**NEURAL CORRELATES OF FATIGABILITY IN OLDER ADULTS**

 **BY 7T MAGNETIC RESONANCE IMAGING (MRI)**

by

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**ABSTRACT**

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There is increasing evidence to support that fatigability, a term for feelings of fatigue anchored to a defined activity at a fixed intensity and duration, may have neurobiological origins. The identification of brain regions associated with fatigability may illuminate vulnerable structural neuronal networks related to the disablement pathway. This work will examine whether structural brain MRI metrics are associated with physical and mental fatigability in older adults. Cross-sectional data collected at the baseline visit for the Lifestyle Interventions and Independence for Elders Study was used to conduct analyses. The analytic sample included participants with complete data for brain MRI metrics and the Pittsburgh Fatigability Scale. Grey matter volumes (GMV) for a priori identified brain regions of interest based on previous literature were normalized to intracranial volume (ICV) and fatigability was dichotomized to higher (HF) and lower(LF) physical and mental fatigability status based on established cutpoints. T-tests and non-parametric methods were performed to compare normalized GMV by higher and lower physical and mental fatigability. An exploratory significance level of p<0.1 was used. The analytic sample (n=29) had a mean (SD) age of 77.2(5.5) years (range=70.3 to 88.3 years), was mostly female (86.2%), 37.9% White and 31.0% had completed greater than a high school education. A majority of participants reported higher fatigability for physical and mental categories (65.5% for each). For the right hippocampus, mean (SD) GMV was lower for those with HF (0.261(0.039)) compared to LF (0.273(0.022)) for physical measures, p=0.07. Similar associations were found for the right putamen (HF: 0.273(0.030), LF: 0.292(0.030), p=0.05) and left (HF: 0.254(0.043), LF: 0.314(0.024), p=0.04) and right thalamus (HF: 0.285(0.032), LF: (0.307(0.023), p=0.08). The associations were similar for mental fatigability for the right hippocampus and thalamus with addition of the right cingulum posterior (HF: 0.260(0.040), LF: 0.276(0.015), p=0.05) and left (HF: 0.075(0.012), LF: 0.080(0.006), p=0.02) and right amygdala (HF: 0.081(0.015), LF: 0.086(0.010), p=0.05). Analyses are suggestive of neural correlates of physical and mental fatigability in older adults. These findings are significant to public health, because they will advance neuroepidemiologic knowledge about the role of the brain and fatigability in the disablement pathway.

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Emily E. Wasson, MPH

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preface

I would like to thank my essay mentors Dr. Rosso, Dr. Glynn and Dr. Butters for their overwhelming support and guidance during my essay-writing process. Additionally, I would like to thank my Pitt Public Health friends for their encouragement and for the precious memories I will forever cherish of my time in Pittsburgh. Lastly, to my family and loved ones, thank you for a lifetime of continuous support and love.

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Introduction

By the year 2050, the world’s population age 60 and older is anticipated to rise from 900 million to two billion people (“WHO | 10 facts on ageing and health,” 2017). In the United States alone, adults age 65 and older represent one of the fastest growing segments of the population, with estimates expected to reach 23.5% by 2060 (Bureau, 2014; Colby & Ortman, 2015). Increasing life expectancy has contributed to these trends. Older adults are living longer as a result of advances in public health, medical care, and technology. However, longevity is often accompanied by a number of chronic health conditions. In 2012, it was estimated that approximately half of US adults have at least one major chronic condition (Ward, Schiller, & Goodman, 2014). This anticipated growth in the population of older adults and persons living with chronic disease has led to a rise in prevention efforts that target age-associated physical function decline and disability (Guralnik, Fried, & Salive, 1996). Additionally, public health resources have been redirected to understand ‘healthy aging’, which is defined by the US Center for Disease Control and Prevention as, “the development and maintenance of optimal physical, mental and social well-being and function in older adults” (“Preventing Chronic Disease: January 2006: 05\_0054,” n.d.). Critical to this definition is the concept of function and implications for independence in the community.

Functional independence is recognized as a public health challenge, as maintaining independence is critical for the prevention of disability and can significantly reduce health complications (Branch et al., 1991). Decline in physical performance and subsequent impaired or reduced mobility may be preceded by fatigue (Avlund, Pedersen, & Schroll, 2003; Mueller-Schotte, Bleijenberg, van der Schouw, & Schuurmans, 2016). In a study of community-living adults age 70 and older, fatigue was the primary reason for restriction of activity (Gill, Desai, Gahbauer, Holford, & Williams, 2001). Among middle aged and older adults, fatigue is often reported as one of the top five complaints in primary care settings (Kenter, Okkes, Oskam, & Lamberts, 2003; Meng, Hale, & Friedberg, 2010). Thus, fatigue is also considered to be a growing health problem, because fatigue is both an independent predictor of mortality and incident disability, and it has implications for functional limitation and utilization of social and health services (Ekmann, Petersen, Mänty, Christensen, & Avlund, 2013)

Many fatigue questionnaires offer information about fatigue in the context of tiredness or exhaustion, but are only limited to perceived global fatigue measures. Rather, fatigability measures can be used to better characterize fatigue in the context of daily activities that are not necessarily attributed to a state of tiredness due to sleep behaviors. The pathophysiology of perceived physical and mental fatigability has largely been understudied, but there is evidence to suggest that fatigue may have neurobiological origins (Harrington, 2012; Kluger, Krupp, & Enoka, 2013; Nakagawa et al., 2016; Rocca et al., 2014; Shan et al., 2016).

Advances in neuroimaging technology have made it possible for researchers to explore the brain in the context of fatigability. Thus, this paper will 1) provide a review of the fatigue and fatigability literature to identify a critical gap in fatigability knowledge and 2) address this gap by examining the relationship between regional brain volume and physical and mental fatigability using cross-sectional baseline data from the Lifestyle Interventions and Independence for Elders Study collected at the University of Pittsburgh field center.

## FATIGUE

### Overview

Fatigue is a chronic complaint among both young and older adults and a common reason for seeking medical care (Kenter, Okkes, Oskam, & Lamberts, 2003; Watt et al., 2000). Previously, fatigue has been described as a state of tiredness, strain and weakness associated with a feeling of exhaustion, and or a response to physical or psychological stress (Tralongo, Respini, & Ferraù, 2003). Generally, fatigue can be acute, where feelings of fatigue are rapid and do not affect a person’s quality of life, or chronic, where feelings of fatigue are long-lasting and generalized (Shen, Barbera, & Shapiro, 2006; Tralongo et al., 2003). The word, “fatigue,” is also used interchangeably with sleepiness, apathy, exhaustion, tiredness, weakness or lack of vigor. In a clinical setting, fatigue is a symptom of tiredness related to a medical condition or a side effect of a drug or surgery. However, in many cases, the cause of fatigue is unknown.

A previous review of the literature on fatigue highlighted that although fatigue remains a common complaint among both healthy and diseased individuals, the definition of fatigue remains under debate (Finsterer & Mahjoub, 2014). As a result, prevalence estimates are highly variable. Various sources suggest that the prevalence of fatigue may range from 5% to as high as 68% (Alexander et al., 2010; Liao & Ferrell, 2000; Moreh, Jacobs, & Stessman, 2010). Variation in prevalence estimates may be attributed to differences in cutpoints used to interpret levels of fatigue, the tool used to measure fatigue, timeframe of interest (present fatigue or past fatigue), as well as the study population of interest (White, 2007).

 Risk Factors for Fatigue

A multitude of individual factors may influence a person’s level of fatigue. These include age, sex and physical condition. Additionally, environmental factors such as diet, life experiences and activity level may influence whether or not a person experiences fatigue. More specifically, risk factors for fatigue have been explored in adolescents, where being female, having anxiety, depression and or conduct disorder was associated with fatigue. Additionally, older age may increase risk for fatigue (Rimes et al., 2007). In a prospective study of working adults, being overweight and being physically inactive were modifiable lifestyle factors associated with fatigue in men, and women were at an increased risk for fatigue if they were underweight (BMI<18.5) (Bültmann et al., 2002). Additionally, a study used the Northern Sweden MONICA population survey to investigate the associations between fatigue and age, sex, socioeconomic status, and self-reported physical activity, sitting time and self-rated health. They found that older men who are highly educated, physically active, and have less sedentary behavior are generally least likely to experience fatigue (Engberg, Segerstedt, Waller, Wennberg, & Eliasson, 2017).

As such, epidemiologic studies of fatigue show that the risk factors for fatigue are varied and often differ depending on the population studied. For example, health status and presence of a chronic condition can influence feelings of fatigue. In patient populations with chronic diseases such as cancer, Hepatitis C, chronic pulmonary disease, hypothyroidism, and rheumatoid arthritis, fatigue symptoms are often reported (Carlson et al., 2004; Feldthusen, Grimby-Ekman, Forsblad-d’Elia, Jacobsson, & Mannerkorpi, 2016; Gupta et al., 2013; Irshad, Mankotia, & Irshad, 2013; Jonklaas et al., 2014; Poort et al., 2017). Among neuropsychiatric disorders, fatigue risk is associated with Multiple Sclerosis, Amyotrophic Lateral Sclerosis, Parkinson’s Disease, depression, traumatic brain injury, and stroke (Targum & Fava, 2011). In a longitudinal study of working age persons with rheumatoid arthritis, higher feelings of fatigue were reported in winter months, suggesting feelings of fatigue may be driven by the body’s response to seasonal changes (Feldthusen et al., 2016) Various cancer treatments such as radiation and chemotherapy are also associated with feelings of fatigue (Poort et al., 2017). Fatigue was also associated with illicit drug use, and it is also frequently reported as a symptom from taking medication for various conditions. (Zlott & Byrne, 2010).

