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QEEG Correlates of Cognitive Deficits in Multiple Sclerosis During Targeted Cognitive Tasks

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ABSTRACT

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Multiple sclerosis (MS) is the most common neurological disorder of young adulthood and is often associated with cognitive impairment and emotional dysfunction. Due to the nature of the disease, the cognitive deficits in MS are often variable in their presentation, and consist of deficits in processing speed, attention, working memory, and executive functioning. The purpose of the present study was to explore common methods of documenting MS-related cognitive deficits, to elucidate the relationship between the cognitive deficits seen in MS and physiological markers of cognitive functioning (i.e., quantitative EEG), and to analyze the relationship between cognitive deficits and mood dysfunction in MS. There were 26 participants diagnosed with remitting-relapsing multiple sclerosis and 18 age, sex, and education matched controls. Results of cognitive testing indicated deficits in gross cognitive functioning, language, attention, processing speed, working memory, and executive functioning. A MANOVA encompassing group, task (PASAT and SPT) and load (light and heavy) showed significant group and load effects, but no main effect of task. The MS group performed worse than the controls and both groups performed better on the light load than the heavy load. Post hoc analysis indicated that performance on the PASAT 3 second trial was worse than on the PASAT 2 second trail compared to controls. Given that the PASAT 3 trial is theoretically easier than the PASAT 2 trial and that the PASAT 3 was administered first, the above results likely reflect learning effects. A Repeated Measures ANCOVA encompassing EEG and cognitive data (PASAT and SPT) indicated group-level differences on task performance, and suggested that at rest mean peak alpha frequency (PAF) is associated with performance on the PASAT, but not the SPT. EEG coherence during cognitive tasks was reduced between short-range connections in the theta, alpha, and beta frequency bins and enhanced in a limited number of long-range, anterior to posterior connections in the theta frequency bin in the MS group compared to controls. Finally, the MS participants had significantly more symptoms of depression and anxiety compared to normal controls. A hierarchical multiple regression analysis suggested that cognitive functioning is deleteriously affected by depression and anxiety. Overall, the results of this study substantiate the feasibility of utilizing QEEG as a physiological indicator of cognitive and cortical dysfunction in MS and show the importance of recognizing depression and anxiety and their contributions to cognitive deficits in individuals with MS.

Keywords: multiple sclerosis, QEEG, electroencephalogram, peak frequency, coherence

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TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

QEEG Correlates of Cognitive Deficits in Multiple Sclerosis During Targeted Cognitive Tasks

Multiple sclerosis (MS) is a chronic inflammatory disease of the central nervous system in which myelin, the insulating sheath surrounding axons that facilitates the conduction of action potentials, is the initial site of degeneration, with eventual expansion of the disease process to include axonal dysfunction and destruction (Frohman et al., 2005). Multiple sclerosis was first recognized as a distinct disease in the 1800's and was initially considered to be fairly rare (Talley, 2008). Presently, MS is the single most common neurological disease of young adults in Western countries (Compston & Coles, 2002; Lassmann, 2008). Multiple sclerosis affects approximately 30 per 100,000 people, ranging from a low of 0.3/100,000 in Africa to a high of 176/100,000 in Hungary (Organization, 2008). The estimated prevalence of MS in the United States is 250,000 to 400,000 cases, with approximately 200 new cases diagnosed each week (Anderson et al., 1992; Health, 2010; Kurtzke, 2000). Multiple sclerosis is a disease of young to middle adulthood with a mean age of onset of 29.2 years. The prevalence of MS is higher in females than in males with a ratio of approximately 3 to 1. Additionally, a diagnosis of MS is associated with a modest decrease in life expectancy (Pryse-Phillips & Sloka, 2006; Sadovnick, Ebers, Wilson, & Paty, 1992; Vukusic & Confavreux, 2001).

The disease course in MS is variable and several subtypes have been identified based on disease presentation, which include: benign, relapsing-remitting, primary-progressive, secondary-progressive, and relapsing-progressive (Lublin & Reingold, 1996). Disease presentation of acute neuronal dysfunction is typically followed by periods of improvement or relative stability (e.g. benign, relapse-remitting, and relapse-progressive), but may also present as progressive deterioration of neuronal processes (e.g., primary/secondary-progressive), which

results in heterogeneous symptoms across individuals with MS (Noseworthy, Lucchinetti, Rodriguez, & Weinshenker, 2000). Regardless of the initial course of disease, the chronic effects of repeated inflammation in the central nervous system (CNS) eventually lead to functional decline in a significant portion of individuals with MS (Frohman et al., 2005).

The etiology of multiple sclerosis and the mechanisms of neuronal injury are unclear, but likely include abnormal t-cell activation and proliferation, astrocytic blockage of remyelination, increased influx of intracellular calcium resulting in neuronal injury, and retroviral-like infection (Compston & Coles, 2002; Frohman et al., 2005; Keegan & Noseworthy, 2002; Noseworthy et al., 2000). One well described mechanism of neuronal injury is the repetitive and continual destruction of myelin (Lassmann, 2008), which is thought to be due to an autoimmune, inflammatory response in which the immune system attacks the oligodendrocytes that form myelin sheath in the CNS (Perry, 2008). After an inflammatory episode, remyelination of neuronal processes typically occurs, however repeated inflammatory insults result in permanent axonal damage and subsequent neuronal loss (Frohman et al., 2005; Gauthier et al., 2009). This continual process of myelin insult and remyelization may account for the variable and progressive pattern of symptoms and functional morbidity observed in relapsing-remitting MS (Rao, Leo, Haughton, St. Aubin-Faubert, & Bernardin, 1989).

Genetic predisposition and environmental risk factors are also thought to play a role in the development of MS (Ebers, Sadovnick, & Risch, 1995). Population based studies suggest that MS susceptibility is likely linked to multiple genes and may be representative of genetic equifinality (Sadovnick et al., 1993). Chemical exposure, stress, and vitamin deficiencies are also thought to play a formative role in the development of MS (Marrie, 2004).

Rating Scales

Historically, MS severity was measured by the degree of physical disability (Kurtzke, 1983). Consequently, the majority of the items on the most commonly used MS disability rating system, the Expanded Disability Status Scale (EDSS), predominately assess physical dysfunction (Kurtzke, 1983). The EDSS rates nine body systems (pyramidal, cerebellar, brain stem, sensory, bowel and bladder, visual, cerebral-total, cerebral-mentation, and other), with scores ranging from 0 (normal) to 6 (essential loss of function), with higher total scores indicating worse function (Kurtzke, 1983). One reason that MS disability rating scales assess physical dysfunction, rather than cognitive dysfunction, is largely due to the fact that physical complaints are the most common presenting symptom of MS (Compston & Coles, 2002). Further, physical disability is often not directly associated with intellectual or cognitive impairments, which are difficult to accurately assess using rating scales (Satori & Edan, 2006; Sepulcre et al., 2006). Two important limitations of the EDSS are its poor association with cognitive functioning and the lack of an assessment of quality of life (Benedict et al., 2005; Foong et al., 1997; Ziemssen, 2009).

Studies indicate that 40 to 70 percent of individuals with MS have cognitive impairments (Calabrese, 2006; Rao, Leo, Bernardin, & Unverzagt, 1991; Rao, Leo, Ellington, et al., 1991; Rogers & Panegyres, 2007). As noted previously, physical symptoms have enjoyed a position of primacy over cognitive symptoms when assessing and quantifying disease progression. Cognitive function has not been used to assess disability associated with MS due to three related issues: 1) physical symptoms are often the presenting complaint, 2) cognitive symptoms in MS are typically heterogeneous and difficult to quantify using simple rating systems, and 3)

cognitive symptoms often do not correlate with physical dysfunction (Benedict et al., 2006; Foong et al., 1997; Rao, Leo, Bernardin, et al., 1991; Satori & Edan, 2006).

New MS disability rating systems are needed due in part to the historical dearth of measures that attempt to quantify cognitive dysfunction, and the recent desire for short, repeatable assessment tools for use in clinical trials (Cutter et al., 1999b; Rudick et al., 1997) In response to this need, the Multiple Sclerosis Functional Composite (MSFC) was developed. The MSFC is comprised of a gross motor task (25-foot walk), a fine motor task (9-hole peg board), and a cognitive attention task (Paced Auditory Serial Addition Task; PASAT) (Fischer, Jak, Knicker, Rudick, & Cutter, 2001). The MSFC can be used to track the fluctuating status of disease processes, which allows for assessment of change over time (Fischer et al., 2001; Rudick et al., 2009). Psychometric studies of the MSFC find good intra-rater (0.99) and inter-rater (1.0) reliability, but significant practice effects are reported for both the 9-hole peg board and PASAT subtests (Rosti-Otajarvi, Hamalainen, Koivisto, & Hokkanen, 2008). While the MSFC has some limitations, it represents an emphasis shift from a primary focus on physical dysfunction to the acknowledgment that cognitive deficits need to be assessed in individuals with MS.

Cognitive Function

Cognitive deficits in individuals with MS are heterogeneous within and between diagnostic categories (e.g. relapse-remitting, progressive). Despite the variable presentation of cognitive deficits, common cognitive impairments include: slowed mental processing speed, impaired attention, executive dysfunction, and impaired memory (i.e., working memory, long-term storage and retrieval) (Calabrese, 2006; Kail, 1998; Thornton & DeFreitas, 2009).

Impairments in working memory are the most widely reported cognitive deficit in individuals with MS, although the relationship between working memory deficits and impaired

attention and slow mental processing speed is unclear (Calabrese, 2006; Lengenfelder et al., 2006). Slow mental processing speed and attention deficits in MS are common and affect focused, sustained, and divided attention (Calabrese, 2006; De Sonneville et al., 2002; Demaree, DeLuca, Gaudino, & Diamond, 1999; Forn, Belenguer, Parcet-Ibars, & Ávila, 2008). Frontal lobe pathology is associated with executive dysfunction in MS, although global pathology appears to play a prominent role as well (Foong et al., 1997). Neuropsychological measures of phonemic and semantic fluency and measures of executive functioning appear to discriminate healthy controls from MS participants (Henry & Beatty, 2006). As noted by Rao et al., (1991) the above pattern of cognitive deficits resembles a subcortical dementia. A review of the literature by Calabrese (2006) also found that the pattern of cognitive deficits in MS that effects working memory, mental processing speed, attention, and executive functions is indicative of subcortical dementia like pathology.

While many cognitive functions are impaired in MS, verbal intelligence, implicit memory and visuo-spatial skills typically remain intact (Rao, Leo, Bernardin, et al., 1991). Further, general intellectual function is also not typically affected by MS. The preservation of general intellectual abilities is hypothesized to be due to: 1) cortical recruitment of additional cortical regions to perform tasks that would normally be performed by fewer brain regions (Prakash, et al., 2008) and 2) brain reorganization due to neuronal plasticity resulting in the appearance of normal intellectual functioning despite underlying cortical lesions (Audoin et al., 2008; Mainero, Pantano, Caramia, & Pozzilli, 2006; Prakash et al., 2008).

Psychological Functioning

Symptoms of depression are prevalent in MS (Minden & Schiffer, 1990) and may interact with cognitive functioning in a "capacity-reducing" way. That is, depression in multiple

sclerosis tends to degrade performance on tasks that demand increased attention, working memory, and multi-step complex cognition (Arnett et al., 1999). Evidence to date suggests that depressive symptoms are the result of increased cortical and subcortical dysfunction and may be separable from major depression (Sadovnick et al., 1996). Additionally, psychological changes, including depression, play a prominent role in the self-ratings of quality of life in the MS population (Ziemssen, 2009), with individuals who endorse depressive symptoms reporting reduced quality of life. As such, psychological functioning in general and depression in particular are important factors to assess when evaluating the effects of MS on cognitive function.

Magnetic Resonance Imaging (MRI)

Structural MRI studies provide a way to assess anatomical correlates of the cognitive deficits observed in MS. Anatomical correlates include lesion location, extent and severity of lesions (lesion burden), cortical and sub-cortical atrophy, and lesion progression over time (Bermel & Bakshi, 2006; Lazeron et al., 2005; Lazeron, de Sonneville, Scheltens, Polman, & Barkhof, 2006). In MS, lesions tend to be widespread including areas of the cortical mantle, subcortical white matter, brainstem, cerebellum, and spinal cord (Ge, 2006). Brain atrophy develops early on in the disease and represents generalized neuronal loss, which is only partially moderated by discrete lesion load (Bermel & Bakshi, 2006; Filippi et al., 2003). Gross brain atrophy is associated with cognitive impairment, while regional atrophy and lesion burden, correlate modestly with specific neuropsychological impairments (Lazeron et al., 2005; Lazeron et al., 2006; Rovaris et al., 2000). For example, Foong, et al. (2007) found that frontal lesion load was associated with deficits in planning abilities. That is, increased frontal lesion load was associated with a decrease in the ability to plan complex, sequenced actions. Similarly, Lazeron,

et al. (2006) found that lesion load was associated with some measures of processing speed, while total brain atrophy was associated with impaired attention and memory, and slow mental processing speed.

Functional Magnetic Resonance Imaging (fMRI)

Functional magnetic resonance imaging (fMRI) in conjunction with measures of working memory and attention/processing speed have also been used to elucidate the relationship between neural pathology and cognitive deficits (Reddy et al., 2000; Staffen et al., 2002). A review of the fMRI literature that assessed the neural correlates of working memory, attention, and processing speed in MS, found increased activation in the prefrontal cortex, bilateral middle and superior temporal cortex, left thalamus, basal ganglia, and left parietal lobe relative to controls during sustained attention and speeded processing tasks (Mainero et al., 2006). Other studies have also shown increased activation in the frontal and parietal lobes in MS populations during working memory tasks (Staffen et al., 2002).

