THE EFFECT OF EXERCISE ON EXECUTIVE FUNCTIONING AND GAIT SPEED IN PATIENTS WITH MILD COGNITIVE IMPAIRMENT

BY

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LIST OF ABBREVIATIONS

AD	Alzheimer's Disease
MCI	Mild Cognitive Impairment
MoCA	Montreal Cognitive Assessment
MMSE	Mini-Mental State Exam
SES	Social Economic Status
SPPB	Short Physical Performance Battery
400MWT	400 Meter Walk Test
LIFE	Lifestyle and Independence for Elders
EF	Executive Function
DSST	Digit Symbol Substitution Test
TMT	Trail Making Test
DAD	Disability Assessment for Dementia
HRR	Heart Rate Reserve
SOPT	Self-Ordered Pointing Test

ABSTRACT

Background: It is estimated that approximately 16 million older Americans have mobility disability[1]. Although there are many factors that influence mobility disability, several studies utilizing diverse study designs have found interesting relationships among executive function (EF) and mobility in older adults. Aerobic exercise offers a potential modality to investigate the relationships between executive functioning and mobility. **Objective:** Examine the relationships among measures of EF and gait speed in older adults with diagnosed MCI. **Methods:** Seventy-one older adults with MCI (mean age 65 years, 66% female, and mean gait speed of 1.4±0.20 m/s) were included using data from the Piedmont Aging, Cognition, & Exercise Study 2 (PACE-2). Participants were randomized into an aerobic or stretching/balance intervention group for the 6-month study. Gait speed (m/s) was measured via the 400MW. EF Was assessed with the trail making test A (TMT-A), B, (TMT-B) and B-A (TMT B-A), and verbal fluency. **Results:** There were no statistically significant differences between intervention groups in gait speed at follow up ($p = 0.989$). A regression model that included race, sex, treatment condition, age, measures of EF significantly predicted gait speed changes (R^2adj = 0.47; $p < 0.05$). Furthermore, TMT-B was the only variable in the regression analysis that was statistically significant (Standardized B = -0.002; $p = 0.002$). **Conclusion:** Although the present study did not find improvements in gait speed resulting from exercise interventions in patients with diagnosed mild cognitive impairment, it did find a significant relationship between a component to EF (i.e., shifting) and improvements in gait. Future research is needed that seeks to integrate cognitively challenged activities with physical activity to maximize benefits to mobility.

INTRODUCTION

It is estimated that approximately 16 million older Americans have mobility disability, which is defined here as the inability to ambulate without assistance[1]. Mobility disability is extremely devastating because it takes away the individual's independence and increases isolation, institutionalization, and risk of falls[1]. Obstacles like these also create a major healthcare burden, coming either from the needs of the patient or requirements of caregivers. Although there are many factors that influence mobility disability, several studies utilizing diverse study designs have found interesting relationships among executive function (EF) and mobility in older adults. EF is an essential component of cognition as it is responsible for inhibition, shifting, and updating. Dual tasking trials, which compare mobility and cognitive performance while completing a single task (e.g., walking) to dual tasks (e.g., simultaneously completing a cognitive or motor task) consistently demonstrating declines in performance in dual tasks compared to single tasks. A massive longitudinal study[2] (N = 4,431) was conducted with older adults examining the effects of both a cognitive and motor task while ambulating. During the motor task the participants walked at a normal pace while carrying a full glass of water. The cognitive task required the subjects to recite alternating letters of the alphabet. Both of these tasks challenge the EF function portion of the brain by stressing the working memory and one's ability to switch their attention between tasks. Immediate recall and processing speed were both significantly reduced when participants were given tasks while walking.

Although the majority of studies have been done on healthy older adults, Holtzer and colleagues[3] found those with neurological disorders not only had decreased attention, memory, and language but were found to have much worse gait speed than those without. This population showed decreased gait speed during usual walking, simple task, complex task, and serial 7's[3]. Although studies have documented consistent relationships between cognition and mobility, the direction of the relationship remains unclear. From the results of this study it is unknown whether improvements in cognition can lead to improvements in mobility.

Aerobic exercise offers a potential modality to investigate the relationships between executive functioning and mobility. Numerous studies have shown that aerobic exercise can improve aspects of brain structure and function in older adults[4]. Additionally, several studies have shown that aerobic exercise can improve mobility in older adults[5,6]. For example, the LIFE Study, the largest randomized controlled trial to test the impact of regular aerobic exercise on mobility in older adults with impairments in lower extremity functioning, found that older adults participating in aerobic exercise had decreased risk of mobility disability, defined as the inability to complete the 400 meter walk test (400MWT) as compared to a healthy aging education condition[6]. Interestingly, however, this study did not find significant improvements in cognition resulting from exercise[7]. This may be because a) the LIFE Study sample was cognitively healthy and b) the sample was not able to achieve the exercise intensity required to produce changes in cognition due to lower extremity impairment[8].

To date only one study has looked at the association between changes in improved EF with improved mobility[9]. Analyses showed changes in selective attention, self-efficacy, and conflict resolution are related to improved gait speed in individuals with MCI[9]. However, this study only involved women participating in a program of resistance training only.

Currently, evidence consistently demonstrates that exercise can improve aspects of mobility, such as gait speed. there is a consistent relationship between EF and gait. However, the relationships among improvements in gait speed and EF in older adults with diagnosed cognitive impairment is unknown. This information could potentially help us discover a treatment option to decrease mobility disability, thereby decreasing the rate of falls in individuals with MCI. There is overwhelming evidence that cognitive tasks disrupt gait speed during dual tasking, so this study sought to understand the effects of EF on mobility disability. That is, improvements in cognitive functioning would lead to the improvements seen in mobility disability.