Biomarkers of fatigue and genetic predispositions to fatigue have been explored using twin studies to assess the heritability of fatigue. A genome-wide association study (GWAS) found that significant genetic correlations were identified between tiredness and physical and mental health factors in the GWAS consortia, suggesting that tiredness or fatigue is partly heritable, but heterogeneous in nature (Deary et al., 2017). Based on these findings, the heritability of fatigue remains a complex phenomenon associated with affective, cognitive, personality and physiological processes.

In summary, risk factors for fatigue may be both inherent and environmental, and known modifiable risk factors are (Targum & Fava, 2011)presently targets for intervention to reduce fatigue in the general population.

Fatigue and Aging

Fatigue is considered to be a growing topic in the field of aging research, as feelings of fatigue in mid-life may be an early marker of age-related decline in health (Kirsten Avlund, 2010). Among middle age and older adults, fatigue is often reported as one of the top five complaints in a primary care setting (Kenter et al., 2003; Meng, Hale, & Friedberg, 2010). The Health and Retirement Study reported that prevalence of fatigue in older adults was approximately 31.2% among those that are community-dwelling (Meng et al., 2010). A comparison of these reports to prevalence reported for the general population suggests that older adults may share one of the highest burdens of fatigue. However, the lack of consistency in fatigue measures has made it difficult to distinguish the true burden of fatigue in older adults.

Of primary concern in older adults is the implication of fatigue in functional independence. Functional limitation can prevent individuals from seeking preventative services in a timely manner, increasing the risk for additional health problems in the future (Fitzpatrick, Powe, Cooper, Ives, & Robbins, 2004).

Mobility decline is recognized as an increasing problem in older adults. In a study of adults age 70 and older, fatigue was the primary reason for restriction of physical activity and mobility (Gill, Desai, Gahbauer, Holford, & Williams, 2001). In many cases, fatigue symptoms may be an indicator of an undiagnosed condition, but in many reports fatigue cannot be attributed to other underlying health abnormalities. The concern lies in these cases, where many adults are subject to feelings of unexplained fatigue, which have implications for mobility decline and loss of functional independence. Sedentary lifestyle, poorer functional performance and higher levels of disability have been strongly associated with depressive symptoms in both younger and older adults (Mänty, Rantanen, Era, & Avlund, 2014). High quality of life is often compromised as individuals with limitations in older age experience additional challenges in the community due to deficits in mobility.

## FATIGABILITY

###  Overview

The term fatigability has emerged in the literature to describe fatigue in a measurable and quantifiable dimension. Measures of global perceived fatigue typically describe a person’s whole body experience of fatigue, but fatigability can be used to understand fatigue as a whole-person construct in which fatigue is anchored to a defined activity at a fixed intensity and duration (Eldadah, 2010). An individual’s fatigability is their susceptibility to fatigue, which may be perceived or performance based. Accordingly, fatigability measures can be both subjective and objective in nature. The relationship between subjective and objective measures of fatigability are presented in **Figure 1.**



Figure 1. Fatigability Diagram

### Subjective vs. Objective Fatigability

Subjective fatigability is best defined as, “a phenotype characterized by the relationship between self-reported fatigue and level of activity with which the fatigue is associated” (Eldadah, 2010). Generally, subjective fatigue can also be interpreted as perceived fatigability. Perceived fatigability is a subjective measure of fatigue that captures an individual’s opinion of how fatigued they would imagine they would feel in the context of a specific task. Individuals with experience performing specific activities may have already experienced feelings of fatigue that influence their response. Thus, subjective fatigability is based on an opinion response about feelings of fatigue *without performing* an activity to objectively measure physical or mental functioning.

Objective fatigability can be thought of as performance fatigability. Performance fatigability can be measured after an individual completes a specific physical or mental task. For example, a measurement of performance deterioration after a standardized walking distance of 400m can be used to objectively measure an individual’s physical fatigability(Simonsick, Schrack, Glynn, & Ferrucci, 2014). Additionally, perceived exertion after completing a five minute treadmill walk is an example of how a person’s fatigue can be objectively measured by *performing* an activity(Simonsick et al., 2014).

### Physical vs. Mental Fatigability

Physical fatigability encompasses the body’s susceptibility to fatigue related to activities that involve physical movement. Mental fatigability is a measure of the body’s susceptibility to fatigue related to physical and mental activities that engage cognitive function. It can be measured by asking participants to engage in mental or cognitive activities and to rate their level of fatigue during a task or after imagining the task. As subjective measures, both physical and mental fatigability can capture feelings of fatigue a person would perceive they would feel directly after completing a specific task. Objective tools of physical and mental fatigue measure feelings of fatigue during or after a person completes, performs, or engages in a physical or mental task.

## FATIGABILITY VS. FATIGUE

A review of the literature indicates that there are a multitude of assessments used to capture fatigue and fatigability in older adults. In the following sections, the assessments used in the LIFE study to measure fatigue and fatigability will be described and critiqued. To summarize, a justification for the measure used to investigate the neural correlates of fatigue will be provided.

### Measures of Fatigue

Fatigue measures generally capture perceived global fatigue. These subjective measures of fatigue can be used to assess global fatigue across whole populations. Generally, fatigue instruments are simple in nature and can be completed by self-report in a few minutes making them highly utilized in aging studies. Fatigue is commonly measured using various questionnaires including the Modified Exercise-Induced Feelings Inventory (MEFI), which is a 6-item scale with each item scored at 0-5 (Rejeski, Reboussin, Dunn, King, & Sallis, 1999). Additionally, perceived global fatigue can be measured using two questions from the Center for Epidemiologic Studies Depression (CES-D) Scale “I felt that everything is an effort,” and “I could not get going”(Radloff, 1977). Higher fatigue is categorized as those who answered “some”, “moderate” or “most of the time” and lower fatigue was agreement with the response “rarely or none of the time.”

The Avlund Mobility-Tiredness scale was an early measure of fatigue associated with cardiovascular diseases, musculoskeletal pain, various medications, walking speed, and depressive symptoms(Fieo, Mortensen, Rantanen, & Avlund, 2013; Mänty et al., 2012). This six-item scale requires subjects to self-report on whether they become tired performing mobility-related tasks. However, a major disadvantage with this scale is that intensity and duration are not taken into consideration. In order to understand the pathophysiological mechanisms of fatigue, intensity and duration must be taken into consideration. Inclusion of both intensity and duration associated with mobility tasks in measurement tools of fatigability allows for a more accurate characterization of fatigability associated with fatigue-inducing task.

Alternatively, the Situational Fatigue Scale has previously been used to measure fatigability (Yang & Wu, 2005). This scale is valid, but it was only validated in a younger sample of adults (mean age=31.1), suggesting that it may not be appropriate to use in an older adult population. Also, activities were not normalized to an intensity level and self-pacing could not be accounted for. Additionally, this 13 item scale included activities not as common for older adults, limiting the application of this measurement tool.

Although these measures explore global fatigue, they do not account for self-pacing. Previous studies have shown that human adults walk at a characteristic speed, but preferred walking speed is related to perception of effort (Willis, Ganley, & Herman, 2005). In order to reduce fatigue or avoid fatigue, older adults may alter the amount of energy they exert when they complete certain tasks. In other words, older adults may engage in self-pacing (Eldadah, 2010). For example, when faced with a challenging task that requires effort, older adults may slow down or shorten the task duration to reduce or avoid fatigue. This may be done to maintain a tolerable effort while completing various activities, where activities are paced according to an individual’s perception of their own fatigue while performing tasks. Fatigue measures cannot account for self-pacing, because they do not generally ask about intensity or duration of tasks, which may alter perception of fatigability. Additionally, fatigue measures are limited to use in younger adult populations, as many of the scales have not been validated in an older adult population nor do they include activities commonly performed by older adults. Generally, fatigability may be better at distinguishing fatigue in relationship to intensity or duration of tasks and identify common activities that may prevent or dissuade an older adult from engaging in physically or mentally demanding tasks.

### Measures of Fatigability

There currently exists a few different tools to measure fatigability, both performance and perceived. Fatigability can be classified as a performance or perceived measure. Performance fatigability captures a decrement in performance due to tiredness (simonsick 2014). This is typically measured during a standardized physical task. Performance measures may capture a fatiguing task alone, such as performance deterioration during a fast-paced 400m walk (simonsick 2014) or may measure a fatiguing task followed by a probe task, i.e., self-reported fatigue and demand are measured in separate instruments.(Schnelle et al., 2012;). Further, perceived fatigability measures capture fatigability characteristics based on an individual’s self-report feeling of tiredness as a function of the duration and intensity of a demanding task or activity. Examples of perceived fatigability measures include perceived exertion, which measures self-reported fatigue while objectively measuring demand during a five minute treadmill test plus rate of perceived effort (Simonsick et al., 2014). However, one disadvantage of these performance-based fatigability measures in research settings is that it is not always feasible for individuals to complete performance tasks due to low resources or remote data collection.

The Pittsburgh Fatigability Scale measures self-reported fatigue and demand using a single instrument (Glynn et al., 2014). The PFS has been used to assess fatigability in older adults and has previously demonstrated that high performance fatigability was associated with slow gait speed, worse physical function and lower fitness (Glynn et al., 2014). This scale asks individuals to rate both the physical and mental fatigue they would expect or imagine they would feel after completing a certain activity. The activities used in this questionnaire target the normal day to day activities in which older adults engage. The assessment can be completed in a few minutes, and also provides researchers information about whether or not an individual engaged in a specific activity in the last month. The PFS is not only reliable and valid for measuring perceived fatigability, but it can also serve as an adjunct for performance-based fatigability measures. A major strength of using this scale in a geriatric population is that it includes activities that are relevant or commonly performed by older adults, where measures like the Situational Fatigue Scale has only been validated in ages 18 to 60. It also normalizes all the activities to a specific intensity and duration, and can be practically performed in a clinical setting, administered over the phone, or mailed out as a questionnaire making it a relatively simple and inexpensive tool to assess fatigability in older adults. Unlike the fatigue measures described, the PFS directs an individual to only think about physical and mental fatigue in the context of the activity mentioned. Thus, the response collected elucidates which activities are related to physical and mental fatigability, and subsequently the activities that are most demanding and limiting physically and mentally for a specific individual. Thus, the Pittsburgh Fatigability Scale (PFS) was developed to overcome weaknesses of perceived global fatigue measures and can also be used in the absence of performance tasks as it has been validated against objective measures of fatigability like the 400 meter walk and five minute treadmill walk (Glynn et al., 2014; Simonsick et al., 2014).

 In summary, it is important to highlight that for some measures of fatigability, fatigability is defined as fatigue in relation to a defined activity of a specific intensity or duration. Others define fatigability as a change in performance deterioration. Despite the variability in the definitions, fatigability has recently been adopted as a new concept in the geriatric literature. For example, a recent review of fatigability measures highlights fatigability as it relates to clinical outcomes (Kim et al., 2017). A cross-sectional study on performance fatigability found that severity of perceived fatigability was correlated with greater oxygen consumption, lower physical activity, low walking distance and higher severity of performance fatigability (Barbosa et al., 2016). Another study found that performance and perceived fatigability severity were associated with physical activity related expenditure (Buchowski et al., 2013). Perceived exertion and performance fatigability measures have also been associated with tiredness, weakness and reported and observed mobility deficits (Simonsick et al., 2016). These findings highlight that fatigability measures may have stronger implications for clinical outcomes than fatigue measures alone.

### Justification

Fatigability measures may better capture fitness and health status than other measures of fatigue. Fatigability measures have been studied in the context of mobility and fitness, and the findings from these studies support the continued use of fatigability measures over traditional fatigue measures. Among older adults in the Baltimore Longitudinal Study of Aging (BLSA), fatigability was associated with almost a 20% greater likelihood of meaningful decline in usual and faster gait speed, physical performance, and reported walking ability (Simonsick et al., 2016). Additionally, slow walking was associated with greater fatigability in older adults (Richardson, Glynn, Ferrucci, & Mackey, 2015). Fatigability was significantly associated with a number of measures that assess individual mobility and fitness. In all cases, fatigability was associated with poorer performance measures.

Generally, measures of perceived global fatigue only measure general feelings of fatigue, which may not completely reflect an individual’s perception of the level of fatigue they may feel while completing different activities. For example, an individual’s perceived global fatigue may be low (no fatigue), but if asked to complete an activity at a specific intensity and duration, his or her perception of their fatigue may change based on the activity described. Objective measures of fatigability offer insight into how an individual’s feelings of fatigue limit them in everyday life. The PFS has previously been validated against objective measures of fatigability, and thus, the PFS can accomplish this task. Also, the level of fatigue that a person perceives she or he would feel accompanied with a workload may be indicative of a different fatigue response compared to questions that relate to a person’s overall state of tiredness, which may be interpreted as a measure of sleep. A self-reported rating of fatigability allows determination of a score of susceptibility to feelings of fatigue that are linked back to feelings or behaviors toward completion of a specific task. Hence, fatigability measures can allow researchers to understand fatigue as it relates to specific activities that are engaging both physically and mentally for a defined age group. Thus, we contend that fatigability measures should be used to investigate the underlying mechanisms of perception of fatigue, due to the strong implications for mobility and fitness outcomes in older adults.

## PATHOPHYSIOLOGY OF FATIGABILITY

In many older adults, feelings of fatigue are not accompanied by other chronic conditions. There are no specific biological markers of fatigue that explain the common complaint reported by older adults. However, there is growing evidence to support that the origins of perceived fatigability are tied to the central nervous system, specifically the brain. The following sections outline and describe the main theories for the pathophysiology of perceived physical and mental fatigability.

### Motivation Theory

There is growing evidence to support the central nervous system playing a vital role in perception of fatigue, where the brain guides decision-making and effort while completing specific tasks (Roerink, van der Schaaf, Dinarello, Knoop, & van der Meer, 2017). Perception of fatigue related to completion of certain tasks may be influenced by how motivated an individual is as they complete a specific task. Alternatively, motivational behavior related to the completion of specific tasks may be related to how an individual adapts to fatiguing tasks, which may influence their perception of their own fatigue (“A motivational control theory of cognitive fatigue”).

### Energy Theory

Feelings of fatigue are theorized to be attributed to a shift in the production and utilization of Adenosine triphosphate (ATP). The relationship between utilization of energy and fatigue outcomes may be related to both brain function and muscle fatigability. First, changes in cognitive neuro-circuitry related to brain atrophy may contribute to age related sensory deficits (Eldadah, 2010). Thus, metabolic costs and reduced executive function and cognitive control have implications for greater brain functional activity to compensate for brain changes. Increased cognitive demand on certain brain regions may have implications for perceived fatigability. Alternatively, capacity for oxidative phosphorylation in quadriceps among older adults was associated with higher fatigability, which suggests that a shift in skeletal muscle mitochondrial energy production may also play a role in fatigability in older adults (Santanasto et al., 2015).

### Immune Activation Theory

In older adults, high levels of fatigue and fatigability may also be attributed to suppression of a neural drive from the circadian clock (Harrington, 2012). Healthy older adults may spend more time awake during a night’s sleep compared to younger adults. Brain regions that express circadian rhythms in neural activity may have impaired or altered function with a loss of such synchrony. These features may impact metabolism and immune system function. Such changes in the body may lead to reduced energy levels and impaired concentration which is often accompanied by fatigue and fatigability. However, it is unknown if age-related sleep disruption derives from circadian or homeostatic sleep regulation, and thus if age-related sleep disruption is the cause of fatigability in older adults (Schmidt, Peigneux, & Cajochen, 2012). It is postulated that circadian rhythms that influence cognitive function are weakened in older healthy adults, which may contribute to observed fatigability.

### Pharmacologic Agent Theory

Fatigue can also be a side effect of some medications (Zlott & Byrne, 2010). This theory is based on a disturbance of excitatory activity in the central nervous system that can manifest as depression and result in fatigue-like symptoms. While the pathophysiological mechanisms of fatigability are not completely understood, the implications of medication on subsequent feelings of fatigue are apparent. However, these findings are interpreted with caution, because the mechanistic pathways are not well-defined. Additionally, opioid use may contribute to excitatory mechanisms that may contribute to fatigability through similar pathways. Many drugs, including placebo drugs, have been reported to cause fatigue where other drugs are known to relieve feelings of fatigue through unknown pathways.

### Environment vs. Genetic Theory

Lifestyle decisions, including diet, exercise, and environmental influences like stress may contribute to an individual’s perceived physical and mental fatigability. Additionally, age and sex are individual factors that may influence fatigability status (Finsterer & Mahjoub, 2014). A review of the genetics and epigenetics of fatigue reported that fatigue may be associated with altered functioning in the hypothalamic-pituitary-adrenal axis, the serotonergic system and infectious agents. However, there is not a clearly defined fatigue phenotype (Landmark-Høyvik et al., 2010). A more recent study investigated the genetics of tiredness linking a number of inherited factors to self-reported tiredness or fatigue (Deary et al., 2017). Thus, there is increasing evidence to support that fatigability may have an inheritance component that is highly heterogeneous. As such, it is presumed that both environmental and genetic components contribute to perceived fatigability, but there is a lack of clarity in the pathophysiology of fatigability, and thus it is not certain which factor contributes most to the fatigability pathway.

## BRAIN AND AGING

Aging influences brain size, cognition and vasculature (Peters, 2006). Over the life-course, both white and grey matter exhibit different patterns, and where white matter deteriorates faster with age than grey matter (Giorgio et al., 2010; Gunning-Dixon, Brickman, Cheng, & Alexopoulos, 2009). Loss of grey matter volume and white matter integrity over time is associated with greater cognitive decline (Debette & Markus, 2010; Karas et al., 2004). It has been shown that healthy lifestyle factors such as physical exercise, healthy diet, and low to moderate alcohol intake can be protective against cognitive decline (Marques-Aleixo, Oliveira, Moreira, Magalhães, & Ascensão, 2012; Masley et al., 2017; Oleson et al., 2017).

Based on what is known about the aging brain, it appears that the rate of brain changes, and many of the processes involved with these biological changes are unknown. Thus, in order to fully conceptualize fatigability in the context of the brain, neuroimaging can be used to identify potential neural correlates of fatigability in cases where deterioration is most abundant or non-existent in various regions of interest.



Figure 2. Conceptual Model of Fatigability and Brain Health

NEUROEPIDEMIOLOGY

Population Neuroscience

The population neuroscience approach has been adopted in neuroepidemiologic research to answer research questions that add to the map of complex relationships between neuro-psychological processes and behavioral outcomes at a population level. Data collected using neuroimaging techniques, such as magnetic resonance imaging, have been used to assess structural and functional properties of the human brain in epidemiology studies. Comparison of inter-individual variations of brain anatomy is critical for understanding the brain among both the healthy and sick. Heterogeneity in research samples allows researchers to assess a number of variables across diverse groups to uncover trends to drive future neuroscience research. This approach to neuroepidemiologic research may help lay the foundation for personalized preventative medicine, and subsequently reduce the burden of poor brain health and cognitive decline.

#### Magnetic Resonance Imaging (MRI)

Magnetic Resonance Imaging can be used to study the brain in the context of fatigability. In a strong magnetic field, atom nuclei absorb and pulse radiofrequency energy. This energy is emitted as radio waves and are constructed using computerized software (“Magnetic Resonance Imaging - MeSH - NCBI,” n.d.). In the context of neurobiology and population neuroscience, MRI is referred to as the key phenotyping tool, and the instrumentation can run several scans of the brain to assess a number of structural and functional properties (Shen et al., 2006). Due to the widespread availability of MR scanners, and the noninvasive nature of the MRI scan, this neuroimaging modality is often used in neurobiology research at the population level. In the present study, 7T MRI scanners were used to capture whole brain, gray matter and white matter volume. This technology offers a highly detailed superior soft tissue contrast and has a molecular imaging capability that makes it a particularly novel instrument for studying the neural correlates of fatigability.

#### Grey Matter

MRI technology is useful for imaging grey matter volume to examine structural regions of interest of the brain. Grey Matter is a component of the central nervous system and is typically darker in color than white matter. It is composed primarily of neuronal cell bodies, and is distinctly different from white matter, because it contains fewer myelinated nerve fibers.

#### White Matter

White matter consists of nerve fibers and myelin. It serves many different functions, ranging from insulation of the axon to connecting nerve cells. Acceleration of electrical impulse conduction takes place in the white matter, which has been shown to be crucial for normal cognitive function. These white-matter fiber tracts connect cortical regions in the brain.

## PREVIOUS RESEARCH

There is considerable evidence to suggest that fatigability may have neurobiological origins, and as such, a number of studies have been carried out to observe neural correlates of fatigue in animal models, populations with specific diseases, as well as in healthy, younger adults. Neural correlates of fatigue have traditionally been investigated among patients who present with a secondary medical condition and studies are starting to investigate fatigue in a relatively healthy population. Potential neural correlates of fatigue have been identified for Parkinson’s disease, traumatic brain injury, stroke and multiple sclerosis, but there is little consensus on specific brain regions associated with fatigue (Harrington, 2012; Kluger, Krupp, & Enoka, 2013; Nakagawa et al., 2016; Rocca et al., 2014; Shan et al., 2016).

 The normal aging process is associated with atrophy of cortical brain regions, but specific regions associated with fatigability in older adults are presently unknown (Fjell et al., 2009; Raz, Gunning-Dixon, Head, Dupuis, & Acker, 1998; Scahill et al., 2003). It is plausible that changes in whole brain atrophy may be related to fatigability, and as such, whole brain volume may be considered as a potential neural correlate of fatigability. Based on previous literature, and what is known about the functional networks in the brain, the following regions of interest have been highlighted as potential neural correlates of fatigability: the amygdala, caudate, cingulate, middle frontal gyrus, orbitofrontal cortex, medial superior frontal gyrus, hippocampus, putamen, and thalamus.

The amygdala is a part of the neural circuitry for emotion and emotional learning through a reward or aversive event (Gallagher & Chiba, 1996). It is postulated that emotional learning may have an impact on behavioral motivation, and consequently may be related to subjective fatigability. A recent study using animal models to explore the effects of social stress on fatigue discovered that gene-expression was altered in inflammation pathways and G-protein coupled receptors in the prefrontal cortex and the amygdala (Azzinnari et al., 2014). These findings suggest that the amygdala and frontal cortices may be potential regions of interest for future study. The amygdala has largely been understudied in the context of fatigue, and therefore, the addition of this region of interest may contribute to the current literature on what is known about the amygdala’s role in fatigue.

The hippocampus is also a part of the limbic system and plays a role in long-term memory and working memory (Axmacher et al., 2010; Poch & Campo, 2012). The hippocampus is involved with the stress response, and emerging evidence suggests that it interacts with dopaminergic systems relative to synaptic plasticity, adaptive memory, and motivated behavior (Calabresi, Castrioto, Di Filippo, & Picconi, 2013). As such, fatigue mechanisms may be implicated in the dopaminergic neuronal loss in the hippocampus (Calabresi et al., 2013).

In healthy subjects, regional grey and white matter integrity of the basal ganglia and frontal lobes have been explored as potential correlates of fatigue only in younger adults. The basal ganglia are subcortical masses located in the basal regions of the cerebral hemispheres. Their functions are highly related to movements combined with reward-related activity (“Reward functions of the basal ganglia | SpringerLink,” n.d.). Lesions of specific sub-regions of the basal ganglia, namely the nucleus accumbens, are related to self-stimulation of dopamine neurons and reward and motivation. These processes are often related to habit-learning to determine actions necessary to achieve rewards. Additionally, cytokines involved in motivational dysfunction and dopaminergic mechanisms may have implications for fatigue (Yohn et al., 2016). Dopamine is a neurotransmitter that carries signals for a limited number of behavioral events, but is most intensely related to reward (Schultz, 2010). Animal models demonstrate that motivational behavior is altered by depletion in dopamine and can be reversed by dopamine treatment (“Suppression of Locomotor Activity in Female C57Bl/6J Mice Treated with Interleukin-1β: Investigating a Method for the Study of Fatigue in Laboratory Animals,” n.d.; Yohn et al., 2016). Thus, alterations in dopamine receptor functioning may influence feelings of fatigue, or subjective fatigability.

 The caudate is a sub-region of the basal ganglia involved in cognition that is thought to contribute to behavior through excitation of correct action based on evaluation of action outcomes (Grahn, Parkinson, & Owen, 2008). The caudate nucleus and the putamen are both the principle input nuclei of the basal nuclei and serve different functions. The caudate is generally associated with cognitive functions where the putamen is primarily associated with motor functions (Patestas & Gartner, 2016).

 The putamen is the largest and most lateral part of the basal ganglia (“Putamen - MeSH - NCBI,” n.d.). The putamen has previously been explored in childhood chronic fatigue syndrome patients where activity of the putamen under low motivational reward conditions is negatively correlated with severity of fatigue, suggesting altered dopaminergic function, decreased reward sensitivity and lower motivation to learn (Mizuno et al., 2016).

 The thalamus is located in the middle of the brain and serves as the relay center of the brain, and is involved in regulation of consciousness, sleep and sensory interpretation (Patestas & Gartner, 2016). It is also responsible for sending motor signals to the cerebral cortex. A study recently investigated sub-regional thalamic abnormalities among patients with Multiple Sclerosis and found that abnormalities contributed to fatigue (Hidalgo de la Cruz et al., 2017). An fMRI study found that under a motor fatigue state, which is related to the exercised induced reduction of neural activity to drive muscle groups, the intensity and size of activation of volumes in the thalamus and the basal ganglia were significantly decreased during a motor fatigue state (Hou et al., 2016). These subcortical areas contributed to a decreased activity in the central nervous system during a motor fatigue, and thus, perceived fatigability may be related to these regions.

 The orbitofrontal cortex is a component of the prefrontal cortex in the frontal lobe of the brain. It is highly involved in cognitive processing of decision making (Patestas & Gartner, 2016). The motivational behavior theory of fatigability suggests that decision making is a factor involved in perception of one’s fatigue. Additionally, one study used a functional-connectivity based method to study mental fatigue and found fatigue discriminatory patterns were associated with the volume of? middle frontal gyrus and several other motor areas (Sun et al., 2014). Another study found that participants who performed executive control work related to working memory and task-switching showed a decrease in brain activity in the left middle frontal gyrus (Blain, Hollard, & Pessiglione, 2016). Additionally, the superior frontal gyrus is associated with self-awareness, which may have implications for perception of fatigability (Goldberg, Harel, & Malach, 2006).

 The cingulate cortex is a component of the limbic lobe of the brain and has previously been explored in neuro-connectivity research and has been identified as a potential neural correlate of subjective fatigue in patients with multiple sclerosis (MS) (Pardini et al., 2015). Among patients with MS, deterioration of networks was found in the cingulate, prefrontal areas and the caudate, which suggests that these regions could also be involved in fatigability outcomes.

 While no one has studies the neural correlates of fatigability in healthy older adults, there are some plausible regions located in the limbic system, basal ganglia, and frontal regions that have been identified from studies of neurologic disease and healthy younger adults.

### Gap in Knowledge

Presently, there have been no studies to our knowledge that explore brain structure and perceived fatigability in an aged population. This study will be the first of its kind to examine the neural correlates of fatigability in older adults. Our work will elucidate the brain structures that may be responsible for or related to perceived fatigability including the amygdala, caudate, cingulate, middle frontal gyrus, orbitofrontal cortex, medial superior frontal gyrus, hippocampus, putamen, and thalamus.