Interestingly, an fMRI study found that MS participants with cognitive impairments had greater cortical activation on a working memory task compared to MS participants without cognitive impairments and healthy controls, i.e. cognitive impairment separated individuals on measures of brain activation not disease state (Chiaravalloti et al., 2005). Contrary to expectations, the cognitively impaired MS group did not differ from the non-impaired MS group on measures of lesion load, length of disease, or physical disability. In another study, participants with MS showed greater cerebral activation in general and in the right prefrontal cortex in particular during an attention task compared to controls (Prakash et al., 2008). In this study, increased cerebral activation did not correlate with better task performance, suggesting

increased cerebral activation may actually reflect the presence of cortical/subcortical deficits, and hence cognitive dysfunction, rather than functional adaptation to underlying cortical dysfunction.

Functional MRI to date supports both the cortical recruitment and cortical reorganization theories in MS (Mainero et al., 2006), but these theories are difficult to tease apart due to poor temporal resolution, afferent/efferent ambiguity, and relatively poor spatial discrimination of fMRI. Overall, fMRI findings suggest that cognitive deficits in attention and working memory in MS are common, and provide some evidence for cortical recruitment/plasticity models in individuals with MS (Chiaravalloti et al., 2005; Mainero et al., 2006; Prakash et al., 2008; and Thornton & DeFreitas, 2009). However, increased cortical activation does not always result in improved cognitive performance. Thus, cortical recruitment/plasticity may not be a functional adaptation, but rather a significant indicator of cognitive dysfunction in MS.

Electroencephalogram (EEG)

The electroencephalogram (EEG) is a graphic representation of extra-cellular and cell surface electrical gradients recorded by means of scalp electrodes (Binnie & Prior, 1994; Levitan & Kaczmarek, 2002). It is a temporally sensitive measure of physiological processes. Positive and negative field gradients between two points are represented by the falling and rising waveforms that make up the EEG signal. The main components of the EEG are time/frequency and waveform amplitude (Tyner, Knott, & Mayer, 1983). The EEG has classically been divided into the frequency, or cycles per second, bins of: Delta (δ; 0-4hz), Theta (θ; 4-8hz), Alpha (α; 8-12hz), Beta (β; 12-30hz), and Gamma (γ; >30hz) (Buzsaki, 2006). Whereas the frequency bins were created out of necessity for clear description and communication about the EEG, it is recognized that there are individual differences in frequencies (Van Albada, Rennie, & Robinson, 2007). Source localization techniques indicate that the frequency bins are discretely

generated by specific cortical and subcortical structures and are sensitive to neuronal dysfunction and death (Binnie & Prior, 1994; Michel, Lehmann, Henggeler, & Brandeis, 1992).

Quantitative Encephalogram (QEEG)

Quantitative encephalography (QEEG) is a method of analyzing EEG signals algorithmically, rather than visually. QEEG allows for real time analysis of cortical activity under a variety of conditions (Thatcher & Lubar, 2009). During QEEG, recordings are simultaneously taken from many cortical regions, which can be compared to generate information about regional differences in frequencies, region to region activity, activity migration across regions, and the relative diffuseness of activity (Thatcher, Biver, & North, 2009). For QEEG to be an effective method of neurophysiological investigation four parameters must be met; first, electrode application has to be uniformly named and consistently placed, e.g., 10-20 system (Jurcak, Tsuzuki, & Dan, 2007), second, the EEG data must be relatively artifact free, allowing for accurate analysis of signals of interest, third, the EEG must be recorded during comparable conditions, and fourth, EEG features must be relatively stable within condition and across time (Gudmundsson, Runarsson, Sigurdsson, Eiriksdottir, & Johnsen, 2007). These four requirements determine the degree to which QEEG is an effective tool for measuring and comparing cortical activity and is the underpinning of normative QEEG databases (Thatcher, 1998; Thatcher, Walker, Biver, North, & Curtin, 2003).

QEEG has been used to evaluate the relationship between cell groups (coherence), the relative magnitude within frequency bands (peak frequency analysis; PFA), and the changes in frequency characteristics during resting/tonic and active/phasic states (event related desynchronization/synchronization; ERD/ERS) (Bazanova & Aftanas, 2008; Klimesch, Doppelmayr, Schimke, & Ripper, 1997; Sauseng, Klimesch, Schabus, & Doppelmayr, 2005).

Coherence is a measure of phase coupling or synchronization of EEG waveforms over distance and time, is an indirect measure of functional/structural connectivity in the brain, and can be expressed by the formula "Number of connections (N) x Strength of connections (S) in a network" (Thatcher, 2010; Thatcher, Krause, & Hrybyk, 1986). As such, EEG coherence has been used to identify cortical structures that are involved in discrete tasks, most prominently memory, executive function, attention and processing speed tasks (Sauseng & Klimesch, 2008; Sauseng et al., 2005). While, coherence has been associated with cognitive impairment and lesion load (Kamel, S., & Hashem, 2004), the relationship between coherence and lesion load appears to be moderated by cortical location and EEG frequency bin (Leocani et al., 2000). Some studies question the use of coherence as a useful marker of functional connectivity, primarily because the reliability of coherence is typically poor due to the use of average referenced electrode montages (electrode maps) (Gudmundsson et al., 2007). Thatcher (2010) notes the unreliability in coherence analysis is primarily due to the selection of an average referent rather than a common or active referent, as an average referent produces phase shifting towards the apex of the head in the EEG signal, and hence changes the morphology of the EEG. This effectively diminishes any utility for coherence analysis from the get-go. An important standardization of coherence studies would be to enact an active or common reference and prohibit the use of an average reference, which would theoretically increase fidelity and reliability.

Spectral analysis is the reduction of a frequency band (delta, theta, alpha, beta, gamma) into its statistical components; i.e., into the frequency with the highest density for that band (peak frequency) or into the statistical mean of the band (individual frequency), etc. (Angelakis, Lubar, Stathopoulou, & Kounios, 2004). A significant portion of the spectral research has focused on

peak alpha frequency analysis as a measure of cognitive function (Angelakis et al., 2004; Klimesch, 2000). Research indicates that "faster" brains, that is, those that exhibit greater EEG signal density higher in the discrete frequencies bins, typically perform better on discrete cognitive tasks, particularly memory and attention tasks, including verbal and nonverbal measures (Angelakis et al., 2004; Bazanova & Aftanas, 2008; Tzyy-Ping, Makeig, Stensmo, & Sejnowski, 1997), however, the findings are mixed for general intellectual abilities (Doppelmayr, Klimesch, Stadler, Pöllhuber, & Heine, 2002; Posthuma, Neale, Boomsma, & de Geus, 2001). As such, peak alpha frequency has been described as a measure of cognitive preparedness rather than a general measure of intellectual functioning (Angelakis et al., 2004).

Electroencephalographic activity can be split into two categories: tonic and phasic. Tonic refers to the baseline or at rest EEG, while phasic refers to changes in the EEG due to task or stimulus demands. Event related desynchronization (ERD) refers to changes in the EEG between a tonic condition and a phasic condition and has been noted to affect frequency bins (delta, theta, alpha, beta, gamma) differently (Klimesch, 1999). The discrete electroencephalogram frequencies respond differentially to diverse cognitive tasks (Klimesch, Doppelmayr, Russegger, Pachinger, & Schwaiger, 1998; Klimesch et al., 1997). The relationship between tonic and phasic activity may be mediated by relative power of the tonic frequency bands (Doppelmayr, Klimesch, Pachinger, & Ripper, 1998). Doppelmayr et al. (2002) found tonic alpha power tone was associated with the extent of ERD during phasic EEG. While most ERD research to date has focused on working memory tasks, which show a double-dissociation between lower theta and upper alpha on measures of task performance (Klimesch, 1999), preliminary results indicate that the lower alpha frequency range of 9.75 – 10.25hz responds selectively to calculation tasks (Klimesch, 1999). Overall, the relationship of ERD to

tonic EEG activity during calculation tasks has only recently been explored and is still in the process of being elucidated.

Research in MS has begun to assess the relationship of cognitive and neuronal functioning using QEEG. Historically, spectral analysis has been used to discriminate MS participants from healthy controls on measures of peak alpha frequency, coherence, and general slowing (Facchetti et al., 1994), but the relationship of QEEG findings and clinical significance is unclear due to the relatively few studies that have assessed QEEG in MS populations. Recent investigations find MS participants have slower reaction times during attention tasks which are associated with increased activation of the high beta and gamma spectrum (Gonzalez-Rosa et al., 2006; Vazquez-Marrufo et al., 2008). Within MS subgroups (benign, relapsing-remitting, etc.) there are spectral differences in the high beta and gamma bins. Although, a study by Vazquez-Marrufo et al. (2008) failed to find tonic EEG differences within MS subgroups, this may have been due to the relatively few cranial electrodes used (13), which only allowed the use of a spectral density analysis rather than a peak frequency analysis, and/or the use of EEG segments directly following stimulus presentation rather than throughout the task.

Purpose of Current Study

A weakness of current QEEG studies in MS populations is the lack of consistently used testing procedures - such as uniform EEG configuration (number and placement), use of standardized tests to assess cognitive domains of interest (memory, attention, executive function), and limited use of neuropsychological tests to determine the extent and severity of cognitive impairments. Few investigations into common themes in the body of QEEG research such as spectral analysis, peak frequency analysis, and event related desynchronization has been carried out in MS populations. The primary purpose of this study was to use a 24 EEG array to

assess the relationship between QEEG features and cognitive performance (working memory, attention/processing speed, and executive function) during EEG in MS participants who report cognitive deficits.

Aims and Hypotheses

Aim 1: To assess the relationship between cognitive functioning and disability scores.

1a: MS participants' scores on the RBANS (total and index scores), a measure of global cognitive function, will be lower than matched control participants' RBANS scores.

1b: The MSFC disability score will correlate with RBANS scores for both MS participants and matched controls.

Aim 2: To assess the relationship between QEEG features and performance on cognitive measures administered during EEG.

2a: Peak Alpha Frequency will discriminate between light and heavy cognitive loads on the PASAT and SPT. Lower PAF will more accurately predict performance on heavy cognitive load tasks than on light cognitive load tasks for both the MS and control groups.

2b: Multiple Sclerosis participants will show impairment on measures of coherence (the degree to which diverse neuronal groups are coupled across space and time, and, as such, is an indicator of functional connectivity in the brain) during the PASAT compared to normal controls.

Aim 3: To assess QEEG and its relationship to cognitive performance.

3a. Spectral analysis will show regional QEEG differences between groups, that is the MS participants will have frequency slowing in delta, theta, alpha, and beta frequencies compared to matched controls.

3b. MS participants with intact cognitive function, as measured by the RBANS overall score, will have reduced QEEG frequency slowing compared to MS participants with cognitive impairments.

Aim 4: To assess the relationship between psychological functioning (depression and anxiety) and cognitive functioning.

4a: Psychological functioning will account for a unique portion of variance in cognitive functioning, controlling for group membership, education, and PAF.

Methods

Participants

Participants included 26 individuals diagnosed with relapsing-remitting multiple sclerosis and 18 age, sex, and education matched controls. The MS participants were recruited and screened by a Board Certified Neurologist (Dr. John F. Foley, MD) from the Rocky Mountain Neurological MS Clinic in Salt Lake City, Utah. Diagnosis of MS was made using the McDonald criteria, an internationally used diagnostic criteria, which includes the identification of at least two cortical or spinal lesions across time and space and one year of disease progression, retrospective or prospective (McDonald et al., 2001; Polman et al., 2005). Study inclusion criteria include diagnosis of relapsing-remitting MS, patient self-report of cognitive impairments, and age 18 to 70 years. Study exclusion criteria included non-English-speaking, use of sedative hypnotic agents within 72 hours of study, prominent visual deficits, dense dominant limb paralysis, comorbid disorders with known cognitive impairment (e.g. traumatic brain injury, stroke resulting in severe cognitive deficits, Parkinson's disease, Huntington's disease, Alzheimer's disease, severe dementia), and age < 18 years old or > 70 years.

There were 18 control participants who were recruited from family members of the MS participants as well as from the community by use of flyers, which were placed on announcement boards at local grocery stores, university campuses, hospitals, and clinics. Controls were matched to the MS participants for sex, age ± 3 years, and education ± 2 years. The same inclusion and exclusionary criteria were used for MS participants and controls.

Procedures

The institutional review board at Brigham Young University approved the study protocol. Written informed consent was obtained from participants prior to initiation of study procedures. After obtaining informed consent, participants were scheduled for one 3 to 4 hour testing session. The testing session consisted of cognitive testing, psychological questionnaires, and EEG recording while performing cognitive tasks.

Demographic and medical history. Demographic and medical history was collected using a questionnaire. Medical history included types and dates of medical diagnosis, medication usage, traumatic injuries, and medical treatments.

Cognitive function. Standardized cognitive tests to assess general intellectual function, attention, and executive function were administered. The Repeatable Battery for the Assessment of Neuropsychological Status (McKay, Casey, Wertheimer, et al., 2007) assessed general cognitive function. Processing speed, sustained attention and working memory were assessed using the Paced Auditory Serial Addition Task (Gronwall, 1977), Digit Symbol Modalities Test (Strauss, Sherman, & Spreen, 2006), and a Sternberg Paradigm Task (Smith, A., 1982). Executive function was assessed using the Trail Making Test Parts A and B (Reitan & Wolfson, 1993), Controlled Oral Word Association Test (Gladsjo, Shuman, Miller, & Heaton, 1999), and

the Wisconsin Card Sorting Test (Heaton, et al., 1993). Detailed test descriptions are provided below.

A priori the presence of cognitive deficits are defined as scores on two or more neuropsychological tests that were greater than 1 standard deviations (*SD*) below the normative population mean. This definition of cognitive impairment in this study is similar to those used in standard clinical neuropsychological evaluations (Binder, Iverson, & Brooks, 2009; Heaton, Miller, Taylor, & Grant, 2004).

