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FATIGUE IN MULTIPLE SCLEROSIS: A MULTIFACETED APPROACH

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ABSTRACT

INTRODUCTION: Fatigue is a debilitating symptom that affects the quality of life for many individuals living with multiple sclerosis (MS). The nature of this elusive disease feature is still not well understood, leaving possibility for further exploration and potential for clinical intervention. While depression has been tied to fatigue in the MS population, research has suggested that recovery of depression does not lead to recovery from high levels of fatigue. The purpose of this thesis is to examine fatigue from psychological, structural, and behavioral angles in order to better understand fatigue and its relationship with depression in MS. METHODS: (a) The sample (n=54) was sorted into three depression groups (never depressed, remitted depression, and currently depressed). Total, physical, social, and cognitive fatigue impacts were examined among depression groups using a series of ANOVAs. (b) A series of Pearson Correlations were conducted between proportioned structural volumes (hippocampus, third ventricle, and thalamus) and cognitive fatigue as well as total fatigue. This analysis was done for the overall sample (n=51) and the three-group divided sample. The relationship between proportioned hippocampus volume and level of depression was also examined. (c) Response time variance and mean response time were calculated from the Computerized Assessment of Response Bias (CARB) and analyzed in relation to different fatigue indices for the overall sample (n=48). RESULTS: (a) Never and remitted depressed groups were found to have significantly lower levels of total fatigue severity, total fatigue impact, physical fatigue impact, and social fatigue impact than the currently depressed group. Cognitive fatigue impact levels were significantly higher in the ever-depressed groups compared to the never depressed group. (b) Hippocampal volume was the one structural region found to meaningfully correlate with total fatigue impact and cognitive fatigue impact. No significant correlations were found between fatigue indices and hippocampus volumes for any of the divided three-groups. DISCUSSION: (a) Findings suggest cognitive fatigue and depression have a different relationship than depression and other fatigue types. It is clinically relevant that cognitive fatigue does not appear to remit with depression.

(b) Findings support hippocampal volume involvement in total and cognitive fatigue but not level of depression, despite fatigue's high correlation with depression. (c) Findings were limited in statistical power due to small sample sizes. While no significant findings were found, fatigue severity positively trended with response time variance and mean response time, suggesting potential for these measures to serve as objective measures of total fatigue.

TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

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Chapter 1 Introduction

Multiple Sclerosis: an Overview

Multiple Sclerosis, or MS, is a chronic, inflammatory disease that targets the central nervous system (CNS). Current diagnosis criteria, dubbed the McDonald Criteria, are based on a combination of characteristic CNS lesions and a year of progressive disability and/or clinical attacks. These criteria also require eliminating other potential diagnoses that may share clinical features (Thompson et al., 2018). The aforementioned flares of progressive symptoms are highly individualized and multisystemic in nature, ranging from vision-related, cognitive, and speech changes, to gait disturbance, muscle weakness, and bowel, bladder, and sexual dysfunction (Reich, Lucchinetti, & Calabresi, 2018) (Lizarraga & Sheremata, 2017).

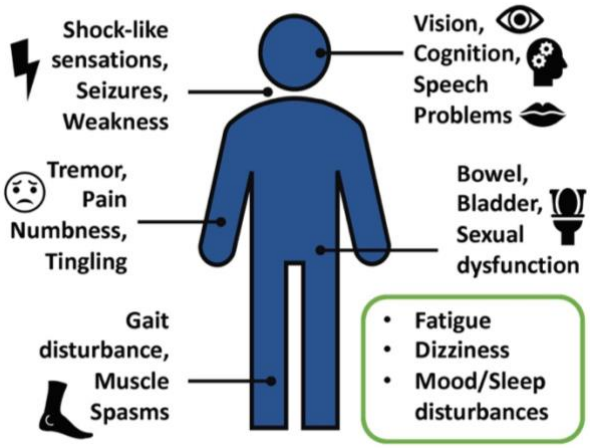

Figure 1.1 Common MS Symptoms
(Reich et al., 2018) (Lizarraga & Sheremata, 2017)

There are three primary subtypes of MS, which are characterized by symptom presentation and duration: relapsing-remitting, primary progressive, and secondary progressive. The majority of MS

patients present with relapsing-remitting MS, which is constituted by periods of remittance and remission of symptoms. Between these periods, some improvement is often recorded. At times, this subtype can progress into secondary progressive MS in which function begins to steadily decline. Alternately, primary progression is diagnosed during an initial "attack" of clinical symptoms, with function declining from onset (Lizarraga & Sheremata, 2017). Several other less common MS subtypes also exist, such as progressive relapsing (in which progressive presentation is interrupted by instances of relapse) and "benign" MS (in which no clinical features exist despite autopsy evidence suggesting disease presence). Benign MS is sometimes grouped under relapsing-remitting, and is still not well understood (Hurwitz, 2009).

MS lesions, or plaques, in the brain and spinal cord are characterized by demyelination of neurons, activation of protective glial cells, and elevated inflammation (Reich et al., 2018). Immune system involvement has led to the wide theorization that MS is autoimmune in nature. This theory is based on various pathological features of the disease. From an innate immunological standpoint, evidence has suggested that decreased gene expression of several phosphatases in MS patients leads to increased cytokine release and inhibition of macrophages after activation of particular receptors (Goodin, 2014). These receptors, called Toll-like receptors, help guide immune response, and have been implicated in other autoimmune conditions like systemic lupus erythematosus (Richez et al., 2019). Their dysfunction can trigger a mounted inflammatory response.

On an adaptive immune system level, abnormal T-cell and B-cell activation and attack of brain tissue has been evidenced to produce inflammatory areas of damage and demyelination. T-cell activation-against-self is still under intensive study, and rodent models have suggested that while myelin-targeted antibody production enhances autoimmune responses, it does not initiate MS itself. A current leading theory on the initiation of the disease itself is called "cumulative autoimmunity" (Goodin, 2014). This concept proposes that pathogenic T-cells that can self-react to more than one autoantigen at once could

lead to an overwhelming, additive response that could develop into a widespread autoimmune disease (Krishnamoorthy et al., 2009).

On an epidemiological level, various environmental, biological, and genetic risk factors exist that elevate risk for developing MS. Like in many other autoimmune diseases, females are at an elevated risk for developing MS when compared to their male counterparts. From a genetic standpoint, family history of the disease elevates risk by about twenty times, and over 200 genes have been implicated in development of MS. The majority of genes implicated in MS are related to immune system regulation and function. It is important to note, however, that this elevated risk in no way completely explanatory of the disease, and hovers at 3% for those with an immediate family member with MS (Reich et al., 2018).

Environmental triggers and risk factors hold notable implications in development of the disease as well. Interestingly, MS presence is magnified in locations of higher latitude, with various explanations for this distribution proposed. These theories range from insufficient vitamin D exposure in utero/development to lack of potentially protective UVB exposure (Olsson, Barcellos, & Alfredsson, 2016). The exact mechanism and significance of these models is unclear at this time. Other risk factors include adolescent obesity, history of smoking, and history of Epstein Barr virus infection (Lizarraga & Sheremata, 2017).

Currently, there is no "cure" for Multiple Sclerosis, though myriad treatment options exist to target symptoms and slow disease progression. Long term disease modifying therapies are typically immuno-regulatory pharmacologics that aim to suppress inflammation and promote neuron survival. Medications and treatments for non-disease specific symptoms such as nerve pain, muscle spasms, gait concerns, and more are treated on a case by case basis and are helpful during relapse periods (Bazzari, 2018). As MS is a chronic neurological disease directly impacting the brain in addition to changing one's lifestyle, relationships, and even outlooks on life, treatments at the intersection of both neurology and psychology are key to ensure quality of life and better outcomes for individuals with the disease.

Pharmacologics, psychotherapy, and lifestyle changes are often used to target disease manifestations such as depression and fatigue (Bazzari, 2018).

Fatigue and Depression in Multiple Sclerosis

As mentioned in the previous section, one of the hallmark symptoms of MS is fatigue. In fact, it has been estimated that 75-87% of patients with MS (PwMS) report this symptom, and ~40% of patients classify it as their most disabling symptom. This finding is quite remarkable considering the multitude of debilitating and painful manifestations of the disease (Aygünoğlu et al., 2015). But what exactly is fatigue, and how does it impact the life of a PwMS?

Multidimensional and largely unexplained in nature, countless definitions of this phenomenon have been developed over the years without a consensual classification being met. Broadly, DeLuca (2005, p. 320) suggests the term can be described as "reduction in performance with either prolonged or unusual exertion." However, it is important to note that many living with chronic illness experience lack of energy that is not a direct result of increased effort or activity. In this case, the MS Council for Clinical Practice Guidelines classifies fatigue as an entity characterized by subjective energy decline "that is perceived by the individual or caregiver to interfere with usual and desired activities" (Kinkel et al., 1994, p. 2). It is important to note that the fatigue of PwMS has been found as clinically distinct from other populations. Studies have suggested that MS-specific fatigue is often triggered not only by mental/physical activity, but also by humidity, infection, consuming food, and even with no apparent cause at all. It is reversible and is elevated in severity compared to premorbid manifestations (Mills & Young, 2007).

While the broad physiological origin of fatigue is still not quite understood, theories and an amalgam of studies tackle this elusive construct. Before delving into these explorations, it is important to note that no correlation has been found between severe fatigue & immunosuppressive/modulating

medications or disease duration (Putzki et al., 2008). At the same time, however, a positive correlation between physical fatigue (MFIS) & disability (EDSS) for PwMS has been found. Additionally, fatigue in PwMS may be related to motivational disturbances (Penner et al., 2007).

It has been proposed that fatigue targeting the central nervous system may be driven by pro-inflammatory cytokine release and HPA-axis activation/neurotransmitter effects in response to environmental and disease-related triggers (DeLuca, 2005). Additionally, structural changes in regions such as the hippocampus, corpus callosum, parietal lobe, and more have been implicated in fatigue specifically in MS populations (Hanken et al., 2015) (Induruwa, Constantinescu, Gran, 2012). Studies have indicated between 2- and 12x magnified prevalence of fatigue in PwMS versus the general population (Aygünoğlu et al., 2015) (Junghaenel, 2013). Resultantly, it has been proposed that the etiology of fatigue is different in the MS population, or is amplified due to the disease.

One convergent explanation theorizes that primary fatigue due to a neurological/immunological disease process is exacerbated by secondary fatigue. Secondary fatigue can be thought of as the feeling or experience of fatigue brought on by various factors, such as lack of sleep, pain or even mood (DeLuca, 2005). One does not need to experience primary fatigue to feel secondary fatigue, providing an explanation of fatigue existing in the general population independent of underlying disease.

Depression is another characteristic condition that presents comorbidly with both MS and fatigue. Clinically, a diagnosis of depression requires experiencing a combination of specific symptoms such as deflated mood, lack of interest, pleasure, and motivation, and cognitive difficulties lasting consistently for two weeks or more (American Psychiatric Association, 2013). It is important to consider someone's MS diagnosis when evaluating for depression, as symptoms from both often overlap, especially ones related to cognitive function or stemming from mobility limitations. Even when accounting for this intersection, there is an estimated 25-50% lifetime prevalence of major depression in PwMS, which is about a 3.5x greater risk than the general population (Feinstein, 2014).

Just as in fatigue, the exact cause of depression is not fully understood. To further complicate this field of study, it has been hypothesized that different cases of depression may stem from different origins. On a physiological level, implicated mechanisms typically involve the nervous and immune systems. Some of these theories involve the HPA axis, inflammation, and/or structural brain changes. For the first mentioned hypothesis, studies have examined HPA axis changes in those with severe depression, revealing they result in increased cortisol levels and suppressed feedback inhibition of this stress hormone. These changes have been implicated in cognitive effects as well. The inflammation hypothesis proves particularly notable in why those with autoimmune conditions, like MS, may be more susceptible to depression. Studies in this area suggest that elevated cytokine levels may lead to neuroinflammation and resultant depression or worsened depression. It is also important to note that, structurally, changes such as reduced hippocampal volume, amygdala hyperactivity, and decreased prefrontal activation have all been associated with depression (Malhi & Mann, 2018). Risk factors such as genetics, stress, and even vitamin D deficiency (as in MS) have also been tied to this condition (Parker, Brotchie, & Graham, 2017). For PwMS, the added lifestyle changes and stressors that come with living with a chronic illness must be considered. It is notable, however, that studies have revealed that PwMS have higher fatigue levels than peers with similar chronic health concerns (Siegert, Abernethy, 2005).

What is significant when considering these two co-morbidities in MS is the relationship between them. Not only are depression and fatigue highly prevalent in PwMS, but they appear to have a fascinating relationship. Fatigue and depression tend to cluster together, and depression rarely occurs without fatigue. As a result, it has been proposed that fatigue in PwMS is simply a manifestation of depression or overlapping symptom of depression and MS. However, several key findings complicate this view point. First of all, depression's predictable partnership with fatigue is not bidirectional: severe fatigue often occurs independently of depression (Chwastiak et al., 2005). Furthermore, studies have supported that "MS fatigue" is distinct from depression in that it lasts a few hours daily vs. all day, improves from naps, and is triggered by heat exposure (Patten & Metz, 2000).