## PUBLIC HEALTH IMPLICATIONS

Due to the increasing size of the aged population and the high prevalence of fatigue in older adults, studying fatigability in the context of brain structure is imperative for the efficient distribution of public health resources to interventions that focus on lasting change and improved quality of life.

It has been established that tiredness in mobility is an independent predictor of mortality (K. Avlund, Schultz-Larsen, & Davidsen, 1998). Among non-mobility limited older adults, ratings of perceived exertion after completing a slow walk for five minutes was associated with a greater likelihood of functional decline over a two year period (Simonsick et al., 2016). Slower walking speed and higher rates of energy expenditure was also associated with greater fatigability (Richardson et al., 2015). Therefore, older adults with higher fatigability may be at risk for mobility decline, and fatigability may be a target for intervention to prevent poor health outcomes among older adults.

Previously, attempts to institute effective strategies for healthy aging through mobility intervention have been challenging and expensive to carry out in research, policy and clinical practice. As such, public health aging research has investigated age-related diseases and the implications of early intervention on the aging process. Critical to this healthy aging process is brain health. Aging brains are subject to deterioration and in some cases neurological disease and impairment. Therefore, the aging brain serves as a unique and important structure to study in the context of public health, because anatomical differences in brain structure may elude to risk for poorer health outcomes, including fatigability.

There is evidence to support that brain anatomical structures can be preserved through adult life by maintaining a healthy lifestyle and through physical activity. Overtime, the brain is subject to structural changes and current research technologies offer a unique window of opportunity to study brain anatomy as a predictor of fatigability outcomes in older adults. Future work may benefit from crude identification of brain anatomical correlates associated with fatigue by allowing investigators to concentrate connectivity research on specific brain regions.

Presently, the literature on fatigability is limited, especially in the context of brain studies. This work will help clarify how the brain may be critical for fatigability specifically in relatively healthy older adults and the importance of fatigability and its relationship to the brain in the disablement pathway. In summary, interventional success for fatigability and related mobility outcomes is dependent on a clear understanding of the disablement pathway. Our work will help advance the knowledge of the disablement pathway in older adults and draw attention to the importance of physical and mental fatigability and its relationship to brain health.

# OBJECTIVES

We aim to examine whether brain MRI metrics are associated with fatigability in an older adult population. We hypothesize that higher fatigability scores will be inversely related to grey matter volumes for basal ganglia and frontotemporal cortices compared to people with lower fatigability.

# Methods

## Ethics Statement

The Lifestyle Interventions and Independence for Elders study was approved by the Institutional Review Board for all eight field centers, including the University of Pittsburgh, Pittsburgh, Pennsylvania field center (Marsh et al., 2013).

## Design and Setting

### Overview of the Parent Study

The Lifestyle Interventions and Independence for Elders (LIFE, U01 AG022376; http://clinicaltrials.gov/ct2/show/NCT01072500) study was a phase three single-masked randomized controlled clinical trial. The goal of the study was to evaluate the effects of long-term moderate-intensity physical activity on physical and cognitive function in sedentary older adults (N=1635) age 70-89 with impaired function with a Short Physical Performance Battery Score (SPPB) of <10.

###  Recruitment

Recruitment for the LIFE study began in March 2010 and ended in December 2011. Participants were eligible for the LIFE study if they were sedentary, defined as less than 20 minutes per week of regular physical activity in the past month and reporting less than or equal to 125 minutes per week of moderate to vigorous physical activity based on the Community Healthy Activities Model Program for Seniors (CHAMPS) physical activity questionnaire. Additionally, participants who were at high risk for mobility disability based on Short Physical Performance Battery (score ≤9) were eligible for participation in the LIFE study. Participants enrolled were able to walk 400 m in less than or equal to 15 minutes without sitting, leaning against a wall or getting assistance from another person or walking aid. Lastly, participants were eligible to be enrolled if they were safely able to participate in the intervention, which was a combination of structured exercise and physical activity focused on walking and included strength, flexibility, balance, training or a successful aging health information and education program(Marsh et al., 2013). A total of 1,818 adults were telephone-screened at the Pittsburgh field center, 880 were screened for eligibility and 216 were enrolled in the study and randomized to the health education intervention or the physical activity group starting in March 2010.

In December 2010, the Lifestyle Intervention and Independence for Elders initiated the Magnetic Resonance Imaging ancillary study (LIFE-MRI)(Rosano et al., 2017). Participants were screened to for willingness to complete an MRI scan at baseline and two years later and for exclusion criteria, including known claustrophobia or having a metal in the body not cleared for a 7T MR scanner. Among those who were eligible and completed the neuroimaging study, 45 participants had complete data for the first 7T MRI scan in the study.

In May of 2011, LIFE participants from the Pittsburgh field center were also screened and if eligible were asked to take part in a muscle mitochondria ancillary study (LIFE-Mito) prior to starting the intervention program. Participants were eligible if they met the 31P Magnetic Resonance Spectroscopy (MRS) scan criteria. The Pittsburgh Fatigability Scale was administered to these participants (Santanasto et al., 2016). The scans and PFS were completed approximately two to three weeks from each other. Exclusion criteria for the LIFE-Mito study were as follows: history of hip fracture, heart attack, angioplasty, or heart surgery within the past 3 months, cerebral hemorrhage within the past 6 months, stroke within the past 12 months, or symptomatic cardiovascular or pulmonary disease (Santanasto et al., 2016).

The final analytic sample size for the present study was N=29, as these participants had complete data for both the 7T MRI scan and Pittsburgh Fatigability Scale (PFS).

### Data Collection

#### Fatigability Measures

At baseline, individuals from the LIFE-Mito study were asked to complete the Pittsburgh Fatigability Scale (PFS), which assessed perceived physical and mental fatigability (Glynn et al., 2014). The 10 item scale scores 0-5 for physical fatigue, with 0 being no fatigue and 5 being extreme fatigue. The Physical and Mental Fatigability scores were calculated by summing the raw scores and were analyzed as a continuous variable, respectively. Fatigability was dichotomized based on total physical fatigability score and total mental fatigability score to characterize higher and lower fatigability status. Fatigability status was based on established cut points for physical and mental fatigability (Physical: Higher fatigability= ≥15, Lower fatigability=<15; Mental: Higher fatigability=≥13, Lower fatigability=<13).

#### Brain Volume Measures

This study used magnetic resonance imaging (MRI) data of the brain. This method is a non-invasive scan that can be used to examine internal anatomy. In the present study, we were interested in structural rather than functional characteristics of the brain. Therefore, this study will focus on grey matter volumes derived from MRI scans to investigate neural correlates of fatigability.

Magnetic Resonance Images were acquired at the MR Research center at the University of Pittsburgh on a 7-Tesla human scanner (Magnetom, Siemens Medical Solutions, Erlangen Germany) using an eight-channel head coil (Rapid Biomedical GmbH, Rimpar, Germany). High-resolution T1-weighted 3D MPRAGE sequences were used for volumetric analyses and were acquired in the axial orientation (TR/TE = 3,430/3.54, voxel size: 0.7 × 0.7 × 0.7 mm, 256 slices) (Rosano et al., 2017).

Neuroimaging variables were assessed for normality and outliers and were transformed as appropriate. Selection of neuroimaging variables was based on previous fatigue literature including the amygdala, caudate, cingulate, middle frontal gyrus, orbitofrontal cortex, medial superior frontal gyrus, hippocampus, putamen, and thalamus. Additionally, grey matter volume was normalized to intracranial volume (ICV). ICV was obtained using Brain Extraction Tool (BET), as the volume contained within the “inner skull” (Smith, 2002). A ratio of GMV to ICV volume was obtained and used in analyses.

#### Covariates

This study used covariate data from the main LIFE study collected at baseline. Covariates included age, sex, race, education level, and body mass index (BMI). Additional comorbidities such as cardiovascular disease, diabetes mellitus, and depression measured by the Center for Epidemiologic Study Depression Scale (depression: ≥16) were included in adjustment analyses.

#### Physical and Cognitive Performance Measures

A number of performance measures were obtained from the LIFE study data including usual gait speed (m/s), usual paced 400-m walk time (seconds), the Short Physical Performance Battery (SPPB, [0-12], score of >8) the Modified Mini-Mental State Examination (3MS) score (range 0-100) and the Digit Symbol Substitution Test score (Guralnik et al., 2000; Teng & Chui, 1987). The SPPB metric is a combined score of performance measures for gait speed, chair stands and balance testing and has been used as a predicative tool of possible disability (Guralnik et al., 2000). The 3MS is a cognitive screening measure that has been widely used to detect dementia (Teng & Chui, 1987). The DSST is a subtest of the Wechsler Adult Intelligence Scale and requires response speed, sustained attention, visual spatial skills and set shifting, and can be used as a screening tool for general cognitive impairment or dementia (Bettcher, Libon, Kaplan, Swenson, & Penney, 2011).

## Statistical Analysis

Descriptive statistics for the overall LIFE study population and the analytic sample by fatigability status were calculated. With N=29, this analysis was exploratory, and tests of significance of demographic characteristics for were not conducted between the sample from the Pittsburgh field center and the analytic sample. Average brain regions were examined by fatigability status, and t-tests were performed at significance level set at p<0.1. The ratio of GMV to ICV for each brain region was expressed as a percentage.