The purpose of this study is to examine the relationships among measures of EF and gait speed in older adults with diagnosed MCI. It is hypothesized that individuals participating in the aerobic group will experience faster gait speed at follow up compared to the stretching and balance group. It is also hypothesized that improvements in EF will be related to improvements in gait speed. To test these hypotheses, this study will analyze data from the Piedmont Aging, Cognition, and Exercise-2 (PACE-2) study. The purpose of PACE-2 was to examine the influence of aerobic exercise on cognition in older adults with MCI. 71 participants were randomized to 6-months of either moderate to high intensity aerobic exercise or stretching, balance, and range of motion exercise. Measures of EF and 400MWT gait speed were collected at baseline and 6-months.

REVIEW OF LITERATURE

Prevalence and Epidemiology of Dementia

Dementia currently affects 50 million people worldwide[10]. It is more prevalent in women, with one in five women being diagnosed by age 85[10]. With 10 million new cases each year, dementia is currently the most common neurological disorder in the world[11]. The annual population cost for dementia is roughly $159 billion, or $215 billion when informal costs, costs accrued outside of direct hospital care, are included[12]. The health and retirement longitudinal study examined demented adults aged 51 years and older and all monetary costs associated with their care[12]. Over this period of time the study accumulated 31,936 person years and found four different domains in which money was spent, including: out of pocket spending, spending covered by Medicare, net nursing home spending, and formal and informal home care[12]. The estimated annual cost per person that could be directly attributed to dementia was roughly $33,329, such that an individual with dementia will likely pay this much more in health care costs[12]. Considering America's rapidly growing older adult population, it is highly likely there will be an even greater health care burden in the future due directly to costs of dementia[12]. It is estimated that the total global cost of dementia is roughly $818 billion[11]. The slow deterioration of the brain causes all bodily processes to gradually deteriorate leading to such a large burden on the healthcare system[13].

Pathophysiology of Dementia

Dementia is caused by the breakdown of neurons and their subsequent synapses with other neurons causing a disruption in the function within the cell, and communication between the cells[14]. Although there are many different causes of dementia, Alzheimer's disease (AD) is the most common cause[11]. AD is thought to be brought about by the buildup of amyloid plaque and tangles of a protein, tau, on the neurons of the brain[15]. Researchers believe the buildup of plaque and tau block communication between neurons and disrupt the processes needed for these cells to survive[13]. If a patient's cognitive decline is thought to be caused by AD a physician may use genetic testing or brain scans. If a brain scan is used, clinicians look for excess amyloid plaque[15]. Although some authors speculate that the presence of amyloid plaque is necessary and sufficient for the diagnosis of AD[15], not all researchers are in agreement of the exact etiology of this neurodegenerative disease[14]. Some believe the aforementioned plaque buildup occurs due to the mutation of the APOE4 gene[10]. The APOE4 gene increases your risk of AD greatly but does not necessarily explain the degeneration of neurons in individuals with AD[13]. The unclear etiology of AD has made the identification of specific risk factors and developing effective therapeutic interventions very difficult.

Assessing Dementia

Exacerbating the challenges in developing effective therapies is the diversity of symptoms and impairments associated with AD-related dementia. The American Psychiatric Association[16] describes dementia as problems with short- and long-term memory, impaired judgement, and personality changes. All such impairments are likely to lead to disturbances in social life, work, or other relationships[16]. There are currently three known stages of dementia: early, middle, and late. In the "early" stage, patients require assistance in common tasks due to the decline in memory, however as the disease progresses, they require help with simple motor tasks, like walking[13]. The "early" stage represents minor forgetfulness and losing track of time[11]. Mild cognitive impairment (MCI) is thought to occur in this early stage of dementia[17]. However, patients with MCI tend to be independent in their activities of daily living and do not see significant detriment to their social or occupational functioning even though there is an observable decline in memory[17]. Individuals experiencing "middle" stage dementia will become forgetful of names, found wandering, or have difficulty communicating[11]. This is typically the stage where individuals begin to lose their independence. For those in the "late" stage of dementia the individual will often have difficulty recognizing friends and family, have trouble walking and taking care of themselves, and may experience mood changes[11]. These different stages help clinicians determine how far along the patient's cognitive decline is and what assistance should be offered so they can be comfortable and successful in their environment.

Further tests have been created in an attempt to standardize the stages of dementia and confirm the diagnosis. The Montreal Cognitive Assessment (MoCA) and the Mini-Mental State Exam (MMSE) are commonly used assessments[17]. Both of these tests are screening tools to identify individuals with more cognitive impairment than expected for their age. The MoCA was found to have an 80-100% sensitivity and 50-76% specificity for detecting disease[17]. The MMSE has a lower sensitivity of 45-60%, but a high specificity at 65-90% detection[17]. MCI may lead to minor inconveniences in the daily lives of those afflicted but is not likely to create major challenges like those that are presented to individuals who are demented. Importantly, MCI has also been linked to movement difficulties[14].

Prevalence and Defining Mobility Disability

Mobility disability, defined here as the inability to ambulate without assistance, is a major public health issue[1]. 13.7% of the United States population is currently living with a mobility disability, 19.4 million of these individuals cannot walk a quarter mile[1]. Over the past eight years ambulatory disability has been the most common type of disability compared to hearing, vision, and cognitive issues[1]. