NeuroRegulation

The Official Journal of

ISNR
INTERNATIONAL SOCIETY FOR NEUROFEEDBACK & RESEARCH

Volume 3, Number 1, 2016

NeuroRegulation

NeuroRegulation (ISSN: 2373-0587) is published quarterly by the International Society for Neurofeedback and Research (ISNR), 1350 Beverly Road, Suite 115, PMB 114, McLean, VA 22101-3633, USA.

Aim and Scope

NeuroRegulation is a peer-reviewed journal providing an integrated, multidisciplinary perspective on clinically relevant research, treatment, and public policy for neurofeedback, neuroregulation, and neurotherapy. The journal reviews important findings in clinical neurotherapy, biofeedback, and electroencephalography for use in assessing baselines and outcomes of various procedures. The journal draws from expertise inside and outside of the International Society for Neurofeedback and Research to deliver material which integrates the diverse aspects of the field. Instructions for submissions and Author Guidelines can be found on the journal website (http://www.neuroregulation.org).

NeuroRegulation

Volume 3, Number 1

2016

Contents

NeuroRegulation

Editorial – Volume 3, Number 1

Citation: Cannon, R. L. (2016). Editorial – Volume 3, Number 1. *NeuroRegulation*, *3*(1), 2. http://dx.doi.org/10.15540/nr.3.1.2

***Address correspondence to**: Rex L. Cannon, PhD, BCN, Neural Potential, 10151 Enterprise Center Blvd, Ste 207, Boynton Beach, FL 33437, USA. Email: rex.cannon@neuralpotential.com

Welcome to *NeuroRegulation*, Volume 3, Number 1. We have experienced a growing interest by both clinicians and researchers submitting quality works to our journal and hope to see this trend continue. It is interesting to note that a search on the term *neurofeedback* in Pubmed returns 870 articles. This is not only important to the field of neurofeedback and its growing application across numerous disciplines; it is a sign of growth and success in our respective craft. We envision *NeuroRegulation* being a primary source for publishing data concerning neurofeedback, self-regulation, and applied neurosciences across disciplines in a short amount of time. We encourage all researchers, clinicians, students, and theorists to publish your work in *NeuroRegulation*.

The current issue is comprised of a variety of topics pertaining to neurofeedback and applied neuroscience. Dr. Lauren Frey presents pilot data demonstrating the effects of SMR neurofeedback on quality of life in medically refractory seizures. Drs. Alycia Roberts, Paul Fillmore, and Scott Decker present research discussing the clinical applicability of test-retest reliability of qEEG coherence. Drs. Hsin-Yi Tsai, Erik Peper, and I-Mei Lin present research evaluating the effects of posture on the EEG during emotional recall tasks. Drs. Marcie Zinn, Mark Zinn, and Leonard Jason provide a review of Myalgic Encephalomyelitis and functional network correlates. Finally, Dr. Randall Lyle presents a book review of "The Good Life: Wellbeing and the New Science of Altruism, Selfishness and Immorality."

NeuroRegulation thanks these authors for their valuable contributions to the scientific literature for neurofeedback and quantitative EEG. We strive for high quality and interesting empirical topics. We encourage the members of ISNR and other biofeedback and neuroscience disciplines to consider publishing with us. We are planning a special issue later in the year and will be soliciting papers from experts in the field in the near future. We thank you for reading *NeuroRegulation*!

Rex L. Cannon, PhD, BCN
Editor-in-Chief
Email: rexcannon@gmail.com

Published: March 9, 2016

NeuroRegulation

Impact of Sensorimotor Rhythm Neurofeedback on Quality of Life in Patients with Medically Refractory Seizures: A Pilot Study

Lauren Frey

University of Colorado, Denver, Colorado, USA

Abstract

Introduction: Published studies suggest that augmentation of the sensorimotor rhythm (SMR), a commonly-used neurofeedback protocol for patients with epilepsy, changes thalamocortical regulatory systems and increases cortical excitation thresholds. Recent meta-analyses showed that at least 50% of patients with medically refractory epilepsy had a post-therapy reduction in seizure frequency after neurofeedback training. However, data on neurofeedback outcomes outside of seizure frequency are limited. **Methods:** The records for all consecutive patients trained using SMR neurofeedback in the University of Colorado Neurofeedback Clinic prior to March 2015 (n = 9) were retrospectively reviewed, abstracted, and analyzed. Patients completed the Quality of Life in Epilepsy-31 (QOLIE-31) survey as a part of their clinic intake interview and at intervals throughout their training. **Results:** 214 total training sessions were reviewed. The average total QOLIE-31 baseline score in our patients was 49.3 ± 8.8. Seven patients completed follow-up QOLIE-31 surveys with an average score of 54.9 ± 6.5. Seventy-eight percent of the patients had improvement in their QOLIE-31 scores with training. The largest absolute improvements were in the seizure worry and cognitive subscores of the QOLIE-31. **Conclusion:** In this small case series, SMR neurofeedback training modestly improved short-term follow-up QOLIE-31 scores in patients with epilepsy.

Keywords: seizure; epilepsy; sensorimotor rhythm; neurofeedback; quality of life

Citation: Frey, L. (2016). Impact of Sensorimotor Rhythm Neurofeedback on Quality of Life in Patients with Medically Refractory Seizures: A pilot study. *NeuroRegulation*, *3*(1), 3–6. http://dx.doi.org/10.15540/nr.3.1.3

***Address correspondence to**: Lauren Frey, MD, Department of Neurology, University of Colorado, Anschutz Medical Campus, 12401 East 17th Avenue, Mail Stop L950, Aurora, CO 80045, USA. Email: Lauren.Frey@ucdenver.edu

Edited by:
Sarah Prinsloo, PhD, The University of Texas MD Anderson Cancer Center, Houston, Texas, USA

Reviewed by:
John Davis, PhD, McMaster University, Hamilton, Ontario, Canada
Genomary Krigbaum, PsyD, Marian University, College of Osteopathic Medicine, Indianapolis, Indiana, USA

Introduction

Epilepsy can be defined as a recurrent predisposition to unprovoked seizures (Fisher et al., 2014). Across the spectrum of persons with epilepsy, seizures occur with a wide range of frequencies and can originate in many different areas of the brain. Approximately 30% of persons with epilepsy are medically refractory, meaning that their seizures are not completely controlled with appropriately chosen and administered antiseizure medications (Kwan et al., 2010). Comorbid mood disorders are common in patients with epilepsy, affecting 40–70% of patients at some point in their lifetime, with depression and anxiety the most commonly reported (Hermann, Seidenberg, & Bell, 2000).

Quality of life (QOL) can be defined as a subjective perception of a patient's own wellness/functionality. QOL is multidimensional and, in patients with epilepsy, is influenced by multiple interacting factors. These factors include: degree of seizure control, psychiatric comorbidity, medication side effects, socioeconomic status, and strength of social support network. Two of the most important factors associated with QOL in patients with medically refractory epilepsy are symptoms of depression and seizure worry (Loring, Meador, & Lee, 2004), suggesting that both seizure and non-seizure

manifestations of epilepsy contribute to a patient's QOL.

Neurofeedback is a form of biofeedback that assesses and analyzes EEG signals to help train individuals to produce healthier brain rhythms. In the case of people with epilepsy, these rhythms are those that are less likely to be proconvulsant. Neurofeedback can be a powerful tool for reregulation of the dysfunctional brain rhythms that are driving the clinical manifestations of epilepsy. Augmentation of the sensorimotor rhythm (SMR) is a commonly used neurofeedback protocol for patients with epilepsy. Published studies suggest that augmentation of the SMR changes thalamocortical regulatory systems and increases cortical excitation thresholds (Sterman, 2000; Sterman & Egner, 2006). As such, SMR augmentation can be an effective means of reducing seizure frequency in patients with medically refractory seizures (Sterman, 2000; Sterman & Egner, 2006; Tan et al., 2009). Recent meta-analyses assessing neurofeedback training in patients with medically refractory epilepsy showed that at least 50% of patients had a post-therapy reduction in seizure frequency (Sterman 2000; Tan et al., 2009). Many protocols for depression and/or anxiety, common psychiatric comorbidities in patients with epilepsy, also involve training within the sensorimotor cortex (Soutar & Longo, 2011). As such, there is potential for SMR training to affect both seizure and non-seizure manifestations of epilepsy. The data on neurofeedback outcomes outside of seizure frequency are currently limited, however. This case series will explore whether SMR neurofeedback training in patients with epilepsy potentially impacts overall QOL.

Methods

The records for all consecutive patients trained using SMR neurofeedback (see below for protocol details) in the University of Colorado Neurofeedback Clinic prior to March 2015 (n = 9) were retrospectively reviewed. This study was reviewed and approved by the Colorado Multi-Institutional Review Board (COMIRB) as an exempt study.

Data on patient demographics, duration of epilepsy prior to training, seizure types and frequencies, antiepileptic drugs (AEDs), degree of seizure control, psychiatric and medical comorbidities, imaging results, neurophysiological results, Quality of Life in Epilepsy-31 (QOLIE-31) scores, and the duration of neurofeedback training were abstracted and analyzed. Patients in this clinic routinely complete the QOLIE-31 survey as a part of their clinic intake interview and at intervals throughout their training. The QOLIE-31 is a validated, epilepsy-specific, QOL measure that measures constructs such as: seizure worry, emotional well-being, energy/fatigue, cognition, medication effects, and social function (Borghs, de la Loge, & Cramer, 2012). In this measure, higher scores represent greater patient-reported QOL. The reported minimal clinically important change for the total QOLIE-31score is between 5 and 12 points (Borghs et al., 2012; Wiebe, Matijevic, Eliasziw, & Derry, 2002). Patients also reported the number of seizures experienced each week before each session.

All patients were trained by a certified neurofeedback provider (LF) using a BrainMaster Atlantis system (BrainMaster Technologies, Inc., Bedford, Ohio). The training protocol rewarded increased amplitude of the 12–15 Hz frequency band and, simultaneously, decreased amplitude of the 4–8 Hz (theta) frequency band at Cz. A second (also simultaneous) inhibit of the 4–8 Hz (theta) frequency band was included at a second site if the individual had a focus of increased theta amplitude outside of C3, Cz, or C4 on their baseline quantitative EEG (qEEG). Training was performed using 2-min training intervals for at least 20 total training minutes per session and one session per week.

For descriptive means of population descriptors and QOLIE scores and subscores, all patient measures were averaged. For the mean change in QOLIE-31 scores and subscores, the change in QOLIE-31 score for each patient was calculated and then averaged over all patients.

Results

A total of 214 training sessions were reviewed. Summary data for our patient population are given in Table 1. One of the seven patients remained seizure-free throughout training. Five of the other six patients reported a subjective decline in seizure frequency or severity.

Table 1
Summary data for case population

Population Descriptor	Summary Data
N	9 patients
Total number of training sessions studied	214 sessions
Mean number of training sessions per patient (± SEM)	22.8 ± 4 sessions
Gender	4 male; 5 female
Mean patient age (± SEM)	47.4 ± 5.9 years
Mean duration of epilepsy prior to training (± SEM)	18.7 ± 3.6 years
Mean number of antiseizure drugs (± SEM)	1.7 ± 0.3
Focal onset epilepsy syndrome?	8 of 9 patients
Structural lesion on MRI?	4 of 9 patients
History of comorbid mood disorder	7 of 9 patients
Number of patients with both initial and follow-up QOLIE-31 scores	7 of 9 patients

Note. SEM = Standard error of the mean

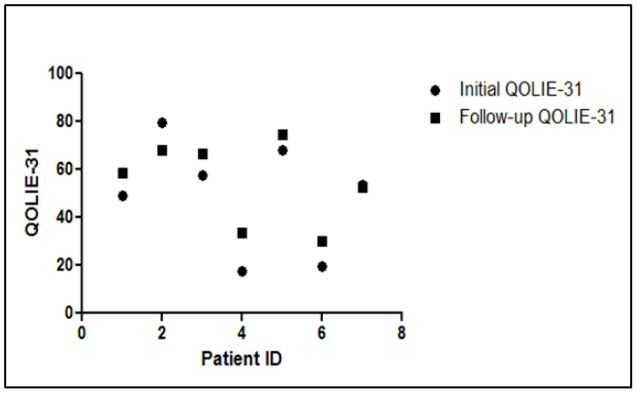

Figure 1. Total QOLIE-31 scores before and after at least 18 sessions of SMR neurofeedback training.

All nine patients completed the QOLIE-31 at the beginning of their training with an average baseline score of 49.3 ± 8.8. Seven patients completed follow-up QOLIE-31 surveys. Initial and follow-up total QOLIE-31 scores for these seven patients are plotted in Figure 1. Five of the seven patients (78%) had an absolute improvement in their follow-up total QOLIE-31 score. One patient's follow-up score was essentially unchanged, and one patient's follow-up score reflected a worsening of reported QOL after training.

As shown in Table 2, the mean (± SEM) post-training QOLIE-31 score was 54.9 ± 6.5 (*n* = 7). The changes in QOLIE-31 scores from initial to follow-up measure averaged 5.6 ± 3.4 (range: -11.6 to 16).

Table 2
QOLIE-31 summary data

QOLIE-31 Parameter	Summary Data
Mean QOLIE-31 score before training (± SEM)	49.3 ± 8.8
Mean QOLIE-31 score after training (± SEM)	54.9 ± 6.5
Mean QOLIE-31 change with training (± SEM)	5.6 ± 3.4
Range of QOLIE-31 score changes	-11.6 to 16
Percent of patients with QOLIE-31 improvement after training	78%

Note. SEM = Standard error of the mean

Table 3 shows the mean (± SEM) of each subscore of the QOLIE-31 before and after neurofeedback training (*n* = 7). Pairs with changes greater than 5 points are highlighted in red. The largest absolute improvements were in the seizure worry and cognitive domains of the QOLIE-31.

Table 3
Mean (± SEM) subscores of QOLIE-31 before and after neurofeedback training

QOLIE-31 Subscore	Before Training	After Training
Seizure Worry	47.7 (± 10.8)	54.0 (± 9.9)
Overall QOL	62.1 (± 9.1)	68.9 (± 4.9)
Emotional Well-being	64.6 (± 8.5)	68.6 (± 6.9)
Energy/Fatigue	41.4 (± 10.5)	44.3 (± 8.1)
Cognitive	44.9 (± 8.5)	54.7 (± 6.0)
Medication Effects	40.5 (± 15.9)	40.5 (± 12.5)
Social Function	41.9 (± 14.9)	44.3 (± 11.0)

Note. Pairs with changes greater than 5 points are highlighted in red

Discussion

In this small case series of patients with medically refractory epilepsy, SMR neurofeedback training improved QOLIE-31 scores, with an average change of 5.6 ± 3.4. The reported minimal clinically important change for the total QOLIE-31score is between 5 and 12 points (Borghs et al., 2012; Wiebe et al., 2002). This range encompasses our finding within the lower end of this range, suggesting that our mean change in QOLIE-31 scores, although modest, may be clinically meaningful. This is the first study that we are aware of that looks at QOL after NFB training in persons with epilepsy.

While QOL in persons with epilepsy is heavily influenced by the degree of seizure control, we know that both seizure and non-seizure manifestations of epilepsy contribute to a patient's QOL (Loring et al., 2004). The improvements in QOLIE-31 scores in our series of medically refractory patients occurred despite a range of changes in seizure control in the individual patients, supporting this concept.

There are a number of limitations to this study. First, we had a small sample size, limiting our power to detect differences between mean QOLIE-31 scores at our two time points. This also limited our analysis to descriptive statistics only. Secondly, our results are based on a subjective measure done only once at two individual time points. Future studies may need to include repeated measures before and after training to try to adjust for day-to-day variability and/or mood dependence of subjective QOL scores.

Overall, in our series of patients with medically refractory epilepsy, we documented modestly improved follow-up QOLIE-31 scores after SMR neurofeedback training, although larger studies are needed to confirm the value of the QOLIE-31 as an outcomes measure. In addition, larger studies are also needed to determine the psychosocial constructs that may underlie changes in QOL after neurofeedback training in patients with epilepsy.

References

Borghs, S., de la Loge, C., & Cramer, J. A. (2012). Defining minimally important change in QOLIE-31 scores: Estimates from three placebo-controlled lacosamide trials in patients with partial-onset seizures. *Epilepsy and Behavior, 23*(3), 230–234. http://dx.doi.org/10.1016/j.yebeh.2011.12.023

Fisher, R. S., Acevedo, C., Arzimanoglou, A., Bogacz, A., Cross, J. H., Elger, C. E., ... Wiebe, S. (2014). ILAE Official Report: A practical clinical definition of epilepsy. *Epilepsia, 55*(4), 475–482. http://dx.doi.org/10.1111/epi.12550

Hermann, B. P., Seidenberg, M., & Bell, B. (2000). Psychiatric Comorbidity in chronic epilepsy: Identification, consequences, and treatment of major depression. *Epilepsia, 41*(Suppl. s2), S31–S41. http://dx.doi.org/10.1111/j.1528-1157.2000.tb01522.x

Kwan, P., Arzimanoglou, A., Berg, A. T., Brodie, M. J., Hauser, W. A., Mathern, G. W., ... French, J. (2010). Definition of drug resistant epilepsy: Consensus proposal by the ad hoc Task Force of the ILAE Commission on Therapeutic Strategies. *Epilepsia, 51*(6), 1069–1077. http://dx.doi.org/10.1111/j.1528-1167.2009.02397.x

Loring, D. W., Meador, K. J., & Lee, G. P. (2004). Determinants of quality of life in epilepsy. *Epilepsy and Behavior, 5*(6), 976–980. http://dx.doi.org/10.1016/j.yebeh.2004.08.019

Soutar, R., & Longo, R. (2011). *Doing Neurofeedback: An Introduction*. San Rafael, CA: ISNR Research Foundation.

Sterman, M. B. (2000). Basic concepts and clinical findings in the treatment of seizure disorders with EEG operant conditioning. *Clinical EEG and Neuroscience, 31*(1), 45–55. http://dx.doi.org /10.1177/155005940003100111

Sterman, M. B., & Egner, T. (2006). Foundation and practice of neurofeedback for the treatment of epilepsy. *Applied Psychophysiology and Biofeedback, 31*, 21–35. http://dx.doi.org/10.1007/s10484-006-9002-x

Tan, G., Thornby, J., Hammond, D. C., Strehl, U., Canady, B., Arnemann, K., & Kaiser, D. A. (2009). Meta-analysis of EEG biofeedback in treating epilepsy. *Clinical EEG and Neuroscience, 40*(3), 173–179. http://dx.doi.org/10.1177 /155005940904000310

Wiebe, S., Matijevic, S., Eliasziw, M., & Derry, P. A. (2002). Clinically important change in quality of life in epilepsy. *Journal of Neurology, Neurosurgery, and Psychiatry, 73*, 116–120. http://dx.doi.org /10.1136/jnnp.73.2.116

Received: January 15, 2016
Accepted: February 13, 2016
Published: March 9, 2016

NeuroRegulation

Clinical Applicability of the Test-retest Reliability of qEEG Coherence

Alycia M. Roberts[1], Paul T. Fillmore[2], and Scott L. Decker[3]*

[1]Rainbow Babies & Children's Hospital, Division of Developmental and Behavioral Pediatrics & Psychology, Cleveland, Ohio, USA
[2]Baylor University, Department of Communication Sciences and Disorders, Waco, Texas, USA
[3]University of South Carolina, Psychology Department, Columbia, South Carolina, USA

Abstract

Measurement reliability is an important aspect of establishing the utility of scores used in clinical practice. Although much is known about the reliability of quantitative electroencephalographic (qEEG) metrics related to absolute power, less is known about the reliability of coherence metrics. The current study examined the measurement reliability of coherence metrics across standard frequency bands during an eyes-closed resting state. Reliability was examined both within channel pairs, and averaged across spatially contiguous channels, to summarize global patterns. We found that while most channel pairs were highly reliable on average, there was substantial variability across channels. Finally, we estimated the effect of measurement reliability on the detection of treatment-related neural change. We concluded that estimates of reliability for treated channels are crucial, and should factor into clinical assessment of treatment efficacy for EEG biofeedback (neurofeedback), especially in cases where large cross-channel variability is present.

Keywords: qEEG; coherence; reliability; reliable change

Citation: Roberts, A. M., Fillmore, P. T., & Decker, S. L. (2016). Clinical Applicability of the Test-retest Reliability of qEEG Coherence. *NeuroRegulation*, *3*(1), 7–22. http://dx.doi.org/10.15540/nr.3.1.7

***Address correspondence to**: Alycia M. Roberts, Rainbow Babies & Children's Hospital, Division of Developmental and Behavioral Pediatrics & Psychology, W.O. Walker Center, 10524 Euclid Avenue, Cleveland, OH, 44195, USA. Email: Alycia.Roberts@UHhospitals.org

Edited by:
Nancy L. Wigton, PhD, Grand Canyon University, Phoenix, Arizona, USA

Reviewed by:
Rex L. Cannon, PhD, Neural Potential, Boynton Beach, Florida, USA
Wesley D. Center, PhD, Liberty University, Lynchburg, Virginia, USA

Introduction

Technological advances in basic measures of electroencephalographic (EEG) recordings have led to a significantly expanded range of quantitative metrics of brain functioning. For example, quantitative EEG (qEEG) has been useful in the assessment of neurological conditions, such as traumatic brain injury (TBI; Ronne-Engstrom & Winkler, 2006; Bozorg, Lacayo, & Benbadis, 2010). Indeed, qEEG was found to have 96% sensitivity for detecting postconcussive syndrome (Duff, 2004). Furthermore, qEEG abnormalities have been linked to numerous other neurological and psychological disorders, including Alzheimer's disease (Gawel, Zalewska, Szmidt-Sałkowska, & Kowalski, 2009; Herrmann & Demiralp, 2005), attention deficit hyperactivity disorder (Fonseca et al., 2008; Koehler et al., 2009; Monastra et al., 1999), antisocial personality disorder (Calzada-Reyes, Alvarez-Amador, Galán-García, Valdés-Sosa, 2012), autism (Cantor & Chabot, 2009; Christakou et al., 2013; Lynch et al., 2013; Sheikhani, Behnam, Mohammadi, Noroozian, & Mohammadi, 2012), learning disabilities (Cantor & Chabot, 2009), schizophrenia (Boutros et al., 2008; Knyazeva et al., 2008), anxiety (Koberda, Moses, Koberda, & Koberda, 2013) and mood disorders (Begić et al., 2011; Koek et al., 1999).

Measurement reliability is a prerequisite and critical foundation for establishing the clinical validation of any measure (Haynes, Smith, & Hunsley, 2011). However, most reliability studies of qEEG have been limited to metrics related to absolute power (Chabot, Merkin, Wood, Davenport, & Serfontein, 1996; Corsi-Cabrera, Galindo-Vilchis, del-Río-Portilla, Arce, & Ramos-Loyo, 2007; McEvoy, Smith, &

Gevins, 2000; Salinsky, Oken, & Morehead, 1991). Indeed, the reliability of absolute power has been extensively researched and found to be suitable for clinical applications. Additionally, several studies have demonstrated the excellent reliability and stability of qEEG metrics at rest (Burgess & Gruzelier, 1993; Pollock, Schneider, & Lyness, 1991). McEvoy and colleagues (2000) also investigated test-retest reliability during cognitive tasks. They found that task-related reliability was higher (i.e., $r > .9$ for working memory tasks, $r > .8$ for psychomotor vigilance tasks) than that at rest (mean $r > .7$ across 4 resting state recordings). However, mean r remained ≥ .80 for theta and alpha regardless of condition. Another study (Corsi-Cabrera et al., 2007) examined within-subject variability and inter-session stability of EEG power in women over time, and found coefficients of $r = .92$ to $r = .98$ for absolute power. Gudmundsson, Runarsson, Sigurdsson, Eiriksdottir, and Johnsen (2007) investigated the effects of montage selection and length of the raw data epochs on test-retest reliability and similarly found that most of the frequency bands had reliability coefficients of $r \geq .80$. Finally, Thatcher (2010) reported test-retest reliability of qEEG is both high and stable with small samples sizes. He claimed that even as little as a 20-s epoch results in r ≈ .80, and suggested that test-retest reliability follows an exponential function, such that as the size of the sample of raw EEG data increases, so too does the reliability coefficient (i.e., 20 s, $r \approx .80$; 40 s, $r \approx .90$; 60 s, $r \approx .95$).

Although research has found uniformly high reliabilities in absolute power, variations in reliability have also been found depending on spectral band and electrode location. For example, Gasser, Bächer, and Steinberg (1985) studied test-retest reliability of both relative and absolute power. While they found mean reliabilities ranging from $r = .47$ to $r = .80$ and $r = .58$ to $r = .80$ for relative and absolute power, respectively, reliability in the alpha band was consistently the highest, with mean $r = .80$ for both. Salinsky, Oken, and Morehead (1991) also studied relative and absolute power, and using a 5-min test-retest interval, they found reliability coefficients ≥ .90, with a median $r = .93$ across all frequency bands. Additionally, Salinsky et al. found that this remained relatively stable over time.

Although numerous studies have investigated a variety of aspects of absolute power reliability, much less is known about the reliability of qEEG coherence. Though the term “coherence” can be used to describe comodulation, here we will refer to it as in Thatcher’s conception, that it is “a measure of the variability of time differences between two time series in a specific frequency band” (Thatcher, 2012). In this view, signals with complete phase-locking will display coherence values of 1.0, with a full absence of phase-locking representing a value of 0, and the magnitude of coherence representing the degree of functional association between two signals (e.g., brain regions). Currently, reliability research is mixed with some studies suggesting that coherence is a relatively stable measure of qEEG (Cannon et al., 2012; Chabot et al., 1996; Corsi-Cabrera et al., 2007; Corsi-Cabrera, Solís-Ortiz, & Guevara, 1997; John, 1977; Thatcher, Krause, & Hrybyk, 1986; Thatcher, Walker, Biver, North, & Curtin, 2003), and other studies finding it to be one of the least reliable measures (Gudmundsson et al., 2007). There is some evidence that coherence tends to be higher in the right hemisphere in comparison to the left hemisphere (Gootjes, Bouma, Van Strien, Scheltens, & Stam, 2008; Miskovic, Schmidt, Boyle, & Saigal, 2009; Tucker, Roth, & Bair, 1986). Additionally, previous studies have found a variety of gender differences in coherence (e.g., higher intra-hemispheric connectivity for males, differential patterns of local coherence changes after photic stimulation or completion of cognitive tasks), with some suggesting that this is due to differences in lateralized brain organization between the sexes (e.g., Gootjes et al., 2008; Koles, Lind, & Flor-Henry, 2010; Rappelsberger & Petsche, 1988; Shaywitz et al., 1995; Volf & Razumnikova, 1999; Voyer, Voyer, & Bryden, 1995; Wada et al., 1996). However, many of these results have been found during cognitive tasks (i.e., verbal and/or spatial tasks), rather than during resting state. Coherence has been linked to a number of cognitive processes (Thatcher & Lubar, 2009) and sensorimotor tasks (Minc et al., 2010; Silva et al., 2012) as well as neuropsychiatric disorders, such as attention deficit hyperactivity disorder (Murias, Swanson, & Srinivasan, 2007), anxiety disorders (Velikova et al., 2010), and depression (Leuchter, Cook, Hunter, Cai, & Horvath, 2012). As such, understanding the reliability and validity of this metric is of utmost importance as the use of EEG increases in the treatment of these disorders.

Clinical Implications of Measurement Reliability

Understanding the measurement reliability of coherence is important for several reasons. First, the utility of qEEG coherence is directly related to its reliability. Indeed, few would support using unreliable measures for making important clinical decisions concerning the care and treatment of individuals with various disorders. Second, as coherence is often targeted as an outcome measure

in neurofeedback treatment (i.e., Friedrich et al., 2014; Gruzelier, 2014; Keizer, Verment, & Hommel, 2010), it is important to establish objective parameters for determining whether treatment has led to a change in brain functioning. Finally, the amount of change needed to determine a meaningful clinical difference as a result of treatment is also directly related to the reliability of the measures used (i.e., Evans, Margison, & Barkham, 1998; Jacobson & Truax, 1991). Specifically, less reliable measures require greater change for demonstrating clinical effects, whereas more reliable measures are more powerful for detecting differences. The Reliability of Change (RC) index provides a formal association between measurement reliability and clinical outcomes. For example, the reliable change definition provided by Jacobson and Truax (1991) formulates whether a client has made clinically significant change. The following equation was used in this study to calculate the reliable change (RC) metric:

$$RC = \frac{x_1 - x_2}{S_{diff}} \quad (1)$$

As indicated by the formula, reliable change is determined by the measured difference of functioning at two time points (X_1-X_2) divided by the standard error of the difference (S_{diff}). The S_{diff} represents the variability in the difference between the two time points as a result of measurement error alone (Christensen & Mendoza, 1986). The S_{diff} characterizes variability of the measure through the use of the test-retest reliability coefficient (r_{xx}) and the standard deviation of the pre-test score (s_1) using the following formula (see Jacobson & Truax, 1991 for further computational details):

$$S_{diff} = \sqrt{(2*(s_1(\sqrt{1-r_{xx}}))^2)} \quad (2)$$

Thus, the RC metric can be interpreted similarly to a one-tailed *z*-score, in which values larger than 1.96 are unlikely to occur by chance if actual change is not present. As an important caveat, the reliability estimate used in the equation should provide an accurate gauge of measurement error related to the measurement instrument. Consequently, test-retest estimates should be based on relatively small intervals of time to ensure the change in scores is not due to a change in the underlying construct being tested.

The Current Study

The goal of this study was to demonstrate how the use of reliability statistics can be used to provide a basis from which to evaluate qEEG data as a pre- and post-test measure of treatment efficacy. Whereas most coherence reliability research has been conducted either during resting state or while participants were completing cognitive tasks (e.g., Fernández et al., 1993; Thornton & Carmody, 2009), this study examined the test-retest reliability of resting-state coherence before and after the completion of a cognitive task. The methodology used in this study limited the duration of time between recordings but also provided an intermediary event (cognitive task) to ensure a change in brain activity occurred between the two sessions prior to return to resting state, which may impact coherence metrics. This approach was used in an attempt to replicate what might occur during a cognitive, behavioral, or neurofeedback treatment session. As such, this study aimed to extend previous literature in the following ways: (1) by examining the test-retest reliability of qEEG coherence in a sample of healthy young adults across different frequency bands and regions of the brain, and (2) by translating this information into a more user-friendly format for clinical practice through the use of reliability of change metrics described below.

Method

Participants

Participants included 40 university students (30 females, 10 males) ranging in age from 19 to 28 years (mean chronological age = 21.33 years, *SD* = 1.80). This study was approved by the University of South Carolina's Institutional Review Board, and informed consent was completed with each participant prior to participation in the study.

Challenging Cognitive Tasks

The measures used in the current study were the Woodcock-Johnson Tests of Cognitive Abilities, Third Edition (WJ III COG; McGrew, Schrank, & Woodcock, 2007) and the Wisconsin Card Sorting Task (WCST; Computer Version 2, n.d.). As previously stated, these measures were used as an interference task, in order to evaluate the test-retest reliability of qEEG after the performance of a cognitively challenging task. Although the scores obtained were not analyzed in this study, future studies will examine the relationship between subjects' working memory and/or executive functioning performance and their qEEG.

Equipment and Software

Dell laptop and desktop computers were used in the collection and analysis of the electroencephalography (EEG) recordings. The

BrainMaster Discovery 24 amplifier and corresponding Discovery software (Version 1.8, 2011) were used to record raw EEG data at a sampling rate of 256 Hz. During data collection, the 60 Hz notch filter was used to filter out noise due to other electronic devices in the laboratory. The BrainMaster Discovery amplifier was selected as a result of its compatibility with Neuroguide (Version 2.6.4., n.d.), which was used to analyze the raw EEG data as well as to produce the qEEG maps. MATLAB (Release 2007b, 2007), SPSS (Version 19, 2007), and Microsoft Excel (2007) were also used for data exportation and final data analysis.

Procedure

Participants were fitted with a standard 19-channel Electro-Cap (Electro-Cap International, Inc., Eaton, OH), which used the international 10-20 system for electrode placement. Impedance was kept below 20 kΩ (below 10 kΩ for most subjects) for each of the electrodes. Additionally, reference leads were placed on participants' ears, and impedance was kept at or below 5 kΩ. These leads were used as a common point of reference for the data collection, and the linked ears montage was used during subsequent data analysis (in Neuroguide). Baseline recordings were taken for 3 min each while the participants' eyes were closed and then open. Participants were also asked to complete one standardized measure of cognitive ability between the baseline EEGs. The average time of completion for the cognitive measure was 5 min 26 s (*SD* = 5 s). Upon completion of the measure, participants then completed secondary baseline EEG recordings with their eyes closed and then open for another 3 min each. The average time between the start of the two eyes-closed conditions was 11 min 33 s (*SD* = 5 s). Thirty-nine of the 40 subjects completed the WJ III numbers reversed subtest between the baselines, while one subject performed the WCST. As these were used as an interference task, it is unlikely that the nature of the cognitive task significantly impacted the test-retest reliability. Additionally, the authors did not find any significant differences as a result of the two intermediary cognitive tasks.

Data Analysis

Prior to running analyses, all EEG data was visually inspected by a single examiner to select a minimum of ten seconds of artifact-free data within the first minute of each sample. Care was taken to select data in 2-s epochs whenever possible. This allowed for the use of the drowsiness and eye movement rejection options in Neuroguide, which helped to eliminate artifact from the data that followed recognizable patterns due to eye movement and/or drowsiness. Additionally, the automatic selection function was employed, which used the ten seconds of selected data as a template to automatically select similar data within the sample. This was done to ensure a minimum of one minute of artifact-free data for each session. Following artifacting, data from the eyes-closed EEG recordings were processed into qEEG metrics through fast-Fourier analysis. A variety of qEEG measures (e.g., absolute power, coherence, phase lag, peak amplitude) were obtained through Neuroguide. MATLAB R2007b was used to collate the relevant raw coherence data from the full Neuroguide reports and to run correlations between Time 1 (T1) and Time 2 (T2) for each of the 171 electrode pairings. Data were then exported to Microsoft Excel and SPSS for additional summary and analysis. Note that while eyes-closed data were used here as an illustration of our method, equivalent eyes-open data are available from the authors, upon request.

In order to summarize patterns in the data, the electrode pairings were grouped into seven zones, based on location in the brain. The first region (FP1, F3, F7) represented the left frontal lobe, while zone two (FP2, F4, F8) represented the right frontal lobe. Zones three (C3, T3) and four (C4, T4) represented the left and right centro-temporal areas, respectively, while zones five (T5, P3, O1) and six (T6, P4, O2) represented the left and right posterior areas of the brain. The final zone, zone seven (Fz, Cz, Pz), represented the midline (see Figure 1). The electrode pairings were then coded based on the regions in which the electrodes fell, such that each pairing was given two codes. For example, the coherence between the left prefrontal (FP1) and left posterior (O1) electrodes would be coded for zones one and five, respectively. After all of the electrode pairs were assigned dual-codes, the pairings were regrouped, such that there were groups representing the coherence between the different zones. For example, one group represented the coherence within the left frontal area of the brain, while others represented the coherence between the frontal, centro-temporal and posterior areas in addition to the midline. There were seven zones (see Figure 1), and four EEG bands (delta [0.5–4.0 Hz], theta [4–8 Hz], alpha [8–12 Hz], beta [12–25 Hz]), forming 28 groups in all. The reliability coefficients were then averaged and collapsed within each group, which significantly reduced the number of statistical comparisons.

Within each group, correlations were run for each electrode pair at T1 and T2 in order to calculate the test-retest reliability of the coherences between the

two electrodes. Although a Pearson Product Moment Correlation (*r*) can be interpreted in terms of size, it cannot be directly combined, as it is restricted in range, and is subject to reduced variances near its extremes (i.e., $-1 \leq r \leq 1$; Cohen, Cohen, West, & Aiken, 2003). As such, these correlations were then transformed using the Fisher's *Z'* transformation:

$$[z'_r = \tfrac{1}{2} [\ln (1+r) - \ln (1-r)] \quad (3)$$

This was completed in order to calculate mean reliability coefficients for each of the 28 groups, because previous research has suggested that average $r_{z'}$ values are less biased than average *r*-values (Corey, Dunlap, & Burke, 1998). Additional statistics were then calculated based on these z'_r values (e.g., mean, standard deviation, and standard error of the mean [SEM]) in order to calculate confidence intervals (CI). The average z'_r scores and the confidence intervals were then inverse transformed back to the *r* metric for ease of interpretation. For additional information regarding this transformation, the reader is directed to Cohen, et al. (2003) and Corey et al. (1998).

Finally, the authors used the most and least reliable zones to demonstrate the clinical applicability of these reliability estimates using Equation 1. These metrics were chosen to demonstrate the vast variability in the amount of change needed to establish the effectiveness of a given treatment, based solely on the reliability of the measure being used.

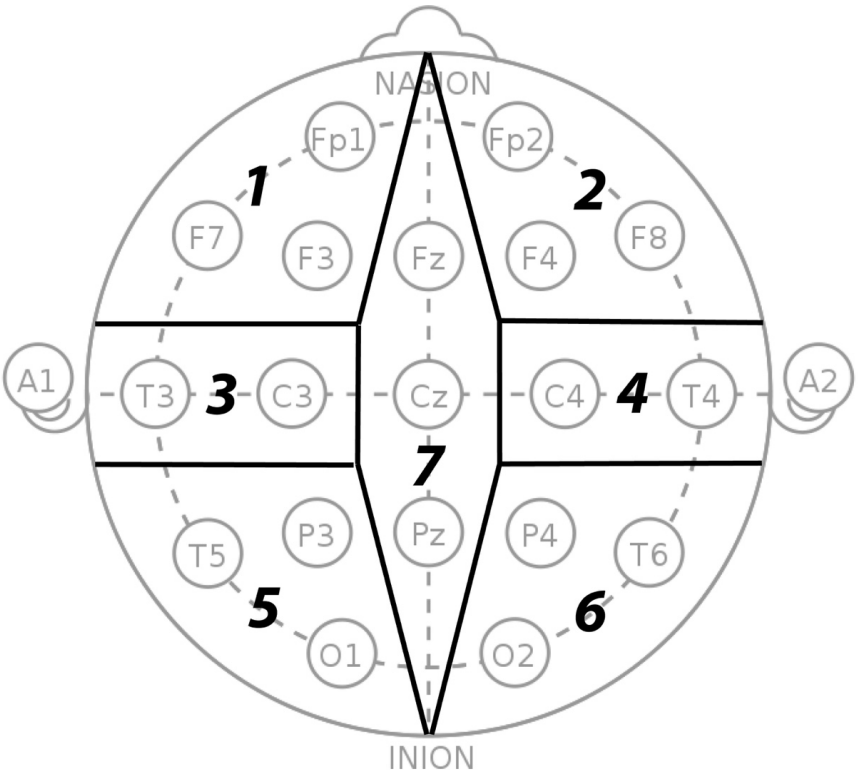

Figure 1. Depiction of the zones used for analysis. The bold black lines demarcate the seven zones as defined above (i.e., Zone 1 represents coherence within the left frontal region, between electrode sites FP1, F3, and F7; Zone 6 represents the coherence between electrodes in the right posterior region, P4, T6, and O2).

Results

Bands

The data were first analyzed by EEG band. Overall, coherence in the alpha band was the most reliable across the two time points, with reliability coefficients ranging from .87 to .97. The next highest reliability for coherence was within the theta range, with reliability coefficients ranging from .83 to .98. Theta was followed by beta (r = .80 to r = .99), and finally delta (r = .74 to r = .96), suggesting that both the low and high extremes are less reliable than the mid-range brain waves. These results are consistent with previous research, which has shown that alpha waves contribute significantly to the base rhythm of electrical activity in the brain, and are frequently associated with the default brain network in resting state with eyes closed (Noachtar et al., 1999).

Coherence within the bands was further analyzed, and additional patterns emerged in specific areas of the brain. For instance, reliability of coherence within zones 3 (T3, C3) and 4 (T4, C4) was the highest of any other areas, regardless of band, with reliability coefficients ranging from r = .86 to r = .97 and r = .82 to r = .98, respectively. On the other hand, the reliability of coherence between anterior and posterior areas of the brain (i.e., zones 1 and 2 with zones 5 and 6) demonstrated the least test-retest reliability, with coefficients ranging from r = .74 to r = .99. This too is consistent with previous literature, in that areas close together have been shown to have higher test-retest reliability for coherence than areas that are further apart.

Zones

Due to the differential pattern of results from the band analysis, the data were also analyzed based on location. Zone 1 had the lowest average reliabilities for coherence (r = .74 to r = .98, mean r = .90), while zone 7 had the highest (r = .90 to r = .98, mean r = .93). In ranking the zones from lowest to highest average reliabilities, zone 1 was followed by zones 2 and 6 (r = .80 to r = .99; r = .74 to r = .98, mean r = .91), zones 5, 3, and 4 (r = .78 to r = .99; r = .84 to r = .98; r = .87 to r = .98, mean r = .92) respectively, and finally, zone 7. Additionally, clearer patterns emerged from these analyses than from those based solely on the type of wave. In fact, the reliability of coherence within zones as well as between zones appeared to cluster together based on bands, and followed different patterns across each area of the brain. For the sake of time and space, these zoned reliability coefficients are depicted in graphical form (see Figure 2). To assess numerical patterns among the mean reliabilities across bands and zones, a two-way (7 zones by 4 bands) ANOVA was conducted on the mean reliability values for each zone and band. We found a main effect of band, $F(3,168) = 15.52$, $p < .0001$, but no effect of zone, $F(6,168) = 1.64$, $p = .14$, and no band by zone interaction, $F(18,168) = 1.42$, $p = .13$. Post-hoc tests revealed that Delta had lower reliability than all other bands, but that no other bands differed from each other. Detailed means for the coherence reliability coefficients, including additional frequency bands, are summarized in Supplementary Table 1, with further detail available upon request from the authors.

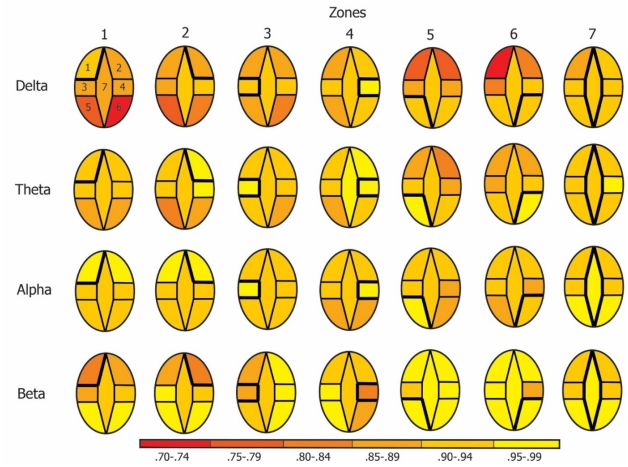

Figure 2. Mean reliabilities by zone and band. For this study, the bands were defined as follows: delta (0.5–4 Hz), theta (4–8 Hz), alpha (8–12 Hz), and beta (12–25 Hz). Reliabilities were generally high (> .90) across zones and bands, with the highest average values in the alpha band, and lowest in the delta band. Within-zone reliabilities, denoted by bold lines, also tended to be higher than cross-zone values.

Reliable Change

As previously reviewed, one of the primary benefits of estimating measurement reliability is to help inform parameters for determining clinically significant change as a result of an intervention. To demonstrate the implications for the impact of reliability on clinically significant outcomes, a case demonstration will be given for using the reliable change method for the least and most reliable individual coherence metrics found in the current study. Starting first with a lower reliability estimate such as Delta O2-F8 coherence, which had a reliability estimate of approximately (r_{12} = .70). To establish Reliability of Change parameters, the coherence reliability metric will first be used to calculate the standard error of measurement:

$$SEM = SD_1 \sqrt{(1-r_{12})}$$

$$SEM = 1 \sqrt{(1-.70)}$$

$$SEM = .55$$

The calculated SEM is then used to calculate the standard error of the difference. Technically, the reliable change equation examines the SEM at two different measurement periods. Here, we assume the reliability estimate for time 1 is also an accurate estimate of the reliability of measurement at time 2. Thus, the standard error of the difference (SE_{diff}) can be calculated as follows:

$$SE_{diff} = \sqrt{(SEM_1)^2 + (SEM_2)^2}$$

$$SE_{diff} = \sqrt{(.55)^2 + (.55)^2}$$

$$SE_{diff} = \sqrt{(.55)^2 + (.55)^2}$$

$$SE_{diff} = \sqrt{.60}$$

$$SE_{diff} = .78$$

The standard error of the difference provides an estimate to be used for confidence intervals. Confidence intervals are arbitrary set values to determine range of score difference needed to conclude a change in score values is beyond what would be expected from measurement error. The 90% confidence interval would be created by multiplying the SE_{diff} by a *z*-score of 1.64. The estimated range (.78*1.64 = 1.28) suggest an obtained *z*-score coherence score with a reliability of .70 would need to change approximately by 1.28 *z*-score points to determine a significantly clinical effect of intervention (e.g., neurofeedback) to be 90% confident. That is, if a client obtained a *z*-score of -2.0 on a *z*-score coherence measure and neurofeedback intervention procedure was implemented to normalize the coherence metric, then a score difference of 1.28 is needed to determine with a 90% confidence level that the intervention has had an impact on the *z*-score metric, which would be obtained with a *z*-score of -.72 or higher (-2.0 + 1.28 = -.72).

To further demonstrate the impact of reliability on treatment outcomes, a confidence interval will be calculated for coherence values with higher reliability metrics such as Beta coherence in FP2-O1, which was (r = .99). Using the same equation as above, the SEM would be .1. Entering this estimate into the SE_{diff} equation would yield an estimate of .14. For establishing 90% confidence intervals, this estimate would be multiplied by 1.64 to yield an estimate of .23. Thus, the standardized coherence value would need to change by an estimate of .23 to conclude a significant amount of change as occurred beyond what may be attributed to measurement error. To allow use by interested clinicians, individual channel pair reliabilities, as well as SE_{diff} values for each channel pair are given in Supplementary Table 2.

Discussion

Overall, the results of this study suggest that the test-retest reliability of coherence is sufficiently high for most areas (i.e., $r \geq .80$). Although not all frequency bands or all areas of the brain demonstrated reliabilities above r = .80, consistent with the power literature, alpha and theta had the highest reliability coefficients. Furthermore, certain patterns emerged, which were also consistent with previous research. For instance, in examining the reliability coefficients by band, the inter-hemispheric reliability of T3-C3 and T4-C4 was the highest of any other areas, across bands. Corsi-Cabrera et al. (2007) found similar results, suggesting that interhemispheric reliabilities tend to be higher than those of intrahemispheric electrode pairs. Also consistent with their study, is that many of the highest reliabilities in the current study involve the right hemisphere (i.e., zone 4, zone 2 with zones 4, 5, and 6), which could be due to the higher coherences typically found in the right hemisphere. In general, the results from the current study demonstrate that qEEG coherence, much like absolute power, is a reliable measure of qEEG.

Additionally, as demonstrated with the above examples, the reliability estimates from qEEG metrics may have a large impact on concluding whether or not a treatment has worked. The current study found a large range of reliability estimates for coherence measures. Although most metrics were considered highly reliable, a fair percentage of metrics had low reliability and some were completely unreliable. Although the causative factors for differences in reliability metrics is unknown and beyond the scope of the current study, coherence values with lower reliability (.70) may require a change in coherence values of over a standard deviation (z = 1.28) due to a large amount of measurement error. In contrast, highly reliable metrics (> .90) require much smaller changes to infer meaningful clinical change (z = .23). The difference in clinical change needed between a highly reliable versus a less reliable metric is over 1 standard deviation. This provides a concrete demonstration of the importance of reliability in

determining treatment outcomes. Given the fact that reliability values may vary differentially across channel pairings, and that this may impact the assessment of clinical effectiveness, both researchers and practitioners may consider incorporating Reliability of Change metrics as part of NF efficacy demonstrations. Although such parameters are not typically provided in most software packages, the current study provides the basic procedures for estimating these parameters.

Limitations

The current sample was sufficiently large to estimate test-retest reliability; however, larger sample sizes generally provide more stable parameter estimates. Future studies may benefit by replicating the current study with larger samples sizes as well as systematically varying the time interval between the measurement periods. Additionally, although the 60 Hz pass filter was used to filter out typically occurring electrical interference, for some subjects the 50 Hz pass filter was also used (e.g., experimenter error), resulting in low estimations of delta, specifically below the 0.5 Hz range, due to overlap in the two filters between 0 Hz and 0.5 Hz. As coherence within the delta range was found to be one of the least reliable, it is possible that these results could be due to this underestimation. Alternatively, delta can be contaminated by EMG and EOG. Thus the method of artifacting used in this study might have included artifact in the delta frequency. Future studies should examine these possibilities.

Clinical Implications for Assessing Intervention Effectiveness

The applications of qEEG are far reaching, as shown by the immense literature base on the topic. The use of qEEG in psychology is growing, and with it, the importance of research such as this study. However, the validity of qEEG for practical applications will always be limited by its measurement reliability. This study focused on test-retest reliability for coherence because it has been less reported in the research, yet has become a primary qEEG measure used in clinical practice. Indeed, as reported by Thatcher, North, and Biver (2005), coherence is a better predictor of IQ and various cognitive abilities than power. Regardless of the mechanism, cognition has consistently been demonstrated to be an important construct within psychology. In fact, qEEG data has already been linked to a variety of neurocognitive profiles, as well as neuropsychiatric disorders, specifically through the measurement of coherence. As such, the reliability and validity of qEEG have become increasingly important. This study has demonstrated consistency with previous literature in showing that coherence is a reliable and stable measure of qEEG, and identified patterns of reliability, which can provide further confidence in the use of such methodology for treating cognitive and/or neuropsychiatric deficiencies. Additionally, the study demonstrated the utility of these reliability estimates in measuring reliable change, thereby extending the utility of qEEG to a progress-monitoring tool as well.

References

Begić, D., Popović-Knapić, V., Grubišin, J., Kosanović-Rajačić, B., Filipčić, I., Telarović, I., & Jakovljević, M. (2011). Quantitative electroencephalography in schizophrenia and depression. *Psychiatria Danubina, 23*(4), 355–362.

Boutros, N. N., Arfken, C., Galderisi, S., Warrick, J., Pratt, G., & Iacono, W. (2008). The status of spectral EEG abnormality as a diagnostic test for schizophrenia. *Schizophrenia Research, 99*(1–3), 225–237. http://dx.doi.org/10.1016/j.schres.2007.11.020

Bozorg, A. M., Lacayo, J. C., & Benbadis, S. R. (2010). The yield of routine outpatient electroencephalograms in the veteran population. *Journal of Clinical Neurophysiology*, *27*(3), 191–192. http://dx.doi.org/10.1097/wnp.0b013e3181e0a950

BrainMaster Discovery 24 (Version 1.8) [Computer software and hardware]. (2011). Bedford, OH: BrainMaster Technologies, Inc.

Burgess, A., & Gruzelier, J. (1993). Individual reliability of amplitude distribution in topographical mapping of EEG. *Electroencephalography and Clinical Neurophysiology, 86*(4), 219–223. http://dx.doi.org/10.1016/0013-4694(93)90101-z

Calzada-Reyes, A., Alvarez-Amador, A., Galán-García, L., & Valdés-Sosa, M. (2012). Electroencephalographic abnormalities in antisocial personality disorder. *Journal of Forensic and Legal Medicine, 19*(1), 29–34. http://dx.doi.org/10.1016/j.jflm.2011.10.002

Cannon, R. L., Baldwin, D. R., Shaw, T. L., Diloreto, D. J., Phillips, S. M., Scruggs, A. M., & Riehl, T. C. (2012). Reliability of quantitative EEG (qEEG) measures and LORETA current source density at 30 days. *Neuroscience Letters*, *518*(1), 27–31. http://dx.doi.org/10.1016/j.neulet.2012.04.035

Cantor, D. S., & Chabot, R. (2009). QEEG Studies in the Assessment and Treatment of Childhood Disorders. *Clinical EEG and Neuroscience, 40*(20), 113–121. http://dx.doi.org/10.1177/155005940904000209

Chabot, R. J., Merkin, H., Wood, L. M., Davenport, T. L., & Serfontein, G. (1996). Sensitivity and specificity of QEEG in children with attention deficit or specific developmental learning disorders. *Clinical EEG and Neuroscience, 27*(1), 26–34. http://dx.doi.org/10.1177/155005949602700105

Christakou, A., Murphy, C. M., Chantiluke, K., Cubillo, A. I., Smith, A. B., Giampietro, V., ... Rubia, K. (2013). Disorder-specific functional abnormalities during sustained attention in youth with Attention Deficit Hyperactivity Disorder (ADHD) and with Autism. *Molecular Psychiatry*, *18*(2), 236–244. http://dx.doi.org/10.1038/mp.2011.85

Christensen, L., & Mendoza, J. L. (1986). A method of assessing change in a single subject: an alteration of the RC index. *Behavior Therapy, 17*, 305–308.

Cohen, J., Cohen, P., West, S. G., & Aiken, L. S. (2003). *Applied multiple regression/correlation analysis for the behavioral sciences* (3rd ed.). Mahwah, NJ: Lawrence Erlbaum Associates.

Corey, D. M., Dunlap, W. P., & Burke, M. J. (1998). Averaging correlations: Expected values and bias in combined Pearson *r*s and Fisher's *z* transformations. *The Journal of General Psychology, 125*(3), 245–261. http://dx.doi.org/10.1080/00221309809595548

Corsi-Cabrera, M., Galindo-Vilchis, L., del-Río-Portilla, Y., Arce, C., & Ramos-Loyo, J. (2007). Within-subject reliability and inter-session stability of EEG power and coherent activity in women evaluated monthly over nine months. *Clinical Neurophysiology, 118*(1), 9–21. http://dx.doi.org/10.1016/j.clinph.2006.08.013

Corsi-Cabrera, M., Solís-Ortiz, S., & Guevara, M. A. (1997). Stability of EEG inter- and intrahemispheric correlation in women. *Electroencephalography and Clinical Neurophysiology*, *102*(3), 248–255. http://dx.doi.org/10.1016/s0013-4694(96)95179-6

Duff, J. (2004). The usefulness of quantitative EEG (QEEG) and neurotherapy in the assessment and treatment of post-concussion syndrome. *Clinical EEG and Neuroscience, 35*(4), 198–209.

Evans, C., Margison, F., & Barkham, M. (1998). The contribution of reliable and clinically significant change methods to evidence-based mental health. *Evidence-Based Mental Health*, *1*(3), 70–72. http://dx.doi.org/10.1136/ebmh.1.3.70

Fernández, T., Harmony, T., Rodríguez, M., Reyes, A., Marosi, E., & Bernal, J. (1993). Test-retest reliability of EEG spectral parameters during cognitive tasks: I Absolute and relative power. *International Journal of Neuroscience*, *68*(3–4), 255–261. http://dx.doi.org/10.3109/00207459308994280

Fonseca, L. C., Tedrus, G. M. A. S., Moraes, C. d., Machado, A. d. V., Almeida, M. P. d., & Oliveira, D. O. F. d. (2008). Epileptiform abnormalities and quantitative EEG in children with attention-deficit/hyperactivity disorder. *Arquivos de Neuro-Psiquiatria, 66*(3a), 462–467. http://dx.doi.org/10.1590/s0004-282x2008000400004

Friedrich, E. V. C., Suttie, N., Sivanathan, A., Lim, T., Louchart, S., & Pineda, J. A. (2014). Brain–computer interface game applications for combined neurofeedback and biofeedback treatment for children on the autism spectrum. *Frontiers in Neuroengineering*, *7*, 21. http://dx.doi.org/10.3389/fneng.2014.00021

Gasser, T., Bächer, P., & Steinberg, H. (1985). Test-retest reliability of spectral parameters of the EEG. *Electroencephalography and Clinical Neurophysiology, 60*(4), 312–319. http://dx.doi.org/10.1016/0013-4694(85)90005-7

Gawel, M., Zalewska, E., Szmidt-Salkowska, E., & Kowalski, J. (2009). The value of quantitative EEG in differential diagnosis of Alzheimer's disease and subcortical vascular dementia. *Journal of the Neurological Sciences, 283*(1–2), 127–133. http://dx.doi.org/10.1016/j.jns.2009.02.332

Gootjes, L., Bouma, A., Van Strien, J. W., Scheltens, P., & Stam, C. J. (2008). Attention modulates hemispheric differences in functional connectivity: Evidence from MEG recordings. *NeuroImage, 30*(1), 245–253. http://dx.doi.org/10.1016/j.neuroimage.2005.09.015

Gruzelier, J. H. (2014). EEG-neurofeedback for optimising performance. III: A review of methodological and theoretical considerations. *Neuroscience and Biobehavioral Reviews, 44,* 159–182. http://dx.doi.org/10.1016/j.neubiorev.2014.03.015

Gudmundsson, S., Runarsson, T. P., Sigurdsson, S., Eiriksdottir, G., & Johnsen, K. (2007). Reliability of quantitative EEG features. *Clinical Neurophysiology, 118*(10), 2162–2171. http://dx.doi.org/10.1016/j.clinph.2007.06.018

Haynes, S. N., Smith, G. T., & Hunsley, J. D. (2011). *Scientific Foundations of Clinical Assessment*. New York, NY: Taylor & Francis/Routledge.

Herrmann, C. S., & Demiralp, T. (2005). Human EEG gamma oscillations in neuropsychiatric disorders. *Clinical Neurophysiology, 116*(12), 2719–2733.

Jacobson, N. S., & Truax, P. (1991). Clinical significance: a statistical approach to defining meaningful change in psychotherapy research. *Journal of Consulting and Clinical Psychology*, *59*(1), 12–19. http://dx.doi.org/10.1037/0022-006x.59.1.12

John, E. R. (1977*). Functional Neuroscience, Vol II: Neurometrics: Clinical Applications of Quantitative Electrophysiology*. Hillsdale, NJ: Lawrence Erlbaum Associates.

Keizer, A. W., Verment, R. S., & Hommel, B. (2010). Enhancing cognitive control through neurofeedback: A role of gamma-band activity in managing episodic retrieval. *NeuroImage*, *49*(4), 3404–3413. http://dx.doi.org/10.1016/j.neuroimage.2009.11.023

Knyazeva, M. G., Jalili, M., Meuli, R., Hasler, M., De Feo, O., & Do, K. Q. (2008). Alpha rhythm and hypofrontality in schizophrenia. *Acta Psychiatrica Scandinavica, 118*(3), 188–199. http://dx.doi.org/10.1111/j.1600-0447.2008.01227.x

Koberda, J. L., Moses, A., Koberda, P., & Koberda, L. (2013). Clinical Advantages of Quantitative Electroencephalogram (QEEG)–Electrical Neuroimaging Application in General Neurology Practice. *Clinical EEG and Neuroscience, 44*(4), 273–285. http://dx.doi.org/10.1177/1550059412475291

Koehler, S., Lauer, P., Schreppel, T., Jacob, C., Heine, M., Boreatti-Hümmer, A., ... Herrmann, M. J. (2009). Increased EEG power density in alpha and theta bands in adult ADHD patients. *Journal of Neural Transmission, 116*(1), 97–104. http://dx.doi.org/10.1007/s00702-008-0157-x

Koek, R. J., Yerevanian, B. I., Tachiki, K. H., Smith, J. C., Alcock, J., & Kopelowicz, A. (1999). Hemispheric asymmetry in depression and mania: A longitudinal QEEG study in bipolar disorder. *Journal of Affective Disorders, 53*(2), 109–122. http://dx.doi.org/10.1016/s0165-0327(98)00171-2

Koles, Z. J., Lind, J. C., & Flor-Henry, P. (2010). Gender differences in brain functional organization during verbal and spatial cognitive challenges. *Brain Topography, 23*(2), 199–204. http://dx.doi.org/10.1007/s10548-009-0119-0

Leuchter, A. F., Cook, I. A., Hunter, A. M., Cai, C., & Horvath, S. (2012). Resting-state quantitative electroencephalography reveals increased neurophysiologic connectivity in depression. *PLoS ONE, 7*(2), e32508. http://dx.doi.org/10.1371/journal.pone.0032508

Lynch, C. J., Uddin, L. Q., Supekar, K., Khouzam, A., Phillips, J., & Menon, V. (2013). Default mode network in childhood autism: posteromedial cortex heterogeneity and relationship with social deficits. *Biological Psychiatry*, *74*(3), 212–219. http://dx.doi.org/10.1016/j.biopsych.2012.12.013

MATLAB (Release 2007b) [Computer software]. (2007). Natick, MA: The Math Works, Inc. Retrieved from: http://www.mathworks.com/products/new_products/release2007b.html

McEvoy, L. K., Smith, M. E., & Gevins, A. (2000). Test-retest reliability of cognitive EEG. *Clinical Neurophysiology, 111*(3), 457–463. http://dx.doi.org/10.1016/s1388-2457(99)00258-8

McGrew, K. S., Schrank, F. A., & Woodcock, R. W. (2007). Technical Manual. *Woodcock-Johnson III Normative Update.* Rolling Meadows, IL: Riverside Publishing.

Minc, D., Machado, S., Bastos, V. H., Machado, D., Cunha, M., Cagy, M., … Ribeiro, R. (2010). Gamma band oscillations under influence of bromazepam during a sensorimotor integration task: An EEG coherence study. *Neuroscience Letters, 469*(1), 145–149. http://dx.doi.org/10.1016/j.neulet.2009.11.062

Miskovic, V., Schmidt, L. A., Boyle, M., & Saigal, S. (2009). Regional electroencephalogram (EEG) spectral power and hemispheric coherence in young adults born at extremely low birth weight. *Clinical Neurophysiology*, *120*(2), 231–238. http://dx.doi.org/10.1016/j.clinph.2008.11.004

Monastra, V. J., Lubar, J. F., Linden, M., VanDeusen, P., Green, G., Wing, W., … Fenger, T. N. (1999). Assessing attention

deficit hyperactivity disorder via quantitative electroencephalography: An initial validation study. *Neuropsychology, 13*(3), 424–433. http://dx.doi.org/10.1037/0894-4105.13.3.424

Murias, M., Swanson, J. M., & Srinivasan, R. (2007). Functional connectivity of frontal cortex in healthy and ADHD children reflected in EEG coherence. *Cerebral Cortex, 17*(8), 1788–1799. http://dx.doi.org/10.1093/cercor/bhl089

Neuroguide (Version 2.6.4) [computer software]. St. Petersburg, FL: Applied Neuroscience, Inc.

Noachtar, S., Binnie, C., Ebersole, J., Mauguière, F., Sakamoto, A., & Westmoreland, B. (1999). A glossary of terms most commonly used by clinical electroencephalographers and proposal for the report form for the EEG findings. The International Federation of Clinical Neurophysiology. *Electroencephalography and Clinical Neurophysiology, Supplement 02*, *52*(1), 21–41. http://dx.doi.org/10.1055/s-2003-812583

Pollock, V. E., Schneider, L. S., & Lyness, S. A. (1991). Reliability of topographic quantitative EEG amplitude in healthy late-middle-aged and elderly subjects. *Electroencephalography and Clinical Neurophysiology, 79*(1), 20–26.

Rappelsberger, P., & Petsche, H. (1988). Probability mapping: Power and coherence analyses of cognitive processes. *Brain Topography, 1*(1), 46–54. http://dx.doi.org/10.1007/bf01129339

Ronne-Engstrom, E., & Winkler, T. (2006). Continuous EEG monitoring in patients with traumatic brain injury reveals a high incidence of epileptiform activity. *Acta Neurologica Scandinavica, 114*(1), 47–53. http://dx.doi.org/10.1111/j.1600-0404.2006.00652.x

Salinsky, M. C., Oken, B. S., & Morehead, L. (1991). Test-retest reliability in EEG frequency analysis. *Electroencephalography and Clinical Neurophysiology, 79*(5), 382–392. http://dx.doi.org/10.1016/0013-4694(91)90203-g

Shaywitz, B. A., Shaywitz, S. E., Pugh, K. R., Constable, R. T., Skudlarski, P., Fulbright, R. K., ... Gore, J. C. (1995). Sex Differences in the Functional Organization of the Brain for Language. *Nature, 373,* 607–609. http://dx.doi.org/10.1038/373607a0

Sheikhani, A., Behnam, H., Mohammadi, M. R., Noroozian, M., & Mohammadi, M. (2012). Detection of abnormalities for diagnosing of children with autism disorders using of quantitative electroencephalography analysis. *Journal of Medical Systems, 36*(2), 957–963. http://dx.doi.org/10.1007/s10916-010-9560-6

Silva, F., Arias-Carrión, O., Teixeira, S., Velasques, B., Peressutti, C., Paes, F., … Ribeiro, P. (2012). Functional coupling of sensorimotor and associative areas during a catching ball task: A qEEG coherence study. *International Archives of Medicine, 5*, 9. http://dx.doi.org/10.1186/1755-7682-5-9

Thatcher, R. W. (2010). Validity and reliability of quantitative electroencephalography. *Journal of Neurotherapy, 14*(2), 122–152. http://dx.doi.org/10.1080/10874201003773500

Thatcher, R. W. (2012). Coherence, phase differences, phase shift, and phase lock in EEG/ERP analyses. *Developmental Neuropsychology*, *37*(6), 476–496. http://dx.doi.org/10.1080/87565641.2011.619241

Thatcher, R. W., Krause, P. J., & Hrybyk, M. (1986). Cortico-cortical associations and EEG coherence: A two-compartmental model. *Electroencephalography and Clinical Neurophysiology, 64*(2), 123–143. http://dx.doi.org/10.1016/0013-4694(86)90107-0

Thatcher, R. W., & Lubar, J. F. (2009). History of the scientific standards of qEEG normative databases. In T. H. Budzynsky, H. K. Budzynski, J. R. Evans, & A. Abarbanel (Eds.), *Introduction to Quantitative EEG and Neurofeedback: Advanced theory and applications* (2nd ed., pp. 29–59). San Diego, CA: Academic Press. http://dx.doi.org/10.1016/b978-0-12-374534-7.00002-2

Thatcher, R. W., North, D. M., & Biver, C. J. (2005). EEG and intelligence: Relations between EEG coherence, EEG phase delay and power. *Clinical Neurophysiology, 116*(9), 2129–2141. http://dx.doi.org/10.1016/j.clinph.2005.04.026

Thatcher, R. W., Walker, R. A., Biver, C., North, D., & Curtin, R. (2003). Quantitative EEG Normative databases: Validation and clinical correlation. *Journal of Neurotherapy, 7*(3–4), 87–122.

Thornton, K. E., & Carmody, D. P. (2009). Eyes-closed and Activation qEEG databases in predicting cognitive effectiveness and the inefficiency hypothesis. *Journal of Neurotherapy, 13*(1), 1–21. http://dx.doi.org/10.1080/10874200802429850

Tucker, D. M., Roth, D. L., & Bair, T. B. (1986). Functional Connections Among Cortical Regions: Topography of EEG Coherence. *Electroencephalography and Clinical Neurophysiology, 63*(3)*,* 242–250. http://dx.doi.org/10.1016/0013-4694(86)90092-1

Velikova, S., Locatelli, M., Insacco, C., Smeraldi, E., Comi, G., & Leocani, L. (2010). Dysfunctional brain circuitry in obsessive-compulsive disorder: Source and coherence analysis of EEG rhythms. *NeuroImage*, *49*(1), 977–983. http://dx.doi.org/10.1016/j.neuroimage.2009.08.015

Volf, N. V., & Razumnikova, O. M. (1999). Sex differences in EEG coherence during a verbal memory task in normal adults. *International Journal of Psychophysiology, 34*(2), 113–122. http://dx.doi.org/10.1016/s0167-8760(99)00067-7

Voyer, D., Voyer, S., & Bryden, M. P. (1995). Magnitude of sex differences in spatial abilities: a meta-analysis and consideration of critical variables. *Psychological Bulletin, 117*(2)*,* 250–270. http://dx.doi.org/10.1037/0033-2909.117.2.250

Wada, Y., Nanbu, Y., Kadoshima, R., Jiang, Z.-Y., Koshino, Y., & Hashimoto, T. (1996). Interhemispheric EEG coherence during photic stimulation: Sex differences in normal young adults. *International Journal of Psychophysiology, 22*(1–2), 45–51. http://dx.doi.org/10.1016/0167-8760(96)00011-6

Wisconsin Card Sorting Test (Computer Version 2) [Computer software]. Lutz, FL: Psychological Assessment Resources, Inc.

Received: January 31, 2016
Accepted: February 24, 2016
Published: March 9, 2016

Appendix

Supplementary Table 1

Detailed means for the coherence reliability coefficients (including additional frequency bands), by zone.

Zone	Delta	Theta	Alpha	Beta	High Beta	Alpha 1	Alpha 2	Beta 1	Beta 2	Beta 3	Mean
	1.0–4.0 Hz	4.0–8.0 Hz	8.0–12.0 Hz	12.0–25.0 Hz	25.0–30.0 Hz	8.0–10.0 Hz	10.0–12.0 Hz	12.0–15.0 Hz	15.0–18.0 Hz	18.0–25.0 Hz	
1	0.85	0.91	0.94	0.91	0.79	0.92	0.92	0.86	0.93	0.84	0.90
2	0.87	0.91	0.94	0.93	0.80	0.92	0.92	0.89	0.94	0.84	0.91
3	0.90	0.93	0.92	0.93	0.82	0.89	0.92	0.89	0.93	0.86	0.92
4	0.91	0.93	0.92	0.92	0.80	0.91	0.90	0.87	0.94	0.83	0.92
5	0.88	0.91	0.92	0.97	0.80	0.88	0.91	0.88	0.97	0.84	0.92
6	0.86	0.90	0.92	0.96	0.81	0.89	0.91	0.90	0.97	0.86	0.91
7	0.92	0.93	0.93	0.95	0.87	0.92	0.92	0.89	0.96	0.89	0.93
Mean	0.89	0.92	0.93	0.94	0.81	0.90	0.91	0.88	0.95	0.85	0.92

Supplementary Table 2

Individual channel pair reliabilities and SE_{diff} values for each channel pair.

		Delta	Theta	Alpha	Beta	High Beta	Gamma
Site1	Site2	1.0–4.0 Hz	4.0–8.0 Hz	8.0–12.0 Hz	12.0–25.0 Hz	25.0–30.0 Hz	30.0–40.0 Hz
FP1	FP2	0.93(5.93)	0.98(3.11)	0.99(2.68)	0.78(12.13)	0.77(13.29)	0.74(13.34)
FP1	F3	0.94(5.72)	0.96(3.88)	0.95(4.87)	0.68(13.78)	0.75(13.27)	0.75(12.47)
FP1	F4	0.86(7.24)	0.94(4.53)	0.96(4.57)	0.82(8.88)	0.80(7.70)	0.72(8.44)
FP1	C3	0.89(5.22)	0.87(5.31)	0.88(8.51)	0.91(5.88)	0.75(5.63)	0.72(6.31)
FP1	C4	0.87(5.92)	0.90(4.69)	0.90(7.13)	0.86(6.17)	0.79(3.62)	0.77(6.54)
FP1	P3	0.82(3.76)	0.88(3.04)	0.92(4.31)	0.99(2.03)	0.76(2.67)	0.83(3.75)
FP1	P4	0.84(3.46)	0.83(3.51)	0.93(4.85)	0.99(1.84)	0.82(2.33)	0.83(5.58)
FP1	O1	0.70(2.47)	0.78(1.38)	0.94(5.52)	0.99(1.62)	0.71(2.24)	0.78(5.43)
FP1	O2	0.65(2.31)	0.85(1.41)	0.95(5.26)	0.99(2.15)	0.64(1.39)	0.92(1.83)
FP1	F7	0.91(7.03)	0.93(5.26)	0.94(5.97)	0.84(8.63)	0.79(10.03)	0.77(11.36)
FP1	F8	0.81(9.56)	0.90(6.49)	0.97(4.89)	0.90(7.10)	0.80(6.64)	0.72(7.56)
FP1	T3	0.87(5.06)	0.88(4.71)	0.92(6.44)	0.94(4.59)	0.77(4.00)	0.77(4.80)
FP1	T4	0.82(5.29)	0.88(4.05)	0.94(4.31)	0.98(2.56)	0.77(2.12)	0.82(4.19)
FP1	T5	0.78(2.71)	0.84(1.72)	0.94(4.74)	0.99(1.7)	0.72(1.88)	0.88(2.69)
FP1	T6	0.74(2.55)	0.86(2.14)	0.95(5.18)	0.99(2.03)	0.83(1.58)	0.82(4.21)
FP1	Fz	0.91(6.10)	0.93(5.17)	0.98(3.13)	0.81(10.82)	0.79(10.98)	0.77(12.33)
FP1	Cz	0.91(5.02)	0.88(5.63)	0.88(8.44)	0.89(6.21)	0.81(4.87)	0.73(6.17)

Supplementary Table 2

Individual channel pair reliabilities and SE_{diff} values for each channel pair.

		Delta	Theta	Alpha	Beta	High Beta	Gamma
Site1	**Site2**	**1.0–4.0 Hz**	**4.0–8.0 Hz**	**8.0–12.0 Hz**	**12.0–25.0 Hz**	**25.0–30.0 Hz**	**30.0–40.0 Hz**
FP1	Pz	0.86(3.55)	0.84(3.60)	0.88(5.37)	0.98(2.53)	0.80(2.49)	0.83(3.42)
FP2	F3	0.91(6.92)	0.95(4.56)	0.93(5.70)	0.72(11.39)	0.77(9.61)	0.79(8.47)
FP2	F4	0.90(6.55)	0.97(3.47)	0.95(4.93)	0.71(13.68)	0.77(13.05)	0.82(12.52)
FP2	C3	0.90(4.93)	0.87(5.27)	0.86(8.76)	0.91(5.76)	0.75(5.92)	0.92(5.48)
FP2	C4	0.89(6.13)	0.93(4.43)	0.89(7.79)	0.84(7.32)	0.76(5.80)	0.70(6.77)
FP2	P3	0.82(3.41)	0.84(3.24)	0.93(4.33)	0.99(1.93)	0.87(3.99)	0.96(4.03)
FP2	P4	0.87(3.54)	0.86(3.66)	0.93(4.77)	0.98(2.20)	0.63(2.90)	0.81(3.20)
FP2	O1	0.72(2.27)	0.74(1.72)	0.94(5.56)	0.99(2.23)	0.51(2.02)	0.86(2.68)
FP2	O2	0.69(2.25)	0.80(1.57)	0.95(5.21)	0.98(2.64)	0.80(3.06)	0.98(2.85)
FP2	F7	0.87(8.16)	0.92(6.09)	0.94(7.02)	0.86(7.63)	0.82(6.75)	0.83(6.55)
FP2	F8	0.87(8.27)	0.94(4.90)	0.96(4.71)	0.81(10.39)	0.84(9.74)	0.85(10.65)
FP2	T3	0.90(3.56)	0.87(4.27)	0.92(6.04)	0.98(2.61)	0.68(3.22)	0.93(4.03)
FP2	T4	0.86(5.97)	0.94(3.91)	0.93(5.01)	0.94(4.19)	0.81(3.59)	0.79(4.63)
FP2	T5	0.76(2.26)	0.77(1.86)	0.94(5.09)	0.99(2.05)	0.89(3.32)	0.98(2.62)
FP2	T6	0.78(2.71)	0.85(2.20)	0.95(4.71)	0.99(2.09)	0.48(2.55)	0.83(2.09)
FP2	Fz	0.90(6.58)	0.94(4.96)	0.97(3.99)	0.79(11.73)	0.82(9.94)	0.84(9.92)
FP2	Cz	0.92(4.92)	0.91(5.31)	0.87(8.81)	0.86(7.46)	0.79(7.37)	0.87(7.72)
FP2	Pz	0.86(3.63)	0.84(3.82)	0.89(5.45)	0.98(2.78)	0.79(4.39)	0.96(3.74)
F3	F4	0.94(5.13)	0.97(3.29)	0.96(4.51)	0.90(5.81)	0.93(5.71)	0.93(5.34)
F3	C3	0.95(4.29)	0.96(3.58)	0.92(7.11)	0.90(6.10)	0.88(7.30)	0.90(6.28)
F3	C4	0.90(5.99)	0.96(4.07)	0.93(7.21)	0.93(5.15)	0.88(5.41)	0.84(7.19)
F3	P3	0.88(5.32)	0.93(4.14)	0.93(4.81)	0.88(4.98)	0.82(4.95)	0.85(5.25)
F3	P4	0.86(5.84)	0.91(4.43)	0.91(4.67)	0.91(4.02)	0.81(3.74)	0.79(5.72)
F3	O1	0.80(4.08)	0.81(2.09)	0.93(4.90)	0.99(1.59)	0.62(2.86)	0.72(5.51)
F3	O2	0.81(3.42)	0.77(1.95)	0.94(5.08)	0.95(2.80)	0.68(2.54)	0.88(3.04)
F3	F7	0.93(5.73)	0.95(5.13)	0.97(4.45)	0.84(9.85)	0.74(13.12)	0.72(14.99)
F3	F8	0.85(8.27)	0.92(5.54)	0.93(6.88)	0.84(6.89)	0.82(4.82)	0.81(4.99)
F3	T3	0.92(5.50)	0.94(4.76)	0.93(6.20)	0.76(7.66)	0.83(6.32)	0.82(6.73)
F3	T4	0.89(5.21)	0.93(3.79)	0.94(4.63)	0.91(3.62)	0.80(2.89)	0.79(5.47)
F3	T5	0.87(4.25)	0.93(2.35)	0.93(4.07)	0.96(2.68)	0.80(2.98)	0.89(3.66)
F3	T6	0.81(3.90)	0.90(1.73)	0.94(4.87)	0.98(2.11)	0.68(2.68)	0.76(4.02)
F3	Fz	0.98(3.28)	0.97(3.47)	0.98(2.86)	0.96(5.16)	0.96(5.49)	0.94(6.43)
F3	Cz	0.92(5.36)	0.95(4.28)	0.93(6.46)	0.89(5.76)	0.89(6.44)	0.89(6.28)

Supplementary Table 2

Individual channel pair reliabilities and SE_{diff} values for each channel pair.

		Delta	Theta	Alpha	Beta	High Beta	Gamma
Site1	**Site2**	**1.0–4.0 Hz**	**4.0–8.0 Hz**	**8.0–12.0 Hz**	**12.0–25.0 Hz**	**25.0–30.0 Hz**	**30.0–40.0 Hz**
F3	Pz	0.88(5.36)	0.91(4.42)	0.90(5.50)	0.90(4.51)	0.85(4.56)	0.84(5.15)
F4	C3	0.93(4.86)	0.94(4.43)	0.89(8.54)	0.96(4.09)	0.90(4.82)	0.94(4.75)
F4	C4	0.95(4.38)	0.97(3.50)	0.94(6.68)	0.95(4.93)	0.95(5.37)	0.88(6.11)
F4	P3	0.87(5.49)	0.89(4.38)	0.92(4.70)	0.98(2.33)	0.75(5.67)	0.95(4.46)
F4	P4	0.90(5.78)	0.92(5.19)	0.91(5.12)	0.98(2.77)	0.84(4.19)	0.81(4.61)
F4	O1	0.85(3.53)	0.73(2.30)	0.93(5.15)	0.99(1.13)	0.56(2.57)	0.83(3.29)
F4	O2	0.87(3.49)	0.70(3.05)	0.92(5.46)	0.99(1.53)	0.70(3.74)	0.95(4.10)
F4	F7	0.83(7.53)	0.88(6.69)	0.94(6.87)	0.89(5.61)	0.87(4.23)	0.89(3.94)
F4	F8	0.89(7.28)	0.98(3.20)	0.98(2.88)	0.90(7.54)	0.86(10.01)	0.87(10.63)
F4	T3	0.90(4.51)	0.91(4.25)	0.92(6.46)	0.97(2.93)	0.72(3.85)	0.88(5.51)
F4	T4	0.92(6.20)	0.97(3.39)	0.95(5.64)	0.89(6.45)	0.81(6.78)	0.70(8.39)
F4	T5	0.85(3.51)	0.84(1.92)	0.94(4.05)	0.99(1.57)	0.72(4.53)	0.98(3.01)
F4	T6	0.89(4.48)	0.90(3.16)	0.92(5.02)	0.99(1.81)	0.75(3.31)	0.82(3.41)
F4	Fz	0.98(2.81)	0.98(3.09)	0.99(2.06)	0.99(2.71)	0.96(4.99)	0.97(4.06)
F4	Cz	0.93(5.21)	0.96(3.96)	0.92(6.80)	0.92(5.14)	0.91(5.73)	0.94(4.86)
F4	Pz	0.89(5.46)	0.90(4.93)	0.90(5.93)	0.97(3.25)	0.83(5.75)	0.91(5.91)
C3	C4	0.95(4.78)	0.96(4.32)	0.93(7.28)	0.92(5.75)	0.92(5.72)	0.88(5.90)
C3	P3	0.95(4.35)	0.95(4.23)	0.95(5.34)	0.92(5.14)	0.87(6.87)	0.90(6.71)
C3	P4	0.90(7.21)	0.94(5.08)	0.94(4.64)	0.97(3.67)	0.90(4.92)	0.86(5.68)
C3	O1	0.87(6.33)	0.88(4.88)	0.90(5.71)	0.97(3.52)	0.79(5.36)	0.78(6.24)
C3	O2	0.88(5.68)	0.87(4.38)	0.88(4.83)	0.97(2.67)	0.79(5.03)	0.91(5.75)
C3	F7	0.86(6.37)	0.91(5.50)	0.91(7.88)	0.89(5.59)	0.83(6.14)	0.83(5.90)
C3	F8	0.88(4.93)	0.93(3.94)	0.87(8.28)	0.98(3.07)	0.79(5.04)	0.93(5.17)
C3	T3	0.92(6.32)	0.97(4.14)	0.96(5.34)	0.86(9.45)	0.88(8.13)	0.87(9.69)
C3	T4	0.91(5.33)	0.94(3.55)	0.91(5.57)	0.97(2.70)	0.76(3.00)	0.78(3.67)
C3	T5	0.92(5.49)	0.94(4.35)	0.89(6.80)	0.94(4.50)	0.83(6.43)	0.89(6.81)
C3	T6	0.84(6.78)	0.90(3.32)	0.89(4.00)	0.99(2.07)	0.81(3.98)	0.82(4.55)
C3	Fz	0.95(3.93)	0.93(4.84)	0.91(8.02)	0.95(4.84)	0.91(5.51)	0.92(5.12)
C3	Cz	0.98(3.11)	0.98(2.80)	0.94(5.51)	0.92(5.69)	0.92(6.38)	0.93(6.06)
C3	Pz	0.93(4.91)	0.94(4.52)	0.95(5.00)	0.96(4.05)	0.90(5.66)	0.93(5.24)
C4	P3	0.92(5.73)	0.89(5.79)	0.92(5.82)	0.90(5.11)	0.85(5.50)	0.83(6.22)
C4	P4	0.94(5.04)	0.95(5.09)	0.94(5.85)	0.91(5.76)	0.91(6.02)	0.90(6.90)
C4	O1	0.90(5.27)	0.87(4.18)	0.88(4.66)	0.96(2.90)	0.65(4.49)	0.75(6.96)

Supplementary Table 2

Individual channel pair reliabilities and SE_{diff} values for each channel pair.

		Delta	Theta	Alpha	Beta	High Beta	Gamma
Site1	**Site2**	**1.0–4.0 Hz**	**4.0–8.0 Hz**	**8.0–12.0 Hz**	**12.0–25.0 Hz**	**25.0–30.0 Hz**	**30.0–40.0 Hz**
C4	O2	0.91(5.17)	0.83(5.85)	0.89(6.20)	0.91(4.15)	0.78(5.83)	0.78(6.79)
C4	F7	0.84(5.03)	0.88(4.96)	0.94(5.65)	0.91(4.25)	0.85(2.67)	0.84(5.87)
C4	F8	0.88(6.50)	0.96(4.04)	0.91(7.60)	0.92(5.41)	0.84(6.05)	0.79(6.49)
C4	T3	0.89(5.28)	0.91(4.42)	0.93(5.38)	0.95(3.34)	0.74(3.33)	0.84(3.66)
C4	T4	0.96(5.23)	0.98(3.03)	0.96(5.27)	0.82(10.79)	0.76(11.86)	0.6(17.68)
C4	T5	0.90(5.12)	0.90(3.33)	0.91(3.22)	0.97(2.32)	0.78(3.26)	0.86(4.14)
C4	T6	0.90(6.05)	0.89(5.87)	0.88(6.04)	0.86(5.76)	0.78(7.13)	0.79(7.85)
C4	Fz	0.95(4.53)	0.96(4.24)	0.93(7.29)	0.93(6.04)	0.94(5.30)	0.88(7.00)
C4	Cz	0.96(4.35)	0.98(2.82)	0.97(4.46)	0.95(4.8)	0.96(5.39)	0.93(5.41)
C4	Pz	0.94(4.64)	0.92(5.08)	0.94(5.75)	0.90(5.37)	0.92(5.89)	0.88(6.45)
P3	P4	0.93(6.11)	0.94(5.14)	0.92(6.54)	0.98(3.19)	0.92(5.20)	0.91(5.53)
P3	O1	0.95(4.79)	0.96(3.87)	0.94(6.65)	0.94(5.29)	0.90(7.12)	0.89(7.39)
P3	O2	0.91(6.02)	0.94(4.39)	0.91(7.80)	0.97(3.62)	0.91(5.70)	0.93(5.94)
P3	F7	0.72(4.75)	0.88(4.10)	0.92(4.52)	0.94(3.44)	0.78(3.15)	0.84(3.87)
P3	F8	0.84(2.46)	0.87(2.64)	0.93(4.13)	0.99(1.58)	0.82(3.73)	0.98(3.01)
P3	T3	0.88(6.61)	0.94(4.77)	0.95(6.07)	0.85(7.76)	0.81(7.64)	0.81(8.97)
P3	T4	0.88(5.51)	0.92(3.37)	0.86(4.29)	0.98(2.24)	0.64(3.17)	0.79(3.70)
P3	T5	0.94(5.14)	0.97(3.31)	0.95(4.70)	0.97(3.53)	0.94(5.24)	0.91(7.08)
P3	T6	0.87(7.71)	0.91(4.69)	0.83(7.38)	0.97(3.01)	0.84(4.93)	0.85(5.38)
P3	Fz	0.90(5.21)	0.91(4.48)	0.93(4.81)	0.98(2.87)	0.79(4.84)	0.86(4.95)
P3	Cz	0.93(5.37)	0.93(4.98)	0.95(5.48)	0.97(3.87)	0.89(5.73)	0.93(5.28)
P3	Pz	0.96(4.27)	0.98(3.08)	0.97(4.22)	0.95(4.16)	0.93(5.70)	0.95(4.94)
P4	O1	0.94(5.00)	0.94(4.08)	0.92(6.39)	0.95(4.17)	0.83(6.65)	0.86(7.66)
P4	O2	0.92(5.55)	0.97(3.65)	0.95(6.06)	0.97(3.54)	0.89(7.12)	0.91(6.50)
P4	F7	0.71(2.91)	0.80(3.47)	0.93(4.69)	0.99(1.66)	0.78(1.54)	0.72(5.34)
P4	F8	0.87(3.66)	0.92(3.52)	0.91(4.72)	0.99(2.25)	0.73(2.90)	0.77(3.81)
P4	T3	0.85(5.35)	0.93(3.33)	0.92(3.81)	0.99(1.88)	0.83(3.05)	0.85(3.55)
P4	T4	0.92(5.99)	0.95(4.41)	0.92(6.67)	0.84(8.08)	0.77(8.27)	0.68(10.95)
P4	T5	0.92(6.14)	0.93(4.35)	0.89(6.82)	0.98(2.43)	0.89(4.17)	0.87(5.61)
P4	T6	0.92(6.46)	0.94(4.55)	0.92(6.18)	0.96(4.15)	0.92(5.88)	0.92(6.11)
P4	Fz	0.90(5.74)	0.92(4.78)	0.89(5.21)	0.98(2.99)	0.88(4.22)	0.86(6.28)
P4	Cz	0.90(7.20)	0.95(5.26)	0.96(5.03)	0.96(4.40)	0.93(4.55)	0.89(5.69)
P4	Pz	0.97(4.03)	0.98(3.12)	0.98(3.69)	0.98(2.65)	0.96(4.70)	0.96(4.31)

Supplementary Table 2

Individual channel pair reliabilities and SE_{diff} values for each channel pair.

		Delta	Theta	Alpha	Beta	High Beta	Gamma
Site1	**Site2**	**1.0–4.0 Hz**	**4.0–8.0 Hz**	**8.0–12.0 Hz**	**12.0–25.0 Hz**	**25.0–30.0 Hz**	**30.0–40.0 Hz**
O1	O2	0.92(5.81)	0.98(3.15)	0.92(6.06)	0.94(4.88)	0.86(8.62)	0.90(7.55)
O1	F7	0.45(1.98)	0.80(1.31)	0.93(5.22)	0.99(1.36)	0.44(2.26)	0.60(6.06)
O1	F8	0.65(1.90)	0.87(1.76)	0.94(5.49)	0.99(1.53)	0.73(1.20)	0.92(1.85)
O1	T3	0.79(5.24)	0.91(3.21)	0.87(5.94)	0.97(3.50)	0.74(6.11)	0.77(6.15)
O1	T4	0.87(4.07)	0.89(1.88)	0.73(3.79)	0.99(1.12)	0.55(2.23)	0.81(4.15)
O1	T5	0.94(4.78)	0.96(3.56)	0.96(4.47)	0.95(5.55)	0.88(9.15)	0.81(11.18)
O1	T6	0.91(6.13)	0.93(4.10)	0.82(8.91)	0.97(3.30)	0.77(6.90)	0.82(7.93)
O1	Fz	0.86(4.00)	0.81(2.25)	0.93(5.28)	0.99(0.97)	0.71(3.55)	0.79(6.19)
O1	Cz	0.91(5.76)	0.90(4.54)	0.90(4.95)	0.98(2.54)	0.76(4.48)	0.80(5.79)
O1	Pz	0.94(4.93)	0.94(4.51)	0.91(7.46)	0.92(5.10)	0.88(6.29)	0.90(5.87)
O2	F7	0.39(1.61)	0.87(1.38)	0.95(5.18)	0.98(2.10)	0.61(1.47)	0.91(2.09)
O2	F8	0.70(1.75)	0.79(1.66)	0.94(5.20)	0.99(1.57)	0.85(2.46)	0.97(2.88)
O2	T3	0.73(4.14)	0.91(2.10)	0.89(3.83)	0.99(1.81)	0.72(3.82)	0.86(5.51)
O2	T4	0.85(5.06)	0.85(3.69)	0.84(5.42)	0.93(3.71)	0.72(5.05)	0.73(5.43)
O2	T5	0.89(6.20)	0.96(3.59)	0.90(7.10)	0.96(3.72)	0.88(6.44)	0.94(6.20)
O2	T6	0.91(7.08)	0.94(4.63)	0.96(4.62)	0.91(6.04)	0.85(9.53)	0.84(10.14)
O2	Fz	0.87(3.60)	0.75(2.62)	0.92(5.54)	0.99(1.32)	0.67(2.87)	0.86(3.56)
O2	Cz	0.91(5.46)	0.87(5.25)	0.86(5.72)	0.99(2.04)	0.81(5.13)	0.92(5.61)
O2	Pz	0.92(5.72)	0.94(4.76)	0.93(7.25)	0.94(4.61)	0.92(5.42)	0.91(6.43)
F7	F8	0.79(7.25)	0.88(6.13)	0.94(6.99)	0.93(4.75)	0.87(2.89)	0.90(3.11)
F7	T3	0.83(7.83)	0.92(5.13)	0.92(6.43)	0.78(7.73)	0.81(7.28)	0.83(6.94)
F7	T4	0.84(2.80)	0.86(3.16)	0.95(3.28)	0.98(1.70)	0.71(1.32)	0.89(3.38)
F7	T5	0.77(3.31)	0.90(2.28)	0.93(4.25)	0.98(2.22)	0.70(2.79)	0.87(3.24)
F7	T6	0.68(1.61)	0.88(2.32)	0.94(5.51)	0.98(2.21)	0.55(2.13)	0.72(3.59)
F7	Fz	0.86(6.96)	0.90(6.58)	0.95(6.38)	0.90(6.36)	0.89(5.33)	0.87(6.69)
F7	Cz	0.84(5.90)	0.89(5.79)	0.92(7.52)	0.85(5.87)	0.83(3.92)	0.86(4.37)
F7	Pz	0.77(4.03)	0.82(4.29)	0.89(5.09)	0.96(2.82)	0.83(1.98)	0.86(3.19)
F8	T3	0.83(3.12)	0.91(2.70)	0.93(5.21)	0.99(1.45)	0.66(2.81)	0.93(4.11)
F8	T4	0.91(5.88)	0.96(4.09)	0.93(6.03)	0.90(6.68)	0.82(7.43)	0.78(7.28)
F8	T5	0.71(1.63)	0.86(1.82)	0.94(5.03)	0.99(1.86)	0.80(3.49)	0.99(2.09)
F8	T6	0.80(3.15)	0.91(2.28)	0.93(4.76)	0.99(1.56)	0.69(2.51)	0.78(3.12)
F8	Fz	0.87(7.77)	0.94(5.37)	0.96(4.96)	0.92(5.97)	0.85(6.01)	0.84(6.50)
F8	Cz	0.89(5.93)	0.95(4.32)	0.89(8.62)	0.92(5.17)	0.84(4.77)	0.93(4.99)

Supplementary Table 2

Individual channel pair reliabilities and SE_{diff} values for each channel pair.

		Delta	Theta	Alpha	Beta	High Beta	Gamma
Site1	**Site2**	**1.0–4.0 Hz**	**4.0–8.0 Hz**	**8.0–12.0 Hz**	**12.0–25.0 Hz**	**25.0–30.0 Hz**	**30.0–40.0 Hz**
F8	Pz	0.85(3.58)	0.89(3.18)	0.89(5.50)	0.98(2.45)	0.80(4.95)	0.94(4.91)
T3	T4	0.84(3.50)	0.89(2.02)	0.91(3.35)	0.99(1.77)	0.63(1.29)	0.90(1.41)
T3	T5	0.89(6.10)	0.93(4.82)	0.87(7.26)	0.85(7.61)	0.83(7.64)	0.83(8.89)
T3	T6	0.76(3.87)	0.79(2.25)	0.92(3.49)	0.99(1.46)	0.80(2.13)	0.83(2.80)
T3	Fz	0.91(4.96)	0.92(4.80)	0.93(6.40)	0.94(4.50)	0.84(3.90)	0.82(5.24)
T3	Cz	0.91(5.61)	0.94(4.70)	0.95(6.24)	0.90(5.82)	0.80(4.94)	0.86(6.64)
T3	Pz	0.85(6.09)	0.93(4.16)	0.95(4.85)	0.94(4.68)	0.82(5.51)	0.87(6.78)
T4	T5	0.89(3.45)	0.87(1.61)	0.84(3.04)	0.99(1.41)	0.68(1.47)	0.92(1.84)
T4	T6	0.91(5.67)	0.92(4.73)	0.89(6.34)	0.82(7.64)	0.73(9.07)	0.68(10.65)
T4	Fz	0.92(5.28)	0.95(3.90)	0.95(5.08)	0.92(4.84)	0.79(4.27)	0.69(6.95)
T4	Cz	0.94(5.40)	0.97(3.44)	0.93(6.24)	0.87(6.32)	0.73(5.67)	0.65(6.54)
T4	Pz	0.92(5.28)	0.94(3.79)	0.88(6.47)	0.91(4.98)	0.77(5.23)	0.71(6.30)
T5	T6	0.90(5.91)	0.90(3.51)	0.87(6.83)	0.99(2.19)	0.84(3.64)	0.88(4.05)
T5	Fz	0.88(3.86)	0.90(2.18)	0.94(4.06)	0.99(1.68)	0.77(2.54)	0.88(3.63)
T5	Cz	0.92(5.25)	0.94(3.67)	0.93(4.03)	0.99(1.88)	0.85(5.59)	0.94(5.29)
T5	Pz	0.93(5.62)	0.96(4.09)	0.91(7.04)	0.94(4.36)	0.88(6.23)	0.90(6.90)
T6	Fz	0.87(4.27)	0.90(2.43)	0.93(4.97)	0.99(1.61)	0.83(3.26)	0.84(4.94)
T6	Cz	0.87(6.93)	0.89(4.97)	0.84(5.22)	0.97(3.06)	0.82(4.36)	0.85(4.42)
T6	Pz	0.89(7.46)	0.92(5.51)	0.86(7.17)	0.95(3.84)	0.84(6.79)	0.84(7.08)
Fz	Cz	0.97(3.49)	0.95(4.25)	0.94(5.87)	0.97(3.53)	0.95(5.22)	0.95(4.82)
Fz	Pz	0.91(5.25)	0.90(4.95)	0.90(5.92)	0.96(3.77)	0.86(4.60)	0.85(5.16)
Cz	Pz	0.94(4.53)	0.94(4.60)	0.95(5.12)	0.90(5.78)	0.94(4.75)	0.94(5.05)

NeuroRegulation

EEG Patterns Under Positive/Negative Body Postures and Emotion Recall Tasks

Hsin-Yi Tsai[1], Erik Peper[2], and I-Mei Lin[1]*

[1]Department of Psychology, College of Humanities and Social Sciences, Kaohsiung Medical University, Taiwan
[2]Institute for Holistic Health Studies, San Francisco State University, California, USA

Abstract

Introduction: Erect and slouch body postures affect access to positive and negative emotions. In an erect sitting posture participants reported more positive emotion and thoughts, while in a slouch position they reported more negative emotion and thoughts. This study explored the electroencephalogram (EEG) patterns under erect and slouch body postures while recalling positive and negative events. **Methods:** Twenty-eight healthy college students were instructed to sit quietly with their eyes closed for 1 min, and then to sit in erect or slouch postures while recalling happy or depressive events for 1 min each. EEG, with linked-ear references, was recorded at Cz and analyzed under five conditions. **Results:** There were significantly higher amplitudes of beta2, beta3, and beta4 in a slouch posture while recalling happy events than in an erect posture while recalling happy or depressive events. There was no significant difference between body posture and emotional recall on low-frequency oscillatory activity. The reaction time was significantly longer to access positive event in the slouched position as compared to the erect position. **Conclusion**: Evoking positive thoughts in a slouch body position takes more effort or arousal than other positions as indicated by the significant increase in high-frequency oscillatory activities. The implication for cognitive behavior therapy is that body posture matters; clients have more difficulty shifting to evoking a positive emotional state when sitting in a collapsed position than when sitting in an erect position.

Keywords: electroencephalogram; body posture; emotional recall; depression

Citation: Tsai, H.-Y., Peper, E., & Lin, I.-M. (2016). EEG Patterns Under Positive/Negative Body Postures and Emotion Recall Tasks. *NeuroRegulation*, *3*(1), 23–27. http://dx.doi.org/10.15540/nr.3.1.23

***Address correspondence to**: I-Mei Lin, PhD, 100, Shih-Chuan 1st Road, Kaohsiung 80708, Taiwan. Email: psyiml@kmu.edu.tw

Edited by:
Nancy L. Wigton, PhD, Grand Canyon University, Phoenix, Arizona, USA

Reviewed by:
Rex Cannon, PhD, Neural Potential, Boynton Beach, Florida, USA
Randall Lyle, PhD, Mount Mercy University, Cedar Rapids, Iowa, USA

Introduction

Body posture might affect our mental state, emotion, and memory recall (Michalak, Micschnat, & Teismann, 2014; Peper & Lin, 2012). Peper and Lin have found that walking in a slouch posture may decrease subjective energy and increase negative emotion, such as sadness, loneliness, isolation, and sleepiness. This slouch posture accompanied feelings of "wanting to just sit down", "low energy," "depressive feelings," or being "zombie-like." While walking in an erect posture and skipping, participants increased their subjective energy and experienced more energetic, happy, and positive feeling. In addition, they found that the erect posture makes subjects much stronger to resist the downward pressure compared to the collapsed position. Nair et al. (2015) found that a slumped posture compared to an upright posture increased the emotional state of high negative arousals including fear, hostility, and nervousness. They also found that an upright-seated posture compared to a slumped posture had a protective effect on the emotion when experiencing a psychological stressor.

The effect of posture on access to positive or negative memories was demonstrated by Wilson and Peper (2004), who found that negative thoughts and memories were easier to access in a collapsed-slump position and that positive thoughts were easier to access when sitting in an upright position.

Michalak et al. (2014) found that patients with depression recalled more negative words in a slump posture, which indicated a recall bias depending upon posture. However, the recall bias of positive and negative words did not occur under an upright sitting posture.

Thibault, Lifshitz, Jones, and Raz (2014) and Zhavoronkova, Zharikova, Kushnir, and Mikhalkova (2012) explored the associations between changes in body posture and electroencephalogram (EEG) activity. Thibault et al. found increased beta (14–30 Hz) and gamma (30–50 Hz) activities in the frontal and occipital regions from lying supine to 45° recline, as well as from 45° recline to sitting upright. Zhavoronkova et al. also found that there were increased beta (12.3–30.1 Hz) and gamma (30.1–40.2 Hz) activities at the parietal and occipital areas from lying to sitting position, whereas there were decreased delta (2.0–3.9 Hz), theta (4.3–7.8 Hz), and alpha (8.1–12.1 Hz) activities from lying to sitting position. In addition, there were increased alpha2 (10.5–12.1 Hz), beta (12.3–30.1 Hz), and gamma (30.1–40.2 Hz) activities from sitting to upright positions (Zhavoronkova et al., 2012). Changes in body posture (e.g., from lying supine to sitting, from sitting to upright) increase high-frequency oscillatory activities.

Previous studies have confirmed changes in body posture related to subject's feelings, memory recall, and brain activity. However, the brain activity when combining the body posture and emotional recall is unknown. The purpose of this study was to explore the EEG patterns under erect or slouch postures while recalling happy or depressive events.

Methods

Participants

Twenty-nine college students were recruited from the Kaohsiung Medical University; one participant was excluded from data analysis due to EEG recording problems. The mean age of the students was 20.64 years (*SD* = 1.06) with 3 men and 25 women. All participants were instructed not to drink caffeinated beverages on the day of the study. Institutional Review Board approval was obtained from the ethics committee of the Kaohsiung Medical University Hospital, and written informed consent was obtained from each participant before the experiment.

Experimental Procedure

Participants were asked to fill out demographic and psychological questionnaires and then sat in a comfortable posture on a sofa. The research procedure consisted of a 2 (erect and slouch postures; Figure 1) × 2 (recalling happy or depressive events) Latin Square design.

Figure 1. The erect and slouch postures.

The experimental stages consisted of a 1-min resting baseline with eyes closed, and then the participants were assigned randomly to experience A–D stages with eyes closed for 1 min each (Figure 2): (A) erect posture while recalling happy event; (B) erect posture while recalling depressive event; (C) slouch posture while recalling happy event; or (D) slouch posture while recalling depressive event.

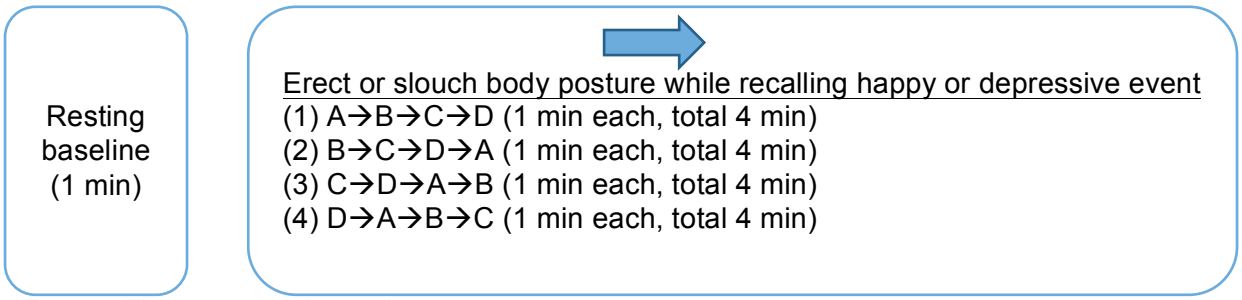

Figure 2. The experimental procedure.

In the erect posture participants were asked to look up and straighten their back, whereas in the slouch posture participants were asked to lower their heads, look down, and sit hunch-backed. The instructions for recalling happy and depressive events were as follows:

> ***Instructions for recalling a happy event****: Please keep the same posture and recall a happy memory from your past. We experience joyful things such as doing the activities we enjoy, getting good scores on exams, gathering with friends, and striving for success. The feeling is very happy and joyful. Now please recall something happy. When you recall such a memory, let me know with a nod. Please maintain the happy feeling for 1 min. When the time is up, I will let you know.*
>
> ***Instructions for recalling a depressive event****: Please keep the same posture and recall a depressive memory from your past. We experience melancholy such as feeling hopeless and helpless, pressure from work, or the stress of school, work, and relationships. The feeling is very depressing and sad. Now please recall something depressive. When you recall such a memory, let me know with a nod. Please maintain the depressive feeling for 1 min. When the time is up, I will let you know.*

After recalling a happy or a depressive event, participants were asked to rate a score from 0 to 100 in relation to how easy it was to recall that event (0 = not easy at all, 100 = extremely easy). The reaction time was recorded when participants nodded their head to tell the researcher that they had a happy or a depressive event come into their mind.

EEG Recording

The one-channel EEG sensor was recorded from Cz with linked-ear reference based on the International 10-20 system. EEG signals were recorded using BioGraph Infiniti software (Version 6.0.4, n.d.) with a band-pass between 1–30 Hz. The sample rate was 256 Hz with 60-Hz notch filters, and the electrode impedances were lower than 5 kΩ.

Data Reduction and Statistical Analysis

After removing eye-blink and movement artifacts, the raw signals of the EEG were analyzed to calculate the EEG amplitude using the following bandwidth: total theta (4–8 Hz), total alpha (8–12 Hz), total beta (12–32 Hz), beta1 (12–15 Hz), beta2 (15–22 Hz), beta3 (22–28 Hz), and beta4 (28–32 Hz) from the five experimental stages. One-way analysis of variance (ANOVA) with repeated measures was used to examine the differences in the EEG amplitudes under the five experimental stages. The analysis was performed using SPSS predictive analytics software (Version 20.0).

Results

The participants reported that it was significantly easier to evoke depressive events in the slouch posture than in the erect posture (70.45 and 63.45), and evoke happiness events in the erect posture than in the slouch posture (80.69 and 73.83), as shown in Table 1. It took significantly longer to recall happy events (7.33 s) in the collapsed position than erect position (3.85 s). In addition, there was shorter reaction time in erect posture for recalling happy events than other conditions (F = 3.52, p < .5).

Table 1

The score of ease to recall and reaction time under different experimental stages.

Variables	Erect while recalling happy event (A)	Erect while recalling depressive event (B)	Slouch while recalling happy event (C)	Slouch while recalling depressive event (D)	*F*	*Post hoc* Comparison
Score of ease to recall	80.69 (13.21)	63.45 (23.83)	73.83 (20.34)	70.45 (19.98)	4.26*	1 > 2, 4; 4 > 2
Reaction time, in seconds	3.85 (4.86)	11.74 (18.25)	7.33 (9.51)	10.96 (13.33)	3.52*	1 < 2, 3, 4

Note. *p < .05.

There were significant differences between the five stages in total beta, beta2, beta3, and beta4 (F = 4.01, p < .05; F = 4.93, p < .01; F = 9.77, p < .001; and F = 17.87, p < .001, respectively). The *post hoc* comparison found the following results (Table 2): (1) while recalling a happy event, there were significantly higher amplitudes of total beta, beta2, beta3, and beta4 in a slouch posture than in an erect posture; (2) while recalling a depressive event, there were significantly higher amplitudes of beta3 and beta4 in a slouch posture than in an erect posture; (3) under congruent body posture and emotional event (sitting collapsed and recalling depressive events; sitting erect and recalling positive events), there was no significant difference in brain activity between the experimental stages; and (4) under incongruent body posture and emotional event (sitting collapsed and recalling positive emotional events; sitting erect and recalling depressive events), there were significantly higher amplitudes of beta2, beta3, and beta4 in a slouch posture with recalling happy events than in an erect posture with recalling depressive events.

Table 2

The EEG amplitude under different experimental stages.

Variables	Baseline (1)	Erect while recalling happy event (A)	Erect while recalling depressive event (B)	Slouch while recalling happy event (C)	Slouch while recalling depressive event (D)	*F*	*Post hoc* Comparison
Total theta	12.51 (5.60)	11.27 (5.22)	11.62 (5.58)	11.49 (5.46)	11.58 (5.38)	6.00***	1 > 2, 3, 4, 5
Total alpha	16.86 (6.10)	15.00 (6.35)	15.26 (6.53)	15.44 (6.13)	15.33 (6.53)	4.09**	1 > 2
Total beta	10.37 (2.26)	9.94 (2.56)	9.87 (2.50)	10.73 (2.66)	10.70 (2.97)	4.01*	1 > 3; 4 > 2
Beta1	5.20 (1.45)	5.02 (1.55)	5.14 (1.55)	5.24 (1.73)	5.31 (1.71)	1.02	
Beta2	6.60 (1.49)	6.10 (1.57)	6.09 (1.60)	6.64 (1.64)	6.60 (1.85)	4.93**	1 > 2, 3; 4 > 2, 3
Beta3	4.16 (0.88)	4.14 (0.98)	4.00 (1.04)	4.72 (1.10)	4.65 (1.35)	9.77***	4 > 1, 2, 3; 5 > 3
Beta4	2.80 (0.54)	2.74 (0.59)	2.61 (0.66)	3.45 (0.77)	3.24 (0.95)	17.87***	1 > 3; 4 > 1, 2, 3; 5 > 1, 3

Note. *p < .05. **p < .01. ***p < .001.

(1) 4 > 3 indicated that under incongruent of body posture and emotion recall there were higher beta2, beta3, and beta4 at slouch posture while recalling happiness event than that at erect posture while recalling depressive event.

(2) 4 > 2 indicated that under recalling happy events there were higher beta 2, beta3, and beta4 at slouch posture than at erect posture.

Discussion

The initial results of this study found that the collapsed posture while recalling positive emotional events had higher beta activities than the other conditions. These results were consistent with the findings of Thibault et al. (2014) and Zhavoronkova et al. (2012) who found increased high-frequency brain activity (such as beta and gamma) under changing body posture. However, this study found that, independent of the body position, recalling happy events in a collapsed position significantly increased the high-frequency oscillatory activity than recalling depressive event in an erect posture. This suggests that it takes much more effort and time to evoke and maintain positive thoughts in a collapsed position. This was also confirmed by the significant increase in reaction time when attempting to recall positive events in the collapsed body position as compared to the erect body position.

This may have significant implications for people who are depressed. Most depressed people or patients have a slumped collapsed posture which would inhibit accessing positive thoughts, thus augmenting their depressive thoughts. To increase

the access to positive thoughts, the person would need to sit erect and look up. In this position, positive and negative thoughts can equally be accessed. Most likely these patterns have been classically conditioned since early childhood.

The EEG findings could explain why subjects reported that it was easier to evoke depressive events as compared to happy events in a collapsed posture because it took more effort and time to think of positive thoughts as indicated by the increase in beta amplitude and reaction time. The EEG finding could not explain why positive thoughts were more easily recalled in the upright posture. Possibly other EEG locations (e.g., left and right frontal) should have been recorded, or an explanation may be because the subjects were healthy students without a history of depression.

Several limitations should be noted in this study. First, most participants were women and gender differences may influence EEG patterns. Second, the recall of memory was a subjective experience, and the quality and intensity of the memory recall may vary between participants, which could affect the findings. Third, the exact psychophysiological mechanisms of posture and emotional regulation remain unknown. Fourth, the EEG recording was only from Cz, and possibly other locations such as frontal EEG may offer more information. Fifth, the study was a cross-sectional study of college students, which limits the generalization to other populations.

In conclusion, this study indicated that body postures and emotional recall were related to high-frequency brainwaves inhibiting the access of positive thoughts in a collapsed position. The finding may have significant implications for people who experience depression. Sitting collapsed will tend to increase access to negative thoughts and emotions and limit access to positive thoughts and emotions, while sitting erect will tend to increase access of positive thoughts and emotions.

Acknowledgements

We greatly thank San-Yu Wang, Ying-Ju Chen, Chia-I Ko, and Pin-Chun Chou for data collection.

References

Michalak, J., Mischnat, J., & Teismann, T. (2014). Sitting posture makes a difference—embodiment effects on depressive memory bias. *Clinical Psychology and Psychotherapy*, *21*(6), 519–524. http://dx.doi.org/10.1002/cpp.1890

Nair, S., Sagar, M., Sollers III, J., Consedine, N., & Broadbent, E. (2015). Do slumped and upright postures affect stress responses? A randomized trial. *Health Psychology*, *34*(6), 632–641. http://dx.doi.org/10.1037/hea0000146

Peper, E., & Lin, I.-M. (2012). Increase or decrease depression: How body postures influence your energy level. *Biofeedback*, *40*(3), 125–130. http://dx.doi.org/10.5298/1081-5937-40.3.01

Thibault, R. T., Lifshitz, M., Jones, J. M., & Raz, A. (2014). Posture alters human resting-state. *Cortex*, *58*, 199–205. http://dx.doi.org/10.1016 /j.cortex.2014.06.014

BioGraph Infiniti (Version 6.0.4) [Computer software]. Quebec, Canada: Thought Technology Ltd. Retrieved from: http://thoughttechnology.com/index.php/software/biograph-infiniti-software-platform.html

Wilson, V. E., & Peper, E. (2004). The effects of upright and slumped postures on the recall of positive and negative thoughts. *Applied Psychophysiology and Biofeedback*, *29*(3), 189–195. http://dx.doi.org/10.1023/B:APBI.0000039057.32963.34

Zhavoronkova, L. A., Zharikova, A. V., Kushnir, E. M., & Mikhalkova, A. A. (2012). EEG markers of upright posture in healthy individuals. *Human Physiology*, *38*(6), 604–612. http://dx.doi.org/10.1134/S0362119712050131

Received: February 19, 2016
Accepted: March 5, 2016
Published: March 9, 2016

NeuroRegulation

Functional Neural Network Connectivity in Myalgic Encephalomyelitis

Marcie L. Zinn[*], *Mark A. Zinn, and Leonard A. Jason*

Center for Community Research, DePaul University, Illinois, USA

Abstract

Myalgic Encephalomyelitis (ME) is a chronic illness with debilitating neurocognitive impairment that remains poorly understood. Previous studies have characterized cognitive deficits as a process by which brain abnormalities are inferred from pre-established testing paradigms using neuroimaging with low temporal resolution. Unfortunately, this approach has been shown to provide limited predictive power, rendering it inadequate for the study of neuronal communication between synchronized regions. More recent developments have highlighted the importance of modeling spatiotemporal dynamic interactions within and between large-scale and small-scale neural networks on a millisecond time scale. Here, we focus on recent emergent principles of complex cortical systems, suggesting how subtle disruptions of network properties could be related to significant disruptions in cognition and behavior found in ME. This review, therefore, discusses how electrical neuroimaging methods with time-dependent metrics (e.g., coherence, phase, cross-frequency coupling) can be a useful approach for the understanding of the cognitive symptoms in ME. By providing a platform for utilizing real-time alterations of the perpetual signals as an outcome, the disruptions to higher-level cognition typically seen in ME can be readily identified, creating new opportunities for better diagnosis and targeted treatments.

Keywords: myalgic encephalomyelitis; chronic fatigue syndrome; functional connectivity; resting-state networks; quantitative EEG (qEEG); electrical neuroimaging

Citation: Zinn, M. L., Zinn, M. A., & Jason, L. A. (2016). Functional Neural Network Connectivity in Myalgic Encephalomyelitis. *NeuroRegulation*, *3*(1), 28–50. http://dx.doi.org/10.15540/nr.3.1.28

***Address correspondence to**: Marcie L. Zinn, PhD, Center for Community Research, DePaul University, 990 W. Fullerton Avenue, Chicago, IL 60614-3504, USA. Email: mzinn1@depaul.edu

Edited by:
Rex Cannon, PhD, Neural Potential, Boynton Beach, Florida, USA

Reviewed by:
Rex Cannon, PhD, Neural Potential, Boynton Beach, Florida, USA
Randall Lyle, PhD, Mount Mercy University, Cedar Rapids, Iowa, USA

Introduction

The 19th-century neurologist John Hughlings Jackson (1835–1911) once said that a major impediment in understanding a neurological disease is a lack of a method for doing so (York & Steinberg, 2011). This problem has challenged the investigation of neurological disease for over a century and, more recently, has posed a significant challenge for the study of Myalgic Encephalomyelitis (ME).[1] ME is a complex, multi-system disease that has remained poorly understood despite decades of empirical research (Afari & Buchwald, 2003; Cockshell & Mathias, 2014; Jason, Zinn, & Zinn, 2015). The most debilitating symptoms pertain to neurocognitive dysfunction; that is, symptoms such as memory impairment, poor concentration and attention, and slow information processing speed are reported by nearly all (at least 90% of) patients as having a severe impact on their everyday living (Capuron et al., 2006; Cho, Skowera, Cleare, & Wessely, 2006; Cook, O'Connor, Lange, & Steffener, 2007; Lange et al., 2005; Marshall, Forstot, Callies, Peterson, & Schenck, 1997; Michiels & Cluydts, 2001; Ropper & Samuels, 2009; Sandman, Barron, Nackoul, Goldstein, & Fidler, 1993; Yancey & Thomas, 2012). This contrasts with a neuropsychological research base documenting only modest levels of cognitive impairment (Attree, Arroll, Dancey, Griffith, & Bansal, 2014; Cockshell & Mathias, 2014; DeLuca, Genova, Capili, & Wylie, 2009) and a paucity of studies investigating the relationship with fatigue severity, sleep quality, and quality of life (Christodoulou et al., 1998; Metzger &

[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.

Denney, 2002; Tiersky et al., 2001; Tiersky, Johnson, Lange, Natelson, & DeLuca, 1997). These paradoxical results might be explainable, however, if one considers the historical context whereby neuropsychological and neuroimaging findings typically do not align well with patient self-reports for patients with brain diseases (DeLuca, 2005; Hillary & DeLuca, 2007; Luria, 1980).

A number of studies using neuropsychological test batteries have provided some support for neurocognitive deficits in ME (Cairns & Hotopf, 2005; Chen, Feng, Zhao, Yin, & Wang, 2008; Deluca et al., 2004; Majer et al., 2008; Michiels & Cluydts, 2001; Thomas & Smith, 2009), while others did not (Cope, Pernet, Kendall, & David, 1995; Krupp, Sliwinski, Masur, Friedberg, & Coyle, 1994; Short, McCabe, & Tooley, 2002). Neurocognitive deficits reported by patients include a lack of mental clarity/mental confusion, sustained attention deficits, verbal working memory deficits, longer reaction times, trouble with multitasking or learning, and problems with response inhibition (Christley, Duffy, Everall, & Martin, 2013; Cockshell & Mathias, 2010; Dobbs, Dobbs, & Kiss, 2001; Hou et al., 2013; Wearden & Appleby, 1997). Notably, these findings have been shown by several authors to be unrelated to psychiatric issues, such as depression, anxiety, etc. (Cockshell & Mathias, 2010, 2012, 2014; Dickson, Toft, & O'Carroll, 2009; Smith, Behan, Bell, Millar, & Bakheit, 1993) as well as pain and medication effects (Attree et al., 2014; Christodoulou et al., 1998; Cockshell & Mathias, 2014; Dickson et al., 2009; Santamarina-Perez et al., 2011).

The assessment of psychiatric influences on neurological symptoms has been studied for a long period of time (Strauss, Sherman, & Spreen, 2006) and remnants of this debate coupled with the continued absence of an established biomarker appear to be, in part, what is contributing to controversy over whether ME is a manifestation of psychopathology (Cope & David, 1996) or an independent neurological disorder (DeLuca et al., 2009). Some investigators have suggested that patients with ME may be exaggerating cognitive symptoms (Ocon, 2013), setting unrealistic expectations (Metzger & Denney, 2002) or underperforming due to lack of effort (Goedendorp, Bleijenberg, & Knoop, 2014). Others posit that emotional or psychological factors are likely responsible for ME symptomology (Cope et al., 1995; Fry & Martin, 1996; Mariman et al., 2013; Warren, Langenberg, & Clauw, 2013; White, 2010), suggesting environmental effects (Wearden & Appleby, 1997) or cultural effects, both resulting in sickness behavior (Abbey & Garfinkel, 1991). More broadly, among neurological disorders overall, it is known that the prevalence of depressive symptoms in people with neurological disorders is higher than that of non-depressed people by nearly 40 percent (Fleminger, Oliver, Williams, & Evans, 2003; Stanton & Carson, 2015).

ME is often misdiagnosed as depression (Griffith & Zarrouf, 2008), and co-morbid depression in patient samples has generated debate over whether it is primary or secondary to ME neurocognitive impairment (Twisk, 2014). For those patients with both conditions, it has been shown that ME and depression are separate disorders sharing some common features (Hawk, Jason, & Torres-Harding, 2006; Maes, 2011; Pazderka-Robinson, Morrison, & Flor-Henry, 2004). Depression in ME does not exhibit symptoms of Beck's cognitive triad (pessimism about the self, world, and future), a core feature of major depressive disorder (Hawk, Jason, & Torres-Harding, 2006). Fatigue, another controversial symptom of ME, is a core feature of major depressive disorder and other forms of depression, and may share a common neuroimaging feature with ME, that is, activity in the anterior cingulate along with its connections (Angelakis & Lubar, 2002; Olvet et al., 2015; Zhang et al., 2015). The primary difference, however, between ME fatigue and fatigue in major depression has been demonstrated empirically to be a reaction to physical activity; people with ME feel considerably worse after physical activity (called post-exertional malaise, PEM), while people with major depression feel better (Griffith & Zarrouf, 2008). This is an important distinction, since PEM is a central feature of ME (LaManca et al., 1998; Nijs et al., 2010), and inducing patients with depression to maintain some physical activity is a core strategy for improvement (Vancampfort, Stubbs, Venigalla, & Probst, 2015). The presence of depression (or other Axis 1 disorders) in ME could be the phenotype of a dysregulated central nervous system with the somatic symptoms as a consequence of the disease process.[2] Regardless of disease etiology, it is well known that neurocognitive impairment found in ME exerts deleterious consequences upon the quality of life for many individuals, and psychiatric factors do not fully account for their level of functional disability (Christodoulou et al., 1998). The problem of finding out what drives this form of neurocognitive

[2]According to DSM-IV-TR, patients with psychiatric comorbidity would be classified under Axis III with the psychiatric problem being secondary general medical condition, unless it can be shown that the primary psychiatric condition existed before the onset of ME.

dysfunction with linkage of brain function to patient symptoms therefore warrants further attention.

Neuroimaging Studies in ME

One crucial issue for ME is a better understanding of the neurocognitive events that underlie behavior and cognition following illness onset. The past several decades have been a time of considerable fluctuation in views of neurocognitive dysfunction for ME seen in the contradictory findings since the early 1990s, while neuroimaging investigations have been unable to establish a clear biological biomarker or signature specific to ME. In a recent literature review, Fischer and colleagues (Fischer et al., 2014) found neuroanatomical differences (using magnetic resonance imaging; MRI) between some patients with ME and healthy controls, but there is still no unifying explanation for the diversity of, or at times absence of, structural findings. Results in some studies have suggested involvement of white matter (Lange et al., 1999; Natelson, Cohen, Brassloff, & Lee, 1993), but other studies found only grey matter abnormalities (de Lange et al., 2005; de Lange et al., 2004; de Lange et al., 2008; Okada, Tanaka, Kuratsune, Watanabe, & Sadato, 2004; Puri et al., 2012) and two studies reported no significant abnormalities in ME (Cope & David, 1996; Perrin, Embleton, Pentreath, & Jackson, 2010). Regarding functional characteristics in ME, cerebral hypoperfusion was found using single-photon emission computed tomography (SPECT) in some (Biswal, Kunwar, & Natelson, 2011; Costa, Tannock, & Brostoff, 1995; Ichise et al., 1992; Schwartz, Komaroff, et al., 1994) but not all studies (Lewis et al., 2001; MacHale et al., 2000; Schmaling, Lewis, Fiedelak, Mahurin, & Buchwald, 2003). Results of metabolic activity from two positron emission tomography (PET) studies were inconclusive (Siessmeier et al., 2003; Tirelli et al., 1998), but abnormalities involving neurotransmitter biosynthesis was suggested in a line of more recent studies (Cleare, Messa, Rabiner, & Grasby, 2005; Nakatomi et al., 2014; Yamamoto et al., 2012). Task-evoked studies using blood-oxygen-level-dependent functional MRI (BOLD fMRI) detected various functional differences in neural activity in ME related to motor imagery (de Lange et al., 2004) and verbal working memory tasks (Lange et al., 2005) depending upon increasing task load (Caseras et al., 2006) and fatigue-inducing tasks (Caseras et al., 2008; Cook et al., 2007; Tanaka et al., 2006). These studies, however, need replication with larger sized sample groups. Taken together, the foregoing results of ME neuroimaging findings are inconclusive and remain unclear. Despite discovering newer ways to assess the symptoms commonly reported in ME neurocognitive impairment, current findings do not fully account for patient symptoms.

Functional Specialization (Segregation)

The primary reason for the disparity between some findings may be due to an over-reliance on classical functional specialization (localizationism models) to examine ME neurocognitive dysfunction. The functional specialization model rests on the premise that individual brain regions are specific and segregated (Deco, Jirsa, & Friston, 2012; Menon, 2012; Rabinovich, Friston, & Varona, 2012). Gay and colleagues (Gay et al., 2015) were first to document regional activation profiles in ME using a functional connectivity approach, suggesting this paradigm may hold promise for identifying the properties of neurocognitive impairment in ME. Due to the knowledge derived from the NIH Human Brain Project in the 1990s, the field of cognitive neuroscience has now established a framework for which complex brain systems can be studied and quantified to support new understandings of cognition and behavior (Thatcher, 2011). Functional brain connectivity is currently the new paradigm focusing on distributed neuronal units or the synchronization of activation of brain regions at rest or when performing a particular cognitive task (Bazhenov & Makeig, 2012; Catani, 2011; Catani, Bodi, & Dell'Acqua, 2012; Rabinovich, Friston, et al., 2012; Thatcher, 2012). Distributed organization within large scale dynamic systems involving multiple brain regions which are spatially distant but functionally linked act together to form a given network (Catani, Dell'Acqua, et al., 2012; Friston, 2010; Rabinovich, Friston, et al., 2012; Thatcher, 2011). Within this system, modular organization, common in complex systems to maximize efficiency, is achieved through use of a relatively small set of modules and hubs, whereby local groupings (clusters) of neurons rely on a small number of long distance connections in order to maximize the metabolic expense of wiring (Havlicek et al., 2015; Menon, 2012; van Straaten & Stam, 2013). In this manner, dysregulation found within and among nodes and hubs of functionally specialized networks may form the primary basis for arriving at a clinical interpretation of symptoms (Thatcher, 2011, 2012, 2015; Thatcher, North, & Biver, 2005; Thatcher et al., 2001).

Models of ME Pathogenesis

Despite decades of research, the definitive causes of ME remain unknown. A common quote in medicine, “the absence of evidence is not evidence for absence,” could apply to ME with some similarity, for example, to Lyme disease where the pathogen

was serendipitously identified after 72 years (Pachner, 2012). There are nonetheless some promising models, which appear to explain patient symptoms. An infectious pathogen in the etiology of ME has been proposed but has not yet been confirmed. Schwartz, Komaroff, et al. (1994) hypothesized ME may be caused by a viral infection of neurons, glia, or vasculature. Support for the deficient metabolism in ME was offered in some PET and SPECT imaging studies (Costa et al., 1995; Schwartz, Garada, et al., 1994; Tirelli et al., 1998). Morris and Maes (2012) proposed an immune-inflammatory model for ME, which accounts for fatigue, post-exertional malaise, and neurocognitive symptoms. Their model suggested the term "post activity relapse" be used for delayed abnormal responses to negligible increases in physical or mental activity that resemble acute phases of influenza (fatigue, malaise, hyperalgesia, brain fog). The authors further suggested that fatigue in ME was suppressing brain function and modulating the autonomic system. In a combined voxel-based analysis of four MRI imaging types (T1 and T2 weighted, grey matter and white matter volume) performed by Barnden et al. (2011), brainstem abnormalities in ME were found to be associated with increasing fatigue duration and hemodynamic scores; white matter atrophy and neuroinflammation in the midbrain was accompanied by impaired cerebrovascular autoregulation.

In a comprehensive review, Dickinson (1997) argued that a viral infection could cause multiple small lesions in the ascending arousal system (AAS). Due to its densely compact size, even microscopic damage to the brainstem could lead to severe disruptions to sleep state transitions, contributing to fluctuations in cognitive symptomology (Saper, Fuller, Pedersen, Lu, & Scammell, 2010; Wright, Lowry, & LeBourgeois, 2012; Wulff, Gatti, Wettstein, & Foster, 2010). In a follow-up study by Barnden, Crouch, Kwiatek, Burnet, and Del Fante (2015) which controlled for depression and anxiety, the brainstem was implicated again and compromised nerve conduction in the midbrain was associated with upregulation of myelination in the prefrontal cortex (PFC; dysregulated signal conduction velocity). The upregulation of myelin (relative to the diameter of axons) may relate to the energy consumption of the fibers mediating the PFC to increase signal conduction velocity and firing capacity (de Hoz & Simons, 2015) at the expense of brain efficiency (more energy consuming ionic channel, axonal transport processes; increased thickness consuming more energy and taking up more space).

Brain Efficiency Hypothesis and ME

The brain's energy expenditure is critically important given that it weighs approximately 3 pounds, yet it consumes about 20–40% blood oxygen consumption, a disproportionate rate of consumption (Raichle, 2010; Shulman, Rothman, Behar, & Hyder, 2004). A significant amount of this baseline energy is budgeted for neuronal signaling processes and glutamate neurotransmission by excitatory glutamatergic neurons (Shulman et al., 2004). Bullmore and Sporns (2012) explain the state of affairs in terms of parsimony; there is a continual drive to minimize the metabolic costs while supporting or creating adaptively valuable functional connectivity. Within this system, the brain is seen as a continual process of negotiating these trade-offs. Glutamate, the chief excitatory neurotransmitter in the brain, is a primary factor, particularly due to its crucial involvement in coupling neuronal activity with glucose utilization and lactate production through reuptake by astrocytes (Pellerin & Magistretti, 1994). Glutamate also plays a key role in regulating α-Amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors for making adjustments to synaptic strength (Bredt & Nicoll, 2003). Nucleotide and protein synthesis secondarily contribute to energy demand, expanding size of synapses, creation of new synapses during wakefulness, regulating excitatory loops, and long-term potentiation (Kennedy, Beale, Carlisle, & Washburn, 2005). 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 energy to neurons (Raichle, 2010).

However, it remains unclear as to how metabolic failures within various brain regions affect neurocognitive function in ME. Recent evidence regarding many neurological disorders suggests that metabolic dysfunction can lead to neuronal hyperexcitability and aberrant neuronal network activities, causing neural dysregulation and producing cognitive deficits through chronic activation of the stress response (McEwen et al., 2015). This can be seen in several diseases whereby metabolic changes are known to cause neural dysfunction (Stranahan & Mattson, 2008), often with the cognitive effects beginning well before the physiological ones are evident (Halassa & Haydon, 2010). Energy deficits can induce unfavorable changes in resting membrane potentials and gamma-aminobutyric acid (GABA-induced) anionic currents, leading to neuronal hyperactivity that may initiate a cascade of pathological events

(Holmgren & Scheffer, 2010). Another possible model posits that neurocognitive dysfunction in ME may emanate from disruption of top-down control within the prefrontal cortex with its normal ability to exert influence over the hypothalamus in modulating sleep/wake parameters (Barnden et al., 2015; Wright et al., 2012). Regardless of the underlying etiology, the "brain fog" (Ocon, 2013) in ME might be described as a generalized failure in the brain's ability to allocate resources in a flexible manner, resulting in widespread inefficiency and producing a state that poses a threat to the adaptive mediation of homeostatic processes. These nonlinear processes may be interactions between the metabolic system, stress system, and inflammatory responses in the immune system (McEwen, 2006). The metabolic changes can, therefore, be taken as signs of allostatic load (effects of chronic stress) and though many of the changes are only partly understood, we are beginning to understand the chronic disruption in these systems and how it affects cognition in chronic disease, especially in ME.

A recurrent theme throughout the ME literature, neuroimaging in particular, is that patients are underperforming, compensating, and otherwise utilizing neural resources more inefficiently than healthy controls (Caseras et al., 2006; Cook et al., 2007; de Lange et al., 2004; Lange et al., 2005; Tiersky et al., 1997). Behaviorally, patients are typically found to be less responsive, less vigilant, and slower to react or initiate movements (Tanaka et al., 2006; Thomas & Smith, 2009; Van Den Eede et al., 2011). Gay et al. (2016) found evidence of reduced functional connectivity in patients with ME. Hypo-connectedness suggests there are fewer links to distant neurons, possibly driven by a homeostatic need to reduce energy costs. All nodes within brain networks can exhibit the same functional properties but with varying degrees of efficiency and the resulting propensity for reorganization. Compensatory activity in the brain appears to be a mechanism of complex self-organizing systems via homeostatic processes (Hellyer, Jachs, Clopath, & Leech, 2015). Nodes are small interacting units in the topology of a network while hubs are units that occupy a highly central position in the network. Due to costly metabolic demands, hubs are more vulnerable to pathology (Crossley et al., 2014), and their failure tends to cause greater disruption within a given network hierarchy (Stam, 2014). Hubs are also crucial for information integration coming in from other widely distributed brain regions (van den Heuvel & Sporns, 2013). The controllability of finite timings within densely connected areas facilitating brain states depend on the underlying integrity of structural connections (Gu et al., 2015; Hagmann et al., 2008). Local "small world" networks operate with local groupings (clusters) of neurons relying on a small number of short-distance connections (thereby maximizing the energy "expense" of wiring) while long distance connections between nodes and modules are inherently less stable (van Straaten & Stam, 2013). Therefore, dysregulation found within and among specialized functional networks may form the primary basis for arriving at a clinical interpretation of neurocognitive symptoms (Menon, 2011; Stam, 2014).

Examining Spatiotemporal Dynamics in ME

Another important facet of ME cognitive dysfunction may be the degree to which measurable spatiotemporal changes in normal dynamic brain function is occurring, thereby contributing to the diminishment of cognitive processes involved in attention, memory, and information transfer rates. Understanding neurocognitive impairment at the spatiotemporal level may sufficiently describe what may be happening to patients because these global state interactions may underpin disturbances to homeostatic systems and represent a failure to adapt in ME, thereby producing measurable deficits in cognition (Rabinovich, Afraimovich, Bick, & Varona, 2012; Rabinovich, Friston, et al., 2012). Highly time-dependent circuits of information flow involve the coordination of time-series segments of large neural populations distributed widely within the brain (Buzsáki, 2006), and the assessment of these subtleties requires analysis of network interactions with high spatiotemporal precision, across extended time periods (Tristan, Rulkov, Huerta, & Rabinovich, 2014). Maintained by an excitatory re-entrant process that alter their dynamics in the face of differing task demands, cognition and action depend upon time-based stability within large-scale brain circuits (Elson, Huerta, Abarbanel, Rabinovich, & Selverston, 1999; Hellyer et al., 2015), whether it is engagement with the environment through sensory systems or by disengagement from the environment, using learned experiences (Sporns, 2013). Neurons are continuously in motion, but it is their synchronization or lack of synchronization that might be most important when studying cognitive control processes (Klimesch, Freunberger, Sauseng, & Gruber, 2008). Accordingly, spatiotemporal dynamics are thought to emerge from homeostatic "tuning" of various factors such as 1) structural network topology, 2) neural noise, 3) time delays, 4) connectivity strength, 5) dynamic balance of excitation/inhibition, and 6) interactions with glial cells (e.g., changes in myelin microarchitecture; de

Hoz & Simons, 2015). All of these factors operate within a narrow window of parameters, outside of which they operate within a pathological state (Buzsáki & Watson, 2012; Hellyer et al., 2015). Each factor co-varies with arousal levels and cognitive state, factors which are vital to performance levels of memory, perceptual, and problem-solving tasks (Tang, Rothbart, & Posner, 2012).

Diverse brain activity visible in the electroencephalogram (EEG) demonstrates how brain function is continually dynamic and in constant flux (Raichle, 2011), and it reflects the spatially diffuse synchronization of large masses of neuronal assemblies which give rise to cognition and behavior (Thatcher, 2015). Quantitative EEG (qEEG) methods are well suited for the task of capturing temporal dynamics at the millisecond time-scale synchronization of brain processes which are largely invisible to other imaging modalities such as fMRI, SPECT, and PET (Thatcher, 2015). Diffusion tensor imaging (DTI) provides an excellent static depiction of white matter and non-dynamic structural mapping of the cortex. fMRI offers excellent spatial resolution but the examination of high temporal fluctuations in connectivity models is limited to constraints of the hemodynamic signal: indirect measurement of neuronal activity with low temporal resolution (on the order of seconds; Poldrack, Mumford, & Nichols, 2011). The spatial resolution of EEG has been adequately addressed through advancements in electrical neuroimaging, a promising approach for noninvasive examination of spatiotemporal interactions in the millisecond domain for mapping of intracortical sources in four dimensions (space and time frequency) through using a variety of distributed inverse methods (Grech et al., 2008).

Electrical neuroimaging involves source analysis procedures to examine the cortex of all frequency bands (delta, theta, alpha, beta, and gamma) through spectrally transformed recordings from the scalp surface using 19-channel EEG (M.A. Zinn et al., 2014). Accurate estimations of the intracranial activity can be achieved with application of inverse methods such as low-resolution electromagnetic tomography (LORETA) and more recent iterations: standardized LORETA (sLORETA) and exact LORETA (eLORETA; Pascual-Marqui, Esslen, Kochi, & Lehmann, 2002; Pascual-Marqui, Lehmann, et al., 2011; Pascual-Marqui, Michel, & Lehmann, 1994). These methods, which allow cross-validation through voxel by voxel co-registration to PET, SPECT, fMRI for matching data to standard coordinate systems, have been used to characterize spatiotemporal dynamics in patients with a wide variety of clinical conditions such as Alzheimer's disease (Babiloni, Binetti, et al., 2004; Babiloni, Cassetta, et al., 2006; Canuet et al., 2012; Gianotti, Künig, Faber, et al., 2008; Gianotti, Künig, Lehmann, et al., 2007), mild cognitive impairment (Babiloni, Carducci, et al., 2013; Babiloni, Del Percio, et al., 2014; Babiloni, Frisoni, et al., 2006), other dementias (Nishida et al., 2011; Styliadis, Kartsidis, Paraskevopoulos, Ioannides, & Bamidis, 2015), epilepsy (Besenyei et al., 2012; Canuet et al., 2011; Clemens et al., 2010), Parkinson's disease (Babiloni et al., 2011; Moazami-Goudarzi, Sarnthein, Michels, Moukhtieva, & Jeanmonod, 2008), multiple sclerosis (Papageorgiou et al., 2007), chronic fatigue syndrome (Sherlin et al., 2007), congestive heart failure (Vecchio et al., 2015), obstructive sleep apnea (Toth, Faludi, Wackermann, Czopf, & Kondakor, 2009), migraine (Clemens et al., 2008), tinnitus (Vanneste et al., 2010), and Down's syndrome (Velikova et al., 2011). LORETA has also been used to investigate neuropsychiatric conditions including locked-in syndrome (Babiloni et al., 2010), anhedonia (Wacker, Dillon, & Pizzagalli, 2009), obsessive-compulsive disorder (Jones & Bhattacharya, 2014; Olbrich et al., 2013; Velikova et al., 2010), posttraumatic stress disorder (Todder et al., 2012), and major depression (Olbrich, Trankner, Chittka, Hegerl, & Schonknecht, 2014). Cross-validation has been demonstrated in multimodal studies combining LORETA with blood oxygen dependent fMRI (Mulert et al., 2004; Musso, Brinkmeyer, Mobascher, Warbrick, & Winterer, 2010; Vitacco, Brandeis, Pascual-Marqui, & Martin, 2002), and structural MRI (Worrell et al., 2000), PET (Dierks et al., 2000; Pizzagalli et al., 2004). Validation of LORETA is further supported by localization findings from invasive, intracranial recordings in humans, as established in several studies of epilepsy and cognitive event-related potentials (Volpe et al., 2007; Zumsteg, Friedman, Wieser, & Wennberg, 2006; Zumsteg, Lozano, Wieser, & Wennberg, 2006). The promising aspect of this method is that it allows researchers to create dynamic causal models of brain networks and mental states, assessing the informational status of the individual nodes, linkages and clustering of connections (Pascual-Marqui et al., 2011). Further advancements have even made it possible to examine cortical dynamics and interrogate causal information flow (Pascual-Marqui et al., 2014).

Results using LORETA have already been reported by Sherlin et al. (2007) by investigating twins with ME, finding slowing of electrical activity in deeper brain structures and parts of the limbic system.

Exploring this further, M. A. Zinn et al. (2014) collected and evaluated pilot data using eLORETA to analyze the current source density in 50 patients with ME compared to 50 healthy controls. This study found that patients had significantly higher current source density within delta (1–3 Hz) affecting widespread bilateral portions of the frontal lobe and limbic lobe. Beta sources (19–21 Hz) were also reduced in the medial posterior parietal regions affecting the sensorimotor region and posterior cingulate in patients. Furthermore, increased delta sources were linked to the Multi-dimensional Fatigue Inventory (MFI-20) reduced motivation subscale in many regions of the left frontal lobe, with maxima localized to Broca's area (Smets, Garssen, Bonke, & De Haes, 1995). The co-occurrence of delta and beta in these brain regions may have provided empirical evidence for a neurobiological basis for patient symptomology including impairment to higher cortical functioning. More importantly, dysregulation in structures such as the parahippocampal gyrus, anterior cingulate, and insula, prefrontal cortex, and orbitofrontal gyrus could explain neurocognitive symptoms in patients (e.g., problems involving attention, memory, multi-tasking, goal-directedness, etc.). Limbic regions, when dysregulated, have generally not been associated with universal domains of attention, working memory and executive function, but instead have been associated with symptoms such as apathy, abulia, reduced motivation, and impaired attention states known as negative (deficit) symptoms (Kuzis, Sabe, Tiberti, Dorrego, & Starkstein, 1999; McPherson, Fairbanks, Tiken, Cummings, & Back-Madruga, 2002). Therefore, the importance of negative symptoms in ME was underscored in this sample. The association of the MFI-20 reduced motivation scale and eLORETA sources further suggested a psychophysiological model may be requisite to understanding this phenomenon.

Use the same dataset, M. L. Zinn et al. (2014) also examined qEEG peak alpha frequency (PAF) computed within the 8–12 Hz frequency band based on each participant's EEG. Mixed ANOVA results found significantly decreased PAF over 58% of the entire cortex in patients with ME when compared to controls. There were significant differences in PAF at 11 electrode sites ($p < 0.05$). Two hierarchical multiple regression models found that subjective scores on both the MFI-20 and FSS (Fatigue Severity Scale; Krupp, LaRocca, et al., 1989) as separate dependent variables predicted fatigue. Findings were consistent with previous reports of reduced efficiency of thalamocortical connections in patients with ME suggesting that PAF measurement may have both diagnostic and prognostic value in patients. The widespread nature of the PAF dysregulation strongly suggests subcortical pathology with some authors suggesting this pathology involves the brainstem (Barnden et al., 2011; Dickinson, 1997; Tirelli et al., 1998). These studies have set the stage for the next steps using network analyses and dynamic relationships to understand a number of cognitive domains where ME deficits have been found (see Table 1 which summarizes the qEEG case-control studies on patients with ME during wakefulness).

Table 1

Case-control qEEG studies involving ME patients during wakefulness

Author (Year)	*N*	Investigation	Behavioral Measures	Significant Findings
Prasher, Smith, and Findley (1990)	25 patients divided into 2 groups with enteroviral antigen VP1 test positive & negative 25 healthy controls	Event-related potentials recorded from Fz, Cz, Pz Visual potentials: Checkerboard pattern Somatosensory potentials: Median nerve stimulation from cervical spine Cognitive potentials: Reaction time to audio tone in ms	None	Greater P3 latency and duration was found in ME sample. Results permit subgrouping patients by P3 amplitude: those with attention problems and those with slower information processing speed.
Billiot, Budzynski, and Andrasik (1997)	28 patients 28 healthy controls matched for age and gender	EEG activity recorded from Cz to measure peak frequency and theta/beta ratio during eyes closed and serial 7s conditions	Profile of Fatigue-Related Symptoms (PFRS cognitive difficulty factors neg. correlated with serial 7s)	Eyes closed: • ME > HC in theta band (5–7 Hz). • Peak alpha frequency (8–13 Hz) correlated with a subjective fatigue rating. • Peak frequency between 4–20 Hz correlated with theta/beta ratio and fatigue scores.* Serial 7s: • ME > HC in theta band (5–7 Hz). • ME < HC in narrow alpha band (9–11 Hz).
Siemionow, Fang, Calabrese, Sahgal, and Yue (2004)	8 patients 8 healthy controls matched by age	58 channel EEG recordings measured subjects while performing handgrip contractions.	None	ME < HCs in maximum voluntary contraction force.* ME > HCs relative power in theta band, indicating higher cortical activity after moderate muscle exercise.
Sherlin et al. (2007)	17 pairs of monozygotic twins discordant for ME	EEG source analysis using LORETA 3D imaging method during eyes closed condition and serial 7s.	None	ME twins > healthy twins in delta (2.0–3.5 Hz) in left uncus and left parahippocampal gyrus. ME twins > healthy twins in theta (4.0–7.5 Hz) in cingulate gyrus and right superior frontal gyrus. Serial 7s data not reported.
Flor-Henry, Lind, and Koles (2010)	61 female patients 80 female controls	EEG source analysis using BK Beamformer algorithm during eyes open and two cognitive conditions: word-finding and dot localization. Only alpha (8–13 Hz) and beta (14–20 Hz) bands were analyzed.	Basic personality inventory Multidimensional Aptitude Battery (MAB-II)	Global source differences were found in both bands for all three conditions. ME < HCs in alpha during eyes-closed condition. ME > HCs in beta during spatial cognitive condition. ME > HCs in alpha in Broca's area during word-finding condition. Spatial EEG patterns separated both groups at 83% classification rate in alpha band during word finding condition.

Table 1

Case-control qEEG studies involving ME patients during wakefulness

Author (Year)	*N*	Investigation	Behavioral Measures	Significant Findings
Neu et al. (2011)	15 patients with ME 15 untreated sleep apnea-hypopnea syndrome (SAHS) 16 healthy controls	Event-related potentials recorded from Fz, Cz, and Pz measuring spectral theta and beta. P300 assessment with standard auditory oddball paradigm WAIS Digit Span Symbol span Rey Auditory Verbal Learning Test Finger-tapping test	Fatigue Severity Scale (FSS) Epworth Sleepiness Scale (ESS) Pittsburgh Sleep Quality Index (PSQ) Beck Depression Inventory 13 item short form (BDI) Hamilton Anxiety Scale (HAS) Hamilton Depression Scale (HDS)	FSS: ME > SAHS > HC ESS: ME < SAHS > HC PSQ: ME < SAHS > HC BDI: ME > SAHS > HC HAS: ME > SAHS > HC HDS: ME > SAHS > HC WAIS: ME > SAHS < HC in both digit span and symbol span RAVLT: ME > SAHS < HC
Duffy, McAnulty, McCreary, Cuchural, and Komaroff (2011)	70 patients with ME 24 patients with MDD 148 patients with general fatigue 390 healthy controls	EEG recordings to measure coherence during awake, alert eyes-closed state	None	EEG spectral coherence measures distinguished ME patients from HCs and MDD groups with nearly 90% accuracy.
M. L. Zinn et al. (2014)	50 patients 50 healthy controls matched by age, gender, educational level.	Used qEEG to measure peak alpha frequency (8–12 Hz) during an eyes-closed resting condition.	Multidimensional Fatigue Inventory (MFI-20) Fatigue Severity Scale (FSS)	Found significantly reduced peak alpha rhythms over 56% of cortex in patients. MFI-20, FSS were strongly associated with peak alpha frequency (8–12 Hz).
M. A. Zinn et al. (2014)	50 patients 50 healthy controls matched by age, gender, educational level.	Used eLORETA to measure current source densities during an eyes-closed resting condition.	Multidimensional Fatigue Inventory (MFI-20) Fatigue Severity Scale (FSS)	ME > HC in delta (1–3 Hz) predominately in bilateral frontal/limbic regions. ME < HC in beta (19–21 Hz) medially in superior parietal lobule (precuneus and sensorimotor areas). Maximal current densities for delta band in left Broca's area predicted by higher scores on the Multidimensional Fatigue Inventory (MFI-20), reduced motivation subscale. No associations found with the FSS.

*$p < .01$.

Importance of Cross-Frequency Interactions, Vertical Brain Organization, and Arousal Systems

All perceptual, cognitive, and emotional processes in the brain arise from precisely coordinated timings (Rabinovich, Friston, et al., 2012) with a vertical organization of structures reflecting the phylogenic scale and forms of consciousness (including sleep/coma) beginning with the earliest reptilian structures (Thatcher & John, 1977). Coupling between subcortical brain structures (e.g., brainstem), the limbic system (e.g., hippocampus) and the neocortex (e.g., dorsolateral prefrontal cortex) allows the brain to achieve multiple levels of adaptation critical for survival with subcortical structures exerting influence over the cortex, and vice-versa. A preponderance of slow-wave (delta, theta) activity cross-frequency coupled with faster rhythms (beta, gamma) is equally involved in the refinement of higher order information processing (Buzsáki & Watson, 2012; Friston, Bastos, Pinotsis, & Litvak, 2015). The nesting of brain rhythms reflects populations of neurons fluctuating in accordance to a hierarchical system modulated by ultraslow (~0.1 Hz) frequencies (Buzsáki & Watson, 2012). This effect demonstrates the inter-dependency of the rhythms; therefore, disruption in any frequency band could produce significant effects on the rhythms in other frequencies.

The correlation between lesions in white matter and increased delta waves was demonstrated by Gloor, Ball, and Schaul (1977). Bilateral lesions of the midbrain tegmentum produced bilateral delta activity in the cortex, while lesions in the reticular formation produced a gradual change in brain state with elevated delta rhythms, suggesting signaling depletion of a biochemical regulator. The authors explained that the lesions themselves did not produce delta activity; rather, the lesions interrupted important afferent connections to the cortex (deafferentation) from white matter, thalamus, hypothalamus, or brain stem leading to delta activity. Elevations in delta activity during the waking state have been a frequent finding in patients with acute phases of encephalitis and are correlated with infection severity, spatial involvement, arousal state, and metabolic factors (Schaul, Lueders, & Sachdev, 1981; Westmoreland, 2005). African trypanosomiasis (sleeping sickness), which has characteristics similar to ME such as disturbance in sleep-wake cycles and excessive daytime drowsiness, is thought to arise from delta disruption during deep sleep stages (Westmoreland, 2005). Delta is also implicated in disturbances of white matter and that is consistent with Purger, Gibson, and Monje (2015) who described in their review how varying levels of neuronal activity can result from subtle changes in myelin microstructure, perturbing neural function, resonances, and attunement of cognition and behavior. Similarly, patients with multiple sclerosis exhibit slow waves (delta) which tend to wax during symptom exacerbation periods and wane during remission while cognitive impairment in those patients is characterized by the extent and degree of slow oscillations found (Westmoreland, 2005).

The earliest clinical correlates of brain pathogenesis are often seen with subtle, fluctuating levels of attention and arousal (Ropper & Samuels, 2009) and concomitant alterations in consciousness are then likely to follow with intracranial disease (e.g., infectious, inflammatory, neoplastic, vascular, and traumatic etiologies; Niedermeyer & Lopes da Silva, 2005). In analyzing patients with deep brain lesions, Luria (1980) noticed that changes in specialized higher cortical processes remained intact, and he observed that the primary symptoms manifested by patients were generalized decreases in “cortical tone” accompanied by a substantial degree of slowness and proneness to fatigue, affecting all the spheres of their activity. Another feature of Luria’s patients was large fluctuations in symptom severity; during some hours or days the patients’ symptoms grew worse, while at other hours or days the same symptoms took on a milder form. Moreover, the changes described by Luria are remarkably characteristic of neurological illnesses involving central fatigue (Chaudhuri & Behan, 2004) with striking similarity to ME. Neurocognitive functioning depends on an intact AAS in promoting effective transmission across many thalamocortical, cortio-basal-thalamic, and cortico-cortical circuits operating continuously during sleep and wakefulness in accordance with circadian rhythms (Heyder, Suchan, & Daum, 2004; Wright et al., 2012). The hierarchical cross-frequency interactions are mediated by reticulothalamic and monoamine projections (e.g., acetylcholine in the basal forebrain, serotonin and norepinephrine in the pons, histamine and orexin in the hypothalamus, dopamine and acetylcholine in the midbrain) which serve to dampen the slower frequencies (delta), reduce the number of refractory neurons (more neurons available for allocation), and sustain the generalized maintenance of alert levels of consciousness (see Figure 1).

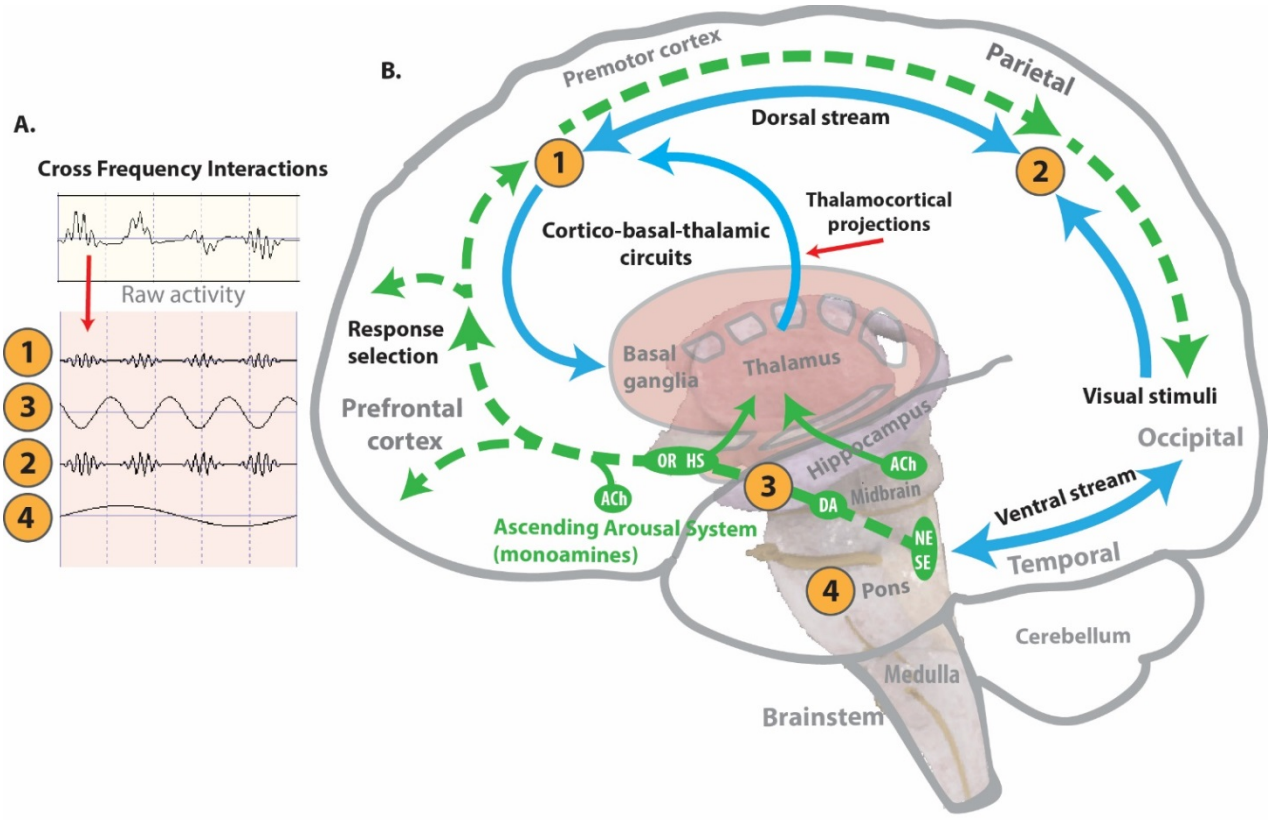

Figure 1. Neurocognitive impairment in ME model based on vertical brain organization, ascending arousal system (AAS), and cross-frequency interactions involved in the metastable dynamic flow of information in higher cortical function [adapted from Rabinovich, Afraimovich, et al. (2012), Stratton and Wiles (2015), Thatcher and John (1977), Wright et al. (2012)]. **A)** Cross-frequency interactions (coupling) showing gamma, theta, and delta frequencies are woven together by phase relationships occurring spontaneously across different brain regions at multiple hierarchical levels. If dysfunction exists in any of the sites (e.g., increased delta), the temporal "fabric" changes accordingly. Inefficient cross-frequency coupling within the raw EEG signal can be separated and analyzed by qEEG and electrical neuroimaging methods (Pinal, Zurrón, Díaz, & Sauseng, 2015). **B)** Brain function at the systems level which is modeled on the vertical organization of the brain circuits in millisecond timings and cycling of oscillatory rhythms (Tristan et al., 2014), accounting for the primary role of arousal promoting nuclei in the brainstem, for example, site 4 (pons) in promoting the encoding and processing of sensory information (e.g., visual stimuli in occipital lobe) influencing the cross-coupled signaling in the dorsal stream of information flow between gamma activity in site 1 (parietal) and site 2 (premotor) coupled with theta rhythms in site 3 (memories recalled by the hippocampus) mediated by prefrontal cortex (filtering out irrelevant stimuli, context-dependent response selection) and cortico-basal-thalamic circuits (anticipatory information), ultimately giving rise to behavior, emotion, and cognition (Fuster, 2009; Rabinovich, Afraimovich, et al., 2012; Stratton & Wiles, 2015). This general hypothesis states that the AAS (dashed green lines) regulates the capacity for neuronal excitability within the information streams (blue arrows) perpetuated by local and long-distance connections within and between networks. Characterizing the metastable dynamics in the brain may be crucial in understanding neurocognitive impairment, particularly in ME; that is, disruptions in signaling at any point (e.g., red arrow pointing to thalamocortical afferent pathways) underpinning information processing deficits and influencing pyramidal neuronal populations in the cortex visible in the qEEG (McCormick & Bal, 1997; Stratton & Wiles, 2015). This model calls for a deeper understanding of dysregulation in the central nervous system in patients; that is, how communication by way of network properties and arousal affects the quality and quantity of the mental representations in the cortex at any given moment in time (Varela, 2014). Within this model, the homeostatic balance of efficient ongoing processing, in turn, produces increased responsiveness of cortical networks that depend on intact subcortical structures. Accordingly, mismatched timings may be indexed by underlying phase mechanisms (Thatcher, North, & Biver, 2014) associated with a variety of conditions such as multiple sclerosis (Yao et al., 2012), autism (Thatcher et al., 2009), Alzheimer's disease (Xu et al., 2008) and short-term memory decline (Pinal et al., 2015). Abbreviations: acetylcholine (ACh), dopamine (DA), histamine (HS), orexin (OR), norepinephrine (NE), serotonin (SE).

The role of brain rhythms and vertical brain organization affecting behavioral performance with time-evolving variability in brain states may be of prime importance to ME. The ability to flexibly switch and maintain brain states to mandate a given performance level is critical to shifting environmental demands (Tang et al., 2012) and ME is known for supporting derangements in set shifting. Delta is associated with potassium (K+) conductance of the membrane potential which can be readily abolished by monoamine-producing nuclei in the pons and midbrain reticular formation (e.g., acetylcholine or norepinephrine) for maintenance of normal consciousness (Steriade, 2006). Severe damage to the midbrain reticular formation produces coma whereby lack of sustained input from the neocortex precludes all function (Nolte, 2009). Cortical arousal becomes initiated by the cholinergic basal forebrain which plays a key role in blocking K+ conductance (Metherate & Ashe, 1993) and strong cholinergic activity during REM and wakefulness is mainly responsible for depolarizing thalamocortical neurons to suppress the occurrence of delta oscillations and diminished excitation in the cortex (McCormick & Bal, 1997). Furthermore, the thalamic neurons projecting to the well-defined areas of the cortex operate in a different manner, and they have essentially two physiological modes: tonic mode and burst mode. Delta rhythms produced by these particular neurons switch their operating mode from tonic mode to burst mode where hyperpolarization of neurons is below the threshold for the tonic mode, thus interrupting normal relay of information back to the neocortex (Sherman & Guillery, 1996). During burst mode, the thalamocortical neurons are operating with increased calcium (Ca^{+2}) influx, making them behave differently; they are more prone to fire in an all-or-none fashion (Zhan, Cox, Rinzel, & Sherman, 1999). This type of irregular transmission produces a type of hyper-responsivity which negates the proper functioning of cortical systems (Elson et al., 1999; Steriade & Paré, 2006). The instability might be semantic in that the remaining information that gets forwarded to the neocortex is compromised, disrupting the ability of neocortical systems to perform their task of discrimination and refinement of incoming sensory information. Likewise, the instability could be produced temporally where the message is the same but the order has been randomized or the tempo of information is too erratic and, with regard to attention, making it difficult to process relevant information (Tristan et al., 2014).

Using EEG Coherence and Phase Metrics to Investigate ME Neurocognitive Impairment

Using time-dependent EEG metrics such as coherence and phase within brain rhythms could form a new conceptual basis of studying neurocognitive impairment in patients with ME. EEG coherence was used by Duffy et al. (2011) as a way of distinguishing ME from depression and healthy control groups. Coherence is the most widely used measure which examines similarity between two cortical regions as well as provides a robust measure of white matter maturation/disease (Nunez, Srinivasan, & Fields, 2014). Coherence looks at phase differences to directly measure the timing of neural activity to elucidate the coordination of action potentials (Klimesch et al., 2008) between any two brain areas and infer a functional relationship is likely happening (phase coupling; Buzsáki & Watson, 2012). Areas with higher coherence are referred to as having increased phase consistency whereby phase differences are clustering very close together over time. However, if the phase differences are fairly scattered over time, there is an inconsistency of phase differences, and those neurons become suppressed. This suggests a fundamental mechanism for selection of neurons: neurons are very likely to fire together when their phases are coupled and the firing threshold is lower, but they become suppressed when their phases are decoupled due to lack of entrainment (decoupling; Hughes et al., 2004). More importantly, high coherence measures demonstrate that neurons are delivering large quantities of neurotransmitters, which rapidly turn neurons on/off, and the neuromodulators, which modulate synaptic transmission and RNA signaling (Kandel, Schwartz, Jessell, Siegelbaum, & Hudspeth, 2012). Findings of intracranial studies show functional coupling in the frontal cortex and connected areas is essentially linked to fundamental memory processes (Johnson & Knight, 2015). Furthermore, a coupling of EEG signals, in addition to power, has been shown to modulate temporal attention intervals contributing to task performance and reaction speed (Stefanics et al., 2010).

We can understand coherence more comprehensively by examining control processes for how the information is being encoded and packaged through analysis of phase reset mechanisms and their constituent subcomponents of phase shift and phase-lock duration. Phase shift and phase lock are fundamental brain mechanisms continually in flux at various frequencies and across nodes of networks during the execution of any behavioral or cognitive

task. According to Canavier (2015), phase-reset performs several functions to represent our thoughts, feelings, and actions: 1) phase alignment to specific reference points, 2) time windows for encoding and decoding, and 3) coordination between mutually connected, phase coupled, brain regions. Recent evidence demonstrates the processes of phase reset on human cognition, especially in clinical disorders (Frey, Ruhnau, & Weisz, 2015). The homeostatic balance of switching dynamics between phase shifting and phase locking and of rhythm patterns has been related to normal brain function, and instabilities have been implicated in pathological conditions such as autism (Thatcher et al., 2009), epilepsy (Chavez, Le Van Quyen, Navarro, Baulac, & Martinerie, 2003; Le Van Quyen, Martinerie, Navarro, Baulac, & Varela, 2001), Alzheimer's disease (Stam et al., 2002), and traumatic brain injury (Sponheim et al., 2011).

At any given moment, millions of neurons are briefly synchronized (phase locked) across domains or networks within milliseconds and then released (phase shift), and this process happens continually with different neurons being involved (Thatcher, 2012). Phase shift refers to the recruitment process of allocating all available neurons for performing a given function and typically varies between 40 and 80 milliseconds in length, and it has been shown to positively correlate with intelligence (Thatcher, North, & Biver, 2008). Phase lock refers to the synchronization of phase-shifted neurons selected for mediating a given function over a sustained period of time, usually between 100 and 600 milliseconds. For example, phase-locking periods of 100 ms in the alpha band in the auditory cortex was recently shown to modulate visual perception in the occipital lobe (Romei, Gross, & Thut, 2012). Longer phase-lock periods were found to be inversely correlated with intelligence due to the brief increase in committed neurons which creates a momentary reduction in neurons available for other phase shifts (Thatcher et al., 2008). It is possible to apply this phase reset model to understanding the inner workings of the brain in ME. If patients were shown to have a higher rate of phase resets than normal in the high beta/gamma range, the information transfer within neocortical local circuits might be happening too quickly. Looking further at phase shift and phase-lock duration, if both of these processes appeared to be significantly shorter, that might further suggest there are fewer neuronal resources allocated in ME for subsequent phase-lock periods. This could lead to inefficiency as a function of time and, if both periods of phase shift/lock durations were too short, that might contribute to an increased rate of phase reset. Also, with phase-locking periods being too brief, that would be consistent with the associated lower rate of information processing and reaction times found in the ME literature.

To create a better understanding, however, it becomes necessary to describe the aberrant coherence and phase within the nodes of large-scale networks dedicated to maintaining higher cognitive functions affecting daily living (e.g., spatial attention, salience recognition, autobiographical memory, sensation and movement, language and sound). Cooperative sequencing and millisecond interactions of dynamic functional systems in the brain (interconnected groupings) are involved in overall function at any given moment of time and can be interrupted by a number of different types of neurological derangements (Menon, 2011; Sporns, 2013). In addition to hierarchical levels of brain rhythms, there are also hierarchical levels of nodes and hub constituents of brain networks. Given their central importance and susceptibility to failure in many clinical disorders (Crossley et al., 2014), coherence and phase analysis within hubs could be another tool for measuring the functional integrity of their connections. The degree to which dysregulation within the nodes or hubs of a given network is found could serve as an index for the inefficiency of information processing and greater energy expenditure, particularly in the compensatory nodes; the dysregulated nodes and hubs continue to function while other nodes attempt to compensate for the information processing deficits, producing greater inefficiency. More powerful and versatile data-driven approaches using independent component analysis to characterize frequencies and spatial correlations simultaneously might yield new insights identifying cortico-cortical, cross-frequency interactions, which can account for compensatory mechanisms (Calhoun, Liu, & Adali, 2009; Pascual-Marqui et al., 2011). Unique to exploring the realm of dynamic connectivity electrical neuroimaging can capture co-varying correlations of regions, including connection strength, direction, and spectral characteristics, from intracranial electric signals. Dynamic connectivity has recently been shown to offer more reliability and sensitivity for measuring network properties in Parkinson's disease (Madhyastha, Askren, Boord, & Grabowski, 2015). Direct paths of effective information flow can be assessed using newly established metrics such as isolated effective coherence (Pascual-Marqui et al., 2014) and phase slope index (Nolte & Müller, 2010; Nolte et al., 2008), which can be used in causal connectivity modeling to describe transmission of preferential oscillations between nodes. In

summary, using electrical neuroimaging methods may help identify dysregulated nodes within large-scale brain networks and dynamic connectivity models which could better characterize the nature and extent of neurocognitive impairment in ME.

Clinical Interpretation of Dysregulated Networks in ME

Clinical interpretation ultimately rests upon linking the patient's symptoms to dysregulated nodes and hubs of large-scale brain systems (Thatcher, 2012). These large distributed networks were mapped through numerous neuroimaging experiments showing areas of endogenous brain activity that were highly correlated and ultimately referred to as resting-state networks (Allen et al., 2011; Fox, Zhang, Snyder, & Raichle, 2009; Raichle, 2011). To gain a deeper understanding of connectivity influences of brain disease on cognitive processing, the assessment of neuropsychological symptoms in patients can be linked to specific alternations in the resting-state networks. Initial steps for investigating neurocognitive impairment in ME could begin with the default-mode network (Raichle et al., 2001). The default-mode network is the first resting-state network to be identified and has been a robust finding in the literature (Raichle, 2011; Raichle et al., 2001). The nodes identified in this network include the medial prefrontal cortex, posterior cingulate/precuneus, and the bilateral temporal-parietal junction. Collectively, these nodes are jointly active during passive moments—while one is recalling past events, ruminating, self-monitoring—but they deactivate during initiation of a goal-directed task (Buckner, 2012). Cognitive symptoms produced by a failure within this network would involve decreased attention, mentalizing, decision-making, self-referential thought, and self-recognition. The default-mode network has been implicated in symptoms of a variety of neurocognitive disorders such as Alzheimer's disease (Greicius, Srivastava, Reiss, & Menon, 2004), Parkinson's disease (van Eimeren, Monchi, Ballanger, & Strafella, 2009), traumatic brain injury (Bonnelle et al., 2011), multiple sclerosis (Zhou et al., 2014), epilepsy (Haneef, Lenartowicz, Yeh, Engel, & Stern, 2014), autism (Jann et al., 2015). In ME, the relative interactions between nodes of the default-mode network could be examined using phase and coherence metrics within LORETA to explore temporal dynamics within a graph theoretical framework; the connectivity of edges between dysfunctional nodes identified as hyper/hypo connected according to EEG frequency band (Pascual-Marqui et al., 2011). To show how it relates to fatigue, the results could then be regressed against scores on neuropsychological tests and subjective behavior measures. These procedures could be then repeated for testing the integrity of other resting-state networks (e.g., salience network, the executive control network, dorsal/ventral attention networks, visual network, sensorimotor network, and auditory networks; (Raichle, 2011) to potentially reveal highly essential clues specific to ME neurocognitive impairment. Specific patterns that are identified using the approach will likely serve as potential targets for treatment (e.g., EEG biofeedback).

Multi-modal EEG Integration

One of the ultimate goals of neuroscience is to find ways of bringing together imaging modalities for the best clinical outcome. Through an integration of neuroimaging (e.g., EEG/MEG with MRI and fMRI techniques), we take advantage of what each modality has to offer to increase our understanding of adverse conditions in the brain (Liu, Ding, & He, 2006). Electrical neuroimaging findings can be co-registered with respect to all these imaging modalities and integrative EEG studies thus far are yielding important noninvasive insights regarding state changes in functional brain architecture (Michel & Murray, 2012). Moreover, DTI modeling of connections in the brain infrastructure forms the basis for understanding and cross-validation of the electric neuroimaging results (Hagmann et al., 2008; Thatcher, North, & Biver, 2012). Finally, combining other modalities is one way to expand our novel approaches for selection of new treatments and differential diagnosis for patients with ME in particular.

Conclusion

Neural dynamics is fundamental for all types of brain processes. Targeting neural dynamics in real time remains attractive but currently poses a significant challenge to researchers and clinicians, particularly in ME. Progress in developing better methods to assess neurocognitive impairment has been limited, possibly due to the lack of newer methods developed and perceived redundancy between animated and static neuroimaging methods. The potential to assess, and possibly treat, neurocognitive problems in ME is evident as per the quantitative EEG methods and preliminary data presented in this article.

An important area of future research is to better understand the manner in which neurons communicate through networks and how that process is truncated in disease. Although it is fairly evident that central nervous system connectivity is a

likely candidate, much more needs to be known about its effect upon neurocognitive dysfunction in ME in order to develop new concepts for the understanding, diagnosis, and treatment of patients.

Conflict of Interest

The authors confirm that this article content has no competing interest.

Our thanks to Linda Clark for generously providing us financial support.

References

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

Afari, N., & Buchwald, D. (2003). Chronic fatigue syndrome: a review. *The American Journal of Psychiatry, 160*(2), 221–236.

Allen, E. A., Erhardt, E. B., Damaraju, E., Gruner, W., Segall, J. M., Silva, R. F., ... Calhoun, V. D. (2011). A baseline for the multivariate comparison of resting-state networks. *Frontiers in Systems Neuroscience, 5*, 2. http://dx.doi.org/10.3389/fnsys.2011.00002

Angelakis, E., & Lubar, J. F. (2002). Quantitative electroencephalographic amplitude measures in young adults during reading tasks and rest. *Journal of Neurotherapy, 6*(2), 5–19. http://dx.doi.org/10.1300/J184v06n02_03

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. http://dx.doi.org/10.2147/prbm.s50645

Babiloni, C., Binetti, G., Cassetta, E., Cerboneschi, D., Dal Forno, G., Del Percio, C., ... Rossini, P. M. (2004). Mapping distributed sources of cortical rhythms in mild Alzheimer's disease. A multicentric EEG study. *NeuroImage, 22*(1), 57–67. http://dx.doi.org/10.1016/j.neuroimage.2003.09.028

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. http://dx.doi.org/10.1002/hbm.22005

Babiloni, C., Cassetta, E., Dal Forno, G., Del Percio, C., Ferreri, F., Ferri, R., ... Rossini, P. M. (2006). Donepezil effects on sources of cortical rhythms in mild Alzheimer's disease: Responders vs. Non-Responders. *NeuroImage, 31*(4), 1650–1665. http://dx.doi.org/10.1016/j.neuroimage.2006.02.015

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, 122*(12), 2355–2364. http://dx.doi.org/10.1016/j.clinph.2011.03.029

Babiloni, C., Del Percio, C., Lizio, R., Marzano, N., Infarinato, F., Soricelli, A., ... Rossini, P. M. (2014). Cortical sources of resting state electroencephalographic alpha rhythms deteriorate across time in subjects with amnesic mild cognitive impairment. *Neurobiology of Aging, 35*(1), 130–142. http://dx.doi.org/10.1016/j.neurobiolaging.2013.06.019

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. http://dx.doi.org/10.1016/j.clinph.2006.01.020

Babiloni, C., Pistoia, F., Sarà, M., Vecchio, F., Buffo, P., Conson, M., ... Rossini, P. M. (2010). Resting state eyes-closed cortical rhythms in patients with locked-in-syndrome: an EEG study. *Clinical Neurophysiology, 121*(11), 1816–1824. http://dx.doi.org/10.1016/j.clinph.2010.04.027

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. http://dx.doi.org/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. http://dx.doi.org/10.1002/nbm.1692

Bazhenov, M., & Makeig, S. (2012). Multiscale electroencephalographic dynamics and brain function. In M. I. Rabinovich, K. J. Friston & P. Varona (Eds.), *Principles of Brain Dynamics: Global State Interactions* (pp. 165–181). Cambridge, MA: The MIT Press.

Besenyei, M., Varga, E., Fekete, I., Puskás, S., Hollódy, K., Fogarasi, A., ... Clemens, B. (2012). EEG background activity is abnormal in the temporal and inferior parietal cortex in benign rolandic epilepsy of childhood: a LORETA study. *Epilepsy Research, 98*(1), 44–49. http://dx.doi.org/10.1016/j.eplepsyres.2011.08.013

Billiot, K. M., Budzynski, T. H., & Andrasik, F. (1997). EEG Patterns and Chronic Fatigue Syndrome. *Journal of Neurotherapy, 2*(2), 20–30. http://dx.doi.org/10.1300/J184v02n02_04

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. http://dx.doi.org/10.1016/j.jns.2010.11.018

Bonnelle, V., Leech, R., Kinnunen, K. M., Ham, T. E., Beckmann, C. F., De Boissezon, X., ... Sharp, D. J. (2011). Default mode network connectivity predicts sustained attention deficits after traumatic brain injury. *The Journal of Neuroscience, 31*(38), 13442–13451. http://dx.doi.org/10.1523/jneurosci.1163-11.2011

Bredt, D. S., & Nicoll, R. A. (2003). AMPA receptor trafficking at excitatory synapses. *Neuron, 40*(2), 361–379.

Buckner, R. L. (2012). The serendipitous discovery of the brain's default network. *NeuroImage, 62*(2), 1137–1145. http://dx.doi.org/10.1016/j.neuroimage.2011.10.035

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

Buzsáki, G. (2006). *Rhythms of the Brain*. New York, NY: Oxford University Press.

Buzsáki, 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.

Cairns, R., & Hotopf, M. (2005). A systematic review describing the prognosis of chronic fatigue syndrome. *Occupational Medicine, 55*(1), 20–31. http://dx.doi.org/10.1093/occmed/kqi013

Calhoun, V. D., Liu, J., & Adali, T. (2009). A review of group ICA for fMRI data and ICA for joint inference of imaging, genetic, and ERP data. *NeuroImage, 45*(Suppl. 1), S163–S172. http://dx.doi.org/10.1016/j.neuroimage.2008.10.057

Canavier, C. C. (2015). Phase-resetting as a tool of information transmission. *Current Opinion in Neurobiology, 31*, 206–213. http://dx.doi.org/10.1016/j.conb.2014.12.003

Canuet, L., Ishii, R., Pascual-Marqui, R. D., Iwase, M., Kurimoto, R., Aoki, Y., ... Takeda, M. (2011). Resting-state EEG source localization and functional connectivity in schizophrenia-like psychosis of epilepsy. *PloS ONE, 6*(11), e27863. http://dx.doi.org/10.1371/journal.pone.0027863

Canuet, L., Tellado, I., Couceiro, V., Fraile, C., Fernandez-Novoa, L., Ishii, R., ... Cacabelos, R. (2012). Resting-state network disruption and APOE genotype in Alzheimer's disease: a lagged functional connectivity study. *PloS ONE, 7*(9), e46289. http://dx.doi.org/10.1371/journal.pone.0046289

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. http://dx.doi.org/10.1038/sj.npp.1301005

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. http://dx.doi.org/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. http://dx.doi.org/10.1017/s0033291708003450

Catani, M. (2011). John Hughlings Jackson and the clinico-anatomical correlation method. *Cortex, 47*(8), 905–907. http://dx.doi.org/10.1016/j.cortex.2011.06.002

Catani, M., Bodi, I., & Dell'Acqua, F. (2012). Comment on "The geometric structure of the brain fiber pathways." *Science, 337*(6102), 1605. http://dx.doi.org/10.1126/science.1223425

Catani, M., Dell'Acqua, F., Bizzi, A., Forkel, S. J., Williams, S. C., Simmons, A., ... Thiebaut de Schotten, M. (2012). Beyond cortical localization in clinico-anatomical correlation. *Cortex, 48*(10), 1262–1287. http://dx.doi.org/10.1016/j.cortex.2012.07.001

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

Chavez, M., Le Van Quyen, M., Navarro, V., Baulac, M., & Martinerie, J. (2003). Spatio-temporal dynamics prior to neocortical seizures: amplitude versus phase couplings. *IEEE Transactions on Biomedical Engineering, 50*(5), 571–583. http://dx.doi.org/10.1109/tbme.2003.810696

Chen, A. C. N., Feng, W., Zhao, H., Yin, Y., & Wang, P. (2008). EEG default mode network in the human brain: spectral regional field powers. *NeuroImage, 41*(2), 561–574. http://dx.doi.org/10.1016/j.neuroimage.2007.12.064

Cho, H. J., Skowera, A., Cleare, A., & Wessely, S. (2006). Chronic fatigue syndrome: an update focusing on phenomenology and pathophysiology. *Current Opinion in Psychiatry, 19*(1), 67–73. http://dx.doi.org/10.1097/01.yco.0000194370.40062.b0

Christley, Y., Duffy, T., Everall, I. P., & Martin, C. R. (2013). The neuropsychiatric and neuropsychological features of chronic fatigue syndrome: revisiting the enigma. *Current Psychiatry Reports, 15*(4), 353. http://dx.doi.org/10.1007/s11920-013-0353-8

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.

Cleare, A. J., Messa, C., Rabiner, E. A., & Grasby, P. M. (2005). Brain 5-HT_{1A} receptor binding in chronic fatigue syndrome measured using positron emission tomography and [^{11}C]WAY-100635. *Biological Psychiatry, 57*(3), 239–246. http://dx.doi.org/10.1016/j.biopsych.2004.10.031

Clemens, B., Bánk, J., Piros, P., Bessenyei, M., Vető, S., Tóth, M., & Kondákor, I. (2008). Three-dimensional localization of abnormal EEG activity in migraine: a low resolution electromagnetic tomography (LORETA) study of migraine patients in the pain-free interval. *Brain Topography, 21*(1), 36–42. http://dx.doi.org/10.1007/s10548-008-0061-6

Clemens, B., Bessenyei, M., Fekete, I., Puskás, S., Kondákor, I., Tóth, M., & Hollódy, K. (2010). Theta EEG source localization using LORETA in partial epilepsy patients with and without medication. *Clinical Neurophysiology, 121*(6), 848–858. http://dx.doi.org/10.1016/j.clinph.2010.01.020

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

Cockshell, S. J., & Mathias, J. L. (2012). Test effort in persons with Chronic Fatigue Syndrome when assessed using the Validity Indicator Profile. *Journal of Clinical and Experimental Neuropsychology, 34*(7), 679–687. http://dx.doi.org/10.1080/13803395.2012.668176

Cockshell, S. J., & Mathias, J. L. (2014). Cognitive functioning in people with chronic fatigue syndrome: a comparison between subjective and objective measures. *Neuropsychology, 28*(3), 394–405. http://dx.doi.org/10.1037/neu0000025

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. http://dx.doi.org/10.1016/j.neuroimage.2007.02.033

Cope, H., & David, A. S. (1996). Neuroimaging in chronic fatigue syndrome. *Journal of Neurology, Neurosurgery, and Psychiatry, 60*(5), 471–473.

Cope, H., Pernet, A., Kendall, B., & David, A. (1995). Cognitive functioning and magnetic resonance imaging in chronic fatigue. *The British Journal of Psychiatry, 167*(1), 86–94.

Costa, D. C., Tannock, C., & Brostoff, J. (1995). Brainstem perfusion is impaired in chronic fatigue syndrome. *Quarterly Journal of Medicine, 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*(8), 2382–2395. http://dx.doi.org/10.1093/brain/awu132

de Hoz, L., & Simons, M. (2015). The emerging functions of oligodendrocytes in regulating neuronal network behaviour. *BioEssays, 37*(1), 60–69. http://dx.doi.org/10.1002/bies.201400127

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*(3), 777–781. http://dx.doi.org/10.1016/j.neuroimage.2005.02.037

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

de Lange, F. P., Koers, A., Kalkman, J. S., Bleijenberg, G., Hagoort, P., van der Meer, J. W. M., & Toni, I. (2008). Increase in prefrontal cortical volume following cognitive behavioural therapy in patients with chronic fatigue syndrome. *Brain, 131*(8), 2172–2180. http://dx.doi.org/10.1093/brain/awn140

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: The MIT Press.

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

DeLuca, J., Christodoulou, C., Diamond, B. J., Rosenstein, E. D., Kramer, N., & Natelson, B. H. (2004). Working memory deficits in chronic fatigue syndrome: differentiating between speed and accuracy of information processing. *Journal of the International Neuropsychological Society, 10(*1), 101–109. http://dx.doi.org/10.1017/s1355617704101124

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. http://dx.doi.org/10.1016/j.pmr.2008.12.007

Dickinson, C. J. (1997). Chronic fatigue syndrome—aetiological aspects. *European Journal of Clinical Investigation, 27*(4), 257–267. http://dx.doi.org/10.1046/j.1365-2362.1997.1120664.x

Dickson, A., Toft, A., & O'Carroll, R. E. (2009). Neuropsychological functioning, illness perception, mood and quality of life in chronic fatigue syndrome, autoimmune thyroid disease and healthy participants. *Psychological Medicine, 39*(9), 1567–1576. http://dx.doi.org/10.1017/s0033291708004960

Dierks, T., Jelic, V., Pascual-Marqui, R. D., Wahlund, L., Julin, P., Linden, D. E., ... Nordberg, A. (2000). Spatial pattern of cerebral glucose metabolism (PET) correlates with localization of intracerebral EEG-generators in Alzheimer's disease. *Clinical Neurophysiology, 111*(10), 1817–1824.

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. http://dx.doi.org/10.1186/1471-2377-11-82

Elson, R. C., Huerta, R., Abarbanel, H. D. I., Rabinovich, M. I., & Selverston, A. I. (1999). Dynamic control of irregular bursting in an identified neuron of an oscillatory circuit. *Journal of Neurophysiology, 82*(1), 115–122.

Fischer, D. B., William, A. H., Strauss, A. C., Unger, E. R., Jason, L. A., Marshall, G. D., Jr., & Dimitrakoff, J. D. (2014). Chronic Fatigue Syndrome: The Current Status and Future Potentials of Emerging Biomarkers. *Fatigue: Biomedicine, Health and Behavior, 2*(2), 93–109. http://dx.doi.org/10.1080/21641846.2014.906066

Fleminger, S., Oliver, D. L., Williams, W. H., & Evans, J. (2003). The neuropsychiatry of depression after brain injury. *Neuropsychological Rehabilitation, 13*(1–2), 65–87. http://dx.doi.org/10.1080/09602010244000354

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

Fox, M. D., Zhang, D., Snyder, A. Z., & Raichle, M. E. (2009). The global signal and observed anticorrelated resting state brain networks. *Journal of Neurophysiology, 101*(6), 3270–3283. http://dx.doi.org/10.1152/jn.90777.2008

Frey, J. N., Ruhnau, P., & Weisz, N. (2015). Not so different after all: The same oscillatory processes support different types of attention. *Brain Research, 1626*, 183–197. http://dx.doi.org/10.1016/j.brainres.2015.02.017

Friston, K. (2010). The free-energy principle: a unified brain theory? *Nature Reviews Neuroscience, 11*(2), 127–138. http://dx.doi.org/10.1038/nrn2787

Friston, K. J., Bastos, A. M., Pinotsis, D., & Litvak, V. (2015). LFP and oscillations—what do they tell us? *Current Opinion in Neurobiology, 31,* 1–6. http://dx.doi.org/10.1016/j.conb.2014.05.004

Fry, A. M., & Martin, M. (1996). Fatigue in the chronic fatigue syndrome: a cognitive phenomenon? *Journal of Psychosomatic Research, 41*(5), 415–426. http://dx.doi.org/10.1016/S0022-3999(96)00190-0

Fuster, J. M. (2009). *The Prefrontal Cortex* (4th ed.). Burlington, MA: Elsevier/Academic Press.

Gay, C. W., Robinson, M. E., Lai, S., O'Shea, A., Craggs, J. G., Price, D. D., & Staud, R. (2016). Abnormal Resting-State Functional Connectivity in Patients with Chronic Fatigue Syndrome: Results of Seed and Data-Driven Analyses. *Brain Connectivity, 6*(1), 48–56. http://dx.doi.org/10.1089/brain.2015.0366

Gianotti, L. R. R., Künig, G., Faber, P. L., Lehmann, D., Pascual-Marqui, R. D., Kochi, K., & Schreiter-Gasser, U. (2008). Rivastigmine effects on EEG spectra and three-dimensional LORETA functional imaging in Alzheimer's disease. *Psychopharmacology, 198*(3), 323–332. http://dx.doi.org/10.1007/s00213-008-1111-1

Gianotti, L. R. R., Künig, G., Lehmann, D., Faber, P. L., Pascual-Marqui, R. D., Kochi, K., & Schreiter-Gasser, U. (2007). Correlation between disease severity and brain electric LORETA tomography in Alzheimer's disease. *Clinical Neurophysiology, 118*(1), 186–196. http://dx.doi.org/10.1016/j.clinph.2006.09.007

Gloor, P., Ball, G., & Schaul, N. (1977). Brain lesions that produce delta waves in the EEG. *Neurology, 27*(4), 326–333. http://dx.doi.org/10.1212/WNL.27.4.326

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. http://dx.doi.org/10.1016/j.jpsychores.2013.12.006

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. http://dx.doi.org/10.1186/1743-0003-5-25

Greicius, M. D., Srivastava, G., Reiss, A. L., & Menon, V. (2004). Default-mode network activity distinguishes Alzheimer's disease from healthy aging: evidence from functional MRI. *Proceedings of the National Academy of Sciences of the United States of America, 101*(13), 4637–4642. http://dx.doi.org/10.1073/pnas.0308627101

Griffith, J. P., & Zarrouf, F. A. (2008). A systematic review of chronic fatigue syndrome: don't assume it's depression. *Primary Care Companion to the Journal of Clinical Psychiatry, 10*(2), 120–128.

Gu, S., Pasqualetti, F., Cieslak, M., Telesford, Q. K., Yu, A. B., Kahn, A. E., ... Bassett, D. S. (2015). Controllability of structural brain networks. *Nature Communications, 6*, 8414. http://dx.doi.org/10.1038/ncomms9414

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. http://dx.doi.org/10.1371/journal.pbio.0060159

Halassa, M. M., & Haydon, P. G. (2010). Integrated brain circuits: astrocytic networks modulate neuronal activity and behavior. *Annual Review of Physiology, 72*, 335–355. http://dx.doi.org/10.1146/annurev-physiol-021909-135843

Haneef, Z., Lenartowicz, A., Yeh, H. J., Engel, J., Jr., & Stern, J. M. (2014). Network analysis of the default mode network using functional connectivity MRI in Temporal Lobe Epilepsy. *Journal of Visualized Experiments,* (90), e51442. http://dx.doi.org/10.3791/51442

Havlicek, M., Roebroeck, A., Friston, K., Gardumi, A., Ivanov, D., & Uludag, K. (2015). Physiologically informed dynamic causal modeling of fMRI data. *NeuroImage, 122*, 355–372. http://dx.doi.org/10.1016/j.neuroimage.2015.07.078

Hawk, C., Jason, L. A., & Torres-Harding, S. (2006). Differential diagnosis of chronic fatigue syndrome and major depressive

disorder. *International Journal of Behavioral Medicine, 13*(3), 244–251. http://dx.doi.org/10.1207/s15327558ijbm1303_8

Hellyer, P. J., Jachs, B., Clopath, C., & Leech, R. (2015). Local inhibitory plasticity tunes macroscopic brain dynamics and allows the emergence of functional brain networks. *NeuroImage, 124*(Pt A), 85–95. http://dx.doi.org/10.1016/j.neuroimage.2015.08.069

Heyder, K., Suchan, B., & Daum, I. (2004). Cortico-subcortical contributions to executive control. *Acta Psychologica, 115*(2–3), 271–289. http://dx.doi.org/10.1016/j.actpsy.2003.12.010

Hillary, F. G., & DeLuca, J. (Eds.). (2007). *Functional Neuroimaging in Clinical Populations*. New York, NY: Guilford Press.

Holmgren, M., & Scheffer, M. (2010). Strong facilitation in mild environments: the stress gradient hypothesis revisited. *Journal of Ecology, 98*(6), 1269–1275. http://dx.doi.org/10.1111/j.1365-2745.2010.01709.x

Hou, J., Lin, Y., Zhang, W., Song, L., Wu, W., Wang, J., ... Li, H. (2013). Abnormalities of frontal-parietal resting-state functional connectivity are related to disease activity in patients with systemic lupus erythematosus. *PloS ONE, 8*(9), e74530. http://dx.doi.org/10.1371/journal.pone.0074530

Hughes, S. W., Lörincz, M., Cope, D. W., Blethyn, K. L., Kékesi, 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. http://dx.doi.org/10.1016/S0896-6273(04)00191-6

Ichise, M., Salit, I. E., Abbey, S. E., Chung, D.-G., Gray, B., Kirsh, J. C., & Freedman, M. (1992). Assessment of regional cerebral perfusion by 99Tcm-HMPAO SPECT in chronic fatigue syndrome. *Nuclear Medicine Communications, 13*(10), 767–772.

Jann, K., Hernandez, L. M., Beck-Pancer, D., McCarron, R., Smith, R. X., Dapretto, M., & Wang, D. J. J. (2015). Altered resting perfusion and functional connectivity of default mode network in youth with autism spectrum disorder. *Brain and Behavior, 5*(9), e00358. http://dx.doi.org/10.1002/brb3.358

Jason, L. A., Zinn, M. L., & Zinn, M. A. (2015). Myalgic Encephalomyelitis: Symptoms and Biomarkers. *Current Neuropharmacology*, *13*(5), 701–734. http://dx.doi.org/10.2174/1570159X13666150928105725

Johnson, E. L., & Knight, R. T. (2015). Intracranial Recordings and Human Memory. *Current Opinion in Neurobiology, 31*, 18–25. http://dx.doi.org/10.1016/j.conb.2014.07.021

Jones, R., & Bhattacharya, J. (2014). A role for the precuneus in thought-action fusion: evidence from participants with significant obsessive-compulsive symptoms. *NeuroImage: Clinical, 4*, 112–121. http://dx.doi.org/10.1016/j.nicl.2013.11.008

Kandel, E. R., Schwartz, J. H., Jessell, T. M., Siegelbaum, S. A., & Hudspeth, A. J. (Eds.). (2012). *Principles of Neural Science* (5th ed.). New York, NY: McGraw Hill.

Kennedy, M. B., Beale, H. C., Carlisle, H. J., & Washburn, L. R. (2005). Integration of biochemical signalling in spines. *Nature Reviews Neuroscience, 6*(6), 423–434. http://dx.doi.org/10.1038/nrn1685

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. http://dx.doi.org/10.1016/j.brainres.2008.06.049

Krupp, L. B., LaRocca, N. G., Muir-Nash, J., & Steinberg, A. D. (1989). The fatigue severity scale. Application to patients with multiple sclerosis and systemic lupus erythematosus. *Archives of Neurology*, *46*(10), 1121–1123. http://dx.doi.org/10.1001/archneur.1989.00520460115022

Krupp, L. B., Sliwinski, M., Masur, D. M., Friedberg, F., & Coyle, P. K. (1994). Cognitive functioning and depression in patients with chronic fatigue syndrome and multiple sclerosis. *Archives of Neurology, 51*(7), 705–710.

Kuzis, G., Sabe, L., Tiberti, C., Dorrego, F., & Starkstein, S. E. (1999). Neuropsychological correlates of apathy and depression in patients with dementia. *Neurology, 52*(7), 1403–1407.

LaManca, J. J., Sisto, S. A., DeLuca, J., Johnson, S. K., Lange, G., Pareja, J., ... Natelson, B. H. (1998). Influence of exhaustive treadmill exercise on cognitive functioning in chronic fatigue syndrome. *The American Journal of Medicine, 105*(3A), 59S–65S.

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. http://dx.doi.org/10.1016/j.neuroimage.2005.02.011

Le Van Quyen, M., Martinerie, J., Navarro, V., Baulac, M., & Varela, F. J. (2001). Characterizing neurodynamic changes before seizures. *Journal of Clinical Neurophysiology, 18*(3), 191–208.

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. http://dx.doi.org/10.1148/radiology.219.3.r01jn18766

Liu, Z., Ding, L., & He, B. (2006). Integration of EEG/MEG with MRI and fMRI. *IEEE Engineering in Medicine and Biology Magazine, 25*(4), 46–53.

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

MacHale, S. M., Lawfie, S. M., Cavanagh, J. T., Glabus, M. F., Murray, C. L., Goodwin, G. M., & Ebmeier, K. P. (2000). Cerebral perfusion in chronic fatigue syndrome and depression. *The British Journal of Psychiatry, 176*, 550–556.

Madhyastha, T. M., Askren, M. K., Boord, P., & Grabowski, T. J. (2015). Dynamic connectivity at rest predicts attention task performance. *Brain Connectivity, 5*(1), 45–59. http://dx.doi.org/10.1089/brain.2014.0248

Maes, M. (2011). An intriguing and hitherto unexplained co-occurrence: Depression and chronic fatigue syndrome are manifestations of shared inflammatory, oxidative and nitrosative (IO&NS) pathways. *Progress in Neuro-Psychopharmacology and Biological Psychiatry, 35*(3), 784–794. http://dx.doi.org/10.1016/j.pnpbp.2010.06.023

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. http://dx.doi.org/10.1097/PSY.0b013e31817b9793

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. http://dx.doi.org/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.

McCormick, D. A., & Bal, T. (1997). Sleep and arousal: thalamocortical mechanisms. *Annual Review of Neuroscience, 20*, 185–215. http://dx.doi.org/10.1146/annurev.neuro.20.1.185

McEwen, B. S. (2006). Protective and damaging effects of stress mediators: central role of the brain. *Dialogues in Clinical Neuroscience, 8*(4), 367–381.

McEwen, B. S., Bowles, N. P., Gray, J. D., Hill, M. N., Hunter, R. G., Karatsoreos, I. N., & Nasca, C. (2015). Mechanisms of

stress in the brain. *Nature Neuroscience, 18*(10), 1353–1363. http://dx.doi.org/10.1038/nn.4086

McPherson, S., Fairbanks, L., Tiken, S., Cummings, J. L., & Back-Madruga, C. (2002). Apathy and executive function in Alzheimer's disease. *Journal of the International Neuropsychological Society, 8*(3), 373–381.

Menon, V. (2011). Large-scale brain networks and psychopathology: a unifying triple network model. *Trends in Cognitive Sciences, 15*(10), 483–506. http://dx.doi.org/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: The MIT Press.

Metherate, R., & Ashe, J. H. (1993). Ionic flux contributions to neocortical slow waves and nucleus basalis-mediated activation: whole-cell recordings in vivo. *The Journal of Neuroscience, 13*(12), 5312–5323.

Metzger, F. A., & Denney, D. R. (2002). Perception of cognitive performance in patients with chronic fatigue syndrome. *Annals Of Behavioral Medicine, 24*(2), 106–112.

Michel, C. M., & Murray, M. M. (2012). Towards the utilization of EEG as a brain imaging tool. *NeuroImage, 61*(2), 371–385. http://dx.doi.org/10.1016/j.neuroimage.2011.12.039

Michiels, V., & Cluydts, R. (2001). Neuropsychological functioning in chronic fatigue syndrome: a review. *Acta Psychiatrica Scandinavica, 103*(2), 84–93. http://dx.doi.org/10.1034/j.1600-0447.2001.00017.x

Moazami-Goudarzi, M., Sarnthein, J., Michels, L., Moukhtieva, R., & Jeanmonod, D. (2008). Enhanced frontal low and high frequency power and synchronization in the resting EEG of parkinsonian patients. *NeuroImage, 41*(3), 985–997. http://dx.doi.org/10.1016/j.neuroimage.2008.03.032

Morris, G., & Maes, M. (2012). A neuro-immune model of Myalgic Encephalomyelitis/Chronic fatigue syndrome. *Metabolic Brain Disease, 28*(4), 523–540. http://dx.doi.org/10.1007/s11011-012-9324-8

Mulert, C., Jäger, L., Schmitt, R., Bussfeld, P., Pogarell, O., Möller, H.-J., ... Hegerl, U. (2004). Integration of fMRI and simultaneous EEG: towards a comprehensive understanding of localization and time-course of brain activity in target detection. *NeuroImage, 22*(1), 83–94. http://dx.doi.org/10.1016/j.neuroimage.2003.10.051

Musso, F., Brinkmeyer, J., Mobascher, A., Warbrick, T., & Winterer, G. (2010). Spontaneous brain activity and EEG microstates. A novel EEG/fMRI analysis approach to explore resting-state networks. *NeuroImage, 52*(4), 1149–1161. http://dx.doi.org/10.1016/j.neuroimage.2010.01.093

Nakatomi, Y., Mizuno, K., Ishii, A., Wada, Y., Tanaka, M., Tazawa, S., ... Watanabe, Y. (2014). Neuroinflammation in patients with Chronic Fatigue Syndrome/Myalgic Encephalomyelitis: An ^{11}C-(R)-PK11195 PET study. *Journal of Nuclear Medicine, 55*(6), 945–950. http://dx.doi.org/10.2967/jnumed.113.131045

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.

Neu, D., Kajosch, H., Peigneux, P., Verbanck, P., Linkowski, P., & Le Bon, O. (2011). Cognitive impairment in fatigue and sleepiness associated conditions. *Psychiatry Research, 189*(1), 128–134. http://dx.doi.org/10.1016/j.psychres.2010.12.005

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

Nijs, J., Van Oosterwijck, J., Meeus, M., Lambrecht, L., Metzger, K., Frémont, M., & Paul, L. (2010). Unravelling the nature of postexertional malaise in myalgic encephalomyelitis/chronic fatigue syndrome: the role of elastase, complement C4a and interleukin-1beta. *Journal of Internal Medicine, 267*(4), 418–435. http://dx.doi.org/10.1111/j.1365-2796.2009.02178.x

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. http://dx.doi.org/10.1016/j.clinph.2011.02.011

Nolte, G., & Müller, K.-R. (2010). Localizing and estimating causal relations of interacting brain rhythms. *Frontiers in Human Neuroscience, 4*, 209. http://dx.doi.org/10.3389/fnhum.2010.00209

Nolte, G., Ziehe, A., Nikulin, V. V., Schlögl, A., Krämer, N., Brismar, T., & Müller, K.-R. (2008). Robustly estimating the flow direction of information in complex physical systems. *Physical Review Letters, 100*(23), 234101.

Nolte, J. (2009). *The Human Brain: An Introduction to its Functional Anatomy* (6th ed.). Philadelphia, PA: Mosby/Elsevier.