Continuous variables were checked for normality using the Shapiro-Wilk test for normality by physical and mental fatigability status. T-tests were performed to assess covariates of fatigability (high versus low for both physical and mental). Chi-squared tests, including Fisher Exact tests for cell counts less than 5, were performed to assess potential categorical covariates of fatigability (high versus low for both physical and mental fatigability).

Logistic regression analyses were performed to assess the associations between *a priori* specified brain regions of interest and fatigability measures as continuous variables with and without adjustments for covariates. Adjustment for covariates was done one at a time to determine whether each covariate might explain any observed associations between brain region volumes and fatigability. Covariates were included as adjustments in multivariable analyses if they were associated with the outcome of interest (the PFS) at p≤0.1. Model fit was examined to verify this analysis approach. Due to the anticipated sample size, correction for multiple comparisons was not included in the analyses. The ratios obtained for GMV to ICV were adjusted by a factor of 100,000 before they were added into the model for meaningful interpretation of parameters associated with fatigability outcomes.

# Results

The descriptive characteristics for the LIFE population at the Pittsburgh field center and the analytic study sample are presented in **Table 1**. The mean age and standard deviation (mean±SD) of older adults at the Pittsburgh site was 78.5±5.1 with a range from 70.1 to 89.8 years and the average age of the analytic sample was 77.2±5.5 with a range of 70.3 to 88.3 years. The Pittsburgh LIFE study population at baseline was 76.7% female, 71.3% White, and 58.8% had completed greater than a high school education. The analytic study sample from the Pittsburgh field center was comparable, with the exception of race 37.9% White (Table 1). Additionally, 20.7% of participants in the study sample had cardiovascular disease, 34.5% were former or current smokers and 34.5% diabetes mellitus. The prevalence of depression measured by the CES-D score was comparable to the Pittsburgh field center. Additionally, mean 3MSE scores and DSST scores were comparable between the overall Pittsburgh site population and analytic sample with MRI and PFS scores (Table 1).

The mean physical and mental fatigability scores were 20.2±9.1 and 15.8±9.7, respectively, and 65.5% of people who completed both the MRI and PFS were categorized as having higher fatigability for both the physical and mental fatigability. There was overlap between participants in high physical and mental fatigability categories, but not all of the participants who scored high for physical fatigability scored high for mental fatigability. The mean usual paced 400m walk time was 491.8±119.6s and the average usual gait speed was 0.81±0.20 m/s.

Table 1. Baseline Characteristics of the Pittsburgh Field Center and Analytic Sample from the Lifestyle Interventions and Independence for Elders Study

|  |  |  |
| --- | --- | --- |
| **Characteristic** | **Pittsburgh Field Center****(N=216)** | **Analytic** **Sample****(N=29)** |
| **Age, years**  | 78.5±5.1\* | 77.2±5.5 |
| **Race, Caucasian/white** | 154(71.3)\*\* | 11(37.9) |
| **Sex, Female** | 166(78.7) | 25(86.2) |
| **Education, ≥ High School, years** | 127(58.8) | 9(31.0) |
| **Smoking Status, Former or Current Smoker**  | 95(44.4) | 10(34.5) |
| **Body mass index (m/kg2)** | 30.6±5.9 | 31.4±4.9 |
| **Cardiovascular disease, Yes, Self-report**  | 63(29.2) | 6(20.7) |
| **Diabetes mellitus, Yes, Self-report**  | 56(25.9) | 10(34.5) |
| **Depression Score, ≥16** | 37(17.6) | 4(13.8) |
| **Physical Fatigability Score, 0-50** | - | 20.2±9.1 |
| **Mental Fatigability Score, 0-50** | - | 15.8±9.7 |
| **Usual gait speed, m/s** | 0.78±0.16 | 0.81±0.20 |
| **Usual-paced 400-m walk time, seconds** | 530.8±123.0 | 491.8±119.6 |
| **Short Physical Performance Battery Score, 0-12** | 7.3±1.6 | 7.6±1.4 |
| **Modified Mini-Mental State Examination Score, 0-100** | 91.6±5.5 | 90.9±5.7 |
| **Digit Symbol Substitution SubTest Score** | 48.0±12.6 | 44.8±13.0 |
| *\* Mean± Standard Deviation**\*\* N(%)* |  |  |

The baseline characteristics of the analytic sample from the LIFE study by fatigability status are presented in **Table 2**. There were no significant differences by higher and lower physical fatigability status for age, race, sex, education, smoking status, BMI, cardiovascular disease, diabetes mellitus, depression, 3MS score or DSST (all p>0.1). Those with higher physical fatigability had significantly lower SPPB scores (p=0.01) than those with lower fatigability.

Higher Mental fatigability status was significantly associated with older age (p=0.09), smoking status (p=0.05), and lower SPPB score (p=0.06) but was not associated with race, sex, education, BMI, cardiovascular disease, diabetes mellitus, depression, 3MS score and/or DSST score(all p>0.1)

For both physical and mental fatigability, usual gait speed and 400 meter walk times were significantly slower for those with higher compared with lower fatigability (Table 2).

Table 2. Baseline Characteristics of the Analytic Sample from the LIFE Study by Fatigability Status (N=29)

|  |  |
| --- | --- |
|  |  **Fatigability Status** |
| **Characteristic** | **Higher** **Physical****(n=19)** | **Lower** **Physical****(n=10)** | **Higher** **Mental****(n=19)** | **Lower** **Mental****(n=10)** |
| **Age, years** | 77.5±5.9\* | 76.6±4.9 | 78.5±5.6a | 74.9±4.6a |
| **Race, Caucasian/White** | 9(47.4)\*\* | 2(20.0) | 8(42.1) | 3(30.0) |
| **Sex, Female** | 17(89.5) | 8(80.0) | 17(89.5) | 8(80.0) |
| **Education≥ High School, years** | 6(31.6) | 3(30.0) | 5(26.32) | 4(40.0) |
| **Smoking Status, Former or Current** | 5(26.3) | 5(50.0) | 4(21.1)a | 6(60.0)a |
| **Body Mass Index(m/kg2)**  | 31.6±5.2 | 30.8±4.4 | 31.3±5.0 | 31.5±5.0 |
| **Cardiovascular Disease, Yes, Self-Report** | 5(26.3) | 1(10.0) | 4(21.1) | 2(20.0) |
| **Diabetes Mellitus, Yes, Self-Report** | 7(36.8) | 3(30.0) | 7(36.8) | 3(30.0) |
| **Depression Score, ≥16** | 4(21.1) | 0(0.0) | 4(21.1) | 0(0.0) |
| **Usual gait speed, m/s** | 0.73±0.15a | 0.96±0.20a | 0.76±0.20a | 0.90±0.16a |
| **Usual-paced 400-m walk time, seconds** | 523.2±131.0a | 432.2±64.1a | 519.5±127.2a | 439.3±86.1a |
| **Short Physical Performance Battery Score, 0-12** | 7.2±1.5a | 8.5±0.7a | 7.3±1.5a | 8.2±1.3a |
| **Mini-Mental State Examination score**  | 91.1±6.0 | 90.3±5.2 | 90.5±5.7 | 91.7±5.8 |
| **Digit Symbol Substitution SubTest Score** | 47.0±13.0 | 40.8±12.8 | 46.4±12.5 | 41.9±14.2 |
| *\* Mean± Standard Deviation**\*\* N (%)*1. *Significant at p<0.1*
 |  |  |  |  |

**Table 3** shows the t-tests and non-parametric test results for *a priori* specified brain regions of interest by fatigability status. For the right hippocampus, mean (SD) grey matter volume (GMV) was lower for those with higher fatigability compared to lower fatigability for physical measures, p=0.07. Similar associations were found for the right putamen (p=0.05) and left and right thalamus, p=0.04 and p=0.08, respectively. The associations were similar for mental fatigability for the right hippocampus and thalamus with addition of the right cingulum posterior (p=0.05) and left (p=0.02) and right amygdala (p=0.05) (Table 3).