Potential explanations of the relationship between fatigue, MS, and depression cross various fields of study. At the same time, an agreement or concrete explanation has yet to be reached on the exact nature of these relationships. On a structural level, white and gray matter changes are consistent in all three conditions, as are dysfunction of regions associated with the HPA axis (DeLuca, 2005; Genova et al., 2013). Furthermore, increased inflammation and immune involvement have also been implicated in depression, fatigue, and MS. Considering psychosocial and lifestyle related factors resulting from MS in the development and/or exacerbation of depression and fatigue and their relationship is also notable. Of relevance in this arena are the costs of treating the disease, limitations in mobility, and potential strain on social relationships due to the disease (DeLuca, 2005; Goodin, 2014; and Malhi & Mann, 2018).

Taking a Neuropsychological Approach

Neuropsychology is a scientific discipline that marries the principles of brain function with behavior. This interdisciplinary approach to health and being offers a comprehensive approach to understanding, evaluating, and treating various diseases. Using an applied combination of assessments in conjunction with neuroimaging allows clinicians and researchers alike to examine the brain-behavior relationship (Lezak et al., 2012). Batteries of tests measuring concepts such as memory, affect, attention, and many more can reveal strengths and deficits that cannot be evaluated with traditional medical tests. Furthermore, they are unique in their ability to estimate aspects of premorbid functioning. It is also important to note that studies on neuropsychological and traditional medical tests have revealed the two to have comparable validity (Meyer et al., 2001).

As outlined previously, diseases such as MS manifest in both physically observable as well as behavioral, mood, and cognitive areas. It is essential to be well-rounded in examining chronic disease to ensure understanding of daily function and quality of life. This thesis integrates neuropsychological

testing with neuroimaging techniques in an effort to study fatigue in a comprehensive manner. Using this lens, fatigue's relationship with brain pathology, depression, and behavior can be evaluated.

Purpose of This Study

The purpose of this study is to take a multifaceted, neuropsychological approach to examining fatigue in MS patients. By studying this phenomenon and its relationship with depression, as well as cognitive function and brain pathology, a balanced perspective can be accomplished. An exploration in this area offers great implications for PwMS and potentially other populations living with chronic disease that are at greater risk for fatigue and depression. These findings can be useful on the path to a better understanding and better treatment of these conditions.

Currently, it is estimated that annually approximately 1,000,000 individuals are living with MS in the US alone, and it has been predicted that this prevalence has been increasing over time (cause unknown) (Wallin, 2019). Worldwide, the predicted cost of this disease is around $10 billion (Reich et al., 2018). As previously mentioned, a large portion of PwMS experience fatigue and/or depression comorbidly. While fatigue is considered to be the most debilitating symptom for PwMS, depression has been found to be the most important symptom in predicting quality of life. In fact, it is estimated that PwMS experience a risk of suicide double that of the general public. From a financial perspective, over 60% of PwMS who are in the "working age" bracket are disabled from their jobs. It is important to consider the role fatigue and depression may play in this figure (Brenner & Piehl, 2016).

Various factors have been implicated in the origins of fatigue as well as depression in MS patients. Whether or not the relationship between fatigue and depression in the MS population lies in one or more biological, psychological, or environmental factors or a combination thereof, the implications of the relationship begs greater exploration. A greater understanding of these comorbidities may allow greater explanation of the physiology and mechanism of the disease itself and how it progresses. With this

greater understanding comes opportunity for improved patient care outcomes and quality of life, as well as optimization of treatment outcomes.

Chapter 2 A Three Depression Group Model of Fatigue

Overview

During this exploration, a novel framework proposed by Cadden, Meyer, and Arnett (2017) will be used to evaluate fatigue in three depression groups rather than a binary fashion: never depressed, currently depressed, and remitted depression. This framework is valuable in that it accounts for the elevated lifetime rate of depression in the MS population without excluding those who are currently remitted.

As depression and fatigue share various characteristics and features, applying this model allows distinctions to be made about their relationship. By examining characteristics of fatigue in individuals who have successfully recovered from depression, similarities and/or distinctions of these comorbidities can be revealed. This area is of particular interest, as the bidirectionality of the relationship between fatigue and depression has come into question: while depressed patients are nearly always fatigued, individuals with high fatigue levels are not always clinically depressed (Chwastiak et al., 2005).

Limited existing research has suggested that fatigue severity is elevated in depressed groups, and remains despite remittance from depression (Cadden et al., 2017). Kroencke et al. (2000) found that while depression predicts fatigue in PwMS, treatment does not lead to fatigue remittance. On related notes, studies have supported that remittance of fatigue is not probable if an individual is depressed (Krupp, Seraphin, Christodoulou, 2010).

Considering previous research, it is predicted that levels of fatigue severity and impact will be elevated for currently depressed participants and remain just as elevated for participants who have recovered from depression. In this chapter, the previous three group analysis on fatigue severity will be

expanded on to consider overall fatigue impact and fatigue impact on physical, cognitive, and social scales.

Sample

Data were extracted from a dataset of 54 participants (16 M, 38 F) recruited from the PA area. This dataset was previously analyzed for Three Group fatigue severity differences by Cadden, Meyer, and Arnett (2017). Patient average age was 52.57 (± 11.44 years), with average years of education being 14.80 (± 1.97 years). Exclusion criteria included a significant substance use history, sensory impairment, additional neurological disorder or condition affecting cognition or motor function, history of learning disability, record of relapse/corticosteroid use four weeks prior to the study, or physical/neurological status that would prevent complete testing.

MS diagnosis was confirmed prior to testing by a board-certified neurologist using the previously mentioned McDonald diagnostic criteria. (39 relapsing-remitting, 12 secondary progressive, 2 primary progressive, and 1 progressive relapsing).

Methods

Measures

This examination included the Fatigue Impact Scale (FIS) as a measure of fatigue. This test accounts for total fatigue impact as well as impact on three subscales: physical, social, and cognitive fatigue. The Beck Depression Inventory - Fast Screen (BDI-FS), Chicago Multiscale Depression Inventory (CMDI), and Structured Clinical Interview for DSM –IV (SCID-IV) were used to assess current depressive status. The SCID-IV and a psychosocial interview were used to assess depression

history. Three depression group classification was made according to criteria established by Cadden, Meyer, and Arnett (2017).

Data Processing

Prior to analysis, normality of data per measure of fatigue and depression group was conducted using the Kolmogorov-Smirnoff statistic, which concluded that the data approximately followed a normal distribution. This analysis was done using Excel.

Box-plot interquartile range (IQR) analysis was performed to assess whether or not outliers were present in the data. For the purpose of this study, an outlier of concern was defined as a value greater than three interquartile ranges below the first or above the third quartiles. An asterisk was used to indicate a data point in this range. This procedure concluded that the data did not present any concerning outliers. However, it is important to note that values outside of 1.5 times the IQR from the mean were indicated by circles on the box and whisker plots. This analysis was done using IBM's SPSS Statistical Analysis software.