Global cognition. The Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) was designed as a screening tool for dementia, but has gained considerable popularity as a screening instrument in a variety of disorders due to its short administration time, co-normed index scores, availability of an easily interpreted summary score, and alternate forms (McKay, Casey, Wertheimer, et al., 2007). The RBANS contains five domain-specific Index Scores including Immediate Memory (List Learning and Story Memory subtests), Visuospatial/Constructional (Figure Copy and Line Orientation subtests), Language (Picture Naming and Semantic Fluency subtests), Attention (Digit Span and Coding subtests), and Delayed Memory (List Recall, List Recognition, Story Recall, and Figure Recall subtests) as well as provides a Total Scale Score. Index scores range from 40 to 160 with higher scores indicating better performance. RBANS subtests correlate with individual neuropsychological tests commonly used to examine similar domains (Aupperle, Beatty, DeNap Shelton, & Gontkovsky, 2002; Beatty, 2004), and has good reliability and validity in MS populations (Aupperle et al., 2002).

Processing speed, attention, and working memory. The Paced Auditory Serial Addition Task (PASAT) measures sustained attention, rate of information processing, and to some degree

simple mathematical calculation skill. Participants are required to add 59 pairs of randomized digits without any aids. Each digit in the sequence is added to the prior digit. Fifty-nine pairs of digits are added for each of two trials, (presenting rates: 3.0s or light load and 2.0s or heavy load due to increased task difficulty) beginning with the 3.0s trial first and progressing to the 2.0s trial (Gronwall, 1977). The PASAT is sensitive to attention, working memory and processing speed in MS and correlates with MRI verified lesion loads (Rao, Leo, Bernardin, et al., 1991; Rao, St. Aubin-Faubert, & Leo, 1989).

The Digit Symbol Modalities Test (DSMT) consists of 105 possible responses, which entail converting numbers from 1 to 9 into random geometric designs during a 120 second testing window (Strauss et al., 2006)Smith, A., 1982). The DSMT measures attention, processing speed, spatial-construction, and non-verbal reasoning skills. The scores range from 0 to 105, with higher scores indicating better performance. The SDMT is sensitive to localized and diffuse cerebral damage. Test-retest reliability is .80 for the paper-pencil version of the SDMT (Smith, 1982).

The Sternberg Paradigm Task (SPT) consists of a light cognitive load (2 stimuli) and a heavy cognitive load (4 stimuli) presentation. During the light cognitive load task the subject is shown two random digits on a monitor and after a brief pause a third digit is presented. The subject responds through a portable device yes if he/she believes that the third digit is the same as one of the two proceeding digits and no if he/she does not. The heavy cognitive load presentation is structurally similar to the light cognitive load except instead of two digits during the stimulus presentation four digits are displayed. Again, during the response digit presentation the subject indicates whether or not the response digit was present in the stimulus sequence (Sternberg, 1969). Scores are represented in accuracy of response and range from 0 percent to

100 percent with greater accuracy indicating better performance. The Sternberg paradigm is an effective measure of information processing speed in general (Gontkovsky & Beatty, 2006) and working memory in particular in MS (Drew, Starkey, & Isler, 2009; Rao, St. Aubin-Faubert, et al., 1989).

Executive function. The Wisconsin Card Sorting Test (WCST) consists of four stimulus cards and 128 response cards that depict figures of varying forms (crosses, circles, triangles, or stars), colors (red, blue, yellow, or green), and numbers of figures (one, two, three, or four) (Heaton, et al., 1993). During administration four stimulus cards are laid before the subject while the subject is given 64 response cards. The subject is instructed to draw from the response cards and place the drawn card with its matching stimulus card. The only feedback provided is whether the "match" is incorrect or correct. After ten correct matches the rules are changed without communication of the rule shift to the subject, which is repeated several times. Values were generated for total categories completed, which is a gross measure of task performance and consists of a score from 0 to 6, with higher scores indicating better performance; trials to complete the first category, which is an indicator of the rapidity of a respondent's adjustment to the implicit rules of the task, with fewer trials indicating a better performance; perseverative responses, which represents consistent responses that match an established sorting rule, with lower scores generally indicating better performance; perseverative errors, which represent responses that match a previous sorting rule and represent poor adjustment to explicit feedback, with lower scores indicative of better performance; and failure to maintain set, which represents a dropping of the sorting pattern after five, but before 10, correct trials, with lower scores representing better performance. The WCST is sensitive to frontal lobe dysfunction. The

WCST: Computerized Version-4 was used in order to ensure consistent test administration across participants.

The Trail Making Test parts A and B are well-documented measures of visual scanning, processing speed, and task switching a component of executive function (Lezak, 1995). The Trail Making Test consists of two parts. In Part A, participants connect consecutively numbered circles, while in Part B participants connect consecutively numbered and lettered circles that alternate between the two sequences. Longer times to complete the tests are associated with worse executive function. Psychometric studies indicate reliability coefficients above .80 (Spreen & Strauss, 1991), and several studies indicate that the two Trail Making tests are sensitive to the global effects of brain injury (Botwinick, Storandt, Berg, & Boland, 1988; Buchanan, Strauss, Kirkpatrick, Breier, & Carpenter, 1994).

The Controlled Oral Word Association test (COWA) requires that participants produce as many words as possible that begin with the letters F, A, and S in one minute (Gladsjo et al., 1999). The greater the number of words produced indicates better performance. Verbal fluency is sensitive to focal cortical dysfunction in a variety of populations and are particularly useful in identifying executive dysfunction (Henry & Crawford, 2004). Verbal fluency has moderate to high correlations (.48 to .84) with verbal intelligence, which has been described as a "hold" test for general intellectual functioning (Henry & Crawford, 2004) and test-retest reliability is high, r = .70 (Tombaugh, Kozak, & Rees, 1999).

Psychological functioning. Psychological functioning appears to play a prominent role in the self-ratings of quality of life, including cognitive deficits, in the MS population (Ziemssen, 2009). To assess depression and general anxiety, participants will complete the Hospital Anxiety and Depression Scale (HADS) (Zigmond & Snaith, 1983). The HADS is a 14 item questionnaire

that is the most widely used survey in medical participants (Herrmann, 1997), has separate subscales for depression and anxiety, and is not heavily reliant on physical symptoms. Scores of 0 to 7 indicated normal, scores of 8 to 10 indicate borderline, and scores ≥11 on either the depression or anxiety indices indicate symptoms of depression or anxiety. The HADS correlates with psychiatric evaluations (Hayes et al., 2000; Zigmond & Snaith, 1983).

Physical dysfunction. The appropriate assessment of physical in participants with multiple sclerosis has long been a concern (Kurtzke, 1983). As such, several rating scales have been developed (Cutter et al., 1999a; Kurtzke, 1983). In order to assess physical dysfunction participants completed the Multiple Sclerosis Functional Composite (MSFC) (Cutter et al., 1999a). The MSFC consists of a twenty-five foot walk, a visual acuity exam, a 9-hole pegboard test, and a version of the Paced Auditory Serial Addition Task. The MSFC score is a *z*-score with a range of -1 to 1 with higher scores indicated better functioning. Psychometric studies of the MSFC find good intra-rater (0.99) and inter-rater (1.0) reliability, but show significant practice effects for both the 9-hole peg board and PASAT subtests (Rosti-Otajarvi et al., 2008).

Electroencephalogram (EEG). The EEG procedure consisted of 24 cranio-facial transdermal electrodes placed according to the *International 10-20 Electrode Placement System* (Jasper, 1958). Electrode sites were cleaned with a mildly-abrasive gel, approved for such purposes, in order to establish and maintain the integrity of the EEG signal at acceptable impedances (≤5kΩ). Recording of the EEG began with bio-calibrations including: eyes open, eyes closed, look left, right, left, right, look up, down, up down, blink five times, smile and grit teeth, and a period of relaxation. Each of these activities did not exceed 20 seconds. After bio-calibrations participants completed approximately 5 minutes of an eyes closed, relaxed condition. This was followed by cognitive testing, with each task followed by approximately 2-

minutes of relaxed, eyes closed EEG recording. After the completion of the cognitive tasks, and before the ending of the EEG recording, participants completed an approximately 5-minute eyes open, relaxed condition.

Cognitive tasks during the EEG consisted of two trials of the Paced Auditory Serial Addition Task (PASAT) (Tombaugh, 2006) and two trials of a Stenberg Paradigm Task (SPT) (Sternberg, 1969). Presentation rates for the PASAT were 3.0s and then 2.0s; and for the STP the heavy cognitive load trial was followed by the light cognitive load trial for all participants.

Quantitative EEG acquisition and processing. Electroencephalogram (EEG) data was recorded from 20 scalp sites using industry standard EEG electrodes and the Cadwell Easy EEG II (v. 2.1) 32-channel digital amplifier system (Kennewick, Washington). Two additional electrode placements adjacent to the outer canthus of either eye enabled recording of vertical and horizontal eye movements reflecting electro-occulographic (EOG) activity. Data from the EEG was referenced to Cz and digitized continuously at 200Hz with a 12-bit analog-to-digital converter. An electrode was placed on both ear lobes; serving the purposes as referents for certain montages. Electrode impedance was maintained below 5kΩ.

EEG was analyzed using NeuroGuide EEG Software (Applied Neuroscience, Inc. Florida, USA). The QEEG software analyzed the EEG for artifact by use of statistical algorithms, source amplitude and frequency, and allowed for temporally sensitive multi-subject EEG comparison. Common artifact rejection included signals associated with ocular movement, muscle tone, and EKG. Artifact rejection was visually reviewed for accuracy by a registered polysomnographer (RPSGT).

Post EEG. After the removal of the EEG apparatus and scalp cleaning, participants completed the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS),

the Controlled Oral Word Association Test (COWAT), and the Wisconsin Card Sorting Test: Computerized Version-4.

Statistical Analysis by Hypothesis

Descriptive statistics were conducted for demographic, medical, psychological, cognitive data (i.e. general intellectual function, attention, and executive function), and physical function. Continuous data are presented as means ± standard deviations (SD) and ranges, while categorical variables are presented as proportions. Continuous data was analyzed by independent samples t tests and categorical data by chi-square analysis; relationships between variables were analyzed with correlations, ANOVA and its variants, and regressions. All statistical analyses were conducted using IBM SPSS Statistics version 20.

Hypothesis 1: To assess the relationship between cognitive function and disability scores.

1a: MS participants' scores on the RBANS (total and index scores), a measure of global cognitive function, will be lower than matched control participants' RBANS scores.

An independent samples t*-test was used to measure group differences. X = group membership (categorical variable); Y = RBANS total and domain scores (quantitative variable).*

1b: The MSFC disability score will correlate with RBANS scores for both MS participants and matched controls.

In order to assess the degree to which cognitive measures correlate with MSFC scores a zero-order Pearson's correlation will be calculated for RBANS scores (total and domain) and MSFC total score for all participants.

Hypothesis 2: To assess the relationship between QEEG features and performance on cognitive measures administered during EEG.

2a: Peak Alpha Frequency will account for subject level differences in performance on light and heavy cognitive loads on the PASAT and SPT.

In order to elucidate the relationship between group membership and task and load on the PASAT and SPT, a repeated measures ANOVA using a group x task x load design was used. A (2(group) × 2(task)) × 2(load) × 1(PAF) repeated measures analysis of covariance was used in order to delineate main effects and interactions of group by task by load by PAF.

In order to compare the PASAT and SPT directly, scores on both measures were converted to z-scores by taking the overall mean of the normal control group for the task and trial and then subtracting this from the individual participants' score for the same task and trial, then dividing this score by the overall normal control standard deviation. Due to significant overlap of signal in PAF across the head, a principle components analysis (PCA) of PAF at all cranial electrode sites (F3, F4, F7, F8, C3, C4, T3, T4, P3, P4, T5, T6, O1, O2, Fz, Cz, and Pz) was used to reduce the dimensionality of PAF across all electrode sites into a single signal. The resulting extraction was used as the PAF covariate in the repeated measures ANCOVA.

2b: Multiple Sclerosis participants will show impairment on measures of coherence (the degree to which diverse neuronal groups are coupled across space and time, and, as such, is an indicator of functional connectivity in the brain) during the PASAT compared to normal controls.

The normal control mean and standard deviation coherence values were used to create z-scores for the MS group. These z-scores, which represent the deviation of the MS group EEG coherence from the control population, were used to create coherence electrode maps.

Hypothesis 3: To assess spectral analysis and their relationship to cognitive performance.

3a. Spectral analysis will show regional QEEG differences between groups, that is the MS participants will have frequency slowing in delta, theta, alpha, and beta frequencies compared to matched controls.

Initially, group means for each electrode site by frequency were computed. Subsequently, mean differences between groups were computed by independent sample t tests for each electrode site across delta, theta, alpha, and beta frequencies; α was adjusted to .01 to control for multiple comparisons.

3b. MS participants with intact cognitive function, as measured by the RBANS overall score, will have reduced QEEG frequency slowing compared to MS participants with cognitive impairments.

The MS group was divided into two groups, a cognitive intact group and a cognitive deficit group. The cognitive deficit group consisted of those participants with an RBANS total scale score at or below the 16th percentile, which is equivalent to a ≤ -1.0 z-score. Subsequently, peak frequency differences between the cognitive intact and deficit groups in the delta, theta, alpha, and beta bins were computed with an independent t-test; α was adjusted to .01 to control for multiple comparisons.

Hypothesis 4: To assess the relationship between psychological functioning (depression and anxiety) and cognitive functioning.

4a: Psychological functioning will account for a unique portion of variance in cognitive functioning, controlling for group membership, education, and PAF.

A two-step hierarchical multiple regression was performed with cognitive functioning as the outcome, or dependent, variable. Cognitive functioning consisted of RBANS Total scores. During the first step group membership (dummy coded), education, and PAF were entered into

the regression. In the second step, psychological functioning was entered. Psychological functioning consisted of HADS total scores.