Table 3. Means (SD) Grey Matter Volume as a Percentage of Intracranial Volume (nm3) by Fatigability Status (LIFE, N=29)

|  |  |  |
| --- | --- | --- |
| **Region of Interest** | **Physical Fatigability** | **Mental Fatigability** |
| **Higher(n=19)** | **Lower(n=10)** | **Higher(n=19)** | **Lower(n=10)** |
|  |  |  |  |  |
| **Whole brain** | 27.21(1.44) | 27.54(1.05) | 27.20(1.49) | 27.56(0.91) |
| **Left Subcortical Structures**  |  |  |  |  |
| **Amygdala** | 0.07(0.01) | 0.08(0.01) | **0.07(0.01)b** | **0.09(0.01)b** |
| **Caudate** | 0.26(0.03) | 0.26(0.03) | 0.26(0.03) | 0.26(0.04) |
| **Cingulate Anterior** | 0.24(0.05) | 0.23(0.04) | 0.24(0.03) | 0.24(0.04) |
| **Cingulate Middle** | 0.28(0.06) | 0.25(0.04) | 0.27(0.06) | 0.26(0.04) |
| **Cingulate Posterior d** | 0.07(0.02) | 0.06(0.01) | 0.07(0.02) | 0.07(0.01) |
| **Frontal Middle** | 0.69(0.06) | 0.69(0.05) | 0.69(0.06) | 0.68(0.05) |
| **Frontal Middle Orbital d** | 0.12(0.03) | 0.12(0.02) | 0.12(0.03) | 0.11(0.02) |
| **Frontal Superior Medial** | 0.41(0.06) | 0.42(0.04) | 0.41(0.06) | 0.41(0.04) |
| **Hippocampusd** | 0.28(0.04) | 0.28(0.02) | 0.27(0.04) | 0.28(0.02) |
| **Putamend** | 0.25(0.04) | 0.27(0.04) | 0.25(0.03) | 0.28(0.06) |
| **Thalamus** | **0.29(0.03)b** | **0.31(0.02)b** | **0.29(0.03)b** | **0.31(0.02)b** |
| **Right Subcortical Structures** |  |  |  |  |
| **Amygdala** | 0.08(0.02) | 0.09(0.01) | **0.08(0.01)a** | **0.09(0.01)a** |
| **Caudate** | 0.29(0.04) | 0.29(0.06) | 0.29(0.04) | 0.28(0.04) |
| **Cingulate Anterior** | 0.23(0.04) | 0.22(0.03) | 0.22(0.03) | 0.23(0.04) |
| **Cingulate Middle** | 0.31(0.06) | 0.30(0.04) | 0.31(0.07) | 0.30(0.04) |
| **Cingulate Posterior d** | 0.05(0.01) | 0.05(0.01) | **0.04(0.01)b** | **0.05(0.01)b** |
| **Frontal Middle** | 0.67(0.07) | 0.67(0.05) | 0.68(0.07) | 0.64(0.02) |
| **Frontal Middle Orbital d** | 0.14(0.02) | 0.13(0.02) | 0.14(0.02) | 0.13(0.02) |
| **Frontal Superior Medial** | 0.33(0.05) | 0.33(0.04) | 0.32(0.06) | 0.33(0.04) |
| **Hippocampus d** | **0.26(0.04)b** | **0.27(0.02)b** | 0.26(0.04) | 0.28(0.02) |
| **Putamen d** | **0.27(0.05)b** | **0.29(0.03)b** | 0.27(0.04) | 0.30(0.06) |
| **Thalamus** | **0.28(0.03)a** | **0.31(0.02)a** | **0.28(0.03)c** | **0.31(0.02)c** |
| *a. Significant at p<0.1*1. *Significant at p<0.05*
2. *Significant at p<0.01*
3. *Non=parametric test*
 |

**Table 4** includes the logistic regression models for each brain region that was significantly associated with physical and mental fatigability identified by univariate t-tests. Every one unit decrease in GMV in the left thalamus, the odds of higher mental fatigability significantly increased by 27.6% (OR=0.724, 95%CI: 0.529, 0.991, p=0.04). For every one unit decrease in GMV in the right thalamus, the odds of higher mental fatigability significantly increased by 39% (OR: 0.610, 95% CI: 0.407, 0.912, p=0.02). Adjusting for age, for every one unit decrease in GMV in the right thalamus, the odds of higher mental fatigability significantly increased by 36.5% (OR: 0.635, 95% CI: 0.418, 0.964, p=0.03). Adjusting for smoking status, for every one unit decrease in GMV in the left thalamus, the odds of higher physical fatigability significantly increased by 28.6% (OR: 0.714, 95%CI: 0.517, 0.985, p=0.04). For every 1 unit decrease in GMV in the left thalamus, the odds of higher mental fatigability significantly increased by 35.4% (OR: 0.646, 95% CI: 0.444, 0.939, p=0.02). For every one unit decrease in GMV in the right thalamus, the odds of higher mental fatigability significantly increased by 54.3% (OR: 0.457, 95% CI: 0.240, 0.869, p=0.02). There were no significant associations between brain regions of interest and fatigability except for the thalamus.

Table 4. Associations of Anatomical Brain Regions from 7T MRI Scans on Categorical Physical and MentalFatigability Scale (LIFE, N=29)

|  |  |
| --- | --- |
|  | **Physical Fatigability** |
|  | **Model 1.** **Unadjusted** | **Model 2.** **Adjusted for** **age** | **Model 3.** **Adjusted for** **smoking status** |
| **Region of Interest**  | **OR (95% CI)** | **OR(95% CI)** | **OR(95% CI)** |
| **Amygdala (L)** | 0.600(0.264, 1.367) | 0.600(0.250, 1.441) | 0.622(0.266, 1.454) |
| **Amygdala(R)** | 0.716(0.385, 1.333) | 0.725(0.380, 1.384) | 0.821(0.408, 1.654) |
| **Cingulate Posterior(R)** | 1.016(0.475, 2.174) | 1.039(0.481, 2.243) | 0.918(0.414, 2.038) |
| **Hippocampus(R)** | 0.898(0.712, 1.131) | 0.902(0.714, 1.139) | 0.870(0.683, 1.108) |
| **Putamen(R)** | 0.907(0.756, 1.089) | 0.909(0.756, 1.093) | 0.937(0.770, 1.140) |
| **Thalamus(L)** | 0.745(0.550, 1.010) | 0.747(0.550, 1.014) | **0.714(0.517, 0.985)a** |
| **Thalamus(R)** | 0.750(0.549, 1.024) | 0.730(0.519, 1.028) | 0.724(0.516, 1.015) |
|  | **Mental Fatigability** |
|  | **Model 1. Unadjusted** | **Model 2.****Adjusted for** **age** | **Model 3.****Adjusted for** **smoking status** |
| **Region of Interest** | **OR(95% CI)** | **OR(95% CI)** | **OR(95% CI)** |
| **Amygdala (L)** | 0.408(0.155, 1.073) | 0.490(0.184, 1.304) | 0.385(0.129, 1.153) |
| **Amygdala(R)** | 0.498(0.239, 1.036) | 0.556(0.263, 1.172) | 0.609(0.273 1.357) |
| **Cingulate Posterior(R)** | 0.660(0.307, 1.419) | 0.706(0.313, 1.594) | 0.486(0.199, 1.190) |
| **Hippocampus(R)** | 0.865(0.681, 1.099) | 0.876(0.682, 1.124) | 0.808(0.620, 1.052) |
| **Putamen(R)** | 0.866(0.708, 1.060) | 0.849(0.664, 1.084) | 0.914(0.734, 1.139) |
| **Thalamus(L)** | **0.724(0.529, 0.991)a** | 0.721(0.514, 1.012) | **0.646(0.444, 0.939)a** |
| **Thalamus(R)** | **0.610(0.407, 0.912)a** | **0.635(0.418, 0.964)a** | **0.457(0.240, 0.869)a** |
| *(L)=Left subcortical; (R)=Right subcortical* *a. Significant at p<0.05* |  |

# Discussion

This study is the first to investigate an association between fatigability and brain structures in healthy older adults. We found that higher physical fatigability scores were inversely related to grey matter volumes for the hippocampus, putamen, and thalamus compared to lower physical fatigability. Those with higher mental fatigability had lower grey matter volumes for amygdala, cingulate posterior and thalamus compared to people with lower fatigability.

The direction of these findings is consistent with the hypothesized association between brain metrics and fatigability status, where those with higher fatigability had lower grey matter volume. We evaluated the relationship between various brain regions previously identified as regions of interest in the fatigue and brain literature. All of the regions analyzed in this study were identified as important regions for fatigability, and therefore were incorporated into the analyses. We expected the strongest relationship to be with the basal ganglia, which has previously been identified as neural correlate of fatigue in healthy younger adults (Nakagawa et al., 2016). Our findings suggest that the putamen, a component of the basal ganglia, may play a role specifically for physical fatigability. However, we found that the thalamus may play an even more significant role in physical and mental fatigability outcomes.

Based on our findings, the brain regions associated with the PFS metrics differ by type of fatigability. Physical fatigability was associated with the hippocampus, putamen and the thalamus, where mental fatigability was associated with the amygdala, posterior cingulate, and the thalamus. The thalamus was the only brain region that was consistently observed for both physical and mental fatigability. We speculate that this association may have been observed because the thalamus serves a central network in relaying signals to other regions of the brain, and thus, it may play many different roles in the postulated mechanisms related to fatigability. Our findings highlight the importance of evaluating both physical and mental fatigability. We speculate that the mechanisms involved in fatigability pathophysiology may vary depending on whether or not the task evaluated with the PFS was more or less physically and cognitively demanding.

Both the left and right thalamus and amygdala were associated with fatigability measures. Associations between the posterior cingulate, hippocampus, and the putamen were only observed in the right subcortical structures. Based on the previous literature, the theory of hemispheric lateralization may elude to differences associations by hemisphere type where emotional processing is represented asymmetrically in cerebral hemispheres (Alves, Fukusima, & Aznar-Casanova, 2008; Silberman & Weingartner, 1986). Emotional lateralization refers to the concept that emotions are better recognized and controlled by the right hemisphere. Their work suggests the right hemisphere may be particularly important for interpreting negative emotions, where the left is primarily involved in positive emotions. Although we cannot confirm that perception of fatigability is driven by emotion, it is plausible that perception of fatigability may have an emotional component, which may explain why we observed a greater number of significant associations in the right subcortical structures rather the left.

