EXAMINATION OF THE RELATIONSHIP BETWEEN STARTLE EYEBLINK

MODULATION AND PERCEIVED FATIGUE IN MULTIPLE SCLEROSIS

A THESIS IN
Psychology

Presented to the Faculty of the University of
Missouri-Kansas City in partial fulfillment of
the requirements for the degree

MASTER OF ARTS

by
BRYAN DEREK FOX

B.A., University of Missouri-Kansas City, 2009 & 2010

Kansas City, Missouri
2016

EXAMINATION OF THE RELATIONSHIP BETWEEN STARTLE EYEBLINK

MODULATION AND PERCEIVED FATIGUE IN MULTIPLE SCLEROSIS

Bryan D. Fox, Candidate for the Master of Arts Degree

University of Missouri-Kansas City, 2016

ABSTRACT

Multiple sclerosis (MS) is a neurodegenerative disorder from which fatigue is one of the most commonly reported symptoms. Recently, research into the underlying neural mechanisms of fatigue has focused largely on the relationship between perceived fatigue and neural efficiency. Imaging studies have shown correlations between self-reported fatigue measures and changes in the patterns of neural activation within the sensorimotor network (SMN), suggesting that disruptions of efficient processing within the SMN are related to fatigue perception. Extending this line of research, the present study investigated whether a psychophysiological measure of the sensorimotor network would correlate with perceived fatigue in a sample of individuals with MS. Startle Eyeblink Modulation (SEM), a measure that has been reliably shown to reflect the functioning of the SMN, indexes both the efficiency and timing of sensorimotor processing within the network. SEM involves the examination of the size and the speed of the startle eyeblink reflex elicited in the presence and absence of a non-startling "prepulse" stimulus that is paired with the startle stimulus. The effect of the prepulse is indexed by comparing the prepulse and non-prepulse (baseline) conditions, with changes in the size (amplitude) and timing (latency) of the startle eyeblink reflecting the efficiency of sensorimotor processing. In the current study, it was hypothesized

that measures of SEM efficiency would significantly correlate with a measure of perceived

fatigue for participants with MS. Individuals ($n = 44$) underwent SEM testing and completed

an assessment of perceived fatigue. Results revealed that participants showed larger (i.e.

slower) latencies of the startle eyeblink response, and that these latencies correlated with a

self-report measure of perceived fatigue. These results contrasted with non-significant

correlations between the same measures for a group of age-matched controls, who differed

from the MS group on perceived fatigue measures. These results suggest that changes in the

timing of these responses reflect disrupted sensorimotor gating, which is in turn related to the

perception of fatigue for individuals with MS. Since startle eyeblink latency may represent an

index of the initiation of stimulus processing, these results also provide support for research

examining the relationship between fatigue and changes in processing efficiency within the

sensorimotor network.

APPROVAL PAGE

The faculty listed below, appointed by the Dean of the College of Arts and Sciences have

examined a thesis titled "Examination of the Relationship Between Startle Eyeblink

Modulation and Perceived Fatigue in Multiple Sclerosis," presented by Bryan D. Fox,

candidate for the Masters of Arts degree, and certify that in their opinion it is worthy of

acceptance.

Supervisory Committee

Diane Filion, Ph.D., Committee Chair
Department of Psychology

Jared Bruce, Ph.D.
Department of Psychology

Tamera Murdock, Ph.D.
Department of Psychology

CONTENTS

ILLUSTRATIONS

TABLES

CHAPTER 1

OVERVIEW

The purpose of the present study was to investigate the measures of the startle

eyeblink reflex as indexes of neural efficiency and the relationships of those measures to

perceived fatigue in multiple sclerosis. Multiple sclerosis (MS) is a neurological disease in

which demyelination and subsequent scarring of nerve axons leads to a disruption of efficient

communication within the central nervous system. Symptoms of MS include vision

problems, cognitive and emotional difficulties, and reduced motor control (Compston &

Coles, 2008). Fatigue is one of the most pervasive symptoms, and its negative impact on

daily functioning is reported by a significant majority of diagnosed individuals (DeLuca,

2005). Research has shown significant negative correlations between subjective measures of

fatigue and the ability to engage in activities of daily living, clinical assessments of

cognition, as well as predicted positive treatment outcomes (Strober & DeLuca, 2013).

However, perception of fatigue, and fatigue's impact on activities of daily living and other

response measures, vary greatly between individuals (Thelen, Lynch, Bruce, Hancock, &

Bruce, 2014). Differing from the sensation of muscular fatigue or physical weariness, the

fatigue in these cases is more central in nature, possibly due to changes in processing within

one or more affected cortical or subcortical pathways (Chaudhuri & Behan, 2004). Similarly,

the length or complexity of assessments used in fatigue studies may create additional task

demands for the participant, which may in turn affect perceived fatigue (DeLuca, 2005).

Although the precise mechanisms are not clearly identified or understood at present,

empirical study of the neural basis of fatigue involves examination of the relationship

between measures of fatigue and measures of neural processing assessed from potentially affected areas. Many researchers employing the use of neuroimaging techniques have examined correlations between self-reported fatigue and neural excitability in cortical and subcortical regions (e.g., Cruz Gómez, Ventura Campos, Belenguer, Ávila, & Forn, 2013; Yusuf & Koski, 2013). Recent findings suggest a relationship between perceived fatigue and neural substrates involved in the sensorimotor network (SMN), the neural pathways that conduct information to and from the sensory and motor processing areas of the brain, including both cortical and subcortical structures. Studies using a model of "neural efficiency" to explain fatigue (DeLuca, 2005; Engström, Flensner, Landtblom, Ek, & Karlsson, 2013) theorize that reductions in functional connectivity between various pathways within the SMN are experienced by the individual as elevated fatigue. Examination of the relationship between measures of fatigue and changes in neural processing (or efficiency) continues to add to the present understanding of the neural basis of fatigue, which in turn may shed light on the nature of fatigue perception itself. The present study continues this line of research by investigating the relationship between perceived fatigue and processing efficiency in one pathway within the SMN, a specific pathway that can be assessed using the startle eyeblink reflex.

The startle eyeblink reflex is a part of a robust constellation of physiological changes, triggered via activation of the SMN, by abrupt or sudden onset of sensory stimulation. Activation of this simple, sub-cortical reflex circuit causes the eyelid to close (or "blink"). This reflexive response is triggered automatically prior to any cognitive processing or volitional attentional control. The size (amplitude) and speed (latency) of the startle eyeblink reflex provide a window into the functioning of the SMN circuit that underlies that response.

In addition, by introducing a non-startling stimulus, termed a "prepulse," immediately prior to a startle-eliciting stimulus, the amplitude and latency of the elicited startle response are modified in reliable patterns that also reflect the functioning of that underlying circuit, due to a "sensory gating" mechanism triggered by the prepulse (Dawson, Schell, & Böhmelt, 1999).This technique of presenting a prepulse in close temporal proximity to a startle-eliciting stimulus is termed startle eyeblink modulation (SEM), and refers to modification of the strength (amplitude) and speed (latency) of the elicited startle response (*Figure 1*).

Startle Eyeblink Modulation
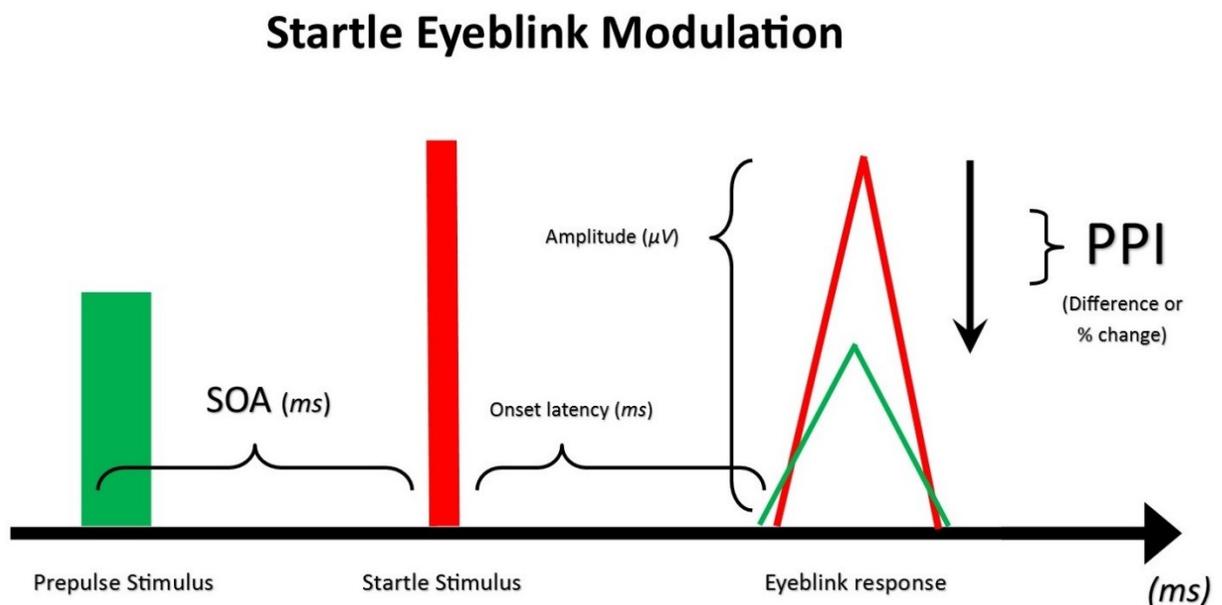
Figure 1: A simplified visual representation of the startle eyeblink modulation paradigm at a short-lead prepulse interval, or stimulus onset asynchrony (SOA). Blink characteristics (amplitude and onset latency, shown here) are measured in response to the startle stimulus. Introducing a non-startling stimulus ("prepulse") prior to the startling stimulus modifies the subsequent response. At small ("short-lead") SOAs, the resulting inhibited response is compared to the individual's response without the prepulse, a phenomenon referred to in the literature as prepulse inhibition (PPI).

Note: Stimulus onset asynchrony (SOA), or prepulse interval, is measured from the onset of the prepulse stimulus in the event of prepulses of significant duration. For clarity, interval measurements are not shown to scale with one another.

As an objective psychophysiological measure, SEM may be useful in providing additional understanding of fatigue in MS because it is thought to reflect the efficiency of the underlying SMN, specifically the cortico-striato-pallido-pontine circuit (c.f. Fendt et al., 2001; Swerdlow et al., 1995). If individual differences in modulated startle eyeblinks reflect changes in the efficiency of the SMN, and if perceived fatigue is similarly related to the efficiency of the SMN, then measures of modulated startle eyeblink amplitude and latency should be correlated with measures of perceived fatigue.