Data analysis was conducted using IBM's SPSS Statistical Analysis software. A series of Analysis of Variance (ANOVA) tests were run on the data, analyzing depression group differences for each measure of fatigue.

Analysis

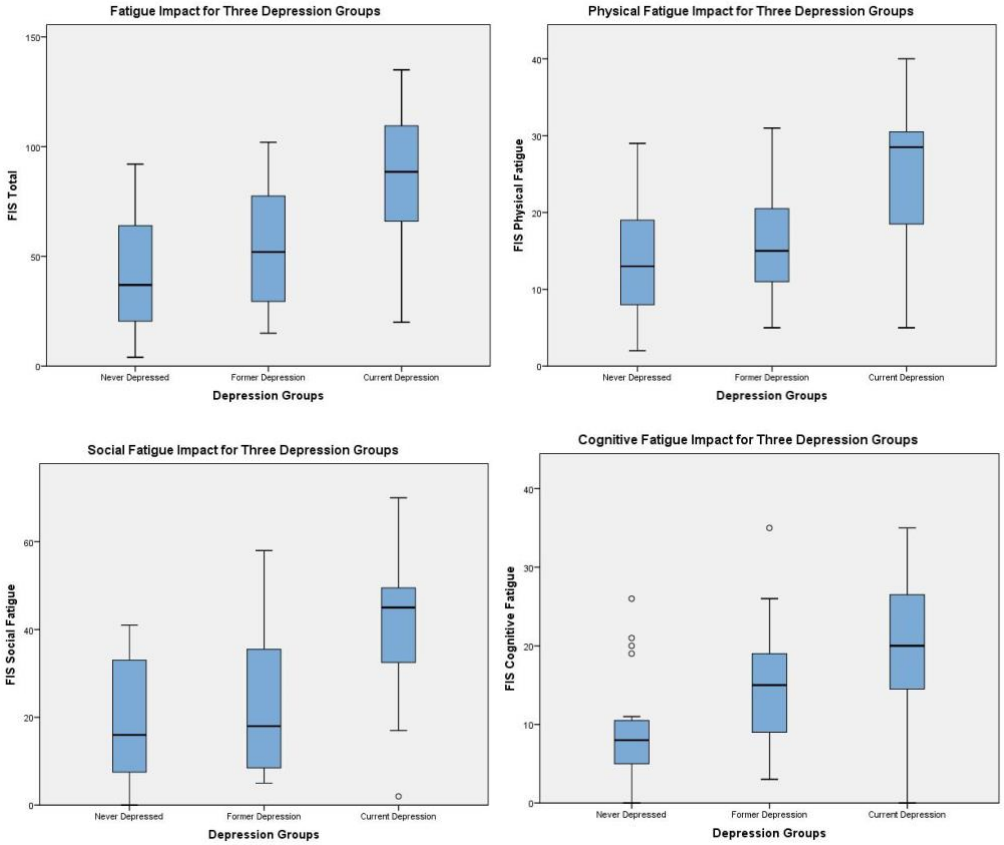

Figure 2.1 Fatigue Impact Scores for Three Depression Groups

Box and whisker plot analysis of total and subscale fatigue impact revealed no concerning outliers in either of the groups. Values outside of 1.5 times the IQR from the mean were indicated by circles on the box and whisker plots and were present in both the cognitive and social fatigue impact subscales.

ANOVA results revealed significant differences for Total Fatigue Impact between currently depressed and not currently depressed groups ($p = 0.000$), formerly and currently depressed groups

(p=.002), and never and ever depressed groups (p=0.001). For never and formerly depressed groups, no significant differences were found (p=.214).

ANOVA evaluation of the Physical Fatigue Impact subscale did not reveal significant fatigue differences between never depressed and formerly depressed groups (p=0.521). However, significant differences were found between groups that were currently depressed and not currently depressed (p=0.000), formerly and currently depressed (p=0.002), and never and ever depressed (p=0.010).

In terms of ANOVA results from the Social Fatigue Impact scale, the only groups found not to be statistically different in terms of social fatigue level were never depressed and formerly depressed (p=0.479). Currently and not currently depressed groups (p=0.000) and formerly and currently depressed groups (p=0.001) as well as never and formerly depressed groups (p=0.005) all demonstrated statistically significant differences.

Cognitive Fatigue subscale analysis revealed lack of statistically significant differences in fatigue between Table 2.1's formerly and currently depressed groups. The remaining never and ever depressed groups shown in this table were found to have significant fatigue differences (p=0.001) as did the currently and not currently depressed groups (p=0.006) and never and formerly groups (p=0.022).

Table 2.1 ANOVA Coefficients for Cognitive Fatigue and Three Groups

Model		Unstandardized Coefficients		Standardized Coefficients		
		B	Std. Error	Beta	t	Sig.
1	(Constant)	14.826	1.156		12.821	.000
	former versus current	2.028	1.437	.175	1.411	.164
	never versus ever	2.834	.806	.437	3.518	.001
Model		B	Std. Error	Beta	t	Sig.
1	(Constant)	14.826	1.156		12.821	.000
2	current depression vs. not currently depressed	2.431	.841	.359	2.889	.006
	never depressed versus former depression	3.237	1.374	.292	2.356	.022

a. Dependent Variable: FIS, Cognitive Fatigue Scale

Discussion

Overall, results of this three-group analysis of fatigue showed a combination of findings, including distinct characteristics of different fatigue subscales and depression groups. As predicted, the group of participants currently experiencing clinical depression experienced elevated fatigue in nearly all tested fatigue measures. At the same time, differences between remitted depression and never depressed groups were not found in total, physical, and social fatigue measures, supporting the idea that depression recovery is correlated with lessened fatigue symptoms in these categories.

An interesting finding, however, was that level of cognitive fatigue did not correlate with remittance from depression. In fact, it remained just as elevated in the remitted depressed as in the currently depressed group. The data supports the idea that recovery from depression is not associated with recovery from cognitive fatigue, leading to many clinically relevant questions. It suggests that cognitive fatigue's relationship with depression is distinct from the other subtypes of fatigue in some way.

These findings with cognitive fatigue coincide with previous research. So, this finding begs the question: why does cognitive fatigue level stay the same for present and remitted depression? This thesis proposes three main theories: (1) separate pathophysiological origins, (2) cognitive fatigue is a milder manifestation of depression, (3) depression and cognitive fatigue are two "parallel phenomena" with differing thresholds of emergence.