We have identified a number of plausible mechanisms for the associations observed in our study. First, hippocampal grey matter volumes were significantly associated with *physical* fatigability. The hippocampus, which is involved with the stress response, has previously been identified as a region of the brain that interacts with dopaminergic systems related to motivational behavior (Calabresi, Castrioto, Di Filippo, & Picconi, 2013). A recent study of younger adults identified the basal ganglia as a critical region involved in fatigue, but not the hippocampus. To our knowledge, we are the first group to identify the hippocampus as a brain region involved in perception of physical fatigability. Plausible mechanisms for the hippocampus’s role in fatigability may be related to neuronal loss in dopaminergic pathways seen in the hippocampus, which has previously been explored in the context of fatigue (Calabresi et al., 2013). Although our work could not explore these mechanisms, previous evidence of hippocampal involvement in the dopaminergic pathway which has been related to fatigue outcomes supports our finding that the hippocampal grey matter volume may be related fatigability in older adults.

The putamen was also significantly associated with *physical* fatigability. The putamen has previously been implicated in motor control and learning habits and skills (Balleine & O’Doherty, 2010; Durieux, Schiffmann, & de Kerchove d’Exaerde, 2011). It is a primary component of the basal ganglion. The basal ganglion has previously been identified as a neural correlate of fatigue in healthy younger adults (Nakagawa et al., 2016). Motivation and reward theories related to fatigue are also associated with the dopaminergic system (Mizuno et al., 2016). Relationships between dopamine functioning and basal ganglia were not explored in the present study however, it is speculated that the relationship between physical fatigability and the putamen may be related to dopamine functioning that plays a role in motivation and reward. Direct measures of dopamine functioning may be useful in future works to better understand if the association observed between the putamen and physical fatigability outcomes was attributed to changes or interruptions in dopaminergic function.

The amygdala was found to be significantly associated with *mental* fatigability. Feelings associated with mental fatigability may have an impact on motivational behavior. Previously, fatigue has been described as an emotion that is affected by factors such as motivation and drive (Gibson et al., 2003). The conscious sensation of fatigue or perception of fatigability may be related to other emotions such as anger, fear and memory of a prior activity (Gibson et al., 2003). As such, these feelings may be implicated in feelings of fatigability associated with a specific activity at a certain intensity or duration. To our knowledge, we are the first to explore the amygdala as a localized brain structure associated with perception of fatigability. However, given that fatigue has been postulated to be a sensation in the conscious awareness of changes in subconscious homeostatic control systems, it is plausible that the amygdala may play a role in neural networks that may induce fatigability states as a result of changes in a level of a specific activity.

Similarly, the posterior cingulate cortex was also associated with *mental* fatigability outcomes. In the present study, we define mental fatigability as a measure of the body’s susceptibility to fatigue related to physical and mental activities that engage cognitive function. Based on our definition, we postulate that mechanisms related to mental fatigability through the posterior cingulate cortex may be related to inefficient cognitive function, which is implicated in perceptions of fatigability related to demanding tasks that specifically involve cognitive control (Leech & Sharp, 2014). The posterior cingulate cortex has notably been identified as a highly connected region of the brain that has a high baseline metabolic rate (Hagmann et al., 2008; Raichle et al., 2001). The high metabolic state of the posterior cingulate is responsive to an individual’s cognitive state, where a demanding task such as a perceptual decision or a motor response is required. Additionally, the activity of the posterior cingulate cortex in a healthy brain is related to cognitive load where failure to appropriately deactivate the brain region is associated with inefficient cognitive function in both the healthy and damaged brain (Singh & Fawcett, 2008) (Bonnelle et al., 2011, 2012; Crone et al., 2011; Sonuga-Barke & Castellanos, 2007; Weissman, Roberts, Visscher, & Woldorff, 2006) These works suggest that control of this region has implications for efficient cognitive function.

Further, the cingulate cortex has previously been identified as a region of interest for fatigue outcomes among multiple sclerosis (MS) patients (Pardini et al., 2015). We did not have participant information available to determine if fatigability outcomes were attributed to MS symptomology. However, participants enrolled in the present study were free of neurologic disease, so it was unlikely that they would have MS symptoms. We postulate that the cingulate may be a brain region that may be related to fatigability outcomes among both clinical and non-clinical cases. Further exploration is necessary to determine the cingulate cortex’s role in fatigability.

Both *physical* and *mental* measures for fatigability were associated with the thalamus. The thalamus, an important relay center in the brain, may be related to fatigability, because all pathways that project to the cerebral cortex do so after synapsing in the thalamus (“Blumenfeld 2E Neuroanatomy Through Clinical Cases.pdf,” n.d.). Previously, it has been speculated that interruption in the striatocortical fiber loop associated with the basal ganglia circuitry may be related to symptoms of central fatigue (Chaudhuri & Behan, 2000). A change in thalamic activity has also been postulated as reasons for perceived higher fatigability (Chaudhuri & Behan, 2000).

The thalamus is the final common pathway of the cortiocofugal projections from the basal ganglia and thus, if there is an increase in thalamic inhibition or a shift in reciprocal state of activation between the thalamus and the subthalamic nucleus the cortical response to the input of the basal ganglia will be modified (Chaudhuri & Behan, 2000). Additionally, in the event the dopaminergic drive to the palliothalamo-cortical loop is reduced, frontal activation will be suppressed. Therefore, there is a motivational influence of the striato-thalamic input to the frontal lobe that may be related to perceived fatigability. It is important to note that alterations in the thalamo-cortical loop have been shown to be associated with Parkinson’s Disease and depression, which commonly report symptoms of fatigue (McCormick, 1999).

The anterior portion of the thalamus has a significant number of connections to the limbic system. More specifically, one of the primary targets of afferent fibers is the hippocampal formation that projects to the cingulate gyrus of the limbic association cortex and the parahippocampal gyrus(Patestas & Gartner, 2016). The association with the limbic system means that this portion of the thalamus plays a role in expression of emotions, and it is believed to be associated with learning and memory processes, and attention. (Patestas & Gartner, 2016). Thus, there are implications for mental fatigability outcomes related to thalamic activity.

Additionally, Dobryakova et al. reported that dopamine may have an important role in fatigue (Dobryakova, Genova, DeLuca, & Wylie, 2015). Their work suggested that fatigue may result from the disruption of communication between the striatum and prefrontal cortex (Dobryakova et al., 2015). These findings have previously been supported by advances in fatigue therapy that suggest fatigue has been alleviated in individuals with brain injury, chronic fatigue syndrome and cancer patients after patients underwent dopaminergic psyschostimulant medication.

There is considerable evidence to support that the neural correlates of fatigability we identified are consistent with previously identified brain regions, specifically regions related to the dopaminergic pathway and motivation and reward behaviors. The motivation theory described previously may best capture the mechanism by which fatigability occurs in older adults. An individual’s perception of their fatigue related to specific tasks may be influenced by how motivated an individual is to complete a specific task. It is plausible that low motivation to complete specific tasks may drive fatigability outcomes, or alternatively, a fatigability state may lead to lower motivation to complete tasks. These mechanisms related to fatigability pathophysiology could not be explored in our work; however, the work of others supports the findings from our identification of neural correlates of fatigability in a small sample of older adults.

A few limitations of this study have been identified. First, the design was cross-sectional and thus, the results cannot be used to determine causality between brain regional volume and fatigability. Additionally, we cannot evaluate differences in fatigability status over time. In order to address this gap in the literature, a prospective study design to confirm causality is necessary. Due to the novel nature of this work, we are limited in our ability to compare findings to the work of others. Lastly, results from these analyses should be interpreted with caution due to the small sample size. However, this work is exploratory in nature and may be imperative for development of future studies that aim to explore the pathophysiology of fatigability. Also, an oversampling of African Americans in the second half of the main LIFE study recruitment period resulted in a greater number of African Americans in our analytic sample compared to the Pittsburgh field center sample. Consequently, the racial imbalance may result in limited generalizability.

We have identified a number of strengths in this work. First, participants enrolled in the LIFE study are relatively representative of a large segment of the older adult population in the United States. As such, the findings from this study have implications for generalizability. Also, the PFS is validated against objective performance fatigability measures and can be used as an easy questionnaire in-person, over the phone, or self-administered. Compared to other scales, the PFS is a better measure of fatigue, and it has never been used to examine these relationships. 7T is a novel neuroimaging modality that allows investigators to capture regions of interest at high resolution.

In conclusion, fatigability outcomes in healthy older adults may be related to volumes of the amygdala, cingulate posterior, hippocampus, putamen, and thalamus. Plausible mechanisms for fatigability outcomes based on existing literature include alterations in dopaminergic function, regulation of sleep and sensory interpretation, and emotional formation and processing, learning and memory, and/or motivational behavior. It is speculated that the neural correlates of fatigability in non-clinical and clinical subjects may overlap. However, more work is necessary to further evaluate the brain regions related to fatigability in healthy older adults.

The literature on fatigability is limited, especially in the context of brain studies. Therefore, future studies at the intersection of neurobiology and population neuroscience research are needed to fully understand the pathophysiology of fatigability in older adults. These findings are significant to public health, because interventional success for fatigability and consequently functional limitation, disability and mortality, relies on a clear understanding of the disablement pathway. The risk factors associated with fatigability in older adults may involve multiple casual pathways. There is evidence to support that the brain may play a critical role in the development of fatigability. We have identified the amygdala, posterior cingulate, hippocampus, putamen and thalamus as brain regions that may play a role in fatigability outcomes, and they should be investigated in the future as brain regions related to downstream effects associated with fatigability.

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