The present study investigated the relationship between fatigue in MS and SEM-based measures of SMN efficiency. It was hypothesized that if perceived fatigue in MS is related to processing efficiency, then baseline and prepulse-modulated startle eyeblink amplitude and latency measures would be correlated with perceived fatigue. At present, results reported in the current literature from studies working to identify what DeLuca (2005) describes as "a neuroanatomic locus for fatigue" (p.64) have been inconclusive, while research examining correlations between measures of fatigue and efficient neural functioning have been more promising (DeLuca, 2005). Support for the present hypothesis contributes to this latter body of work by not only addressing some of the challenges of empirical fatigue research that were discussed above, but by offering converging evidence of the relationship between efficient SMN processing and fatigue perception.

CHAPTER 2

A REVIEW OF THE LITERATURE

The focus of the current study will be on the examination of the relationship between the perceived fatigue of individuals with multiple sclerosis, and the neural efficiency of the sensorimotor network as indexed by the amplitude and latency of the startle eyeblink reflex. The following literature review will first provide a brief description of multiple sclerosis (MS), followed by a summary of common symptoms of MS. Fatigue in MS will be examined more closely, with fatigue defined and research into the nature of fatigue outlined. Literature on the role of the sensorimotor network and neural efficiency on fatigue perception will then be reviewed, followed by a discussion of the startle eyeblink modification paradigm. Following this, a closer look at studies that have measured the amplitude and latency of the startle eyeblink response will be reviewed that support the potential benefit of using this measure to further examine the relationship between perceived fatigue and the efficiency of the sensorimotor network.

Multiple Sclerosis

Multiple sclerosis (MS) is a degenerative neurological disease, affecting approximately one out of every 750 Americans, between 2 and 2.5 million people worldwide (Niedziela, Adamczyk-Sowa, & Pierzchała, 2014). About 65-75% of these individuals are female, with symptom onset usually occurring between the ages of 20 to 50 (National Multiple Sclerosis Society, 2014). With this disease, the body's autoimmune system attacks the myelin sheath surrounding axons in the individual's central nervous system (CNS). This demyelination interferes with neural transmission leading to disruption of communication within the individual's central nervous system, causing the varied symptoms which may be

observed in MS. Neural functionality or efficiency of transmission may be reduced, degraded, or lost altogether, as lesions form within the neural axons. Subsequent scarring over these lesions may lead to additional chronic problems, as plaque (or "sclera") forms after the demyelination has taken place (Polman et al., 2011).

Symptoms of Multiple Sclerosis

Depending on the course of the disease, symptoms in MS can have a sudden or gradual presentation. Clinical subtypes are identified by the pattern of symptom presentation, with symptoms in many cases disappearing only to return after a period of time (Katz Sand & Lublin, 2013; Runia, Jafari, & Hintzen, 2013). The presence of psychiatric disorders is often comorbid with MS, and may be related to overall brain dysfunction. These disorders can also develop during the course of the disease over worry or frustration with symptom management, uncertainty from not knowing when MS symptoms will "flare up" again, or loss of previously-enjoyed activities (Strathopoulou, Christopoulos, Soubasi, & Gourzis, 2010). As many of 50% of all individuals diagnosed with MS will also be diagnosed with Major Depressive Disorder, or will have at least one identifiable depressive episode at some point during the course of their illness (Minden et al., 2014). Many more individuals (beyond the 50%) indicate subclinical symptoms of depression, or report difficulty coping with emotion regulation stemming from depressive thoughts about MS, how the disease has affected them, or thoughts relating to any other symptom of MS (e.g. loss of motor control) that may be present (Pomili et al., 2012).

Other symptoms of MS include reduced or impaired visual acuity, diminishing motor control, and cognitive deficits (Genova, DeLuca, Chiaravalloti, & Wylie, 2013). Slowed information processing speed is the primary cognitive deficit observed by clinicians

(Archibald & Fisk, 2000; Parmenter, Shucard, & Shucard, 2007; Rao, St. Aubin-Faubert, & Leo, 1989), and this symptom occurs early in the progression of MS (Hughes, Denney, & Lynch, 2011; Kail, 1998). For individuals with MS, assessing changes in information processing is not only helpful in monitoring disease progression, but is instrumental for determining treatment strategies (Denney, Gallagher, & Lynch, 2011; Hughes et al., 2011; Kujala, Portin, Revonsuo, & Ruutiainen, 1994).

Fatigue in Multiple Sclerosis

Fatigue, described as an "overwhelming feeling of tiredness, including a reduced or absent sensation of energy" (Ward, 2013, pp. 1-2), is frequently reported as one of the most pervasive symptoms of multiple sclerosis (DeLuca, 2005). Many patients report that fatigue is one of the most difficult-to-manage symptoms of MS (Skerrett & Moss-Morris, 2006), and that its presence adds to the difficulty in coping with other symptoms (Rendas-Baum, Yang, Cattelin, Wallenstein, & Fisk, 2010). It is frequently listed as a secondary factor that may influence neuropsychological test performance (Bruce, Thelen, & Westervelt, 2013), potentially confounding assessments used to measure the impact of MS symptoms. Fatigue often occurs as a side effect of medication designed to manage symptoms of MS (Csatho et al., 2012; Thelen, Lynch, Bruce, Hancock, & Bruce, 2014), and has been found to predict medication adherence (Knoop et al., 2012; Wicks, Massagli, Kulkarni, & Dastani, 2011). Whether the appearance of fatigue was attributed to any comorbid disorder, the primary diagnosis, or both, fatigue has an impact on symptom management strategies (Feinstein, 2004), and how fatigue is perceived to impact daily functioning varies from individual to individual (Cockshell & Mathias, 2013; Csatho, van der Linden, Hernadi, Buzas, & Kalmar, 2012; Skerrett & Moss-Morris, 2006).

Within the clinical literature, fatigue is usually classified into one of several subtypes. Fatigue perceived by the individual (e.g. "I am tired," or "I feel exhausted") usually refers to *central* fatigue, as opposed to *peripheral* fatigue (Ward, 2013). The term "motor weakness" is sometimes used instead of peripheral fatigue (Chaudhuri & Behan, 2000, e.g.), distinguishing centrally-felt "fatigue" from the sensation of muscular "wear and tear" ("My legs are tired") following physical exertion or mechanical energy expenditure. Fatigue may be classified as either *primary* or *secondary*, depending on the temporal ordering of symptoms as they were presented or are experienced (Strober & DeLuca, 2013). For example, individuals with MS who report high levels of fatigue, in the absence of any other explanation, are said to be experiencing primary central fatigue associated with the disease. If an individual with MS reports fatigue existing with a cluster of other symptoms related to another co-morbid disorder (e.g. depression), then depression (in this case) is a primary symptom, and central fatigue is a secondary symptom of MS. Additionally, central fatigue can be experienced either as *physical* fatigue ("lack of energy", regardless of the presence of any peripheral fatigue), *cognitive* fatigue (slowed thinking), or *social* (or *emotional*) fatigue (difficulty regulating one's feelings; Bruce, Bruce, & Arnett, 2010; Knoop et al., 2012). Each of these three domains may be uniformly or differentially experienced, and they all combine to form an individual's overall perception of central fatigue (Csatho et al., 2012).

Despite some consensus in the identification of the various types of fatigue, objectively defining fatigue remains particularly problematic. Individuals may experience central fatigue differently, with variation or inconsistency due to the highly subjective nature of individual self-reports frequently used for assessment (DeLuca, 2005; Shucard et al., 2004; Walker, Berard, Berrigan, Rees, & Freedman, 2012). The distinction between central

and peripheral fatigue is often unclear, as is determining whether the symptoms of fatigue reported from clinical populations (MS, in particular) are primary or secondary in nature (e.g., Patel, Malhotra, Gottlieb, White, & Hu, 2006; Swerdlow et al., 2003). Fatigue may sometimes be induced during the testing process itself (Ward, 2013), due to the necessary length of some neuropsychological assessments. Fatigue may be included as a covariate in discussing any empirical results obtained (Sáez-Francàs, Hernández-Vara, Roso, Martín, & Brugué, 2013), or it may be described as a potential limitation to generalization (e.g. Bol, Duits, Hupperts, Verlinden, & Verhey, 2010).

At present, the majority of assessments of fatigue and fatigue perception involve either a subjective self-report (Rendas-Baum, et al., 2010), or a measure (e.g. increased reaction time) from which fatigue's effect is inferred (Fogt, Kalns, & Michael, 2010). More recently, research into the nature of fatigue has focused on investigating its neural basis (e.g., Yusuf & Koski, 2013), examining how changes in neural processing relate to, or even *enhance,* the perception of fatigue—regardless of a particular cause. Nonetheless, it remains difficult to consistently disentangle the effects of fatigue from psychological tests, or to objectively assess the construct itself, which thereby limits both the understanding of the effect of fatigue perception as well as research into fatigue's etiology.

Neural Efficiency and the Sensorimotor Network (SMN)

At present, a significant portion of research on the neural basis of central fatigue has examined the relationship between changes in neural processing and fatigue perception. In particular, the individual perception of fatigue is hypothesized to reflect the individual's perceptual awareness of changes in the efficiency of processing within neural substrates (DeLuca, 2005). Whether due to lesions, damage, or otherwise pathological changes to

activation of a given area, changes in the processing efficiency of a given area of the brain are interpreted and "felt" as fatigue specific to the domain (e.g. sensory, motor, cognitive) related to that affected area. This perspective has led researchers to use imaging or evoked potential techniques to investigate patterns of activation in domain-specific areas and to correlate them with self-reported measures of fatigue subtypes (e.g., Engström, Flensner, Landtblom, Ek, & Karlsson, 2013). In reviewing studies of neurobiological correlates of fatigue for varying clinical populations, Hergerl and colleagues (2013) reported no single underlying mechanism consistently related to the perception of fatigue across differing disorders. However, when a specific domain was impacted by the disease or pathology (stroke in the motor cortex, or cortical lesions in the frontal lobe, e.g.), the authors indicated that observed differences in affected areas appear to be related to fatigue *perception*, regardless of the measure used for assessing central fatigue (e.g., lesions in the prefrontal cortex correlating with self-reported cognitive fatigue; Hergerl et al., 2013).

It is this examination of physiological mechanisms related to self-reported fatigue that continues to drive current research into the neural basis of fatigue perception in MS. Using functional magnetic resonance imaging (fMRI) and diffusion tensor imaging (DTI) techniques, Rocca and colleagues (2009) found that levels of "abnormal" connectivity between cortical areas of the sensorimotor network were correlated with disease severity in MS (Rocca et al., 2009). These findings also indicated that observed patterns of activation from compensatory mechanisms projecting into the SMN may be in response to decreased efficiency of sensory processing in this affected network. Continuing this line of research by specifically examining the thalamo-striato-cortical pathway with fMRI during a visually-presented cognitive task, Engström and colleagues (2013) found that for MS participants

10

(*n*=15), differential activation patterns indicated weaker cortical-to-subcortical connections when compared to the control group (*n*=12). Additionally, these between-group differences were strongly correlated with individual fatigue ratings, suggesting that along with the processing of both external (sensory input) and internal (cognition) stimuli during the working memory task, this pathway plays a role in the perception of fatigue (Engström et al., 2013).

Another recent study (Cruz Gómez, Campos, Belenguer, Ávila, & Forn, 2013) examined the relationship between self-reported fatigue and functional connectivity between gray and white matter also using volumetric MRI and fMRI. Similar to the results as above, the findings showed that individuals with MS (*n*=60) reported higher levels of central fatigue when compared to a group of healthy controls (*n*=18), and were more likely to show greater white matter atrophy (decreased volume) the thalamus and in the sensorimotor network (SMN) in general. Individuals with MS who reported lower levels of fatigue had higher functional connectivity in the SMN than individuals with higher reported fatigue, suggesting a relationship between atrophy in this network, the loss of efficient processing (decreased activation), and the perception of the "fatigue sensation" (Cruz Gómez et al., 2013, p.1).

For MS populations, other volumetric and fMRI studies like the ones cited above highlight similar findings, that structural abnormalities and functional deficits within the brain correlate with decreased activation of those affected areas, and that these decreases relate to performance on cognitive assessments and self-reports of symptomology, including fatigue (for review, see Sweet & Vandermorris, 2011). Similarly, studies examining functional connectivity through the use of DTI generally find that both altered structure and decreased activity of white matter networks correlate with self-reported fatigue scores for

individuals with MS (e.g. Pardini, Bonzano, Mancardi, & Roccatagliata, 2010). Despite consistently showing that differences in white matter networks appear to be related to perceived fatigue, the researchers are generally unable to conclude whether fatigue perception is related to structural differences, or if fatigue is more related to changes in the *timing* of activation within those networks.

However, examination of the relationship between fatigue and these timing disruptions, using methodologies that are known to be sensitive to the timing of cortical processing, has received relatively little empirical attention. At present, only one study has employed the use of electroencephalography (EEG) to examine fatigue in MS, concluding that perceived central fatigue was unrelated to sleep patterns and the corresponding EEG activity patterns (Caruso, 1995). A study employing the use of event-related potentials (ERPs) to examine the relationship between cognitive functioning and fatigue was similarly inconclusive: Participant accuracy on an auditory task, as well as reaction time, did not significantly differ for participants with MS, separated into high vs. low fatigue groups, and no correlations were found between motor conduction and reaction time (Sandroni, Walker, & Starr, 1992). Both of the aforementioned studies are indicative of the paucity in the literature of research in the last 25 years employing methodologies with a greater temporal resolution assessing the relationship between fatigue and changes in neural activity.

A recent qualitative review by Yusuf and Koski (2013) looked at a group of 40 papers highlighting research using transcranial magnetic stimulation in order to study the relationship between neural excitability in the CNS and the perception of fatigue in individuals with MS. Decreases in neural excitability following adherence to medication were related to increases in self-reported changes in central fatigue. Induced via exercise,

peripheral fatigue was found not to be related to any observed neural excitability changes, lending support to the notion that central fatigue is the appropriate subtype to be considered for models of neural efficiency (Yusuf & Koski, 2013). Showing support for the neural efficiency hypothesis, the authors concluded that the nature of central fatigue experienced by participants in these studies was related to a loss of efficiency due to temporal changes in the functional connectivity of pathways within the sensorimotor network.

Taken together, the studies above provide evidence of the SMN's role in the neural efficiency hypothesis. Imaging studies would seem to indicate that the perception of fatigue in these populations is related to some degree to functional changes in neural processing within the sensorimotor network. Although fatigue did not appear to be related to behavioral measures (e.g. reaction time) used within the EEG and ERP studies cited above, the authors generally concluded that any underlying changes in neural substrates or temporal processing may have been masked by cortical compensatory mechanisms designed to overcome any "perceived" fatigue originating within the SMN (Caruso, 1995; Sandroni, et al., 1992). Although not yet used to investigate perceived fatigue with this population, startle eyeblink modification (SEM) is another psychophysiological measure that is used to assess the SMN. Along with potentially disentangling the mechanisms mentioned above from automatic sensory processing, modulation of the startle eyeblink reflex may provide convergent validity and a greater understanding of the role that efficiency of the SMN plays in fatigue perception.

Modulation of the Startle Eyeblink Reflex as a Measure of the SMN

The human startle reflex (SR) occurs when the body involuntarily responds to a stimulus, serving a protective function that directs the individual's attention to the presence

of that stimulus. Along with identification of related neural pathways, assessment of the SR allows both researchers and clinicians to infer physiological and psychological processes that may be at work (Valles-Sole, 2012). The startle eyeblink reflex occurs when the orbicularis oculi muscles involuntarily activate in response to startling stimuli. This particular response is advantageous for researchers because the robust reflex action can be reliably induced in a variety of research settings, and with differing sense modalities. For example, the startle eyeblink can occur in response to a puff of air blown toward the corner of the eye, from a rapidly approaching visual stimulus, or in response to a loud, aversive sound. As opposed to eyeblinks stemming from voluntary activation of the eyelid muscles (i.e. intentional closing of the eye), assessment of the startle eyeblink reflex allows researchers to infer psychological processes that may be occurring outside of the individual's awareness or control. Measures used in these assessments include the amplitude (or "strength") of the signal recorded by electromyography (EMG), representing the maximum activation of the eyelid muscles during the eyeblink. Though not reported as frequently in the literature as amplitude, the latency of the eyeblink refers to the difference between the onset of the startle stimulus and the subsequent blink. Although there is some overlap in the individual variation of these measures, amplitude and latency measures seem to reflect different aspects of SMN processing. While both reflect the efficiency of the network, latency seems to be more related to the timing of processing within the SMN (Vrana, 1995). Examination of between-group differences of these measures, along with individual variation and changes over time, allows researchers to identify potential neurological phenomena related to presentation of the startle stimulus (Valles-Sole, 2012), or underlying affective traits that affect automatic attentional processes (Haerich, 1994; Hackley and Graham, 1987).

The amplitude and latency of the startle reflex are reliably modified when a non-startling stimulus, termed a "prepulse," presented just prior to the startle stimulus onset. Measures obtained using this protocol are generally referred to as measures of Startle Eyeblink Modification (SEM). The underlying psychological processes that are thought to be at work depend largely on several factors. Changes in blink measures may be related to participant characteristics (e.g. a clinical population versus a control group), the modalities of the startle stimulus and/or the prepulse, modulation of blink measures observed by systematically varying the interval between the prepulse and the startling stimulus (termed the stimulus onset asynchrony, or SOA), or any combination thereof (Blumenthal et al., 2005; Dawson, Schell, Swerdlow, & Filion, 1997). Within-group studies have reliably reported differences in blink response characteristics due to the sense modalities (e.g., a loud sound vs. a sudden puff of air near the eye) of the stimuli used, emotional characteristics of the stimuli used (e.g., differently-valenced pictures used as prepulse stimuli) and emotional states of an individual (e.g., individuals with differing state or trait affect). Additionally, research using what are termed "short lead intervals" (SOAs usually 30-500ms), generally finds that the amplitude of the eyeblink is attenuated or "inhibited" as a function of the SOA, with maximum inhibition occurring around 100-120ms.

Although the neural pathway responsible for the acoustic startle response is relatively simple, extending from the cochlear nucleus to the caudal pontine reticular nucleus, and then outputting through the spinal cord to the orbicularis oculi; the pathway(s) responsible for modifying this response are more complex. Varying with the prepulse modality, the signal from the prepulse stimulus is transduced to the brain from the respective sense organ, entering the sensorimotor network through the thalamo-striato-cortical pathway. Coupled

15

with additional "hard-wired" cortical projections from what Swerdlow (2013) terms "forebrain circuitry" (p.1150), inhibitory processes are then projected onto the pons, attenuating the amplitude and shortening the latency of the subsequent response once the signal from the startle stimulus arrives. Frequently referred to as prepulse inhibition (PPI), this robust effect is thought to reflect a protection of sensory processing, in which sensory information from the startle stimulus is "gated" to allow processing of the prepulse stimulus with minimal disruption (for comprehensive review, see Filion, Dawson, & Schell, 1998).

Demonstrating utility for clinical populations, SEM/PPI has been used for assessing sensorimotor differences between controls and groups of individuals with Alzheimer's disease or dementia (Ueki, Goto, Sato, Iso, & Morita, 2006), Huntington's disease (Swerdlow et al., 1995), fragile-X syndrome (Schneider et al., 2012), hyperekplexia (Brown et al., 1991), schizophrenia (Dawson, Hazlett, Filion, Nuechterlein, & Schell, 1993), and Parkinson's disease (Nakashima, Shimoyama, Yokoyama, & Takahashi, 1993). For SOA intervals between 30-500ms (termed "short lead" intervals), findings in the literature suggest that modification of the subsequent response characteristics are less likely due to cognitive differences (Bitsios, Giakoumaki, Theou, & Frangou, 2006), or volitional attention of the individual. Rather, findings consistently suggest that observed differences in responses at these short lead intervals are more due to state/trait emotionality, automatic preattentive processes, and the functionality of those processes within the sensorimotor network (Corr, Tynan, & Kumari, 2002; Dawson et al., 1997; Swerdlow et al., 2003).

The studies listed above are each examples of the relationship between efficiency in the SMN and sensorimotor gating. Here, differences in the "general ability to inhibit external stimuli" (Filion et al., 1998, p.7) can be indexed by differences in PPI. For example,

16

Zoetmulder and colleagues (2014) found that for 38 individuals diagnosed with Parkinson's disease, better performance on measures of processing speed and attention were associated with greater inhibition of the startle eyeblink response amplitude, compared to worse performers (Zoetmulder et al., 2014). Along with Parkinson's disease, research has shown that a range of other "gating disorders," such as schizophrenia, Huntington's disease, Tourette's syndrome, and obsessive-compulsive disorder each show decreased PPI when compared to healthy controls (for review, see Geyer, Krebs-Thomson, Braff, & Swerdlow, 2001). Regardless of disorder-specific etiology, these results indicate that disruptions in inhibitory processes represent a lack of efficiency in sensorimotor gating, and that this inefficiency can be reliably indexed by assessing PPI differences.

Even though a significant majority of studies assess PPI differences via changes in the amplitude of the modulated eyeblink response, studies that include response latency have shown that it too is modulated in the presence of a prepulse stimulus (Bolino et al., 1993; Filion et al., 1998). PPI studies including latency as a measure have shown it to be reliably modified (lengthened) for populations of adults with schizophrenia (Hasenkamp et al., 2010; Swerdlow et al., 2007), children with autism spectrum disorder (Yuhas et al., 2011), and elderly participants (Salem et al., 2011). Onset latency differences have been shown to relate to measures of sensory processing speed for individuals with Huntington's disease (Swerdlow et al., 1995), individuals with schizophrenia responding to environmental toxins (Pearce et al., 2013), and healthy college-age students (Rissling, Dawson, Schell, & Nuechterlein, 2005). A study by Salem and colleagues (2011) found that differences in the white matter circuitry within the startle response network affected the latency of the startle response. They concluded that the circuitry involved was "more rapidly initiated" (p. 314) in trials which

contained a prepulse stimulus, lending support to the idea that latency modulation reflects changes in the temporal ordering of the processes for modulating the subsequent startle response measure, independent of how the "strength" (amplitude) of the response was modulated (Salem, et al., 2011). The findings from these studies all suggest that latency may be sensitive to changes in sensorimotor processing across a variety of both neurological as well as neurodevelopmental disorders.

Summary and Hypotheses

Multiple sclerosis is a neurological disorder whose varying symptoms frequently include fatigue and disruptions in sensorimotor processing. At present, it is unclear precisely how these two symptoms are related. Research using imaging techniques shows decreased activation in the sensorimotor network (SMN) to be correlated with perceived fatigue, although studies employing more temporally-sensitive measures (i.e. EEG, ERP) are inconclusive in elucidating this relationship. Operating within the neural efficiency hypothesis, these studies would indicate that loss of functionality, individual lesion load, or otherwise slowing of SMN processing due to MS would effectively change the neural activity within this network. Resulting changes in activity, therefore, effectively decrease the efficiency of neural processing, despite any compensatory or effortful processes indexed from measures of cortical projections which would mask such change in bottom-up efficiency. In the present study, the startle eyeblink modification technique, in which changes in the reflexive motor responses are known to vary with the relative timing of antecedent sensory information, was used to investigate the relationship processing in the SMN fatigue, from a clinical population for whom pervasive fatigue symptoms and deficits in sensorimotor efficiency are well-documented.

Participants with a diagnosis of MS had their amplitude and latency responses measured across several short-lead interval conditions, and those were compared to measures of perceived fatigue. It was hypothesized that amplitude and onset latencies of modulated startle eyeblink responses would significantly correlate with one or more subscales of perceived fatigue (physical, cognitive, social), assessed via self-report for participants with MS. In order to examine the effect of MS on these correlations, the same measures were taken from an age-matched control group. Since the startle eyeblink is in response to an acoustic stimulus, and acoustic pathways are not known to be impacted in individuals with MS, it was not expected that baseline (i.e., no visual prepulse to modify the response) blink amplitudes or onset latencies would be significantly different between the two groups. However, response amplitudes were expected to follow the pattern of prepulse inhibition for short lead intervals for all participants, and that the observed PPI would be significantly less pronounced for the MS group. Similarly, onset latencies of eyeblink responses to the startle stimulus following the visual prepulse stimuli were expected to be effectively delayed at each SOA interval when compared to the same intervals from control group participants.

CHAPTER 3

METHOD

The present study was conducted using data from the completed study

Psychophysiological Assessment of Sensory Processing Speed in Multiple Sclerosis

(Lovelace & Bruce, 2010; SSIRB # 090810). This section describes the participants,

measures, and the startle eyeblink protocol that were used in gathering the data.

Participants

Participants ($N=69$) were recruited from a clinic specializing in the treatment of

individuals diagnosed with multiple sclerosis (MS) from the University of Kansas Medical

Center, under the direction of Dr. Sharon Lynch, as well as from flyers and on-line

advertisements at the University of Missouri - Kansas City (UMKC) and the surrounding

community. Participants were selected based on self-identification of diagnosis of MS (for

participants in the experimental group), as well as meeting the inclusion criteria of being

between the ages of 25 and 70, no history of learning disability or severe vision problems, no

significant past or present alcohol or drug use, no severe psychiatric or neurological

conditions (aside from MS), and no past brain injury, disease, or complications. MS

diagnosis ($n=45$) and disease subtype were confirmed using accepted criteria (Polman et al.,

2011). One participant in this group was excluded from the present study due to failing to

meet inclusion criteria, and therefore will not be included in future descriptive statistics or

analyses. The remaining sample (n=44) of the MS Group was between the ages of 28 and 69

($M=46.87$, $s=9.38$); was 86.4% female (n=38), and 13.6% male (n=6); with 86.4% (n=38)

indicating "white" as his or her race/ethnicity, 9.1% (n=4) indicating "African-American",

and 4.5% (n=2) indicating "Hispanic/Latino."

Participants without a diagnosis of multiple sclerosis (n=24) were selected based on the above inclusion criteria, and identified as the "Control Group." These participants' ages ranged between 30 and 58 (*M*=46.01, *s*=8.94); were 87.5% female (n=21) and 12.5% male (n=3); and 95.8% (n=23) identified his or her race/ethnicity as "white", with 4.2% (n=1) as "African-American".

All participation was voluntary. Each participant was informed to the purpose of the study, and signed consent. At the conclusion of the study, each participant was paid $100 in exchange for his or her participation.

Design and Measures

The study *Psychophysiological Assessment of Sensory Processing Speed in Multiple Sclerosis* used a two-group, quasi-experimental mixed design, with all participants assessed on all measures used.

Each participant in the study completed a battery of neuropsychological testing following completion of a short demographic questionnaire, in which he or she provided a list of all current medications taken (if any). The neuropsychological test battery consisted of several self-report surveys, a short psychiatric interview, and a comprehensive set of cognitive assessments to determine cognitive performance and perceived deficits.

The Modified Fatigue Impact Scale (MFIS): A 21-item version of the (40-item) questionnaire frequently used in assessing the effect of fatigue on daily functioning for individuals with MS was administered to each participant during the self-report phase of the testing session. Each item assesses the individual's perceived impact of fatigue on a given activity (e.g. "Because of my fatigue, I have been less alert"; "…I have had difficulty paying attention for long periods of time."), with each participant indicating his or her level of

agreement with each statement via a 5-point Likert scale (0 = "Never"; 4 = "Almost Always"). The MFIS is composed of 3 subscales measuring physical, cognitive, and social fatigue, and has well-documented validity and reliability (Mills, Young, Pallant, & Tennant, 2010; Rendas-Baum, Yang, Cattelin, Wallenstein, & Fisk, 2010). For the present study, the MFIS was used to index each participant's level of perceived fatigue in the domains measured in each of the subscales, as described above.

The startle eyeblink modulation (SEM) of each participant was measured via electromyography (EMG) from two electrodes placed under each participant's left lower eyelid muscle (orbicularis oculi). Another electrode was placed on the left temple, to provide a reference ("ground") for the EMG signal. Signals were amplified and recorded according to established guidelines and practices (Blumenthal et al., 2005). Data for each trial included onset latency, peak latency, and eyeblink amplitude.

Each eyeblink was induced in response to acoustic startle stimuli consisting of brief (50ms), loud (105 dB) bursts of noise. In trials involving a visual prepulse, those stimuli were presented via a brief (20ms) dim (14 μcd) pulse of light from a small light-emitting diode (LED). Prepulses occurred at one of five intervals: 0ms, 50ms, 100ms, 150ms, or 200ms prior to the startle stimulus. Additionally, startle trials involving no prepulse were also recorded, in order to provide each individual with a baseline startle eyeblink response. Including this baseline condition, there were three trials of each interval condition, for a total of 18 trials per run. Trials were randomized across each run, and participants completed two runs for the study.

CHAPTER 4

RESULTS

Correlation of Perceived Fatigue Measures

To test the hypothesis that modulated startle eyeblink amplitudes and onset latencies were related to measures of perceived fatigue, participant SEM responses were compared to their respective totals on each MFIS subscale. Due to the positively skewed nature of these fatigue data for the MS group, MFIS scores from each fatigue subtype and SEM measures were assessed by computing Spearman correlations. For individuals with MS, there were no significant correlations between the amplitude at each interval and the fatigue measures (all ps> .05). Similarly, onset latencies from each interval were not correlated with either cognitive or social fatigue. However, significant correlations were observed between physical fatigue at the 0ms interval condition: $\rho(29) = .358$, $p = .05$; the 100ms condition: $\rho(29) = .357$, $p = .05$; and the 200ms condition: $\rho(29)= .434$, $p = .02$.

In order to examine if this same relationship extended to a non-MS population, Control group fatigue scores were first compared to the scores from the MS group on each of the MFIS subscales. Not surprisingly, independent-samples t-tests revealed that perceived physical fatigue was significantly greater for MS participants that it was for the Control group*: $t(47) = 8.89$, $p < .001$*. Cognitive fatigue [$t(47) = 6.76$, $p < .001$] and social fatigue [$t(47) = 6.35$, $p < .001$] were also significantly greater, meaning that individuals with MS report more perceived fatigue, across the three fatigue domains, than similar individuals without MS. However, perceived fatigue did not appear to be related to either amplitude or onset latency for control participants. Correlational analysis showed that there were no

23

significant correlations between SEM measures and any of the fatigue measures with the Control group (all ps> .05).

Baseline Startle Eyeblink Amplitude

To examine whether baseline (i.e. no visual prepulse) amplitudes of the startle eyeblink were significantly different between the MS and Control groups, group differences in startle amplitude in the baseline condition were compared: $t(47) = 1.20, p = .238$. Transforming the data to correct for non-normality did not affect the result; all ps = n/s. The non-significant findings indicated that the strength of the blink response to the acoustic startle stimuli alone did not differ between groups. Consistent with a priori predictions, this suggested no fundamental between-group difference in the physiological mechanisms behind this eyeblink reflex response.

Baseline Startle Eyeblink Onset Latency

To examine whether baseline (no prepulse) onset latencies of the startle eyeblink were significantly different between the MS and Control groups, group differences in startle onset latency in the baseline condition were compared: $t(47) = 1.39, p = .172$. The non-significant finding indicated that the onset of the blink response to the acoustic startle stimuli alone did not differ between groups, again suggesting no fundamental difference in the mechanism behind this measure of the eyeblink reflex response, consistent with *a priori* predictions.

Modulated Startle Eyeblink Amplitude

Eyeblink amplitudes in response to the startle stimulus following a prepulse were assessed for all conditions (intervals) in which a prepulse was present. The amplitudes for each participant in both the MS group and Control group were submitted to a Group X

Condition repeated-measures ANOVA. As anticipated, the main effect of interval was significant, $F(4, 184) = 5.72$, $p < .001$. However, the main effect of Group was not significant, nor was the Group X Condition interaction, both $p > .05$. Repeating the analysis using log-corrected values for each amplitude yielded the same results. Further post-hoc analysis of the mean amplitude at each condition revealed not only were there no group differences at each condition, but that eyeblink amplitudes were modified contrary to expectation. This anomalous finding would suggest that the presence of the prepulse facilitated (rather than inhibited) the amplitude of the startle eyeblink response in this case.

Modulated Startle Eyeblink Onset Latency

To test the hypothesis that modulated onset latencies would differ between groups, onset latency data from each of the prepulse conditions were submitted to a Group X Condition repeated-measures ANOVA (see *Figure 2*). As with amplitude, results revealed a significant main effect of Condition, $F(4,184) = 16.37$, $p < .001$ as expected, and that group (MS vs. Control) and interaction effects were not significant. These results would indicate that only prepulse interval significantly affected the observed onset latency. However, as seen in Table 1, overall onset latencies for the MS group showed smaller attenuation than those of the control group, as well as consistently-differing ranges of score values at each interval. Post-hoc comparison of onset latencies at each interval separately revealed a significant difference in onset latency at the 100ms interval condition: $t(47) = 2.13$, $p = .04$, when unequal variances were assumed.

25

Blink Onset Latency By Group
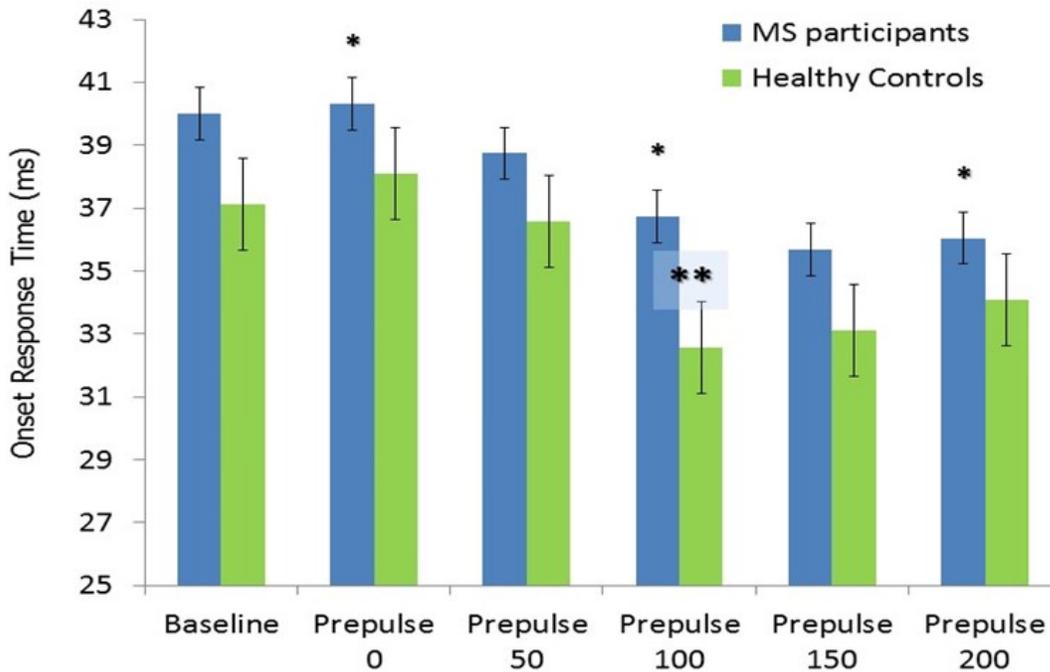
Figure 2: Group differences in startle eyeblink reflex latency at baseline and SOAs. The pattern of latency modification indicates MS participants overall were closer to baseline response than their control counterparts. Group responses were significantly different at the SOA 100ms interval, where the maximum effect of the prepulse is typically observed in PPI studies. Significant correlations between perceived fatigue of the MS group and onset latencies were observed at the 0ms (simultaneous presentation), 100ms, and 200ms SOA intervals. For individuals with MS, this finding would indicate a decreased efficiency in processing of the visual prepulse prior to the introduction of the startle stimulus, in support of the neural efficiency model of fatigue.

Note: * $p \leq .05$, ** $p = .04$

Table 1

Startle eyeblink onset latency means (M), standard deviations (SD), and ranges (with minimum and maximum values) for both MS participants and controls, at each of the prepulse conditions (baseline = no prepulse).

	Condition	*M*	*SD*	Range	Min	Max
MS	*Baseline*	40.001	7.367	30.25	27.25	57.50
(N=31)	*SOA0*	40.323	7.643	29.50	26.50	56.00
	SOA50	38.742	7.081	29.00	27.00	56.00
	SOA100	36.742	8.692	32.50	23.20	55.75
	SOA150	35.667	7.662	32.50	22.00	54.50
	SOA200	36.048	8.226	30.50	23.50	54.00
Control	*Baseline*	37.125	6.278	23.75	27.00	50.75
(N=18)	*SOA0*	38.097	6.156	22.50	27.25	49.75
	SOA50	36.569	5.708	23.00	28.75	51.75
	SOA100	32.569	5.043	16.00	25.75	41.75
	SOA150	33.111	4.352	18.25	23.75	42.00
	SOA200	34.083	7.902	31.00	24.00	55.00

Note: Latency values are measured in milliseconds (ms) following the presentation of the startle stimulus. Groups were significantly different at SOA100: $t(47) = 2.13$, $p = .04$; unequal variances assumed.

27

CHAPTER 5

DISCUSSION

Summary of Findings

The purpose of the present study was to investigate the relationship between startle eyeblink modulation (SEM) and perceived fatigue in individuals with multiple sclerosis (MS). Participants were assessed on their perceived fatigue via completion of the modified fatigue index scale (MFIS), and on their individual levels of efficiency of the sensorimotor network (SMN) via the SEM paradigm. It was hypothesized that individuals with MS would show significant correlations between measures of SEM and one or more measures of self-reported fatigue. For participants with a diagnosis of MS, perceived physical fatigue was significantly correlated with onset latency, indicating that fatigue perception may be related to disruption of efficient processing within the sensorimotor network (SMN). By correlating latency changes with measures of perceived fatigue, the present study not only shows support for the proposed hypothesis that those two measures are related, but also for hypotheses that fatigue perception is related to neural efficiency.

In order to explore further this relationship, the relationship of these measures to a control group was also examined. As expected, MFIS subscale measures significantly differed for MS participants when compared against the Control group, showing greater perceived impact of fatigue for the MS participants. Differences in baseline eyeblink amplitude and onset latency were not observed, indicating no fundamental difference between groups in the startle response mechanism. Although eyeblink response amplitude was significantly modulated at each prepulse interval for all participants, these modified responses did not differ between groups, contrary to expectation. This finding may indicate

28

that since SEM of amplitude reflects processing in the SMN in terms of stimulus impact, the degree of processing efficiency was not related to fatigue. For example, if the visual stimulus would produce, on average, a 50% PPI in a control group at a specific lead interval, but produces 25% PPI in a clinical sample at that same lead interval, then this would indicate an impairment in the efficiency of the SMN, in that the prepulse stimulus did not have the same impact. However, this was not the case here. Observed onset latency at each interval showed a similar pattern to that of amplitude, with prepulse interval significantly affecting the onset response. The pattern of data here indicate that the timing of processing was disrupted between the groups, thereby reflecting a difference in processing efficiency in terms of stimulus timing. If the visual prepulse produces the greatest attenuation (shortest) at the 100ms lead interval for a control group, but produces the shortest latency at a later lead interval for a clinical sample, then this would indicate impairment in the speed of transmission of sensory signals within the SMN. In other words, the processing of the prepulse would take longer to have its impact.

This effective lengthening of the prepulse interval was observed in the present study. Assuming unequal variances in onset latency, the MS group significantly differed from the control group at the 100ms SOA interval. In support of the aforementioned hypothesis, the onset latency at this interval, along with those from the 0ms and 200ms intervals (the minimum and maximum intervals used in this study respectively) were each significantly correlated with perceived physical fatigue for the MS participants. Taken together, these results suggest that the mechanisms at work within the sensorimotor network that effect SEM operate differentially for individuals with MS when compared against control participants,

29

and that these differences are related to perceived physical fatigue, showing support for a neural efficiency model of fatigue.

Limitations

This study is not without several limitations. As stated above, results of amplitude modulation were contrary to expectation based on repeated findings in the literature using short-lead interval PPI designs. More research is needed to effectively elucidate the distinction between effects generated by a passive prepulse and any carryover effects from the startle stimulus in previous trials. It's noteworthy that nearly every study of PPI has directed participant attention to the prepulse in some fashion (Dawson et al., 1997, Filion et al., 1998; Lipp et al., 2001), so consistently controlling attention in some uniform fashion may help future PPI studies disentangle effects from any carryover effects as well as allow for better between-group assessments. Additionally, the psychological significance of onset latency modulation is not well supported in the literature. It would be the recommendation of this author that future PPI studies, as well as SEM in general, incorporate onset latency into their analyses, so that this effect in general, as well as differences from amplitude modulation can be noted and better understood. Finally, the effects observed are very small in nature, and a high degree of variability in these psychophysiological measures exists between individuals (Blumenthal et al., 2005). Any present effects may have been masked altogether, and a the number of correlations involved in finding the prepulse interval conditions associated with the different fatigue measures may have inflated the possibility of Type I error. In both of these cases, specifying the hypothesized relationship between the given constructs (as well as a larger sample size) in future studies of onset latency would address this.

Implications and Conclusion

It is unclear why individuals with MS are impacted by perceived fatigue so pervasively (DeLuca, 2005). Recent research into the neural basis of fatigue has led to the development of neural efficiency hypotheses, in which changes in the efficiency of processing within the sensorimotor network are thought to predict the sensation of fatigue felt by the individual (Hergerl et al., 2013). Therefore, closer examination of the particular subtype of fatigue (e.g. physical, cognitive) reported by the individual may allow researchers or clinicians to infer intra-individual differences in processing, and therefore identifying potentially affected areas which are no longer operating efficiently (Cruz Gómez et al., 2013; Engström et al., 2013; Yusuf & Koski, 2013).

As expected, control participants did not show a significant relationship between measures of SMN efficiency and fatigue, possibly due to floor effects for the fatigue measures frequently observed when assessing non-clinical populations (DeLuca, 2005). For the MS participants, significant correlations between physical fatigue and onset latency were observed at the three intervals representing the shortest SOA (0ms), the longest SOA (200ms), and the interval within the range where maximum effect of short lead modification is typically seen (100ms SOA). These findings indicate that the higher the score of self-reported physical fatigue that was reported, the greater the time needed for blink onset, despite any difference of latency when compared to baseline in response to the visual prepulse.

Since the auditory pathway has not been shown to be affected by individuals with MS (Archibald & Fisk, 2000; Diamond, DeLuca, Kim, & Kelley, 1997), the observation that differences were not observed in baseline startle eyeblinks is not surprising. Had differences

here been observed, they possibly would have been due to the mechanisms involved in the elicited response originating in the pons and propagating through the brainstem (Brown et al., 1991). However, this change in reflex action was not observed in this case.

Therefore, observed changes in blink responses can be inferred to be related to the introduction of the visual prepulse stimulus used in this study. Examination of modulated differences influenced by the presence of this "prepulse" has been reliably shown to indicate psychological differences between individuals and groups of individuals (Filion et al., 1998). As in the case of the present study, research using short lead intervals has identified the phenomenon of prepulse inhibition (PPI), in which processing of the startle stimulus is effectively inhibited by the "gating process" (Swerdlow, 2013, p.1151) begun by prepulse processing. Inhibition is assessed by measuring changes in eyeblink amplitude in a significant majority of PPI studies, with the latency of the eyeblink onset receiving what Filion (1998) identifies as "little (empirical) attention" (p.4). Nonetheless, studies including onset latency as a dependent measure have shown that latency is also modulated due to the presence of the prepulse, although the factors influencing latency modulation (possibly different than those influencing amplitude) are not as clear (e.g., Braff, Grillon, & Geyer, 1992), or more related to an attentional salience (Vrana, 1995). In this light, these findings are not wholly surprising, since the stimuli used as short-lead prepulses were emotionally-neutral and did not require a reorienting of attention on the participant's part. The present study contributes to this body of literature by examination of both of these measures within a single study.

There were no significant differences between individuals with MS and healthy controls in modulated amplitude at any of the SOA intervals. Curiously, response amplitude

appeared to be *greater* following the introduction of the prepulse stimulus, following the general pattern seen in "long-lead" SEM studies. Thought to be due to emotional potentiation or a priming effect, these studies generally examine how aversive prepulse stimuli (usually a negative affective picture) enhances or "facilitates" the amplitude of the startle response (Bőhmelt et al., 1999; Dawson et al., 1997; Filion et al., 1998; Lipp et al., 2001). Since the prepulse stimulus used in this study required little cognitive or emotional input for processing, it's possible that the aversive startle stimulus effectively primed participant responses from one trial to the next, acting as a sort of "long-lead" prepulse with the effective SOA equal to the inter-trial interval. However, this supposition would require further testing.

Onset latencies differed for all participants based on the interval of the preceding prepulse. As cited previously, these modulated changes appear to be more related to the timing between prepulse and startle stimuli, and the present study would appear to support this finding. Correcting for significantly differing variances in onset times at each SOA interval, between-group onset latencies significantly differed at the 100ms interval. Since the maximum effect of the prepulse on the amplitude of the startle stimulus in short-lead interval studies has been shown to occur around 100-120ms (Blumenthal et al., 2005; Dawson et al., 1997; Lipp et al., 2001), together these findings would suggest that the timing of this interval is related to the maximum effect observed in these SEM measures, although the processes responsible for those effects may be different. Although there was not a significant overall main effect of group for the MS and control group participants, MS participants showed a general greater delay in onset times than the controls (see *Figure 2* and Table 1).

This study nonetheless contributes to the literature by examining a population which, to the best of my knowledge, has not previously been studied with these particular measures and analyses. Since MS participants in the present study were assessed with a short lead interval paradigm (thereby limiting cognitive influence), and only had to attend to the onset of the visual prepulse (with no other task demands), the results presented here suggest a possible relationship between processing within the sensorimotor network and perceived physical fatigue for this population. Consistent with neural efficiency hypotheses of fatigue (DeLuca, 2005; Engström et al., 2013; Hergerl et al., 2013) changes in the functionality or efficiency of the gating mechanism within this network might be simultaneously measured as differences in the (expected) modification of the startle eyeblink response, as well as an increase in fatigue perception. Examination of both self-reported fatigue and changes in acquired blink onset data will help in understanding the relationship between the delivery of sensory information to the SMN and the nature of perceived fatigue. Additionally, information about SEM and blink characteristics of individuals with MS, and how those differ from healthy controls, may allow for a better understanding of the interaction between the differential processes and neural pathways responsible for the variability in observed outcomes. Since the length of the interval between the prepulse and startle stimulus would modulate the subsequent eyeblink response, and the prepulse stimulus is presented visually, differences in visual processing in the SMN will differentially affect the expected blink modification. Since the auditory neural pathway is not as vulnerable to the effects of MS to the same degree as the visual pathway (Diamond et al., 1997), assessing changes by either comparing the individual's SEM to a control value or their own baseline could therefore

allow for a greater understanding of the progression of vision-related symptoms, along with assessing fatigue's impact on other visually-driven assessments.

Finally, continued support of the hypotheses would indicate that assessing fatigue objectively while potentially disentangling its impact from performance measures would not only be clinically beneficial, but would allow for a greater understanding of the potentially bi-directional nature of fatigue in general. More light will be shed on its role in efficient sensory information processing, as well as the relationship this effect has with an individual's perception of fatigue symptoms.

REFERENCES

Archibald, C. J., & Fisk, J. D. (2000). Information processing efficiency in patients with multiple sclerosis. *Journal of Clinical and Experimental Neuropsychology*, *22*(5), 686-701. doi:10.1076/1380-3395(200010)22:5;1-9;FT686

Bitsios, P., Giakoumaki, S. G., Theou, K., & Frangou, S. (2006). Increased prepulse inhibition of the acoustic startle response is associated with better strategy formation and execution times in healthy males. *Neuropsychologia*, *44*(12), 2494-2499. doi:10.1016/j.neuropsychologia.2006.04.001

Blumenthal, T. D., Cuthbert, B. N., Filion, D. L., Hackley, S., Lipp, O. V., & van Boxtel, A. (2005). Committee report: Guidelines for human startle eyeblink electromyographic studies. *Psychophysiology, 42*(1), 1-15. doi:10.1111/j.1469-8986.2005.00271.x

Bőhmelt, A. H., Schell, A. M., & Dawson, M. E. (1999). Attentional modulation of short- and long-lead-interval modification of the acoustic startle eyeblink response: Comparing auditory and visual prestimuli. *International Journal of Psychophysiology*, *32*(3), 239-250. doi:10.1016/S0167-8760(99)00019-7

Bol, Y., Duits, A. A., Hupperts, R. M., Verlinden, I., & Verhey, F. J. (2010). The impact of fatigue on cognitive functioning in patients with multiple sclerosis. *Clinical Rehabilitation*, *24*(9), 854-862. doi:10.1177/0269215510367540

Bolino, F., di Michele, V., Manna, V., di Cicco, L., Isidori, M. V., & Casacchia, M. (1993). Acoustic and electrically elicited startle reaction: Similar patterns of habituation and reflex modifications in humans. *International Journal of Neuroscience*, *73*(1-2), 13-21. doi:10.3109/00207459308987207

Braff, D., Grillon, C., & Geyer, M. (1992). Gating and habituation of the startle reflex in

  schizophrenic patients. *Archives of General Psychiatry, 49*, 206-215.

Brown, P., Rothwell, J. C., Thompson, P. D., Britton, T. C., Day, B. L., & Marsden, C. D.

  (1991). The hyperekplexias and their relationship to the normal startle reflex. *Brain,*

  114(4), 1903-28.

Bruce, J. M., Bruce, A. S., & Arnett, P. A. (2010). Response variability is associated with

  self-reported cognitive fatigue in multiple sclerosis. *Neuropsychology, 24*(1), 77-83.

  doi:10.1037/a0015046

Bruce, J. M., Thelen, J. M., & Westervelt, H. J. (2013). Secondary influences on cognition in

  multiple sclerosis. In P. A. Arnett, P. A. Arnett (Eds.) , *Secondary influences on*

  neuropsychological test performance: Research findings and practical applications

  (pp. 203-227). New York, NY, US: Oxford University Press.

Caruso, L. S. (1995, January). Sleep disruption in fatigued versus non-fatigued persons with

  multiple sclerosis. *Dissertation Abstracts International*, *55*, 3041.

Chaudhuri, A., & Behan, P. (2000). Fatigue and basal ganglia. *Journal of Neurological*

  Sciences, 179(1), 34-42. doi:10.1016/S0022-510X(00)00411-1

Chaudhuri, A., & Behan, P. (2004). Fatigue in neurological disorders. *The Lancet,*

  363(9413), 978-988. doi:10.1016/S0140-6736(04)15794-2

Cockshell, S. J., & Mathias, J. L. (2013). Cognitive deficits in chronic fatigue syndrome and

  their relationship to psychological status, symptomatology, and everyday functioning.

  Neuropsychology, *27*(2), 230-242. doi:10.1037/a0032084

Compston, A., & Coles, A. (2008). Multiple sclerosis. *Lancet, 372*, 1502-1517.

  doi: 10.1016/S0140-6736(08)61620-7

Corr, P. J., Tynan, A., & Kumari, V. (2002). Personality correlates of prepulse inhibition of

the startle reflex at three lead intervals. *Journal of Psychophysiology, 16*(2), 82-91.

doi:10.1027//0269-8803.16.2.82

Cruz Gómez, A. J., Ventura Campos, N., Belenguer, A., Ávila, C., & Forn, C. (2013).

Regional brain atrophy and functional connectivity changes related to fatigue in

multiple sclerosis. *PLOS One, 8*(10), 1-8. doi: 10.1371/journal.pone.0077914

Csatho, A., van der Linden, D., Hernadi, I., Buzas, P., & Kalmar, G. (2012). Effects of

mental fatigue on the capacity limits of visual attention. *Journal of Cognitive*

Psychology, 24(5), 511-524. doi: 10.1080/20445911.2012.658039

Dawson, M. E., Hazlett, E. A., Filion, D. L., Nuechterlein, K. H., & Schell, A. M. (1993).

Attention and schizophrenia: Impaired modulation of the startle reflex. *Journal of*

Abnormal Psychology, 102(4), 633-641. doi:10.1037/0021-843X.102.4.633

Dawson, M. E., Schell, A. M., Swerdlow, N. R., & Filion, D. L. (1997). Cognitive, clinical,

and neurophysiological implications of startle modification. In P. J. Lang, R. F.

Simons, M. T. Balaban (Eds.). *Attention and orienting: Sensory and motivational*

processes (pp. 257-279). Mahwah, NJ US: Lawrence Erlbaum Associates Publishers.

Dawson, M. E., Schell, A. M., & Böhmelt, A. H. (1999). *Startle modification: Implications*

for neuroscience, cognitive science, and clinical science. New York, NY, US:

Cambridge University Press. doi:10.1017/CBO9780511665523

DeLuca, J. (2005). *Fatigue as a window to the brain*. Cambridge, MA, US: MIT Press.

Denney, D. R., Gallagher, K. S., & Lynch, S. G. (2011). Deficits in processing speed in

patients with multiple sclerosis: Evidence from explicit and covert measures.

Archives Of Clinical Neuropsychology, *26*(2), 110-119. doi:10.1093/arclin/acq104

Diamond, B. J., DeLuca, J., Kim, H., & Kelley, S. M. (1997). The question of

    disproportionate impairments in visual and auditory information processing in

    multiple sclerosis. *Journal Of Clinical And Experimental Neuropsychology*, *19*(1),

    34-42. doi:10.1080/01688639708403834

Engström, M., Flensner, G., Landtblom, A., Ek, A., & Karlsson, T. (2013). Thalamo-striato-

    cortical determinants to fatigue in multiple sclerosis. *Brain and Behavior, 3*(6), 715-

    728. doi: 10.1002/brb3.181

Feinstein, A. (2004). The neuropsychiatry of multiple sclerosis. *The Canadian Journal of*

    Psychiatry / La Revue Canadienne de Psychiatrie, 49(3), 157-163. ISSN: 1497-0015

Fendt, M., & Yeomans, J. (2001). Brain stem circuits mediating prepulse inhibition of the

    startle reflex. *Psychopharmacology*, *156*(2-3), 216-224. doi:10.1007/s002130100794

Filion, D. L., Dawson, M. E., & Schell, A. M. (1998). The psychological significance of

    human startle eyeblink modification: A review. *Biological Psychology, 47*(1), 1-43.

    doi:10.1016/S0301-0511(97)00020-3

Fogt, D., Kalns, J., & Michael, D. (2010). A comparison of cognitive performance decreases

    during acute, progressive fatigue arising from different concurrent stressors. *Military*

    Medicine, 175(12), 939-944.

Genova, H. M., DeLuca, J., Chiaravalloti, N., & Wylie, G. (2013). The relationship between

    executive functioning, processing speed, and white matter integrity in multiple

    sclerosis. *Journal of Clinical And Experimental Neuropsychology*, *35*(6), 631-641.

    doi:10.1080/13803395.2013.806649

Gewirtz, J. C., & Davis, M. (1995). Habituation of prepulse inhibition of the startle reflex using an auditory prepulse close to background noise. *Behavioral Neuroscience*, *109*(3), 388-395. doi:10.1037/0735-7044.109.3.388

Geyer, M. A., Krebs-Thomson, K., Braff, D. L., & Swerdlow, N. R. (2001). Pharmacological studies of prepulse inhibition models of sensorimotor gating deficits in schizophrenia: A decade in review. *Psychopharmacology*, *156*(2-3), 117-154. doi:10.1007/s002130100811

Hackley, S. A., & Graham, F. K. (1987) Effects of attending selectively to the spatial position of reflex-eliciting and reflex-modulating stimuli. *Journal of Experimental Psychology: Human Perception and Performance, 13*(3), 411-424.

Haerich, P. (1994). Startle reflex modification: Effects of attention vary with emotional valence. *Psychological Science*, *5*(6), 407-410. doi:10.1111/j.1467-9280.1994.tb00294.x

Hasenkamp, W., Epstein, M. P., Green, A., Wilcox, L., Boshoven, W., Lewison, B., & Duncan, E. (2010). Heritability of acoustic startle magnitude, prepulse inhibition, and startle latency in schizophrenia and control families. *Psychiatry Research*, *178*(2), 236-243. doi:10.1016/j.psychres.2009.11.012

Hazlett, E. A., Buchsbaum, M. S., Tang, C. Y., Fleischman, M. B., Wei, T., Byne, W., & Haznedar, M. M. (2001). Thalamic activation during an attention-to-prepulse startle modification paradigm: A functional MRI study. *Biological Psychiatry*, *50*(4), 281-291. doi:10.1016/S0006-3223(01)01094-0

Hegerl, U., Lam, R. W., Malhi, G. S., McIntyre, R. S., Demyttenaere, K., Mergl, R., & Gorwood, P. (2013). Conceptualising the neurobiology of fatigue. *Australian and New Zealand Journal of Psychiatry*, *47*(4), 312-316. doi:10.1177/0004867413481505

Hughes, A. J., Denney, D. R., & Lynch, S. G. (2011). Reaction time and rapid serial processing measures of information processing speed in multiple sclerosis: Complexity, compounding, and augmentation. *Journal Of The International Neuropsychological Society*, *17*(6), 1113-1121. doi:10.1017/S1355617711001135

Kail, R. (1998). Speed of information processing in patients with multiple sclerosis. *Journal Of Clinical And Experimental Neuropsychology*, *20*(1), 98-106. doi:10.1076/jcen.20.1.98.1483

Katz Sand, I. B., & Lublin, F. D. (2013). Diagnosis and differential diagnosis of multiple sclerosis. *CONTINUUM: Lifelong Learning in Neurology, 19*(4), 942-943.

Kisley, M. A., Davalos, D. B., Engleman, L. L., Guinther, P. M., & Davis, H. P. (2005). Age-related change in neural processing of time-dependent stimulus features. *Cognitive Brain Research*, *25*(3), 913-925. doi:10.1016/j.cogbrainres.2005.09.014

Knoop, H., van Kessel, K., & Moss-Morris, R. (2012). Which cognitions and behaviours mediate the positive effect of cognitive behavioural therapy on fatigue in patients with multiple sclerosis? *Psychological Medicine, 42*(1), 205-213. doi:10.1017/S0033291711000924

Kujala, P. P., Portin, R. R., Revonsuo, A. A., & Ruutiainen, J. J. (1994). Automatic and controlled information processing in multiple sclerosis. *Brain: A Journal Of Neurology*, *117*(5), 1115-1126. doi:10.1093/brain/117.5.1115

Lipp, O. V., Blumenthal, T. D., & Adam, A. R. (2001). Attentional modulation of blink

    startle at long, short, and very short lead intervals. *Biological Psychology*, *58*(2), 89-

    103. doi:10.1016/S0301-0511(01)00109-0

Lovelace, C., & Bruce, J. (2010). [Psychophysiological assessment of sensory processing

    speed in multiple sclerosis]. Unpublished raw data.

Mills, R. J., Young, C. A., Pallant, J. F., & Tennant, A. A. (2010). Rasch analysis of the

    Modified Fatigue Impact Scale (MFIS) in multiple sclerosis. *Journal of Neurology,*

    *Neurosurgery & Psychiatry, 81(*9), 1049-1051. doi:10.1136/jnnp.2008.151340

Minden, S., Feinstein, A., Kalb, R., Miller, D., Mohr, D., Patten, S.,…Narayanaswami, P.

    (2014). Evidence-based guideline: Assessment and management of psychiatric

    disorders in individuals with MS. Report of the Guideline Development

    Subcommittee of the American Academy of Neurology. *Neurology, 82*(2), 174-181.

    doi: 10.1212/WNL.0000000000000013

Nakashima, K., Shimoyama, R. R., Yokoyama, Y. Y., & Takahashi, K. (1993). Auditory

    effects on the electrically elicited blink reflex in patients with Parkinson's disease.

    Electroencephalography & Clinical Neurophysiology: Electromyography & Motor

    Control, 89(2), 108-112.

National Multiple Sclerosis Society. (2014). Who Gets MS? (Epidemiology). Retrieved on

    April 2, 2014, from: http://www.nationalmssociety.org/What-is-MS/Who-Gets-MS

Niedziela, N., Adamczyk-Sowa, M., & Pierzchała, K. (2014). Epidemiology and clinical

    record of multiple sclerosis in selected countries: A systematic review. *International*

    Journal of Neuroscience, *124*(5), 322-330. doi:10.3109/00207454.2013.840618

Pardini, M., Bonzano, L., Mancardi, G. L., & Roccatagliata, L. (2010). Frontal networks play a role in fatigue perception in multiple sclerosis. *Behavioral Neuroscience*, *124*(3), 329-336. doi:10.1037/a0019585

Parmenter, B. A., Shucard, J. L., & Shucard, D. W. (2007). Information processing deficits in multiple sclerosis: A matter of complexity. *Journal Of The International Neuropsychological Society*, *13*(3), 417-423. doi:10.1017/S1355617707070580

Patel, S. R., Malhotra, A., Gottlieb, D. J., White, D. P., & Hu, F. B. (2006). Correlates of long sleep duration. *Sleep: Journal of Sleep and Sleep Disorders Research, 29*(7), 881-889.