Theory 1 considers the possibility that while cognitive fatigue and depression may both be triggered by a primary process (in this case Multiple Sclerosis), differing pathophysiology or location of damage distinguishes the two comorbidities. In this theoretical example, lesion damage to an unconfirmed region/s of the brain would result in cognitive fatigue independently of depression. As such, treatments for depression may not be effective in reversing damage of this particular "cognitive fatigue" region or origin. A challenge to this theory would be the similarities in leading etiological theories of these conditions, such as previously mentioned structural HPA axis changes and inflammation. If a treatment

were to combat these processes, it would be curious if only one comorbidity responded to this treatment-unless there was more to the picture, which leads into Theory 2.

Theory 2 proposes that fatigue is a milder form or pro-/post-drome of depression. By acting as a cluster of symptoms that lead up to or follow from a period of clinical depression, this theory explains why cognitive fatigue is likely to present independently of full-blown depression. In fact, fatigue has been proposed as a pro-/post-drome of depression in other literature (Pede, Suyong, & Vishal, 2017). This framework also explains why both comorbidities emerge from similar pathologies and alongside MS. As previously outlined, fatigue oscillates in literature between being considered its own entity and being classified as a symptom of depression. Further research in this area is necessitated, particularly in the timing of symptom emergence and impact of each entity on daily functioning in a MS population.

An amalgam of the two previous theories, Theory 3 considers depression and fatigue as two separate but parallel phenomena that stem from the same pathological origin. This theory recognizes that while the two entities are interrelated and prompted by similar conditions, they still have distinct features and presentations. Furthermore, their distinction allows for different thresholds for pathology. In this case, cognitive fatigue may present separately from fatigue as its clinical emergence has a lower threshold for some sort of damage or etiological trigger. While this pathology may be treated down to a level below the emergence threshold for depression, treatment may not lower pathology enough to be effective against

cognitive fatigue. This theory is pictured below in Figure 2.2.

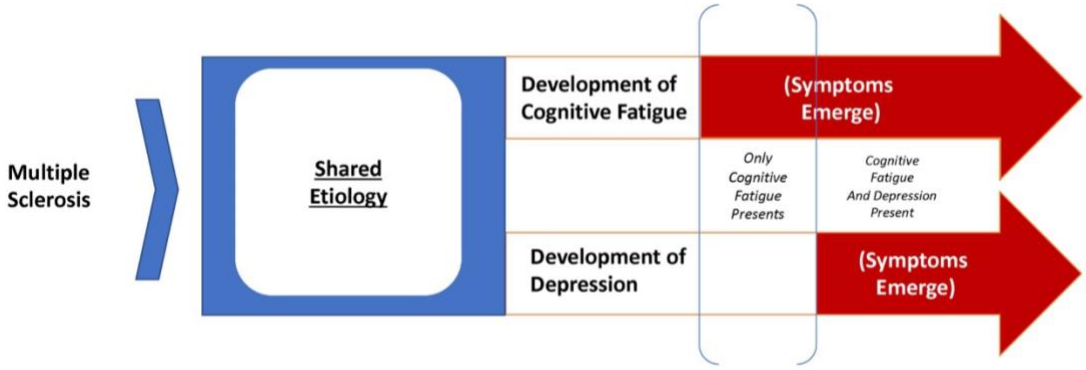

Figure 2.2 Theory 3 Schematic

A multitude of other extraneous factors have not been considered, such as sleep, medication, and social support. It is possible that these and/or other considerations may be mediating or moderating the relationship between cognitive fatigue and depression in PwMS. It is also important to consider how the population of individuals who are able to recover from depression in the first place may differ from their peers who do not successfully remit from depression. Was their depression more "state" than "trait," perhaps brought on by an adjustment period to living with a chronic disease? How does treatment resistant depression differ from depression that is responsive to treatment and do these variations have different relationships with fatigue? These questions warrant further investigation, and illustrate potential limitations of this study.

Further investigation of these three theories would provide insight into the relationship of fatigue and depression in MS. In order to do so, investigation of shared pathologies such as structural damage and immune response would be useful. Additionally, longitudinal study of symptom presentation, pattern, and response to treatment would be as well. Given cognitive fatigue's persistent presentation despite recovery from depression, this particular form of fatigue calls for attention.

Chapter 3 Fatigue as a Continuum and an Exploration of Brain Pathology

Overview

The undetermined relationship between cognitive fatigue and depression in PwMS, as further substantiated in Chapter 2, begs further study. Given the quality of life implications of these comorbidities, understanding their origins and relationship is important from a clinical perspective. One important piece to this puzzle, particularly considering the degenerative and autoimmune nature of MS, is a structural perspective. This approach will be implemented by examining the relationship between cognitive fatigue and level of structural damage in the brain independently and in a three-depression group framework. Proportioned brain region volume will be used as the metric for level of damage, as volumetric loss resulting from atrophy is a significant manifestation of damage in MS (Lizarraga & Sheremata, 2017). Furthermore, total fatigue will also be considered in these analyses to give results a point of comparison/contrast.

While determining regions of the brain to examine during this chapter, consideration was given to presence of MS and cognitive fatigue/cognition. A wide array of studies have been conducted on these issues, with an equally wide array of regions being examined in both. For the purpose of this study, the thalamus, hippocampus, and third ventricle were selected as the structures of interest. In PwMS, the thalamus, hippocampus, and third ventricle have each been associated with severity of cognitive manifestations in the disease (Schoonheim et al., 2015) (Geurts et al., 2007) (Artemiadis et al., 2018). Furthermore, decreased hippocampal activation has been linked to higher levels of cognitive fatigue. It is theorized that this link is a result of the hippocampus affecting HPA axis activation (Klaassan et al., 2013).

Predictions for this part of the study are based on the three theories of cognitive fatigue presented in Chapter Two. For the purpose of this thesis, Theory 3 will be used for hypothesis generation, however, conclusions will give insight into each of the aforementioned theories. Recall that this theory proposes that cognitive fatigue and depression stem from the same pathology yet have different thresholds for damage before symptoms appear. In this chapter, the root of these comorbidities being examined is impaired structural brain integrity due to MS.

Generally, it is predicted that higher levels of cognitive fatigue will be associated with higher levels of damage, as will presence of depression. It is predicted that level of damage in the depressed and remitted depression groups will be more strongly correlated with level of cognitive fatigue than in the never depressed group. This prediction is made as the ever-depressed groups experience a significantly higher level of cognitive fatigue than their counterparts, which may be explained by generally irreversible structural damage above other secondary fatigue-inducing factors.

Sample

Data were extracted from a dataset of 51 participants (15 M, 36 F) recruited from the PA area. This dataset was previously analyzed in Chapter Two of this thesis, however, some data were unusable due to movement during imaging, leading to the decreased sample size. Patient average age was 52.65 (± 11.65 years) with average years of education being 14.80 (± 1.97 years). Exclusion criteria are the same as those listed in Chapter 2, as are diagnosis criteria (37 relapse-remitting, 11 secondary progressive, 2 primary progressive, and 1 progressive relapsing).