Results

Descriptive Statistics

Descriptive statistics for demographic and medical data for the 26 individuals with multiple sclerosis and 18 control participants are shown in Table 1**.** These was no difference for age, $t(42) = .425$, $p = .67$, or education, $t(42) = .11$, $p = .91$ between the multiple sclerosis and normal control groups. The ratio between males and females was 1:7.6 and 1:5 in the MS and control groups, respectively; this difference was not significant, $\chi^2 = .24$, $p = .63$. All MS participants were diagnosed with relapsing-remitting multiple scleroses and none were known to be experiencing an active relapse. The average number of CNS activating medications in the MS group was 5.46, with a mode of 4 and a range from 0 to 10; only three control participants were taking CNS activating medications (Table 1). A significant difference between groups was noted for medications, with the MS group taking a greater number of medications overall.

Descriptive statistics for all cognitive, psychological, and physical variables are presented in Table 2. Participants with MS reported worse cognitive function on a self-report likert scale compared to normal controls. Participants with MS reported more symptoms of anxiety and depression and had worse physical function (MSFC, -0.04 vs. 0.79) than control participants.

Table 1.
Descriptive Statistics for Demographic and Medical Variables by Group.

Variable	Multiple Sclerosis (n = 26) M, SD (range)	Normal Control (n = 18) M, SD (range)	t
Age (years)	49.2, 8.5 (33 – 66)	48.1, 9.0 (30 – 61)	0.42
Education (years)	15.2, 2.0 (11 – 20)	15.2, 1.8 (13 – 19)	0.11
Length of Disease (years)	9.1, 4.9 (0.5 – 19)	*n/a*	*n/a*
	n (%)	n (%)	χ^2
Sex (females)	23 (88.5)	15 (83.3)	0.24
Medications			
MS Specific Medications			
Avonex	4		
baclofen	4		
Copaxone	1		
Detrol	1		
Tysabri	10		
Zanaflex	5		
Other Psychoactive Medications			
Anti-Depressants	25	2	
Opioids	11		
Atypical Antipsychotics	3		
Anxiolytics	4		
Mood Stabilizers	2		
Anti-Epileptics	6		
Stimulants	7	1	

Hypothesis 1: Cognitive Function and Disability Scores

1a: Individuals with MS had worse cognitive function on the RBANS Total Score, Language Index, and Attention Index compared to controls. However, there were no differences for Immediate Memory Index, Visual Construction Index, and Delayed Memory Index between groups.

Similarly, the MS group exhibited slower mental processing speed (SDMT) and worse executive function (Trails A and Trails B) compared to controls. On the two and three second trials of the PASAT the MS group scored significantly lower than the control group indicating deficits in attention, processing speed, working memory, and simple calculation skills. On the

COWA the MS group generated significantly fewer words overall than the control group. Both MS and controls groups completed a similar number of categories within a similar range of trials on the WCST, but the MS group made significantly more perseverative responses and errors compared to controls. On the SPT the MS participants were less accurate and had slower response times than controls for both light and heavy cognitive loads.

Table 2.
Descriptive Statistics for Cognitive and Functional Measures

Measure	Multiple Sclerosis (n = 26) M, SD	Normal Control (n = 18) M, SD	t
Self-Report of Cognitive Deficits (Likert scale ranging from 1 (no deficits) to 7 (significant deficits)	4.4, 0.8	1.83, 1.2	8.57**
Hospital Anxiety & Depression Scale			
Total score	19.8, 7.0	5.5, 3.0	8.07**
Anxiety score	10.5, 4.3	3.9, 2.0	6.02**
Depression score	9.3, 4.0	1.6, 1.7	7.69**
MS Functional Composite Score	-0.04, 0.6	0.79, 0.2	-5.84**
Repeatable Battery for the Assessment of Neuropsychological Status			
Total score	91.3, 12.8	103.8, 11.7	-3.12**
Immediate Memory score	97.6, 15.4	101.9, 14.9	-0.94
Visual Construction score	92.1, 16.6	100.4, 9.8	-1.90
Language score	93.2, 15.4	102.4, 9.8	-2.23*
Attention score	88.9, 15.4	106.2, 11.6	-4.03**
Delayed Memory score	96.8, 12.0	101.8, 13.9	-1.28
Digit Symbol Modalities Test			
Total Correct	58.5, 16.0	81.0, 11.6	-5.07**
Trail Making Test Parts A & B			
Trails A – Time (seconds)	37.2, 14.2	24.6, 5.3	3.59**
Errors	0.1, 0.3	0.3, 0.5	-1.82
Trails B – Time (seconds)	108.1 ± 71.9	58.7, 13.1	2.87*
Errors	0.6 ± 1.0	0.3, 0.6	0.94
Paced Auditory Serial Addition Task			
Trial 3 Correct	40.4, 12.6	54.6, 4.6	-4.60**
Trial 2 Correct	33.9, 13.2	44.7, 8.0	-3.11**
Controlled Oral Word Association Test			
F/A/S Total Correct	32.3, 11.8	41.9, 14.4	-2.45*
F/A/S Total Errors	0.6, 1.0	0.9, 0.9	-0.56

F Correct	10.2, 4.1	13.9, 4.7	-2.83*
A Correct	9.8, 4.4	12.0, 6.1	-1.41
S Correct	12.3, 4.8	16.0, 6.0	-2.25*
Wisconsin Card Sorting Task			
Categories Completed	5.3, 1.3	5.5, 1.5	-0.55
Trials to Complete 1st Category	17.4, 12.9	20.3, 27.3	-0.48
Perseverative Responses	16.42, 10.6	8.9, 6.5	2.69*
Perseverative Errors	14.8, 9.0	8.5, 5.8	2.62*
Failure to Maintain Set	1.42, 1.6	0.6, 0.9	1.96*
Sternberg Paradigm Task			
Light Load Accuracy (percent)	95 %, 0.10	99 %, 0.02	-2.47*
Light Load Response Time (milliseconds)	1038.9, 372.9	711.1, 153.2	3.52**
Heavy Load Accuracy (percent)	91 %, 0.12	96 %, 0.03	-2.22*
Heavy Load Response Time (milliseconds)	1300.8, 509.8	843.0, 163.5	3.67**

Abbreviations are as follows: MS = multiple sclerosis
*p < .05, two-tailed. **p < .01, two-tailed. ***p <.001, two-tailed

1b: In order to test the relationship between the RBANS and the MSFC, zero-order Pearson's correlations were calculated for the MSFC and the RBANS Total and Index scores for MS and control groups combined (Table 3). One MS subject was removed from the analyses due to missing MSFC values. Significant positive correlations were found for the MSFC score and the RBANS Total score, Visual Construction Index, Language Index, and Attention Index. This finding suggests that increased functioning – as measured by the MSFC – is associated with better cognitive functioning – as measured by the RBANS. In the MS group only analysis, MSFC scores were positively correlated with RBANS Total score, Immediate Memory Index, Attention Index, and Language Index, but not with the Visual Construction Index or the Delayed Memory Index, which is similar to the combined groups analysis reported above. The MSFC did not correlate significantly with the RBANS Total score or Index scores for the control group (Table 3). Figure 1 shows a representative example of the correlations between MSFC scores and RBANS scores, in this case MSFC scores with the RBANS Total scores.

Table 3.
Zero-order correlations between the MSFC and RBANS scores

Multiple Sclerosis and Normal Control Combined (n = 43)		
RBANS Global Scores	Pearson's r	p
Total score	.592	<0.00
Immediate Memory	.279	0.07
Visual Construction	.421	0.00
Language	.495	0.00
Attention	.668	<0.00
Delayed Memory	.213	0.17

	Multiple Sclerosis (n = 25)		Normal Control (n = 18)	
RBANS Global Scores	Pearson's r	p	Pearson's r	p
Total score	.616	0.00	-.227	0.36
Immediate Memory	.415	0.04	-.383	0.12
Visual Construction	.352	0.08	.068	0.79
Language	.468	0.02	-.065	0.80
Attention	.576	0.00	-.015	0.95
Delayed Memory	.207	0.32	-.228	0.36

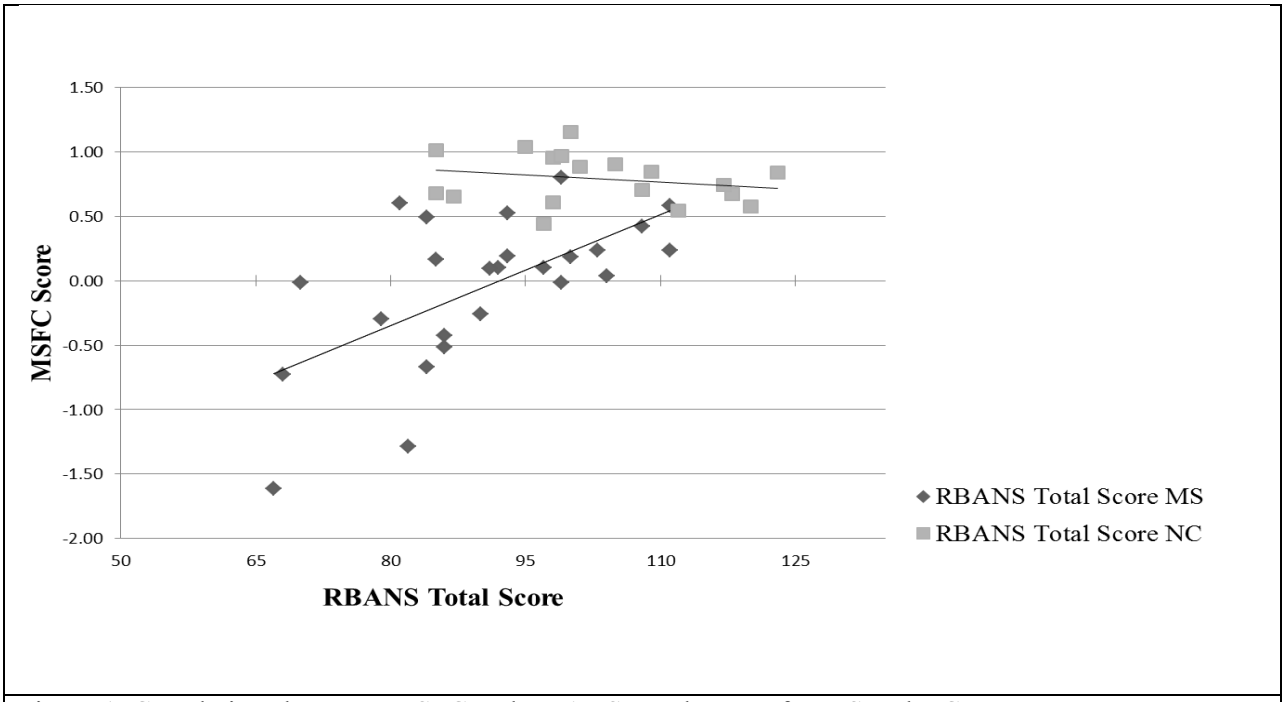


Figure 1. Correlations between MSFC and RBANS Total scores for MS and NC groups

Hypothesis 2: QEEG Features

2a: The normal control mean and standard deviation coherence values were used to create z-scores for the PASAT 2 and 3 second trials and the SPT light and heavy trials. The MS

group's *z*-scores are as follows: PASAT 2 and 3 = -1.36 and -3.12, respectively; SPT Heavy and Light = -1.71 and -1.51, respectively. A principle components analysis (PCA) of peak alpha frequency (PAF) including all cranial electrode sites (F3, F4, F7, F8, C3, C4, T3, T4, P3, P4, T5, T6, O1, O2, Fz, Cz, and Pz) was used to identify a single PAF component (For a description of this technique see Fisher, Talathi, Cadotte, & Carney, 2009, p. 156). The PCA produced a potential of 17 components, with the first accounting for approximately 82 percent of the variance (eigenvalue = 13.93), with significant drop-off noted beyond the first potential component. All electrode sites had extraction values for the main component above .73, with a range from .73 to .92, which indicates that all electrode sites load on the extracted component, as such, all subsequent analysis was restricted to a single component.

In order to elucidate the relationship between group membership and task and load a Repeated Measures ANOVA was completed (Table 4). There was a main effect for group, indicating significant differences between the groups on the PASAT and SPT. Review of the testing data shows that the MS group scored significantly below the normal control group on all measures (Table 2). There was a main effect for load but no main effect for task, showing significant within-subjects effects. Post hoc pairwise analysis with both groups combined indicates significant differences between PASAT 3 and 2 second trials ($t(43) = -4.51$, $p = >.000$) and the PASAT 3and the SPT heavy load ($t(43) = -2.57$, $p = >.01$) but no significant differences between the two loads on the SPT or between other contrasts between the two measures (i.e., light vs. heavy, heavy vs. heavy). Finally, there was a group x task interaction. Review of the data suggests that the PASAT 3 second trial was particularly difficult for the MS group, which is consistent with the above post hoc analysis. The group x task x load interaction was not significant.