Pearce, B. D., Hubbard, S., Rivera, H. N., Wilkins, P. P., Fisch, M. C., Hopkins, M. H., & ... Duncan, E. (2013). Toxoplasma gondii exposure affects neural processing speed as measured by acoustic startle latency in schizophrenia and controls. *Schizophrenia Research, 150*(1), 258-261. doi:10.1016/j.schres.2013.07.028

Polman, C. H., Reingold, S. C., Banwell, B., Clanet, M., Cohen, J. A., Filippi, M., & ... Wolinsky, J. S. (2011). Diagnostic criteria for multiple sclerosis: 2010 revisions to the McDonald Criteria. *Annals of Neurology, 69*(2), 292-302. doi:10.1002/ana.22366

Pompili, M., Forte, A., Palermo, M., Stefani, H., Lamis, D. A., Serafini, G., & ... Girardi, P. (2012). Suicide risk in multiple sclerosis: A systematic review of current literature. *Journal of Psychosomatic Research, 73*(6), 411-417. doi:10.1016/j.jpsychores.2012.09.011

Rao, S. M., St. Aubin-Faubert, P., & Leo, G. J. (1989). Information processing speed in patients with multiple sclerosis. *Journal Of Clinical And Experimental Neuropsychology*, *11*(4), 471-477. doi:10.1080/01688638908400907

Rendas-Baum, R., Yang, M., Cattelin, F., Wallenstein, G. V., & Fisk, J. D. (2010). A novel approach to estimate the minimally important difference for the fatigue impact scale in multiple sclerosis patients. *Quality of Life Research: An International Journal of Quality of Life Aspects of Treatment, Care & Rehabilitation, 19*(9), 1349-1358. doi:10.1007/s11136-010-9704-7

Rissling, A. J., Dawson, M. E., Schell, A. M., & Nuechterlein, K. H. (2005). Effects of perceptual processing demands on startle eyeblink modification. *Psychophysiology, 42*(4), 440-446. doi:10.1111/j.1469-8986.2005.00296.x

Rocca, M. A., Absinta, M., Valsasina, P., Ciccarelli, O., Marino, S., Rovira, A., & ... Filippi, M. (2009). Abnormal connectivity of the sensorimotor network in patients with MS: A multicenter fMRI study. *Human Brain Mapping, 30*(8), 2412-2425. doi:10.1002/hbm.20679

Runia, T. F., Jafari, N. N., & Hintzen, R. Q. (2013). Application of the 2010 revised criteria for the diagnosis of multiple sclerosis to patients with clinically isolated syndromes. *European Journal of Neurology, 20*(12), 1510-1516. doi:10.1111/ene.12243

Sáez-Francàs, N., Hernández-Vara, J., Roso, M. C., Martín, & Brugué, M. C. (2013). The association of apathy with central fatigue perception in patients with Parkinson's disease. *Behavioral Neuroscience, 127*(2), 237-244. doi:10.1037/a003153

Salem, L. C., Hejl, A., Garde, E., Leffers, A. M., Paulson, O. B., & Waldemar, G. (2011). White matter hyperintensities and prepulse inhibition in a mixed elderly population. *Psychiatry Research: Neuroimaging, 194*(3), 314-318. doi:10.1016/j.pscychresns.2011.07.007

Sandroni, P., Walker, C., & Starr, A. (1992). 'Fatigue' in patients with multiple sclerosis:

    Motor pathway conduction and event-related potentials. *Archives of Neurology,*

    49(5), 517-524. doi:10.1001/archneur.1992.00530290105019

Schneider, A., Ballinger, E., Chavez, A., Tassone, F., Hagerman, R. J., & Hessl, D. (2012).

    Prepulse inhibition in patients with fragile X-associated tremor ataxia syndrome.

    Neurobiology of Aging, 33(6), 1045-1053. doi:10.1016/j.neurobiolaging.2010.09.002

Shucard, J. L., Parrish, J., Shucard, D. W., McCabe, D. C., Benedict, R. B., & Ambrus, J. r.

    (2004). Working memory and processing speed deficits in systemic lupus

    erythematosus as measured by the paced auditory serial addition test. *Journal of the*

    International Neuropsychological Society, 10(1), 35-45.

    doi:10.1017/S1355617704101057

Skerrett, T., & Moss-Morris, R. (2006). Fatigue and social impairment in multiple sclerosis:

    The role of patients' cognitive and behavioral responses to their symptoms. *Journal of*

    Psychosomatic Research, 61(5), 587-593. doi:10.1016/j.jpsychores.2006.04.018

Smith, J., & Motl, R. W. (2005). Electromyographic indices of neuromuscular reflexes.

    International Journal of Sport and Exercise Psychology, 3(3), 322-337.

    doi:10.1080/1612197X.2005.9671775

Stathopoulou, A., Christopoulos, P., Soubasi, E., & Gourzis, P. (2010). Personality

    characteristics and disorders in multiple sclerosis patients: Assessment and treatment.

    International Review of Psychiatry, 22(1), 43-54. doi:10.3109/09540261003589349

Strober, L. B., & DeLuca, J. (2013). Fatigue: Its influence on cognition and assessment. In P.

    A. Arnett, P. A. Arnett (Eds.), *Secondary influences on neuropsychological test*

performance: Research findings and practical applications (pp. 117-141). New York, NY, US: Oxford University Press.

Sweet, L. H., & Vandermorris, S. D. (2011). Neuroimaging and cognitive function in multiple sclerosis. In R. A. Cohen, L. H. Sweet, R. A. Cohen, L. H. Sweet (Eds.) , *Brain imaging in behavioral medicine and clinical neuroscience* (pp. 355-367). New York, NY, US: Springer Science + Business Media. doi:10.1007/978-1-4419-6373-4_21

Swerdlow, N. R. (2013). Update: Studies of prepulse inhibition of startle, with particular relevance to the pathophysiology or treatment of Tourette syndrome. *Neuroscience and Biobehavioral Reviews*, *37*(6), 1150-1156. doi:10.1016/j.neubiorev.2012.09.002

Swerdlow, N. R., Paulsen, J., Braff, D. L., Butters, N., Geyer, M. A., & Swenson, M. R. (1995). Impaired prepulse inhibition of acoustic and tactile startle response in patients with Huntington's disease. *Journal of Neurology, Neurosurgery & Psychiatry, 58*(2), 192-200. doi:10.1136/jnnp.58.2.192

Swerdlow, N. R., Sprock, J., Light, G. A., Cadenhead, K., Calkins, M. E., Dobie, D. J., & ... Braff, D. L. (2007). Multi-site studies of acoustic startle and prepulse inhibition in humans: Initial experience and methodological considerations based on studies by the Consortium on the Genetics of Schizophrenia. *Schizophrenia Research*, *92*(1-3), 237-251. doi:10.1016/j.schres.2007.01.012

Swerdlow, N. R., Wasserman, L. C., Talledo, J., Casas, R., Bruins, P., & Stephany, N. L. (2003). Prestimulus modification of the startle reflex: Relationship to personality and psychological markers of dopamine function. *Biological Psychology, 62*(1), 17-26. doi:10.1016/S0301-0511(02)00090-X

Thelen, J., Lynch, S., Bruce, A., Hancock, L., & Bruce, J. (2014). Polypharmacy in multiple
  sclerosis: Relationship with fatigue, perceived cognition, and objective cognitive
  performance. *Journal of Psychosomatic Research*, *76*(5), 400-404.
  doi:10.1016/j.jpsychores.2014.02.013

Ueki, A., Goto, K., Sato, N., Iso, H., & Morita, Y. (2006). Prepulse inhibition of acoustic
  startle response in mild cognitive impairment and mild dementia of Alzheimer type.
  Psychiatry and Clinical Neurosciences, 60(1), 55-62. doi:10.1111/j.1440-
  1819.2006.01460.x

Valls-Sole, J. (2012). Assessment of excitability in brainstem circuits mediating the blink
  reflex and the startle reaction. *Clinical Neurophysiology, 123*(1), 13-20.
  doi:10.1016/j.clinph.2011.04.029

Vrana, S. R. (1995). Emotional modulation of skin conductance and eyeblink responses to a
  startle probe. *Psychophysiology*, *32*(4), 351-357. doi:10.1111/j.1469-
  8986.1995.tb01217.x

Walker, L. S., Berard, J. A., Berrigan, L. I., Rees, L. M., & Freedman, M. S. (2012).
  Detecting cognitive fatigue in multiple sclerosis: Method matters. *Journal of the
  Neurological Sciences, 316*(1-2), 86-92. doi:10.1016/j.jns.2012.01.021

Ward, T. (2013). *Fatigue and its impact on visual vigilance in people with multiple sclerosis*
  (Doctoral dissertation). Retrieved from Proquest Information & Learning (Accession
  Number 2013-99220-429).

Wicks, P., Massagli, M., Kulkarni, A., & Dastani, H. (2011). Use of an outline community to
  develop patient-record outcome instruments: The Multiple Sclerosis Treatment

Adherence Questionnaire (MS-TAQ). *Journal of Medical Internet Research, 13*(1), 172-184. doi:10.2196/jmir.1687

Woodward, N. D., Duffy, B., & Karbasforoushan, H. (2013). Response selection impairment in schizophrenia transcends sensory and motor modalities. *Schizophrenia Research*, *152,* 446-449. doi:10.1016/j.schres.2013.11.038

Yuhas, J., Cordeiro, L., Tassone, F., Ballinger, E., Schneider, A., Long, J., & ... Hessl, D. (2011). Brief report: Sensorimotor gating in idiopathic autism and autism associated with fragile X syndrome. *Journal of Autism and Developmental Disorders*, *41*(2), 248-253. doi:10.1007/s10803-010-1040-9

Yusuf, A., & Koski, L. (2013). A qualitative review of the neurophysiological underpinnings of fatigue in multiple sclerosis. *Journal of the Neurological Sciences*, *330*(1-2), 4-9. doi:10.1016/j.jns.2013.04.012

Zoetmulder, M., Biernat, H. B., Nikolic, M., Korbo, L., Friberg, L., & Jennum, P. J. (2014). Prepulse inhibition is associated with attention, processing speed, and ^{123}I-FP-CIT SPECT in Parkinson's disease. *Journal of Parkinson's Disease*, *4*(1), 77-87.

VITA

Bryan Derek Fox was born on January 17, 1973, in Honolulu, Hawai'i. Following his father's discharge from the United States Army, he moved with his family to southwestern Missouri, graduating from Carl Junction High School in 1991. He began attending the University of Missouri at the Columbia campus the following fall, leaving in the spring of 1994 to work in business management while starting a family. After living in the Chicago area for almost nine years, Bryan moved to the Kansas City area in the fall of 2004. Following the diagnosis of autism spectrum disorder for one of his children, Bryan switched his career path to academia, graduating with bachelor's degrees in Psychology in 2009 and in Communications in 2010, both from the University of Missouri – Kansas City.

Bryan began his graduate training in 2012 when he was accepted into the Experimental Health Psychology PhD program at the University of Missouri – Kansas City (UMKC) where he began studying cognitive psychophysiology under the mentorship of Dr. Diane Filion. Bryan's primary research interests include the subjective nature of fatigue, and the role of attention in the sensory filtering of environmental stimuli.

Bryan is a member of the Society for Psychological Research (SPR), and is a current member and past chapter president of Psi Chi, the International Honor Society in Psychology. At UMKC, Bryan works with the Institute for Human Development (IHD), is a member of the Executive Board of the Graduate Student Council, and is a Preparing Future Faculty fellow. He lives in Kansas City, Kansas, with his youngest two children, and enjoys keeping up with all of their activities.