Methods

Measures

Subcortical grey matter volumes of the left and right thalamus proper, left and right hippocampus, and third ventricle were obtained via MRI imaging using a 3-Tesla Siemens Magneto Trio A Tim System. Functional Magnetic Resonance Imaging of the Brain software was used to analyze imaging and obtain specified structural data.

As in Chapter 2, the Fatigue Impact Scale (FIS) was used to operationalize total and cognitive fatigue. The Beck Depression Inventory - Fast Screen (BDI-FS), Chicago Multiscale Depression Inventory (CMDI), and Structured Clinical Interview for DSM –IV (SCID-IV) were used to assess current depressive status. The SCID-IV and a psychosocial interview were used to assess depression history. The three depression group classification was again made according to criteria established by Cadden, Meyer, and Arnett (2017). The BDI-FS was also used as a measure of total depression outside classification of the three groups.

Data Processing

Prior to analysis, left and right hippocampal regions were summed, as were thalamic regions. Next, volumes were proportioned by dividing each by overall brain volume. This technique is one common method of adjustment that has been supported in various literature (O'Brien et al., 2011).

Data analysis was conducted using IBM's SPSS Statistical Analysis software. A series of Pearson Correlation 2-tailed t-tests were run, looking at correlations between brain volumes and total and cognitive fatigue FIS scores. Significantly correlated regions were next analyzed with fatigue measures in the context of the three-group model.

Finally, significantly correlated brain volumes were examined in relation to level of depression and fatigue measures.

Analysis

Significant correlations were found between total fatigue on the FIS and adjusted hippocampus volumes (Pearson Correlation = -0.349, p = 0.012), while a trending correlation was found between FIS cognitive fatigue and adjusted hippocampal volumes (Pearson Correlation = -0.235, p = 0.097). No significant correlations were found between total fatigue and adjusted thalamic volumes (Pearson Correlation = -0.207, p = 0.145) or cognitive fatigue and thalamic volumes (Pearson Correlation = -0.045, p = 0.756). No significant correlations were found between total fatigue and adjusted third ventricle volumes (Pearson Correlation = 0.040, p = 0.779) or between cognitive fatigue and adjusted third ventricle volumes (Pearson Correlation = -0.041, p = 0.776).

Only hippocampal volumes were further analyzed, as they were the only structural regions found to be significantly correlated with fatigue measures. For the never depressed group, n = 19, no significant correlation was found between total fatigue and adjusted hippocampal volume (Pearson Correlation = -0.232, p = 0.338) or cognitive fatigue and adjusted hippocampal volume (Pearson Correlation = -0.218, p = 0.369). For the remitted depression group, n = 17, no significant correlation was found between total

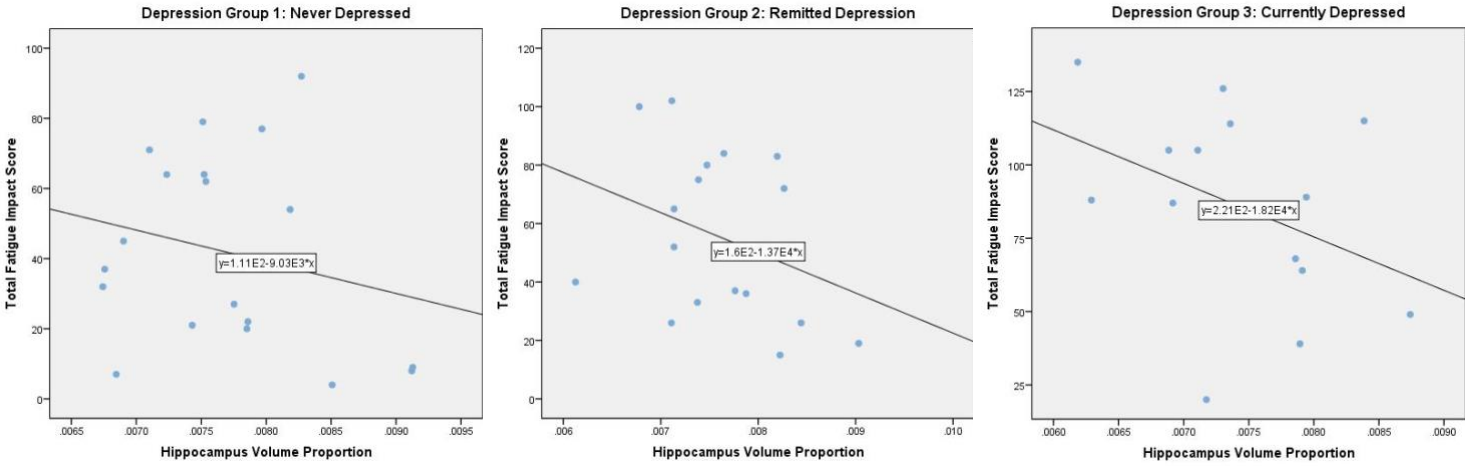

Figure 3.1 Trends in Hippocampal Volume VS Total Fatigue for Three Groups

fatigue and adjusted hippocampal volume (Pearson Correlation = -0.336, p = 0.187) or cognitive fatigue and adjusted hippocampal volume (Pearson Correlation = -0.158, p = 0.544). For the currently depressed group, n = 15, no significant correlation was found between total fatigue and adjusted hippocampal volume (Pearson Correlation = -0.196, p = 0.485).

Figure 3.1 presents correlational trends for adjusted hippocampal volume and total fatigue for each of the three groups. R^2 linear for group one = 0.054, for group two = 0.113, for group three = 0.157).

The total depression score correlated significantly with total fatigue (Pearson Correlation = 0.655, p = 0.000) and cognitive fatigue (Pearson Correlation = 0.486, p = 0.000). However, it did not significantly correlate with adjusted hippocampal volume (Pearson Correlation = -0.180, p = 0.207).

Discussion

Overall, the only significant structural brain-fatigue relationship supported was between total fatigue and hippocampal volume, with a trending correlation also present between this region and cognitive fatigue. These correlations were negative, which fits the convention that as a region loses

volume due to a disease process (in this case MS), cognitive impacts (in this case fatigue) increase. It is quite interesting to note that total depression level did not correlate with hippocampal volume at all, even though depression level significantly correlated with both total and cognitive fatigue. This finding provides support for Theory 1 proposed in Chapter 2. This theory proposes that the origins of damage in cognitive fatigue and depression for PwMS are distinct, and the present data support the idea that the hippocampus is a structural region with implications for cognitive fatigue but not depression.

After finding that hippocampal volume was the only tested region that showed significant correlations with fatigue measures, it was selected to be further analyzed under the three-group framework. Several notable trends were revealed, especially for total fatigue. As indicated in Figure 3.1, each correlation is negative, indicating a decrease in volume is associated with increased total fatigue. Furthermore, the strength of the correlation increases from never depressed to previously depressed to currently depressed. It does not appear that cognitive fatigue follows these patterns (at least as strongly), which suggests another fatigue subtype may be contributing to this total pattern. It is important to note that further subdividing into these three groups reduced sample sizes, and thus limited the power of the statistical analysis. Overall, these findings suggest that perhaps with a larger sample size, hippocampal damage may have a stronger impact on fatigue in ever depressed groups. This could mean that never depressed groups may have some sort of protective factor/s against this particular type of structural damage correlating with fatigue.

While this analysis provides insight into the relationship between fatigue, cognitive fatigue, depression, and structural damage, it is limited in several key aspects. As previously mentioned, the group sizes are notably small, and only one measure of structural brain damage is used on a very limited number of brain regions. It is possible that damage to other tested regions or damage from depression was not captured by a volumetric measure. It would be useful to conduct further analysis on other regions implicated in these phenomena, particularly those directly involved in the HPA axis, which, as previously

discussed, has been tied to fatigue, depression, and MS. Other indices of damage, functioning, and even inflammation may also produce significant findings.

Having a better understanding of the structural contributions to cognitive fatigue in PwMS is key in better understanding this manifestation and for future development of treatment regimens. However, it is likely that a variety of other factors must be considered when painting the picture of this comorbidity of MS. This particular exploration presents the importance of viewing cognitive fatigue and depression as separate-but-related entities, and suggests that a "blanket" approach to treatment of their symptoms may be resulting in some patients continuing to wrestle with debilitating fatigue despite recovery from depression. Continuing to consider the potential for differences between these two comorbidities is essential for quality of life outcomes for PwMS.

Chapter 4

Additional Tests and Remarks

Response Variance and Fatigue

As detailed in Chapter One, cognitive fatigue has yet to be consistently tied to any significant cognitive impairments. However, when such a substantial number of patients report on something that interferes with their daily functioning, it must be considered that the phenomenon may just not be captured by current metrics. Bridging off of the previous chapter's findings on cognitive fatigue and their call for understanding this manifestation, a brief exploration of a behavioral measure of this phenomenon will be explored.

Bruce, Bruce, and Arnett (2010) found that cognitive fatigue in PwMS presented in cognitive testing as increased variability in response time. This chapter will attempt to replicate this finding. If response time follows the same pattern in this dataset, there will be further evidence of this feature as an objective and clinically useful test of cognitive fatigue. Additionally, it may be indicative of the etiology and/or behavior of this phenomenon and be useful in proposing future studies.

Sample

This sample is composed of 48 participants (15 M, 33 F) from the same data set examined in Chapter 2, and satisfied the same exclusion criteria. This dataset was previously analyzed in Chapter Two of this thesis, however, some data were unusable due to movement during imaging, leading to the decreased sample size. Patient average age was 52.04 (± 11.96 years) with average years of education being 14.90 (± 1.96 years). Exclusion criteria are listed in Chapter 2, as are diagnosis criteria (35 relapse-remitting, 10 secondary progressive, 2 primary progressive, and 1 progressive relapsing).

Methods

Measures

As proposed by Bruce, Bruce, and Arnett (2010), the Computerized Assessment of Response Bias (CARB) was used to assess response time variability as well as other similar characteristics of participant response. This test is usually used to assess for effort, however has been adapted to look at the variables of interest and how they vary in response to a repetitive task. The Fatigue Impact Scale (FIS) and Fatigue Severity Scale (FSS) were used to measure total fatigue and fatigue subscales.

Data Processing

A series of Pearson Correlations were run between the different measures of fatigue and response time measures of interest (mean response time and mean standard deviation of response time as a measure of variability).

As a large proportion of participants did not experience much variability in their response, a further series of Independent Sample t-tests was run after participants were grouped into low and high variability to assess for group differences. The cutoff for low variability was made at 500 seconds.

Analysis

There was a trending correlation between response time variance and fatigue severity (Pearson Correlation = 0.271, $p = 0.066$). However, no notable correlations between response time variance were found with total fatigue impact (Pearson Correlation = 0.193, $p = 0.189$), physical fatigue impact (Pearson

Correlation = 0.152, p = 0.301), social fatigue impact (Pearson Correlation = 0.176, p = 0.230), or cognitive fatigue impact (Pearson Correlation = 0.196, p = 0.182).

Trending correlations were found between mean response time and total fatigue impact (Pearson Correlation = 0.249, p = 0.088), and cognitive fatigue impact (Pearson Correlation = 0.247, p = 0.090).

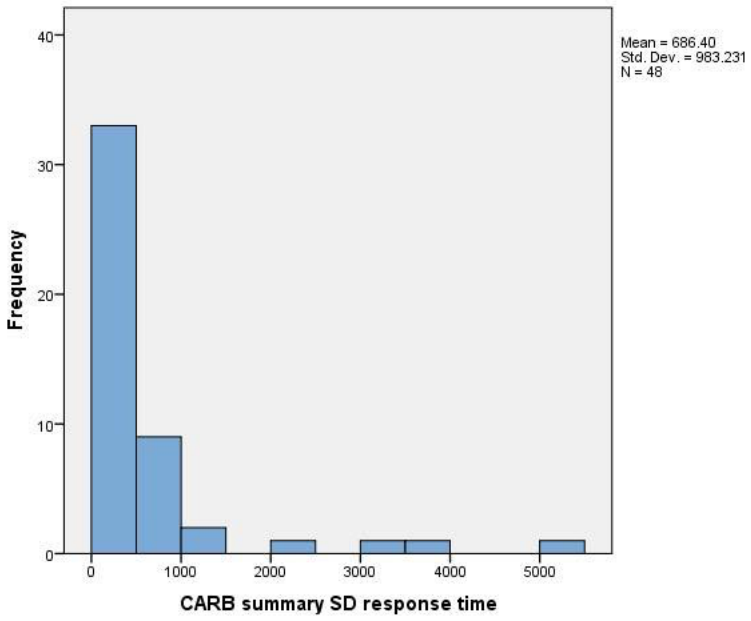

Figure 4.1 Distribution of Response Time Variance

Upon grouping of participants into high and low variability groups, group differences in each of the measures of fatigue were tested for. There were no significant differences found. However, there was a trend for group differences in mean response time (p = 0.078) with fatigue severity and response time variance (p = 0.071) with fatigue severity.