Table 4.
Main effects and interactions for Group (MS, normal control), Task (PASAT, SPT), and Load (Light, Heavy)

Main Effects	*F*	df	*p*	*Partial Eta*^{2}
Between-Subjects Effects				
Group	20.06	1	<0.00	0.32
Within-Subjects Effects				
Task	0.91	1	0.35	0.02
Load	5.30	1	0.03	0.11

Interactions	*F*	df	*p*	*Partial Eta*^{2}
Group x Task	0.91	1	0.35	0.02
Group x Load	5.31	1	0.03	0.11
Group x Task x Load	2.48	1	0.12	0.06
Task x Load	2.47	1	0.12	0.06

In order to test the hypothesis that Peak Alpha Frequency will account for group level differences in performance on light and heavy cognitive loads on the PASAT and SPT a Repeated Measures ANCOVA with group as the between-participants variable, the two conditions of the PASAT and SPT (within-participants task and load), and the PAF component score as a covariate was carried out. Results are shown in Table 5. The assumption of sphericity was not violated (Mauchly's W = 1.0 and Greenhouse-Geisser = 1.0), indicating homogeneity of variance in the dependent variables and signaling that the data is appropriate for analysis with a repeated measures ANCOVA. There was a main effect for group, indicating significant differences between the groups on the PASAT and SPT. Additionally, there continued to be a main effect for task. Similarly, the group x task interaction continued to be significant. There was a significant between-subjects effect for PAF, indicating that PAF was related to performance on the PASAT or SPT, or both. Post hoc analysis utilizing pairwise comparison of mean score differences indicates significant differences for load (mean difference = -.50, p = .02), but not for task (mean difference = -.32, p = .32). Comparison of marginal means shows,

similar to the MANOVA reported on above, that the PASAT 3 trial was largely responsible for the significant results (Table 6). To further analyze the relationship between PAF and the PASAT and SPT, partial correlations, controlling for group membership, for PAF and PASAT were as follows, PASAT 3 (r = .44, p < .00), PASAT 2 (r = .33, p = .03). Partial correlations, controlling for group membership, for PAF and SPT were as follows, SPT Light (r = .12, p = .46), and SPT Heavy (r = .088, p = .58). These results suggest that the effect of PAF was largely due to the relationship between PAF and both trials of the PASAT, whereas the SPT does not appear to be associated with variations in PAF. Overall, these results suggest that there are significant group level differences in cognitive performance on the PASAT and SPT, and that variations in PAF are associated with performance on the PASAT, but not on the SPT.

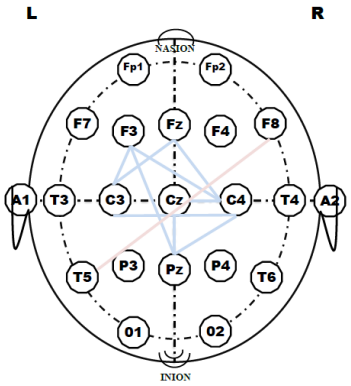
Table 5.
Main effects and interactions for Group (MS, normal control), Task (PASAT, SPT), and Load (Light, Heavy), with PAF as a covariate

Main Effects	*F*	*df*	*p*	*Partial Eta*^{2}
Between-Subjects Effects				
Group	19.36	1	<0.00	0.32
PAF Component Score	5.36	1	0.03	0.12
Within-Subjects Effects				
Task	1.00	1	0.32	0.02
Load	5.54	1	0.02	0.12
Interactions	*F*	*df*	*p*	*Partial Eta*^{2}
Group x Task	0.61	1	0.44	0.02
Group x Load	4.61	1	0.04	0.10
Group x Task x Load	2.12	1	0.15	0.05
Task x Load	2.52	1	0.12	0.06
Task x PAF	2.32	1	0.14	0.05
Load x PAF	1.85	1	0.18	0.04
Task x Load x PAF	0.77	1	0.38	0.02

Table 6.
Comparison of marginal means for Group (MS, normal control), Task (PASAT, SPT), and Load (Light, Heavy), with PAF as a covariate

					95% Confidence Interval	
Group	Task	Load	Mean	Std. Error	Lower Bound	Upper Bound
Multiple Sclerosis	PASAT	Light	-3.02	.395	-3.81	-2.23
		Heavy	-1.31	.268	-1.85	-0.80
	SPT	Light	-1.69	.447	-2.59	-0.80
		Heavy	-1.50	.439	-2.38	-0.60
Normal Control	PASAT	Light	-0.14	.475	-1.10	0.82
		Heavy	-0.10	.322	-0.72	0.60
	SPT	Light	-0.04	.538	-1.23	1.05
		Heavy	-0.03	.529	-1.10	1.04

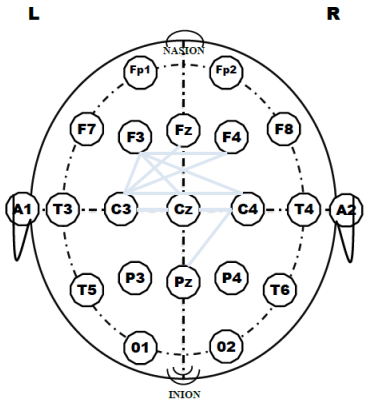
2b. In order to identify possible difference in functional neuronal connectivity between groups, comparison of MS and NC coherence during cognitive tasks was completed. Coherence in the theta, alpha, and beta bands during both trials of the PASAT generally showed reduced coherence for both intra- and inter-hemispheric electrode pairs that were comprised of shorter distance connections. Increased coherence was noted on the PASAT2 and PASAT3 in the theta band for a limited number of electrodes. In summary, while the overall trend was for reduced coherence in the MS group compared to normal controls (see Figures 2, 3, 4, 5, 6, 7), there was increased coherence between a few electrode pairs that were separated by longer distances (see Figures 2 and 5).



	F4	C3	C4	P3	P4	O1	O2	F7	F8	T3	T4	T5	T6	Fz	Cz	Pz
F3	-0.68	-1.24	-1.21	-0.22	-0.39	-0.23	-0.21	0.01	-0.10	-0.35	-0.35	-0.69	-0.32	-1.21	-0.63	-0.75
F4		-0.93	-0.54	-0.29	-0.38	-0.28	-0.24	-0.23	0.25	-0.38	-0.12	-0.26	-0.52	-0.92	-0.47	-0.66
C3			-1.39	-0.04	-0.63	-0.19	-0.31	0.26	-0.34	0.04	-0.68	-0.79	-0.42	-1.40	-0.91	-0.89
C4				-0.55	-0.36	-0.40	-0.28	-0.41	0.42	-0.44	0.24	-0.62	-0.65	-1.50	-1.86	-1.30
P3					-0.27	-0.02	-0.25	0.23	0.16	0.15	-0.26	-0.45	-0.28	-0.35	-0.10	-0.18
P4						-0.30	-0.19	0.32	-0.10	0.10	-0.41	-0.44	-0.51	-0.57	-0.38	-0.54
01							-0.40	-0.10	0.40	0.20	0.36	0.27	-0.12	-0.32	-0.06	0.15
O2								0.28	0.33	0.71	-0.05	0.04	0.05	-0.28	-0.14	0.02
F7									-0.14	-0.03	-0.08	-0.55	0.85	-0.03	0.14	0.09
F8										-0.10	0.41	1.08	-0.48	-0.03	-0.01	-0.30
T3											0.24	-0.68	0.91	-0.45	-0.27	-0.13
T4												0.72	-0.72	-0.46	-0.63	-0.61
T5													0.40	-0.66	-0.54	-0.30
T6														-0.53	-0.42	-0.29
Fz															-0.60	-0.87
Cz																-1.29

Reduced Coherence			***z*-score**			**Increased Coherence**
< -3.0	**-3.0 < -2.0**	**-2.0 < -1.0**	**-1.0 > 0 < 1.0**	**1.0 < 2.0**	**2.0 < 3.0**	**> 3.0**

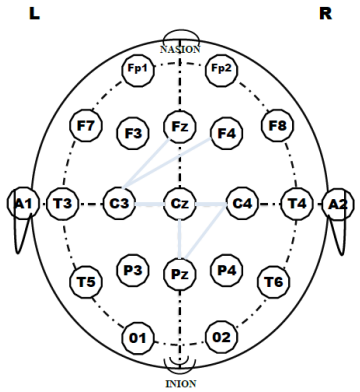
Figure 2. Comparison of MS and normal controls EEG coherence during the **PASAT2** in the **theta** band. Coherence values have been z-transformed and color-coded to aid in interpretation; scores of -1 to <-3 (blue colors) indicate reduced levels of coherence between electrode pairs in the MS group compared to normal controls, while scores of 1 to >3 (red colors) indicate increased coherence. Reduced coherence is noted between frontal and temporal electrodes. Both intra- and inter-hemispheric reductions are noted. Inter-hemispheric increases in coherence between parietal and frontal electrode sites are also present.



	F4	C3	C4	P3	P4	O1	O2	F7	F8	T3	T4	T5	T6	Fz	Cz	Pz
F3	-1.01	-1.23	-1.13	-0.18	-0.36	-0.57	-0.51	-0.44	-0.39	-0.52	-0.50	-0.36	-0.33	-1.12	-0.11	-0.55
F4		-1.20	-0.69	-0.28	-0.14	-0.57	-0.46	-0.58	-0.07	-0.49	-0.33	-0.12	-0.36	-0.97	-0.96	-0.48
C3			-1.37	0.16	-0.36	0.07	-0.28	-0.44	-0.56	-0.29	-0.58	0.02	-0.27	-1.18	-1.44	-0.66
C4				-0.55	0.17	-0.37	0.00	-0.61	-0.19	-0.47	-0.11	-0.02	0.07	-0.95	-1.48	-1.04
P3					-0.31	0.29	-0.08	-0.06	-0.15	0.20	-0.53	-0.05	-0.25	-0.17	0.04	-0.60
P4						-0.22	0.09	-0.31	-0.10	-0.17	-0.06	-0.17	-0.28	-0.20	0.03	-0.31
01							-0.29	-0.54	-0.51	0.04	-0.75	0.22	-0.27	-0.51	0.03	0.43
O2								-0.40	-0.52	-0.38	-0.33	0.03	0.04	-0.43	-0.03	0.40
F7									-0.47	-0.37	-0.46	-0.58	-0.03	-0.40	-0.49	-0.03
F8										-0.40	-0.05	0.16	-0.41	-0.24	-0.33	-0.52
T3											-0.15	-0.21	0.09	-0.44	-0.45	-0.27
T4												0.05	-0.20	-0.42	-0.46	-0.66
T5													0.17	-0.21	0.08	0.17
T6														-0.21	-0.02	-0.01
Fz															-0.83	-0.47
Cz																-0.47

Reduced Coherence			***z*-score**			**Increased Coherence**
< -3.0	**-3.0 < -2.0**	**-2.0 < -1.0**	**-1.0 > 0 < 1.0**	**1.0 < 2.0**	**2.0 < 3.0**	**> 3.0**

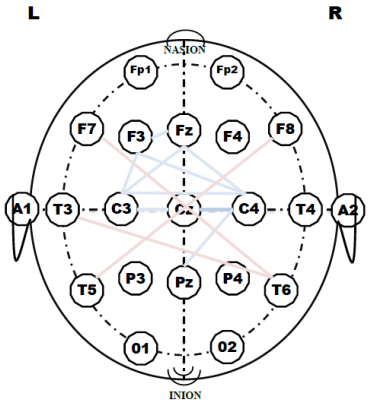
Figure 3. Comparison of MS and normal controls EEG coherence during the **PASAT2** in the **alpha** band. Coherence values have been z-transformed and color-coded to aid in interpretation; scores of -1 to <-3 (blue colors) indicate reduced levels of coherence between electrode pairs in the MS group compared to normal controls, while scores of 1 to >3 (red colors) indicate increased coherence. Reduced coherence is noted between frontal and temporal electrodes. Both intra- and inter-hemispheric reductions are noted.



	F4	C3	C4	P3	P4	O1	O2	F7	F8	T3	T4	T5	T6	Fz	Cz	Pz
F3	-0.68	-0.62	-0.75	-0.24	-0.37	-0.43	-0.49	-0.39	-0.19	-0.17	-0.14	-0.13	-0.31	-0.33	-0.57	-0.61
F4		-1.04	-0.56	-0.44	-0.42	-0.46	-0.49	-0.55	0.09	-0.14	0.19	0.00	-0.37	-0.69	-0.87	-0.64
C3			-0.98	-0.06	-0.50	-0.25	-0.39	-0.25	-0.49	-0.09	-0.39	0.00	-0.27	-1.26	-1.34	-0.92
C4				-0.64	-0.12	-0.44	-0.23	-0.48	0.00	0.00	0.25	0.24	-0.35	-0.83	-1.30	-1.13
P3					-0.41	-0.24	-0.38	0.02	-0.32	0.10	-0.47	0.00	-0.32	-0.36	-0.33	-0.55
P4						-0.32	-0.22	-0.23	-0.20	0.16	-0.02	0.28	-0.68	-0.37	-0.43	-0.59
01							-0.18	-0.43	-0.44	0.08	-0.59	0.59	-0.14	-0.47	-0.20	0.15
O2								-0.39	-0.42	-0.27	0.63	0.57	0.06	-0.49	-0.20	0.10
F7									-0.11	-0.09	-0.10	-0.05	-0.19	-0.39	-0.37	-0.48
F8										0.21	0.32	0.00	-0.39	-0.20	-0.30	-0.57
T3											-0.08	-0.33	-0.14	-0.21	-0.21	-0.14
T4												-0.11	-0.53	0.01	-0.11	-0.29
T5													-0.56	-0.04	0.21	0.32
T6														-0.35	-0.29	-0.21
Fz															-0.79	-0.71
Cz																-1.24

Reduced Coherence			***z*-score**			**Increased Coherence**
< -3.0	**-3.0 < -2.0**	**-2.0 < -1.0**	**-1.0 > 0 < 1.0**	**1.0 < 2.0**	**2.0 < 3.0**	**> 3.0**

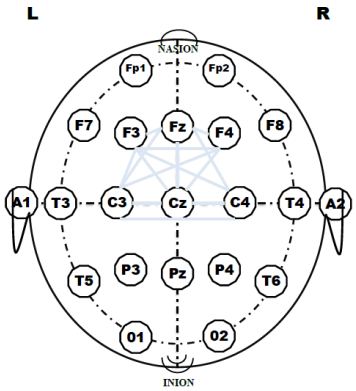
Figure 4. Comparison of MS and normal controls EEG coherence during the **PASAT2** in the **beta** band. Coherence values have been z-transformed and color-coded to aid in interpretation; scores of -1 to <-3 (blue colors) indicate reduced levels of coherence between electrode pairs in the MS group compared to normal controls, while scores of 1 to >3 (red colors) indicate increased coherence. Reduced coherence is noted between frontal and temporal electrodes. Both intra- and inter-hemispheric reductions are noted.



	F4	C3	C4	P3	P4	O1	O2	F7	F8	T3	T4	T5	T6	Fz	Cz	Pz
F3	-0.66	-1.11	-1.16	-0.48	-0.47	-0.49	-0.40	-0.30	-0.08	-0.39	-0.29	-0.63	-0.61	-1.31	-0.64	-0.64
F4		-0.68	-0.62	-0.34	-0.30	-0.45	-0.40	-0.29	0.28	-0.32	-0.03	-0.22	-0.73	-0.83	-0.39	-0.49
C3			-1.38	-0.21	-0.58	-0.45	-0.47	0.13	-0.08	-0.17	-0.44	-0.81	-0.59	-1.13	-1.05	-0.67
C4				-0.73	-0.38	-0.54	-0.49	-0.61	0.38	-0.63	0.16	-0.52	-0.93	-1.35	-2.29	-1.01
P3					-0.48	-0.47	-0.48	-0.02	0.07	-0.27	-0.16	-0.53	-0.33	-0.42	-0.23	-0.26
P4						-0.47	-0.46	-0.23	-0.01	-0.46	-0.15	-0.39	-0.70	-0.52	-0.41	-0.38
01							-0.49	-0.23	0.12	-0.38	-0.06	-0.09	-0.11	-0.54	-0.28	-0.14
O2								0.13	0.05	-0.13	-0.04	0.01	-0.10	-0.51	-0.32	-0.16
F7									-0.16	0.04	-0.34	-0.52	1.57	-0.18	-0.14	-0.23
F8										0.65	0.57	1.06	-0.59	0.08	0.14	-0.14
T3											0.38	-0.84	1.26	-0.39	-0.38	-0.49
T4												0.62	-0.71	-0.28	-0.34	-0.27
T5													0.53	-0.53	-0.52	-0.34
T6														-0.84	-0.68	-0.49
Fz															-0.49	-0.63
Cz																-0.88

Reduced Coherence			**z-score**			**Increased Coherence**
< -3.0	**-3.0 < -2.0**	**-2.0 < -1.0**	**-1.0 > 0 < 1.0**	**1.0 < 2.0**	**2.0 < 3.0**	**> 3.0**

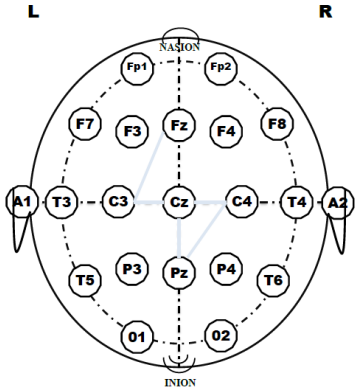
Figure 5. Comparison of MS and normal controls EEG coherence during the PASAT3 in the theta band. Coherence values have been z-transformed and color-coded to aid in interpretation; scores of -1 to <-3 (blue colors) indicate reduced levels of coherence between electrode pairs in the MS group compared to normal controls, while scores of 1 to >3 (red colors) indicate increased coherence. Reduced coherence is noted between frontal and temporal electrodes. Both intra- and inter-hemispheric reductions are noted. Inter-hemispheric increases in coherence between parietal and frontal/temporal electrode sites are also present.



	F4	C3	C4	P3	P4	O1	O2	F7	F8	T3	T4	T5	T6	Fz	Cz	Pz
F3	-1.02	-1.56	-1.19	-0.18	-0.52	-0.56	-0.57	-0.53	-0.56	-0.77	-0.63	-0.40	-0.45	-1.14	-1.04	-0.52
F4		-1.29	-0.89	-0.33	-0.29	-0.54	-0.57	-0.61	-0.23	-0.63	-0.53	-0.17	-0.52	-1.09	-1.13	-0.43
C3			-1.39	0.24	-0.36	-0.09	-0.29	-0.55	-0.70	-0.50	-0.67	0.03	-0.23	-1.46	-1.64	-0.50
C4				-0.55	0.12	-0.29	-0.02	-0.63	-0.43	-0.56	-0.33	-0.17	-0.01	-1.14	-1.57	-0.84
P3					-0.42	0.26	-0.09	0.05	-0.44	0.05	-0.59	-0.15	-0.20	-0.19	0.08	-0.74
P4						-0.18	0.03	-0.34	-0.30	-0.22	-0.15	-0.22	-0.32	-0.36	-0.06	-0.29
01							-0.27	-0.37	-0.52	-0.10	-0.74	0.02	-0.23	-0.47	0.07	0.46
O2								-0.30	-0.57	-0.33	-0.38	-0.09	-0.06	-0.53	-0.07	0.35
F7									-0.54	-0.59	-0.45	-0.49	0.13	-0.45	-0.52	-0.33
F8										-0.45	-0.10	0.01	-0.51	-0.40	-0.51	-0.62
T3											-0.02	-0.25	0.15	-0.67	-0.59	-0.39
T4												-0.07	-0.12	-0.65	-0.66	-0.60
T5													0.14	-0.21	0.10	0.08
T6														-0.49	-0.17	-0.06
Fz															-1.02	-0.45
Cz																-0.39

Reduced Coherence			**z-score**			**Increased Coherence**
< -3.0	**-3.0 < -2.0**	**-2.0 < -1.0**	**-1.0 > 0 < 1.0**	**1.0 < 2.0**	**2.0 < 3.0**	**> 3.0**

Figure 6. Comparison of MS and normal controls EEG coherence during the PASAT3 in the alpha band. Coherence values have been z-transformed and color-coded to aid in interpretation; scores of -1 to <-3 (blue colors) indicate reduced levels of coherence between electrode pairs in the MS group compared to normal controls, while scores of 1 to >3 (red colors) indicate increased coherence. Reduced coherence is noted between frontal and temporal electrodes. Both intra- and inter-hemispheric reductions are noted.



	F4	C3	C4	P3	P4	O1	O2	F7	F8	T3	T4	T5	T6	Fz	Cz	Pz
F3	-0.47	-0.65	-0.79	-0.37	-0.44	-0.42	-0.52	-0.55	-0.07	-0.42	-0.07	-0.33	-0.24	-0.42	-0.63	-0.76
F4		-0.83	-0.46	-0.44	-0.35	-0.48	-0.45	-0.46	0.23	-0.47	0.09	-0.17	-0.25	-0.40	-0.64	-0.65
C3			-0.97	-0.67	-0.54	-0.21	-0.37	-0.25	-0.33	-0.26	-0.24	-0.31	-0.16	-1.15	-1.15	-0.91
C4				-0.69	-0.11	-0.39	-0.10	-0.47	0.18	-0.47	0.18	-0.04	-0.24	-0.75	-1.19	-1.08
P3					-0.35	-0.35	-0.34	-0.05	-0.32	-0.26	-0.36	-0.25	-0.12	-0.45	-0.39	-0.74
P4						-0.27	-0.19	-0.25	-0.09	-0.33	-0.23	0.03	-0.59	-0.42	-0.37	-0.33
01							-0.27	-0.30	-0.51	-0.20	-0.58	0.25	-0.02	-0.44	-0.10	0.10
O2								-0.46	-0.39	-0.57	0.13	0.10	0.11	-0.44	-0.12	0.12
F7									-0.05	-0.21	-0.09	-0.27	-0.15	-0.39	-0.28	-0.55
F8										-0.23	0.11	-0.17	-0.33	0.09	-0.08	-0.52
T3											-0.04	-0.58	-0.25	-0.49	-0.52	-0.58
T4												-0.25	-0.42	-0.16	-0.15	-0.20
T5													0.33	-0.22	-0.05	-0.09
T6														-0.28	-0.16	-0.08
Fz															-0.92	-0.85
Cz																-1.16

Reduced Coherence			**z-score**			**Increased Coherence**
< -3.0	**-3.0 < -2.0**	**-2.0 < -1.0**	**-1.0 > 0 < 1.0**	**1.0 < 2.0**	**2.0 < 3.0**	**> 3.0**

Figure 7. Comparison of MS and normal controls EEG coherence during the PASAT3 in the beta band. Coherence values have been z-transformed and color-coded to aid in interpretation; scores of -1 to <-3 (blue colors) indicate reduced levels of coherence between electrode pairs in the MS group compared to normal controls, while scores of 1 to >3 (red colors) indicate increased coherence. Reduced coherence is noted between frontal and temporal electrodes. Both intra- and inter-hemispheric reductions are noted.

Hypothesis 3: Spectral Analysis

3a. In order to identify possible group difference in QEEG features spectral analysis was carried out for both the MS and normal control group in the delta, theta, alpha, and beta EEG frequency bins. Independent samples t tests, with α adjusted to .01 to control for multiple analysis, were computed in order to compare potential differences between the MS and normal control groups in peak frequency. There were no significant differences in mean peak frequency between groups for delta, theta, alpha, or beta frequency bins. Means, standard deviations, and statistical analysis are presented in Table 7 (Delta), Table 8 (Theta), Table 9 (Alpha), and Table 10 (Beta).

Table 7.
Comparison of Mean Peak Frequency in the Delta Band by Electrode Site by Group

	Multiple Sclerosis (n = 26)	Normal Control (n = 18)		
Electrode	Mean ± SD	Mean, SD	$t_{(42)}$	p
F3	2.09, 0.12	2.13, 0.10	-1.07	0.29
F4	2.10, 0.10	2.13, 0.10	-0.93	0.36
C3	2.18, 0.10	2.19, 0.09	-0.59	0.56
C4	2.15, 0.11	2.19, 0.06	-1.48	0.15
P3	2.18, 0.09	2.19, 0.06	-0.35	0.73
P4	2.16, 0.11	2.18, 0.05	-0.80	0.43
O1	2.20, 0.10	2.15, 0.12	1.63	0.11
O2	2.19, 0.11	2.16, 0.10	0.82	0.42
F7	2.00, 0.17	2.03, 0.07	-0.55	0.59
F8	2.01, 0.14	2.05, 0.13	-0.80	0.43
T3	2.11, 0.13	2.14, 0.10	-1.00	0.33
T4	2.10, 0.12	2.13, 0.13	-0.57	0.57
T5	2.17, 0.14	2.16, 0.11	0.24	0.81
T6	2.16, 0.15	2.16, 0.10	0.11	0.91
Fz	2.15, 0.10	2.17, 0.10	-0.37	0.71
Cz	2.20, 0.09	2.21, 0.08	-0.33	0.74
Pz	2.18, 0.08	2.19, 0.07	-0.46	0.65
Mean	2.14, 0.06	2.15, 0.05	*n/a*	*n/a*

Table 8.
Comparison of Mean Peak Frequency in the Theta Band by Electrode Site by Group

	Multiple Sclerosis (n = 26)	Normal Control (n = 18)		
Electrode	Mean, SD	Mean, SD	$t_{(42)}$	p
F3	5.80, 0.25	5.84, 0.23	-0.49	0.63
F4	5.80, 0.27	5.85, 0.22	-0.66	0.52
C3	5.85, 0.29	5.81, 0.22	0.44	0.66
C4	5.85, 0.29	5.83, 0.21	0.22	0.82
P3	5.88, 0.33	5.77, 0.26	1.22	0.23
P4	5.88, 0.30	5.83, 0.22	0.62	0.54
O1	5.84, 0.31	5.84, 0.18	-0.02	0.99
O2	5.86, 0.30	5.89, 0.18	-0.32	0.76
F7	5.75, 0.26	5.75, 0.29	-0.01	0.99
F8	5.78, 0.24	5.76, 0.27	0.25	0.80
T3	5.77, 0.30	5.71, 0.27	0.69	0.49
T4	5.84, 0.27	5.75, 0.28	1.05	0.30
T5	5.89, 0.34	5.82, 0.06	0.75	0.46
T6	5.93, 0.30	5.89, 0.24	0.56	0.58
Fz	5.80, 0.28	5.84, 0.21	-0.46	0.65
Cz	5.84, 0.31	5.79, 0.20	0.55	0.59
Pz	5.90, 0.33	5.84, 0.18	0.68	0.50
Mean	5.84, 0.05	5.81, 0.05	*n/a*	*n/a*

Table 9.
Comparison of Mean Peak Frequency in the Alpha Band by Electrode Site by Group

	Multiple Sclerosis (n = 26)	Normal Control (n = 18)		
Electrode	Mean, SD	Mean, SD	$t_{(42)}$	p
F3	9.48, 0.30	9.48, 0.28	-0.26	0.98
F4	9.50, 0.30	9.52, 0.27	-0.27	0.79
C3	9.54, 0.32	9.56, 0.27	-0.25	0.81
C4	9.59, 0.37	9.63, 0.26	-0.44	0.66
P3	9.65, 0.39	9.71, 0.33	-0.61	0.55
P4	9.66, 0.41	9.73, 0.30	-0.56	0.58
O1	9.68, 0.42	9.77, 0.36	-0.75	0.46
O2	9.68, 0.43	9.78, 0.38	-0.75	0.46
F7	9.46, 0.27	9.54, 0.27	-0.93	0.36
F8	9.47, 0.26	9.58, 0.28	-1.30	0.20
T3	9.54, 0.30	9.68, 0.27	-1.55	0.13
T4	9.57, 0.33	9.69, 0.29	-1.24	0.22
T5	9.58, 0.40	9.68, 0.28	-0.87	0.39
T6	9.62, 0.43	9.73, 0.34	-0.95	0.35
Fz	9.44, 0.31	9.47, 0.27	-0.33	0.74
Cz	9.50, 0.37	9.55, 0.27	-0.48	0.64
Pz	9.63, 0.45	9.72, 0.32	-0.73	0.47
Mean	9.56, 0.08	9.64, 0.10	*n/a*	*n/a*

Table 10.
Comparison of Mean Peak Frequency in the Beta Band by Electrode Site by Group

	Multiple Sclerosis (n = 26)	Normal Control (n = 18)		
Electrode	Mean, SD	Mean, SD	$t_{(42)}$	p
F3	16.98, 0.96	16.86, 0.42	0.50	0.62
F4	17.01, 1.07	16.91, 0.49	0.38	0.71
C3	16.72, 0.89	16.82, 0.45	-0.43	0.67
C4	16.83, 1.07	16.66, 0.66	0.61	0.55
P3	16.15, 0.94	16.35, 0.71	-0.77	0.44
P4	16.24, 1.01	16.40, 0.75	-0.56	0.58
O1	16.24, 1.05	16.19, 0.87	0.16	0.87
O2	16.26, 1.08	16.32, 0.97	-0.18	-0.86
F7	17.02, 0.78	16.94, 0.55	0.37	0.71
F8	16.87, 0.73	16.80, 0.53	0.37	0.72
T3	17.10, 1.14	16.82, 0.81	0.91	0.37
T4	17.27, 1.24	16.85, 0.73	1.27	0.21
T5	16.44, 1.02	16.37, 0.74	0.27	0.79
T6	16.40, 1.01	16.47, 0.97	-0.21	0.84
Fz	16.65, 0.85	16.61, 0.36	0.21	0.83
Cz	16.57, 0.87	16.63, 0.52	-0.27	0.79
Pz	16.04, 1.01	16.30, 0.75	-0.94	0.35
Mean	16.63, 0.37	16.61, 0.24	*n/a*	*n/a*

3b. The MS cognitively intact group was compared to the cognitive deficit group. Demographic data for the two groups is presented in Table 11. There were no statistically significant differences for any demographic variable between groups.

Table 11.
Demographic Data for the Cognitive Deficit and Cognitive Intact Groups

	Cognitive Deficit (≤ -1.0 z-score) (n = 9)	Cognitive Intact (> -1.0 z-score) (n = 17)		
Variable	Mean, SD	Mean, SD	t	p
Age (years)	45.0, 9.7	51.4, 7.2	-1.92	0.07
Education (years)	14.7, 2.4	15.6, 1.8	-1.25	0.22
LoD (years)	9.9, 5.7	8.7, 4.5	0.60	0.56

LoD = length of disease

Spectral analysis of mean peak frequency was carried out for the MS cognitive intact and cognitive deficit group for the delta, theta, alpha, and beta EEG frequency bins using independent samples t tests, with α adjusted to .01 to control for multiple analysis. There were no significant differences in mean peak frequency between the groups for delta, theta, alpha, or

beta frequency bins. Means, standard deviations, and statistical analysis are presented in Table 12 (Delta), Table 13 (Theta), Table 14 (Alpha), and Table 15 (Beta).

Table 12.
Comparison of Mean Peak Frequency in the Delta Band by Electrode Site by Group

	Cognitive Deficit (≤ -1.0 *z*-score) (*n* = 9)	Cognitive Intact (> -1.0 *z*-score) (*n* = 17)		
Electrode Site	Mean, SD	Mean, SD	*t*	*p*
F3	2.07, 0.13	2.10, 0.13	-0.54	0.59
F4	2.09, 0.06	2.11, 0.11	-0.40	0.69
C3	2.16, 0.10	2.18, 0.10	-0.49	0.63
C4	2.14, 0.11	2.15, 0.10	-0.26	0.79
P3	2.16, 0.07	2.19, 0.10	-0.84	0.41
P4	2.14, 0.14	2.17, 0.09	-0.57	0.57
O1	2.19, 0.13	2.21, 0.08	-0.34	0.73
O2	2.20, 0.11	2.19, 0.11	0.28	0.79
F7	1.95, 0.18	2.04, 0.16	-1.35	0.19
F8	1.98, 0.15	2.03, 0.14	-0.87	0.40
T3	2.04, 0.16	2.14, 0.10	-2.03	0.05
T4	2.07, 0.13	2.12, 0.12	-0.90	0.38
T5	2.15, 0.14	2.18, 0.13	-0.65	0.52
T6	2.16, 0.19	2.16, 0.13	-0.11	0.92
Fz	2.15, 0.11	2.15, 0.10	0.01	0.99
Cz	2.21, 0.12	2.20, 0.08	0.34	0.74
Pz	2.19, 0.07	2.17, 0.09	0.50	0.62
Mean	2.12, 0.07	2.15, 0.05	*n/a*	*n/a*

Table 13.
Comparison of Mean Peak Frequency in the Theta Band by Electrode Site by Group

	Cognitive Deficit (≤ -1.0 *z*-score) (*n* = 9)	Cognitive Intact (> -1.0 *z*-score) (*n* = 17)		
Electrode Site	Mean, SD	Mean, SD	*t*	*p*
F3	5.89, 0.08	5.75, 0.06	1.29	0.21
F4	5.87, 0.31	5.77, 0.25	0.87	0.39
C3	5.96, 0.27	5.79, 0.29	1.50	0.15
C4	5.93, 0.34	5.81, 0.27	0.97	0.34
P3	5.97, 0.35	5.84, 0.32	0.96	0.34
P4	5.96, 0.35	5.84, 0.27	0.98	0.34
O1	5.94, 0.36	5.79, 0.28	1.21	0.24
O2	5.94, 0.34	5.82, 0.28	0.94	0.36
F7	5.84, 0.26	5.70, 0.25	1.36	0.19
F8	5.86, 0.27	5.74, 0.23	1.22	0.23
T3	5.83, 0.34	5.74, 0.29	0.73	0.47
T4	5.89, 0.33	5.81, 0.25	0.68	0.51
T5	5.97, 0.40	5.85, 0.30	0.92	0.37
T6	6.02, 0.42	5.89, 0.21	1.07	0.29
Fz	5.86, 0.32	5.77, 0.25	0.79	0.43
Cz	5.93, 0.35	5.79, 0.28	1.18	0.25
Pz	6.01, 0.38	5.84, 0.30	1.22	0.23
Mean	5.92, 0.06	5.80, 0.05	*n/a*	*n/a*

Table 14.
Comparison of Mean Peak Frequency in the Alpha Band by Electrode Site by Group

Electrode Site	Cognitive Deficit (≤ -1.0 *z*-score) (*n* = 9) Mean, SD	Cognitive Intact (> -1.0 *z*-score) (*n* = 17) Mean, SD	*t*	*p*
F3	9.36, 0.35	9.55, 0.26	-1.56	0.13
F4	9.38, 0.33	9.56, 0.27	-1.46	0.16
C3	9.46, 0.36	9.58, 0.30	-0.92	0.36
C4	9.41, 0.40	9.68, 0.33	-1.80	0.08
P3	9.51, 0.44	9.72, 0.35	-1.31	0.20
P4	9.47, 0.47	9.76, 0.36	-1.80	0.09
O1	9.52, 0.48	9.77, 0.37	-1.47	0.16
O2	9.48, 0.48	9.79, 0.37	-1.88	0.07
F7	9.39, 0.39	9.50, 0.19	-0.96	0.35
F8	9.39, 0.30	9.51, 0.22	-1.13	0.27
T3	9.53, 0.38	9.55, 0.26	-0.19	0.85
T4	9.49, 0.42	9.62, 0.28	-0.92	0.36
T5	9.48, 0.44	9.64, 0.37	-0.93	0.36
T6	9.42, 0.49	9.72, 0.37	-1.80	0.08
Fz	9.31, 0.35	9.51, 0.28	-1.62	0.12
Cz	9.33, 0.39	9.59, 0.34	-1.75	0.09
Pz	9.42, 0.48	9.74, 0.41	-1.78	0.09
Mean	9.43, 0.06	9.63, 0.10	*n/a*	*n/a*

Table 15.
Comparison of Mean Peak Frequency in the Beta Band by Electrode Site by Group

Electrode Site	Cognitive Deficit (≤ -1.0 *z*-score) (*n* = 9) Mean, SD	Cognitive Intact (> -1.0 *z*-score) (*n* = 17) Mean, SD	*t*	*p*
F3	17.26, 0.81	16.84, 1.02	1.07	0.30
F4	17.36, 0.87	16.82, 1.15	1.21	0.24
C3	16.82, 0.59	16.67, 1.03	0.38	0.71
C4	17.05, 0.74	16.72, 1.22	0.73	0.47
P3	16.06, 0.56	16.20, 1.10	-0.35	0.73
P4	16.17, 0.42	16.28, 1.23	-0.26	0.80
O1	16.21, 0.79	16.26, 1.20	-0.13	0.90
O2	16.17, 0.84	16.31, 1.21	-0.30	0.77
F7	17.25, 0.80	16.90, 0.77	1.09	0.29
F8	16.97, 0.46	16.82, 0.85	0.47	0.64
T3	17.25, 1.25	17.02, 1.12	0.48	0.63
T4	17.25, 1.04	17.27, 1.37	-0.05	0.96
T5	16.58, 0.84	16.37, 1.11	0.50	0.62
T6	16.32, 0.69	16.45, 1.16	-0.32	0.76
Fz	16.89, 0.49	16.53, 0.98	1.04	0.31
Cz	17.01, 0.67	16.35, 0.89	1.95	0.06
Pz	15.87, 0.37	16.13, 1.22	-0.63	0.54
Mean	16.73, 0.49	16.58, 0.32	*n/a*	*n/a*

Hypothesis 4: Psychological Functioning

A multiple regression was used to explore the relationship between cognitive functioning and psychological functioning. Overall cognitive function (RBANS Total score) was predicted by Group (coded 0 = Multiple Sclerosis, 1 = Normal Control), Education, Peak Alpha Frequency (PAF), and Psychological Functioning (PF) (i.e., HADS total score). The total sample size was 44; no data points were missing.

Table 16.
Results of a Two-Step Hierarchical Regression to Predict Cognitive Functioning from Group, Education (ED), and PAF, and Psychological Functioning (PF)

	RBANS	Group	ED	PAF	PF		b	β
Group	-0.43						-3.90	-0.14
ED	0.15	0.02					0.45	0.06
PAF	0.40	-0.12	0.14				4.89	0.36
PF	-0.45	0.78	-0.11	-0.04			-0.48	-0.32
						Intercept =	98.32	
Mean	96.16	_____a	15.2	_____b	13.93			
SD	13.60	_____a	1.9	_____b	9.10			
						$R^2 = 0.358$		
						$R^2_{adj} = 0.293$		
						$R = 0.599$***		

Note: Group, ED, and PAF were added in step one; PF was added in step-two. *$p < .05$, two-tailed. **$p < .01$, two-tailed. ***$p < .001$, two-tailed. Table adapted from (Warner, 2008, p. 582).
a. Group was a dummy coded variable (Multiple Sclerosis = 0, Normal Control = 1). As such means and standard deviations are note reported. The sample included 26 MS participants and 18 Normal Controls.
b. PAF is the product of a transformation (i.e., reduction of dimensionality), which decouples PAF from its original metric (i.e., 8 to 12hz) and results in a mean of 0 and a standard deviation of 1.

A two-step hierarchical multiple regression was performed with cognitive functioning as the dependent variable. During the first step group membership, education, and PAF were entered into the regression. In the second step psychological functioning was added to the model (see Table 16). The overall regression in step-one, which included group membership, education, and PAF, was significant, $R = 0.57$, $R^2 = 0.32$, $R^2_{adj} = 0.27$, $F(4, 39) = 6.30$, $p = <.00$. The addition of psychological functioning to the model was significant, and resulted in a slight

increase in predictive power for the overall regression model, $R = 0.60$, $R^2 = 0.36$, $R^2_{adj} = 0.30$, $F(4, 39) = 5.45$, $p = <.00$.

Discussion

Cognitive Function

The current study explored the complex relationship between cognitive deficits, QEEG features, and cognitive performance during EEG in MS participants. The MS participants exhibited significant cognitive impairments compared to matched controls. For instance, the RBANS global cognition score was significantly reduced in the MS group compared to controls (91±13 vs. 103±12; standard score). Specifically, differences in cognitive functioning were found in language and attention; while immediate and delayed memory and visuo-constructional abilities did not differ between the groups. It should be noted that while global cognitive functioning in the MS group was significantly lower than controls, the MS groups' mean scores fell within the low average range of normal cognitive function.

Previous research has identified memory deficits as part of the hallmark pattern of cognitive decline in MS (Rao, Leo, Bernardin, et al., 1991). As noted above, there were no differences between our MS and control group on immediate or delayed memory indices. One study that utilized the RBANS found deficits in the immediate and delayed memory indices in individuals with MS who had a MMSE score of < 27 (impaired cognitive function), while individuals with a MMSE score ≥ 27 (normal cognitive function) had RBANS memory scores that were not impaired (Beatty, 2004). Our findings are similar to those of Beatty et al. (2004) in that our MS group had both relatively normal global cognitive function and preserved memory functions (encoding, storage, and retrieval), which are sub-served by medial temporal lobe structures. In contrast, on a Sternberg Paradigm Test our MS group exhibited significant

impairments on accuracy and speed of response compared to controls, suggesting that our MS participants had impaired working memory, a function of the frontal lobes (Prabhakaran, Narayanan, Zhao, & Gabrieli, 2000). The intact immediate and delayed memory but impaired working memory suggests that brain regions may be differentially affected and lesion location is likely critical in determining the type and severity of cognitive impairments in individuals with MS. Deficits in visuo-spatial function in our MS participants approached significance ($p = 0.07$). This finding is interesting in that visuo-spatial deficits are uncommon in MS populations (Calabrese, 2006). Given our relatively modest sample size, it may be that a larger sample would have found visuo-spatial impairments in our MS participants compared to controls. Another possible explanation for these findings may be limitations in the RBANS complex figure scoring. An analysis by Duff et al. (2007) of the RBANS' complex figure scoring suggests that the published scoring criteria may over-estimate the severity of visuo-spatial impairments, particularly in populations with deficits in motor functioning, making individuals appear to have visuo-spatial impairments where none exist. Deficits in motor functioning can contribute to visuo-spatial impairments including "gap errors," or the inclusion of small spaces between components of the complex figure task, which in the standard RBANS' scoring system are strictly penalized. It is not unreasonable to think that this may contribute, as least in part, to the low performance of our MS participants on this task. As such, the differences, while not significant, in visuo-spatial performance between the MS and control group may be due to over estimation of errors when using the standard RBANS complex figure scoring system, rather than actual visuo-spatial impairments. A final possibility is that there are no differences in visuo-spatial function in our MS participants compared to controls, similar to previous research.