Nunez, P. L., Srinivasan, R., & Fields, R. D. (2014). EEG functional connectivity, axon delays and white matter disease. *Clinical Neurophysiology, 126*(1), 110–120. http://dx.doi.org/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. http://dx.doi.org/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. http://dx.doi.org/10.1186/1471-2377-4-14

Olbrich, S., Olbrich, H., Jahn, I., Sander, C., Adamaszek, M., Hegerl, U., ... Stengler, K. (2013). EEG-vigilance regulation during the resting state in obsessive-compulsive disorder. *Clinical Neurophysiology, 124*(3), 497–502. http://dx.doi.org/10.1016/j.clinph.2012.08.018

Olbrich, S., Tränkner, A., Chittka, T., Hegerl, U., & Schönknecht, P. (2014). Functional connectivity in major depression: increased phase synchronization between frontal cortical EEG-source estimates. *Psychiatry Research, 222*(1–2), 91–99. http://dx.doi.org/10.1016/j.pscychresns.2014.02.010

Olvet, D. M., Delaparte, L., Yeh, F.-C., DeLorenzo, C., McGrath, P. J., Weissman, M. M., ... Parsey, R. V. (2015). A comprehensive examination of white matter tracts and connectometry in major depressive disorder. *Depression and Anxiety, 33*(1), 56–65. http://dx.doi.org/10.1002/da.22445

Pachner, A. R. (2012). *A Primer of Neuroimmunological Disease*. New York: Springer.

Papageorgiou, C. C., Sfagos, C., Kosma, K. K., Kontoangelos, K. A., Triantafyllou, N., Vassilopoulos, D., ... Soldatos, C. R. (2007). Changes in LORETA and conventional patterns of P600 after steroid treatment in multiple sclerosis patients. *Progress in Neuro-Psychopharmacology and Biological Psychiatry, 31*(1), 234–241. http://dx.doi.org/10.1016/j.pnpbp.2006.07.005

Pascual-Marqui, R. D., Biscay, R. J., Bosch-Bayard, J., Lehmann, D., Kochi, K., Kinoshita, T., ... Sadato, N. (2014). Assessing direct paths of intracortical causal information flow of oscillatory activity with the isolated effective coherence (iCoh). *Frontiers in Human Neuroscience, 8*. http://dx.doi.org/10.3389/fnhum.2014.00448

Pascual-Marqui, R. D., Esslen, M., Kochi, K., & Lehmann, D. (2002). Functional imaging with low-resolution brain electromagnetic tomography (LORETA): a review. *Methods and Findings in Experimental and Clinical Pharmacology, 24(*Suppl. C), 91–95.

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 of the Royal Society A, 369*(1952), 3768–3784. http://dx.doi.org/10.1098/rsta.2011.0081

Pascual-Marqui, R. D., Michel, C. M., & Lehmann, D. (1994). Low resolution electromagnetic tomography: a new method for localizing electrical activity in the brain. *International Journal of Psychophysiology, 18*(1), 49–65.

Pazderka-Robinson, H., Morrison, J. W., & Flor-Henry, P. (2004). Electrodermal dissociation of chronic fatigue and depression: evidence for distinct physiological mechanisms. *International Journal of Psychophysiology, 53*(3), 171–182. http://dx.doi.org/10.1016/j.ijpsycho.2004.03.004

Pellerin, L., & Magistretti, P. J. (1994). Glutamate uptake into astrocytes stimulates aerobic glycolysis: a mechanism coupling neuronal activity to glucose utilization. *Proceedings of the National Academy of Sciences of the United States of America, 91*(22), 10625–10629.

Perrin, R., Embleton, K., Pentreath, V. W., & Jackson, A. (2010). Longitudinal MRI shows no cerebral abnormality in chronic fatigue syndrome. *The British Journal of Radiology, 83*(989), 419–423. http://dx.doi.org/10.1259/bjr/85621779

Pinal, D., Zurrón, M., Díaz, F., & Sauseng, P. (2015). Stuck in default mode: inefficient cross-frequency synchronization may lead to age-related short-term memory decline. *Neurobiology of Aging, 36*(4), 1611–1618. http://dx.doi.org/10.1016/j.neurobiolaging.2015.01.009

Pizzagalli, D. A., Oakes, T. R., Fox, A. S., Chung, M. K., Larson, C. L., Abercrombie, H. C., ... Davidson, R. J. (2004). Functional but not structural subgenual prefrontal cortex abnormalities in melancholia. *Molecular Psychiatry, 9*(4), 393–405. http://dx.doi.org/10.1038/sj.mp.4001469

Poldrack, R. A., Mumford, J. A., & Nichols, T. E. (2011). *Handbook of Functional MRI Data Analysis*. New York: Cambridge University Press.

Prasher, D., Smith, A., & Findley, L. (1990). Sensory and cognitive event-related potentials in myalgic encephalomyelitis. *Journal of Neurology, Neurosurgery, and Psychiatry, 53*(3), 247–253.

Purger, D., Gibson, E. M., & Monje, M. (2015). Myelin plasticity in the central nervous system. *Neuropharmacology*. Advance online publication. http://dx.doi.org/10.1016/j.neuropharm.2015.08.001

Puri, B. K., Jakeman, P. M., Agour, M., Gunatilake, K. D. R., Fernando, K. A. C., 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. *The British Journal of Radiology, 85*(1015), e270–273. http://dx.doi.org/10.1259/bjr/93889091

Rabinovich, M. I., Afraimovich, V. S., Bick, C., & Varona, P. (2012). Information flow dynamics in the brain. *Physics of Life Reviews, 9*(1), 51–73. http://dx.doi.org/10.1016/j.plrev.2011.11.002

Rabinovich, M. I., Friston, K. J., & Varona, P. (Eds.). (2012). *Principles of Brain Dynamics: Global State Interactions*. Cambridge, MA: The MIT Press.

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

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

Raichle, M. E., MacLeod, A. M., Snyder, A. Z., Powers, W. J., Gusnard, D. A., & Shulman, G. L. (2001). A default mode of brain function. *Proceedings of the National Academy of Sciences of the United States of America, 98*(2), 676–682. http://dx.doi.org/10.1073/pnas.98.2.676

Romei, V., Gross, J., & Thut, G. (2012). Sounds reset rhythms of visual cortex and corresponding human visual perception. *Current Biology, 22*(9), 807–813. http://dx.doi.org/10.1016/j.cub.2012.03.025

Ropper, A. H., & Samuels, M. A. (2009). *Adams & Victor's Principles of Neurology* (9th ed.). New York, NY: McGraw-Hill.

Sandman, C. A., Barron, J. L., Nackoul, K., Goldstein, J., & Fidler, F. (1993). Memory deficits associated with chronic fatigue immune dysfunction syndrome. *Biological Psychiatry, 33*(8–9), 618–623.

Santamarina-Perez, P., Eiroa-Orosa, F. J., Freniche, V., Moreno-Mayos, A., Alegre, J., Saez, N., & Jacas, C. (2011). Length of illness does not predict cognitive dysfunction in chronic fatigue syndrome. *Applied Neuropsychology, 18*(3), 216–222. http://dx.doi.org/10.1080/09084282.2011.595448

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

Schaul, N., Lueders, H., & Sachdev, K. (1981). Generalized, bilaterally synchronous bursts of slow waves in the EEG. *Archives of Neurology, 38*(11), 690–692.

Schmaling, K. B., Lewis, D. H., Fiedelak, J. I., Mahurin, R., & Buchwald, D. S. (2003). Single-photon emission computerized tomography and neurocognitive function in patients with chronic fatigue syndrome. *Psychosomatic Medicine, 65*(1), 129–136.

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. *American Journal of Roentgenology, 162*(4), 935–941. http://dx.doi.org/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. http://dx.doi.org/10.2214/ajr.162.4.8141022

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. http://dx.doi.org/10.1016/j.neuroimage.2006.11.007

Sherman, S. M., & Guillery, R. W. (1996). Functional organization of thalamocortical relays. *Journal of Neurophysiology, 76*(3), 1367–1395.

Short, K., McCabe, M., & Tooley, G. (2002). Cognitive functioning in chronic fatigue syndrome and the role of depression, anxiety, and fatigue. *Journal of Psychosomatic Research, 52*(6), 475–483. http://dx.doi.org/10.1016/S0022-3999(02)00290-8

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. http://dx.doi.org/10.1016/j.tins.2004.06.005

Siemionow, V., Fang, Y., Calabrese, L., Sahgal, V., & Yue, G. H. (2004). Altered central nervous system signal during motor performance in chronic fatigue syndrome. *Clinical Neurophysiology, 115*(10), 2372–2381. http://dx.doi.org/10.1016/j.clinph.2004.05.012

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. http://dx.doi.org/10.1136/jnnp.74.7.922

Smets, E. M. A., Garssen, B., Bonke, B., & De Haes, J. C. J. M. (1995). The Multidimensional Fatigue Inventory (MFI) psychometric qualities of an instrument to assess fatigue.

Journal of Psychosomatic Research, 39(3), 315–325. http://dx.doi.org/10.1016/0022-3999(94)00125-O

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.

Sponheim, S. R., McGuire, K. A., Kang, S. S., Davenport, N. D., Aviyente, S., Bernat, E. M., & Lim, K. O. (2011). Evidence of disrupted functional connectivity in the brain after combat-related blast injury. *NeuroImage, 54*(Suppl. 1), S21–S29. http://dx.doi.org/10.1016/j.neuroimage.2010.09.007

Sporns, O. (2013). Structure and function of complex brain networks. *Dialogues in Clinical Neuroscience, 15*(3), 247–262.

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

Stam, C. J., van Cappellen van Walsum, A. M., Pijnenburg, Y. A., Berendse, H. W., de Munck, J. C., Scheltens, P., & van Dijk, B. W. (2002). Generalized synchronization of MEG recordings in Alzheimer's Disease: evidence for involvement of the gamma band. *Journal of Clinical Neurophysiology, 19*(6), 562–574. http://dx.doi.org/10.1097/00004691-200212000-00010

Stanton, B. R., & Carson, A. (2016). Apathy: A practical guide for neurologists. *Practical Neurology, 16*(1), 42–47. http://dx.doi.org/10.1136/practneurol-2015-001232

Stefanics, G., Hangya, B., Hernádi, I., Winkler, I., Lakatos, P., & Ulbert, I. (2010). Phase entrainment of human delta oscillations can mediate the effects of expectation on reaction speed. *The Journal of Neuroscience, 30*(41), 13578–13585. http://dx.doi.org/10.1523/jneurosci.0703-10.2010

Steriade, M. (2006). Grouping of brain rhythms in corticothalamic systems. *Neuroscience, 137*(4), 1087–1106. http://dx.doi.org/10.1016/j.neuroscience.2005.10.029

Steriade, M., & Paré, D. (2006). *Gating in cerebral networks*. New York, NY: Cambridge University Press.

Stranahan, A. M., & Mattson, M. P. (2008). Impact of energy intake and expenditure on neuronal plasticity. *NeuroMolecular Medicine, 10*(4), 209–218. http://dx.doi.org/10.1007/s12017-008-8043-0

Stratton, P., & Wiles, J. (2015). Global segregation of cortical activity and metastable dynamics. *Frontiers in Systems Neuroscience, 9*, 119. http://dx.doi.org/10.3389/fnsys.2015.00119

Strauss, E., Sherman, E. M. S., & Spreen, O. (2006). A Compendium of Neuropsychological Tests: Administration, Norms, and Commentary (3rd ed.). New York, NY: Oxford University Press.

Styliadis, C., Kartsidis, P., Paraskevopoulos, E., Ioannides, A. A., & Bamidis, P. D. (2015). Neuroplastic effects of combined computerized physical and cognitive training in elderly individuals at risk for dementia: an eLORETA controlled study on resting states. *Neural Plasticity, 2015,* 172192. http://dx.doi.org/10.1155/2015/172192

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. http://dx.doi.org/10.1186/1471-2377-6-9

Tang, Y.-Y., Rothbart, M. K., & Posner, M. I. (2012). Neural correlates of establishing, maintaining, and switching brain states. *Trends in Cognitive Sciences, 16*(6), 330–337. http://dx.doi.org/10.1016/j.tics.2012.05.001

Thatcher, R. W. (2011). Neuropsychiatry and Quantitative EEG in the 21st Century. *Neuropsychiatry, 1*(5), 495–514. http://dx.doi.org/10.2217/npy.11.45

Thatcher, R. W. (2012). *Handbook of Quantitative Electroencephalography and EEG Biofeedback*. St. Petersburg, FL: ANI Publishing.

Thatcher, R. W. (2015). *Handbook of Quantitative Electroencephalography and EEG Biofeedback*. St. Petersburg, FL: ANI Publishing.

Thatcher, R. W., & John, E. R. (1977). *Foundations of Cognitive Processes (Vol. 1)*. Hillsdale, NJ: Lawrence Erlbaum.

Thatcher, R. W., North, D., & Biver, C. (2005). EEG and intelligence: relations between EEG coherence, EEG phase delay and power. *Clinical Neurophysiology, 116*(9), 2129–2141. http://dx.doi.org/10.1016/j.clinph.2005.04.026

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. http://dx.doi.org/10.1016/j.neuroimage.2008.06.009

Thatcher, R. W., North, D. M., & Biver, C. J. (2012). Diffusion spectral imaging modules correlate with EEG LORETA neuroimaging modules. *Human Brain Mapping, 33*(5), 1062–1075. http:/dx.doi.org/10.1002/hbm.21271

Thatcher, R. W., North, D. M., & Biver, C. J. (2014). LORETA EEG phase reset of the default mode network. *Frontiers in Human Neuroscience, 8*, 529. http://dx.doi.org/10.3389/fnhum.2014.00529

Thatcher, R. W., North, D. M., Curtin, R. T., Walker, R. A., Biver, C. J., Gomez, J. F., & Salazar, A. M. (2001). An EEG severity index of traumatic brain injury. *Journal of Neuropsychiatry and Clinical Neurosciences, 13*(1), 77–87.

Thatcher, R. W., North, D. M., Neubrander, J., Biver, C. J., Cutler, S., & DeFina, P. (2009). Autism and EEG phase reset: deficient GABA mediated inhibition in thalamo-cortical circuits. *Developmental Neuropsychology, 34*(6), 780–800. http://dx.doi.org/10.1080/87565640903265178

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

Tiersky, L. A., DeLuca, J., Hill, N., Dhar, S. K., Johnson, S. K., Lange, G., ... Natelson, B. H. (2001). Longitudinal assessment of neuropsychological functioning, psychiatric status, functional disability and employment status in chronic fatigue syndrome. *Applied Neuropsychology, 8*(1), 41–50. http://dx.doi.org/10.1207/s15324826an0801_6

Tiersky, L. A., Johnson, S. K., Lange, G., Natelson, B. H., & DeLuca, J. (1997). Neuropsychology of chronic fatigue syndrome: a critical review. *Journal of Clinical and Experimental Neuropsychology, 19*(4), 560–586. http://dx.doi.org/10.1080/01688639708403744

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. *The American Journal of Medicine, 105*(3A), 54S–58S.

Todder, D., Levine, J., Abujumah, A., Mater, M., Cohen, H., & Kaplan, Z. (2012). The quantitative electroencephalogram and the low-resolution electrical tomographic analysis in posttraumatic stress disorder. *Clinical EEG and Neuroscience, 43*(1), 48–53.

Toth, M., Faludi, B., Wackermann, J., Czopf, J., & Kondakor, I. (2009). Characteristic changes in brain electrical activity due to chronic hypoxia in patients with obstructive sleep apnea syndrome (OSAS): a combined EEG study using LORETA and omega complexity. *Brain Topography, 22*(3), 185–190. http://dx.doi.org/10.1007/s10548-009-0110-9

Tristan, I., Rulkov, N. F., Huerta, R., & Rabinovich, M. (2014). Timing control by redundant inhibitory neuronal circuits. *Chaos*, *24*(1), 013124. http://dx.doi.org/10.1063/1.4866580

Twisk, F. N. M. (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. http://dx.doi.org/10.1016/j.jpsychores.2013.10.016

Van Den Eede, F., Moorkens, G., Hulstijn, W., Maas, Y., Schrijvers, D., Stevens, S. R., ... Sabbe, B. G. C. (2011). Psychomotor function and response inhibition in chronic fatigue syndrome. *Psychiatry Research, 186*(2–3), 367–372. http://dx.doi.org/10.1016/j.psychres.2010.07.022

van den Heuvel, M. P., & Sporns, O. (2013). Network hubs in the human brain. *Trends in Cognitive Sciences, 17*(12), 683–696. http://dx.doi.org/10.1016/j.tics.2013.09.012

van Eimeren, T., Monchi, O., Ballanger, B., & Strafella, A. P. (2009). Dysfunction of the default mode network in Parkinson disease: a functional magnetic resonance imaging study. *Archives of Neurology, 66*(7), 877–883. http://dx.doi.org/10.1001/archneurol.2009.97

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

Vancampfort, D., Stubbs, B., Venigalla, S. K., & Probst, M. (2015). Adopting and maintaining physical activity behaviours in people with severe mental illness: The importance of autonomous motivation. *Preventive Medicine, 81*, 216–220. http://dx.doi.org/10.1016/j.ypmed.2015.09.006

Vanneste, S., Plazier, M., van der Loo, E., Van de Heyning, P., Congedo, M., & De Ridder, D. (2010). The neural correlates of tinnitus-related distress. *NeuroImage, 52*(2), 470–480. http://dx.doi.org/10.1016/j.neuroimage.2010.04.029

Varela, C. (2014). Thalamic neuromodulation and its implications for executive networks. *Frontiers in Neural Circuits, 8,* 69. http://dx.doi.org/10.3389/fncir.2014.00069

Vecchio, F., Miraglia, F., Valeriani, L., Scarpellini, M. G., Bramanti, P., Mecarelli, O., & Rossini, P. M. (2015). Cortical Brain Connectivity and B-Type Natriuretic Peptide in Patients With Congestive Heart Failure. *Clinical EEG and Neuroscience, 46*(3), 224–229. http://dx.doi.org/10.1177/1550059414529765

Velikova, S., Locatelli, M., Insacco, C., Smeraldi, E., Comi, G., & Leocani, L. (2010). Dysfunctional brain circuitry in obsessive-compulsive disorder: source and coherence analysis of EEG rhythms. *NeuroImage, 49*(1), 977–983. http://dx.doi.org/10.1016/j.neuroimage.2009.08.015

Velikova, S., Magnani, G., Arcari, C., Falautano, M., Franceschi, M., Comi, G., & Leocani, L. (2011). Cognitive impairment and EEG background activity in adults with Down's syndrome: a topographic study. *Human Brain Mapping, 32*(5), 716–729. http://dx.doi.org/10.1002/hbm.21061

Vitacco, D., Brandeis, D., Pascual-Marqui, R., & Martin, E. (2002). Correspondence of event-related potential tomography and functional magnetic resonance imaging during language processing. *Human Brain Mapping, 17*(1), 4–12. http://dx.doi.org/10.1002/hbm.10038

Volpe, U., Mucci, A., Bucci, P., Merlotti, E., Galderisi, S., & Maj, M. (2007). The cortical generators of P3a and P3b: a LORETA study. *Brain Research Bulletin, 73*(4–6), 220–230. http://dx.doi.org/10.1016/j.brainresbull.2007.03.003

Wacker, J., Dillon, D. G., & Pizzagalli, D. A. (2009). The role of the nucleus accumbens and rostral anterior cingulate cortex in anhedonia: integration of resting EEG, fMRI, and volumetric techniques. *NeuroImage, 46*(1), 327–337. http://dx.doi.org/10.1016/j.neuroimage.2009.01.058

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. http://dx.doi.org/10.1016/j.jpsychores.2012.09.002

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. H. Lopes da Silva (Eds.), *Electroencephalography: Basic principles, clinical applications and related fields* (5th ed., pp. 323–337). Philadelphia, PA: 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. http://dx.doi.org/10.1016/j.jpsychores.2010.01.008

Worrell, G. A., Lagerlund, T. D., Sharbrough, F. W., Brinkmann, B. H., Busacker, N. E., Cicora, K. M., & O'Brien, T. J. (2000). Localization of the epileptic focus by low-resolution electromagnetic tomography in patients with a lesion demonstrated by MRI. *Brain Topography, 12*(4), 273–282.

Wright, K. P., Lowry, C. A., & LeBourgeois, M. K. (2012). Circadian and wakefulness-sleep modulation of cognition in humans. *Frontiers in Molecular Neuroscience, 5*, 50. http://dx.doi.org/10.3389/fnmol.2012.00050

Wulff, K., Gatti, S., Wettstein, J. G., & Foster, R. G. (2010). Sleep and circadian rhythm disruption in psychiatric and neurodegenerative disease. *Nature Reviews Neuroscience, 11*(8), 589–599. http://dx.doi.org/10.1038/nrn2868

Xu, Y., Xu, G., Wu, G., Antuono, P., Rowe, D. B., & Li, S.-J. (2008). The phase shift index for marking functional asynchrony in Alzheimer's disease patients using fMRI. *Magnetic Resonance Imaging, 26*(3), 379–392. http://dx.doi.org/10.1016/j.mri.2007.07.007

Yamamoto, S., Ouchi, Y., Nakatsuka, D., Tahara, T., Mizuno, K., Tajima, S., ... Watanabe, Y. (2012). Reduction of [^{11}C](+)3-MPB binding in brain of chronic fatigue syndrome with serum autoantibody against muscarinic cholinergic receptor. *PloS ONE, 7*(12), e51515. http://dx.doi.org/10.1371/journal.pone.0051515

Yancey, J. R., & Thomas, S. M. (2012). Chronic fatigue syndrome: diagnosis and treatment. *American Family Physician, 86*(8), 741–746.

Yao, B., Bagnato, F., Matsuura, E., Merkle, H., van Gelderen, P., Cantor, F. K., & Duyn, J. H. (2012). Chronic multiple sclerosis lesions: characterization with high-field-strength MR imaging. *Radiology, 262*(1), 206–215. http://dx.doi.org/10.1148/radiol.11110601

York, G. K., & Steinberg, D. A. (2011). Hughlings Jackson's neurological ideas. *Brain*, *134*(10), 3106–3113. http://dx.doi.org/10.1093/brain/awr219

Zhan, X. J., Cox, C. L., Rinzel, J., & Sherman, S. M. (1999). Current clamp and modeling studies of low-threshold calcium spikes in cells of the cat's lateral geniculate nucleus. *Journal of Neurophysiology, 81*(5), 2360–2373.

Zhang, B., Lin, P., Shi, H., Öngür, D., Auerbach, R. P., Wang, X., ... Wang, X. (2015). Mapping anhedonia-specific dysfunction in a transdiagnostic approach: an ALE meta-analysis. *Brain Imaging and Behavior*. Advance online publication. http://dx.doi.org/10.1007/s11682-015-9457-6

Zhou, F., Zhuang, Y., Gong, H., Wang, B., Wang, X., Chen, Q., ... Wan, H. (2014). Altered inter-subregion connectivity of the default mode network in relapsing remitting multiple sclerosis: a functional and structural connectivity study. *PloS ONE, 9(*7), e101198. http://dx.doi.org/10.1371/journal.pone.0101198

Zinn, M. A., Zinn, M. L., Norris, J. L., Valencia, I., Montoya, J. G., & Maldonado, J. R. (2014, March). Cortical hypoactivation during resting EEG suggests central nervous system pathology in patients with Chronic Fatigue Syndrome. Paper presented at the Symposium conducted at the meeting of IACFS/ME 2014 Biennial Conference, San Francisco, CA, USA.

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.

Zumsteg, D., Friedman, A., Wieser, H. G., & Wennberg, R. A. (2006). Propagation of interictal discharges in temporal lobe epilepsy: correlation of spatiotemporal mapping with intracranial foramen ovale electrode recordings. *Clinical Neurophysiology, 117*(12), 2615–2626. http://dx.doi.org/10.1016/j.clinph.2006.07.319

Zumsteg, D., Lozano, A. M., Wieser, H. G., & Wennberg, R. A. (2006). Cortical activation with deep brain stimulation of the anterior thalamus for epilepsy. *Clinical Neurophysiology, 117*(1), 192–207. http://dx.doi.org/10.1016/j.clinph.2005.09.015

Received: January 19, 2016
Accepted: January 26, 2016
Published: March 9, 2016

NeuroRegulation

Book Review – *The Good Life: Wellbeing and the New Science of Altruism, Selfishness and Immorality*

by Graham Music. Routledge Press, New York, NY, 2014, 256 pages, ISBN-13: 978-1848722279.

Citation: Lyle, R. R. (2016). [Review of the book *The Good Life: Wellbeing and the New Science of Altruism, Selfishness and Immorality*, by Graham Music]. *NeuroRegulation*, *3*(1), 51–52. http://dx.doi.org/10.15540/nr.3.1.51

***Address correspondence to**: Randall R. Lyle, PhD, Mount Mercy University, 1330 Elmhurst Drive NE, Cedar Rapids, IA 52402-4797, USA. Email: rlyle@mtmercy.edu

Edited by:
Rex Cannon, PhD, Neural Potential, Boynton Beach, Florida, USA

Reviewed by:
Rex Cannon, PhD, Neural Potential, Boynton Beach, Florida, USA

One might wonder why a journal committed to research and theory related to neuromodulation would want to review a book that is essentially about ethics and morality in the 21st century. The reason is that the author does an excellent job of integrating some of our most recent findings about the brain into his discussion of the "science of altruism, selfishness and immorality."

Music is a child and adolescent psychotherapist at the Tavistock and Portman Clinics in London, UK, and an adult psychotherapist in private practice. He does a yeoman's task of bringing together research and findings as diverse as attachment, neuroscience, ethics, history, evolutionary biology, sociology, and psychology. He weaves his way through these diverse topics following a developmental path mirroring human development in order to examine what all of these fields of study might tell us about human beings' capacity for compassion, altruism, selfishness, and immorality in our current times and what this might bode for our future. In a nutshell, he asks: Can we hope to accomplish the "Good Life" given our current state?

Music begins his journey by asking the fundamental question of whether humans are primarily and naturally good and kind, or if are we basically selfish and motivated only by what we can get to satisfy our needs and desires. He presents the research and theoretical literature that supports each point of view and seeks to walk the fine line of holding some of each position in his conclusions for going forward in his discussion of human development and the possibilities for the ethical "Good Life." Music tells us in his introduction that he has three primary reasons for writing this book. The first is his own curiosity about the human situation. He is aware, as I hope we all are, that we can be quite different people at different times. I can be very kind and generous one moment—and cruel and heartless the next. Have the latest developments and research across the various domains of human knowledge helped us to better understand how that might be? The second is his work as a psychotherapist. His work with children who have experienced significant trauma has provided him with glimpses into both the worst and the best of the human condition. He has seen children (and adults) who have been too damaged to ever be able to truly live a "fulfilled" life. He has also witnessed the incredible resiliency of the human spirit and its ability to recover from horrific experiences and, through human bonding and loving care, be fully restored and functional loving people. The third reason is linked to his observation that the western world seems to be moving in a less humane and connected direction, leaving increasing numbers of people disconnected and diminished and just so many cogs in the wheel of economic growth and Gross Domestic Product (GDP).

The book proceeds to examine in a logical and well-articulated fashion the steps necessary to ask and answer the questions required to try and accomplish the overarching concern. He begins by fine-tuning the discussion as to whether humans are primarily destined for good or just a "part of brutal nature." This leads him into a discussion of attachment and how dependent development and connection depends on those initial connections, and then to a discussion of empathy, stress, impulsiveness, self-regulation, and aggression. He carefully links each topic to psychological, developmental, and neurological research and understanding.

These initial chapters might be said to explain the rootedness of our potential for living a life of connection and satisfaction in our birth and early development internally and through our external connections. The remaining chapters move this examination out into what we might describe as the adult world of real relationships and consequences. Here he discusses such topics as aggression and psychopaths, emotion and reason, cooperation and competition, reputations and shaming, and his penultimate chapter "consumerism, society and our divided brain."

This was for me one of the most striking and disturbing chapters. One paragraph may serve to highlight why:

> We are all capable of moving into either more competitive or caring states of mind. As we have seen, the extent to which we do either is influenced by early experiences and family life, and also the kinds of work environments, communities and societies we inhabit. In competitive environments we are more likely to see others as rivals, compare ourselves with them and make judgments. When people feel compared to others, irrespective of whether these comparisons are positive or negative, then several days later they are less empathic and prosocial than control groups (Yip and Kelly, 2013). The huge amount of data on the devastating effects of inequality on levels of trust underscore this (Wilkinson 2005; Wilkinson and Pickett, 2009). (Music, 2014, p. 170).

In the end, Music's book seeks to encourage all those who resonate with his concern that perhaps the world is not headed in a direction that will lead us to the enhanced and more possible place of connection, intimacy, and community but rather towards a place of increased suffering, disconnection and inequality. It is his hope and mine that reading this book might serve as an impetus and motivation to seek to find ways to correct our course so that we can indeed have a chance to live the "Good Life."

Randall R. Lyle, PhD
Mount Mercy University
Cedar Rapids, Iowa, USA
Email: rlyle@mtmercy.edu

Received: January 20, 2016
Accepted: January 26, 2016
Published: March 9, 2016