Discussion

In summary, there were no statistically significant findings during this exploration of fatigue and response time variability. However, fatigue severity was nearly significant in various aspects: it held positive trending correlations with response time variance overall and showed nearly significant group differences between high and low variability for mean response time and response time variance. This finding indicates that perhaps response time variability is a better measure of how severe fatigue is presenting, rather than its daily impact for PwMS.

When considering the results of this examination, it is important to consider the skew and size of the data. While data were split into two groups to explore differences, the highly variable group had only 15 participants while the low variability group had 33. The power of the analyses, thus, may have been hindered by this small sample size, or the trend may only be visible on a larger scale. The study this examination was modeled after had 78 PwMS participate, nearly double this sample size (Bruce et al., 2010).

Further studies with larger sample sizes are necessitated to further analyze response time variance as a behavioral measure of cognitive as well as other measures of fatigue. It would be useful to break down response variability over time within the CARB itself. Additionally, other tests getting at this phenomenon that may produce more variability in response overall would be useful in order to produce data that is less skewed. Perhaps a longer or a more difficult test could manifest these results.

Finding a way to quantify fatigue is key in understanding a patient with fatigue's daily functioning. It provides be a way of interpreting fatigue's response to intervention, a way to substantiate patient's concerns, and a way to predict symptom progression long term or even throughout the day.

Chapter 5 Future Directions and Clinical Implications

As fatigue and depression are so prevalent and have such a significant impact on the well-being and daily functioning of PwMS, understanding their relationship and origins is essential to optimizing treatment and quality of life outcomes. This thesis has approached fatigue from a multifaceted perspective, examining psychological, structural, and behavioral aspects of this elusive construct.

Overall, it appears that cognitive fatigue may act separately from other fatigue factors, and may interact differently with depression as well. Findings suggest that recovery from this sub-component of fatigue does not occur with remitted depression, leading to questions about treating and evaluating this phenomenon. Upon further exploration of cognitive fatigue, both it and total fatigue impact were notably inversely correlated with hippocampal volume. This finding aligned with previous literature tying this region to cognitive concerns in PwMS. The fact that hippocampal volume did not predict depression revealed a possible difference in the structural brain underpinnings of fatigue and depression, or at least the type of damage these comorbidities are connected to.

Understanding cognitive fatigue as an entity is key, however, when it comes to translating findings into a clinical setting, using an objective behavioral measure to quantify its severity is essential. In the final portion of this thesis, response time variability was explored as an indicator of general and cognitive fatigue. As current neuropsychological testing does not typically show deficits associated with high reporting of fatigue, exploring response time variability has been proposed by Bruce et al. (2010) as a way to explore how testing performance and fatigue may be linked. While only trends rather than statistical support for this measure were found, the limited size of the samples in this Chapter illustrate one of the major drawbacks of this fatigue exploration.

In addition to expanding sample sizes, other room for improvement for this research includes testing additional brain regions associated with fatigue in MS and in different ways. Future study of cognitive fatigue particularly is called for, and exploration of factors such as inflammation and immune response, sleep, vitamin D levels, and much more hold interesting opportunity for findings. As a better understanding of these entities in the MS population emerge, quality of life improvements for this and potentially other clinical populations can be made.

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Independent research product design on aspects of fatigue and depression in Multiple Sclerosis. Responsible for lab-wide clinical test data collection, scoring, and cleaning.

RESEARCH SCHOLAR

Department of Infectious Diseases — **Lehigh Valley Health Network**, Summer 2017
Design of and data collection for Lyme Disease retrospective chart review. Creation of comprehensive variable code book for data collection. Coordination with physicians, entomologists, and biostatisticians for comprehensive data collection/analysis. Use of EPIC electronic health record system and RedCap data capture software.

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Department of Civil and Environmental Engineering — **Lafayette College**, Fall/Winter 2014
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LEADERSHIP POSITIONS

EXECUTIVE DIRECTOR, STUDENT FARM CLUB — **The Pennsylvania State University**, Spring 2017-Present

Responsible for communication and outreach with faculty, administration, community, and students. Delegation of tasks for student exec members and running of executive retreats and meetings. Advocate for organization and promote growth in campus and local community.

CODIRECTOR FOR YOUTH EDUCATION, STUDENT FARM CLUB — **The Pennsylvania State University**, Spring 2017-Present

In charge of organizing and running educational outreach events and programs for Penn State's Student Farm. Responsible for coordinating guest lectures at local schools, creating lesson plans and presentations, and forging community partnerships.

COMMUNITY ACCESSIBILITY GARDEN, PROJECT LEAD — **The Pennsylvania State University**, Fall 2017-Present

Initiated the plan for constructing an accessibility and therapy focused garden for Penn State's Student Farm. Upon completion, will serve as a model for communities such as nursing homes and schools. Will demonstrate educational and public health bene its of a hands on garden environment.

THIRD ANNUAL NM-AIST AFRICAN GRAND CHALLENGE — **NMAIST**, Arusha, Tanzania, Jan 24-28, 2017

Selected as Penn State Student Ambassador for conference and competition on emerging technology use in the healthcare and animal sciences/wildlife management fields.

SCHREYER HONORS COLLEGE STUDENT ADVOCATE AT CAPITAL DAY — **Harrisburg, PA**, April 2017

Selected to represent the Pennsylvania State University at "Capital Day" An event where students visit state legislators and advocate for funding and state support of public education.

VICE PRESIDENT OF MARKETING, INNOBLUE ENTRPRENEURSHIP — **The Pennsylvania State University** F 2016

In charge of designing banners, social media, and other promotional items. Social media coverage during event. In charge of emails to sponsors and designing T-Shirts for the event.

PUBLIC RELATIONS AND MARKETING HEAD FOR 3 DAY STARTUP — **The Pennsylvania State University**, Fall-Winter 2015

In charge of designing banners, social media, and other promotional items. Social media coverage during event. In charge of emails to sponsors and designing T-Shirts for the event.

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For those interested in global issues and maintaining an international perspective. In charge of photography for organization. Lead various discussions on global issues.

SCHOLARSHIPS/AWARDS:

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COMMUNITY SERVICE

INFUSION CENTER VOLUNTEER, LEHIGH VALLEY HOSPITAL — **Bethlehem, PA**, 2018-Present

Responsible for tending to patients receiving treatment and assisting nurses/office staff as needed

STUDENT FARM CLUB FOOD SECURITY VOLUNTEER — **State College, PA**, 2016-Present

Participate in activities such as planting, harvesting, and delivery of produce to local food banks and pantries.

COPS 'N' KIDS LEHIGH VALLEY — **Bethlehem, PA**, 2007-Present

Organization that aims to bring literacy to children in underprivileged areas. Have coordinated and participated in numerous community events such as book distribution and public educational events and story times.

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