The MS group had slower processing speed compared to normal controls. Our findings of slow processing speed are consistent with research showing that processing speed deficits are a core component of the cognitive decline in MS (Bellmann-Strobl et al., 2009). Intact motor functioning is a prerequisite to adequate performance on many measures associated with processing speed (D'Orio et al., 2012). Given that we screened and did not find gross motor impairment in the MS group, it is more likely that the differences in processing speed were due to true differences, rather than to differential motor functioning.

On measures of executive functioning, our MS participants exhibited deficits in phonemically constrained word generativity, motor sequencing and planning, perseverative responding, and maintenance of cognitive set. The finding of impaired executive function in individuals with MS has been previously reported. For example, Arnett, et al., (1997) found significant planning deficits on a tower task and Beatty and Monson (1996) found deficits in concept generativity and increased perseverative responding on a sorting task. Also, both Foong, et al., (1997) and Henry, et al., (2006) noted deficits in verbal fluency. In addition to working memory and processing speed deficits, it is likely that deficits are consistent with a subcortical pattern of cognitive impairments (Lazeron et al., 2005), which provides support for the idea that the cognitive deficits observed in MS may represent a type of subcortical dementia.

The neuropsychological findings in this study are consistent with previous research indicating that the cognitive deficits (i.e., deficits in memory, processing speed, attention, and executive dysfunction) in individuals with MS are consistent with a subcortical dementia and likely represent damage to subcortical white matter networks.

MSFC Disability Score and Relationship with RBANS

An area of interest has been the development and application of repeatable, brief screening tools that can be used to assess cognitive function in MS. We assessed the relationship between the MSFC and performance on the RBANS. As predicted, the MSFC score was associated with the RBANS scores for the combined MS and control group, with lower MSFC scores correlated with cognitive impairments on the RBANS (see Figure 1). When we assessed the relationship between the MSFC and RBANS scores for the MS group in isolation, the findings were similar. There was no relationship between MSFC and RBANS scores for the control group. This finding is not terribly surprising, as the MSFC was designed to assess the stereotypical deficits in MS – motor, working memory, and processing speed, rather than normal functioning. As such, one might expect that the MSFC would be a recapitulation of findings on cognitive measures in an MS group, but not necessarily in a normal control group where impairments in motor, working memory, and processing speed difficulties are not expected. Thus, both the MSFC and the RBANS are able to detect cognitive impairments in multiple sclerosis, and can be used as quick, yet valid tools to assess cognitive impairment in this population. There are some benefits of using the RBANS over the MSFC as a cognitive screening tool that should be noted. For example, the MSFC does not sample as many cognitive domains as does the RBANS, and as such may not be as sensitive to the heterogeneous deficits seen in MS. Moreover, the RBANS has an estimated administration time of approximately 30 minutes (Randolph, Tierney, Mohr, & Chase, 1998), which is comparable to the time needed to administer the MSFC, aproximately15 to 20 minutes (Fischer et al., 2001). One advantage of the RBANS is that it does not use the PASAT, which is a challenging test that is often frustrating for participants (Tombaugh, 2006) and can be difficult to administer and score (Rosti, Hämäläinen, Koivisto, & Hokkanen, 2006).

Quantitative EEG

Amid growing interest in clinical applications of EEG to understand cognitive functioning in neurological participants (Koberda, Moses, Koberda, & Koberda, 2013), to our knowledge our study is the first to show the feasibility of QEEG techniques in an MS population in a clinical neurology setting. We used a standardized 10 – 20 electrode placement system (Jurcak et al., 2007) in conjunction with standardized clinical measures of cognition that are sensitive to the deficits seen in MS (e.g., PASAT). This is an innovative use of QEEG techniques in a clinical setting, and meets the requirements set by Gudmundsson et al., (2007) and Jurcak et al., (2007) for a valid and useful cognitive-neurophysiological protocol, and such methods could be used as a guide for future researchers and clinicians who want to implement these techniques in a research or clinical setting.

Peak Frequency

Initial studies of PAF indicated that it might be a marker of general intelligence, but researchers have since determined that PAF is associated with cognitive preparedness (Doppelmayr et al., 2002; Klimesch, 2000). An analysis, utilizing a Repeated Measures ANOVA, comparing the MS and normal control groups' performance on both trials on the PASAT and SPT indicated group level differences in performance for load but not task. Post hoc analysis indicated that this result was primarily due to significant differences between groups on the PASAT 3 (light trial). It should be noted that these results are in contrast with previous research, which has consistently shown that faster presentation (heavier load) is associated with worsening performance (Tombaugh, 2006). Given that the PASAT 3 second trial was administered first, per standard MSFC protocol, it is likely that the above results represent practice effects, which may have been ameliorated by a counter balanced design. Utilizing a

Repeated Measures ANCOVA, with at rest PAF as the covariate, we found that variance in performance on the PASAT (measure of mental preparedness and processing speed) was significantly associated with changes in at rest PAF. Faster at rest PAF correlated with better performance on the PASAT; this was particularly true for the PASAT 3 second trial. These results are similar to previous research indicating PAF is associated with cognitive preparedness in that, as indicated above, a practice effect on the PASAT from the first trial (PASAT 3) to the second trial (PASAT 2) suggests increased cognitive preparedness as a participant acclimates to the demands of the task. In contrast to the PASAT data, despite clear differences in performance accuracy and response speed between the MS and control group PAF was not associated with the Sternberg Paradigm Task, a measure of working memory (Kahana & Loftus, 1999; Sternberg, 1969). Research by Finnigan and Robertson (2011) found working memory was associated with theta rather than alpha frequencies. Other research indicates that gamma frequencies are associated with working memory (Howard et al., 2003). Given the above, at rest PAF would not necessarily be expected to be related to working memory such as measured by the Sternberg Paradigm Test. Another possibility is that our SPT was not sufficiently optimized to find load effects. Thus, PAF is associated with cognitive preparedness and processing speed, both of which are impaired in MS participants, and therefore may be a viable physiological biomarker of cognitive decline in MS populations.

Spectral Analysis

We assessed regional differences between the MS and control groups' peak delta (0-4hz), theta (4-8hz), alpha (8-12hz), and beta (12-30hz) frequencies while engaged in the PASAT and found no differences at any electrode site (F3, F4, F7, F8, C3, C4, T3, T4, P3, P4, T5, T6, O1, O2, Fz, Cz, and Pz). We also compared peak frequencies (delta, theta, alpha, and beta) in MS

participants with intact cognition with MS participants who had cognitive impairments. There were no significant differences between the "normal" and cognitively impaired MS groups for any frequency at any electrode site. This is in contrast with previous research which has shown increased alpha (Facchetti et al., 1994) and faster peak beta frequencies in MS populations (Vazquez-Marrufo et al., 2008), but comports with other studies that have shown grossly normal EEG in the majority of MS participants (Feng, 1981). One possible explanation for the discrepancies between these studies is that the study by Facchetti et al., and Vazquez-Marrufo et al., consisted of relatively few participants (n = 16 and n = 19, respectively) whereas Feng et al., had a larger samples (n = 57), which decreases the likelihood of false positive errors. Thus, one possible reason that we did not find differences in peak frequencies in our cognitively impaired versus "non-impaired" MS participants may be our small sample size (n = 9 and n = 17, respectively), and as such we may not be powered for subgroup analyses. Further studies are needed to explore this issue.

Coherence

Coherence represents the degree to which diverse neuronal groups are coupled across space and time, and, as such, is an indicator of functional connectivity in the brain. Research to date in MS populations is mixed as to whether coherence decreases as a sign of subcortical impairment or increases, indicating cognitive adaptation. Our MS participants exhibited reductions in both intra- and inter-hemispheric coherence in the theta, alpha, and beta bands, with a limited number of electrode pairs in the theta band showing increased coherence. The electrode pairs that showed reduction in coherence were generally closer together, while the electrode pairs in the theta band that showed increased coherence were distant, anterior to posterior electrode pairs. Leocani, et al., (2000) found decreases in coherence in theta and alpha

bands during at rest EEG. In contrast, increases in theta, alpha, and beta coherence in an MS population have also been reported (Schoonheim et al., 2013). While we found a limited number of electrode pairs that showed increased coherence, our data is most similar to that of Leocani et al., (2000) who found decreased coherence, and in contrast to Schoonheim et al., (2013) who found primarily increased coherence. One possible explanation for these discordant findings is that the Leocani et al. study consisted of MS participants that as a group were cognitively impaired in comparison to the control group, while in the Schoonheim et al. study the MS participants had normal cognitive functioning compared to controls. While our MS participants' general cognitive functioning was in the low average range, it was significantly lower than matched controls, which makes our population more similar to the Leocani et al. population who had decreased coherence. It may be that when neuronal networks begin breaking down coherence decreases, and cognitive functioning is subsequently impaired, which would explain both our and Leocani et al.'s findings of decreased coherence. Alternatively, adaptive responses, such as cortical recruitment, may initially result in increased coherence, and maintenance of cognitive abilities, which would explain Schoonheim et al.'s data. Therefore, coherence may be a biomarker of both adaptive brain processes (i.e., increased coherence) and brain dysfunction (i.e., decreased coherence) in MS. While our data is intriguing, our population is small and the differences between groups modest. Further research is needed to determine the role of coherence in MS populations as well as the neural implications (brain injury, adaptation, or both) of such. Finally, while our data did suggest a general reduction in coherence in the MS groups compared to controls, this effect was not drastic. Given that MS is a disease with a heterogeneous presentation (i.e., variable lesion location and load across individuals and time) it may be that group level analysis obscures true differences between groups, and a that

comparison at the level of the individual participant would be more fruitful. More research is needed to explore this issue further.

Psychological Functioning

Our MS participants reported significant symptoms of both depression and anxiety compared to controls (Table 2). These findings are similar to studies that have found depression to be common in multiple sclerosis (Whitlock & Siskind, 1980). Population based studies indicate a two to three fold increase in incidence rates of depression in MS participants compared to non-MS participants (Patten, Beck, Williams, Barbui, & Metz, 2003). Depression is associated with reduced quality of life, greater fatigue, physical dysfunction, and abnormalities on structural neuroimaging (Benedict et al., 2005; Feinstein et al., 2010; Feinstein et al., 2004; Ziemssen, 2009). After accounting for the variance explained by group membership, education, and electrophysiological differences; psychological functioning (depression and anxiety) predicted an additional, albeit small (~4 percent), portion of the variance in cognitive performance (see Table 16) in our MS participants. Data is mixed regarding the relationship between depression and cognitive impairments in MS. For example, Arnett et al., (1999) found that depression was associated with reduced working memory capacity. In contrast, Lovera et al., (2006) found that depression was associated with the perception of cognitive deficits, rather than with cognitive impairments. Our data tend to support those of Arnettt et al., in that psychological functioning accounted for variability (four percent) in cognitive functioning in our MS sample. Given that depression and anxiety are common in MS and that depression appears to account for a portion of the variability of cognitive function in MS, the effects of depression should be assessed in studies of cognitive functioning in MS.

Strengths and Limitations

The strengths of this study include the utilization of quantitative EEG, the inclusion of a well-defined MS group and carefully matched controls, and use of standardized neuropsychological measures of cognitive and psychological functioning. In addition, our data provide support that the RBANS can be used to assess cognitive function in MS participants. Finally, the electrophysiological data suggests that QEEG may be a promising biomarker of cognitive deficits in MS. There are a few limitations of the current study. First, given the amount of data that is generated during a standard EEG and the number of comparisons required when analyzing such data, and our relatively small sample size, there is an increased possibility of a Type II error, especially for the individual electrode peak frequency analysis. Second, the MS group was taking more psychoactive medications than the control group, which may alter EEG activity (Ford, Goethe, & Dekker, 1986). Specifically, benzodiazepines tend to increase diffuse beta activity, mood stabilizers increase both delta and theta activity, and antipsychotics, depending on the method of action, can either decrease or increase alpha frequency (Blume, 2006; Fink, 1969). Given our sample size, we were unable to determine the effect that medications might have had on our analysis, but it is not unlikely that some effect was present. Both of these limitations may be alleviated with a larger sample size, and as such, the relatively small sample size is an important limitation of this study.

Conclusion

In conclusion, our MS population exhibited cognitive impairments in attention, processing speed, working memory, and executive functioning, which is consistent with previous research in MS populations. These findings are consistent with the description of MS as a sub-cortical dementia. We showed that a standardized clinical QEEG protocol used in conjunction

with cognitive measures is feasible, but care needs to be taken to ensure both task and load fidelity. Our data indicates that at rest peak alpha frequency is associated with cognitive preparedness and processing speed, a prominent area of deficit in MS. Coherence was generally reduced during processing speed tasks in MS, which may indicate subcortical dysfunction. The electrophysiological data suggests that QEEG may be a promising biomarker of cognitive deficits in MS. Finally, symptoms of depression and anxiety are prevalent in MS, and depression was associated with cognitive impairments, and, as such, should be accounted for when assessing cognitive dysfunction in MS populations.

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