more experimental groups such as a group with co-morbid depression. Future research should also include neuropsychological measures for comparison to connectivity findings, such as measures of sleep disturbance and executive functioning. Such measures would be most useful if they are found to predict the most commonly found pathological states in patients with ME, such as slowed information processing speed, memory and concentration disturbances and overall feelings of derealization and depersonalization.

## Conclusion

The present study suggests that a clear pattern of substantial CNS hypoactivation in ME patients, finding support for aberrant source localization. Current ME research points to a common finding of cognitive slowing in ME and we identified this with quantifiable reductions in delta and alpha frequency bands as well as relating delta and alpha cortical sources to reduced functional connectivity. By finding support for the Menon Tripe Network model of pathology, we provide one possible explanation for known cognitive deficits in ME, such as incomplete engagement of executive functioning in the awake state.

Our study used eLORETA to explore EEG indices of ME pathophysiology with findings implicating profound CNS involvement. Our results support the hypothesis that there is significant brain dysregulation overall seen in the parietal, occipital, posterior temporal, posterior cingulate and parahippocampal gyrus. Dysregulation is also present within the 3 core networks of the human brain as defined by the triple network model, within ME. Based on high concordance of our findings with other ME source analysis studies, it is possible that eLORETA can provide clinically relevant information about patients with ME, and may be therefore a viable tool for use in clinical as well as research settings.

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**Compliance with Ethical Standards**

**Conflict of interest** The authors declare that there is no conflict of interest. The funder played no role in the design or conduct of this study.

**Ethical Standards** All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This study was approved by the Institutional Review Board at DePaul University in Chicago, Protocol # LJ052615 PSY.

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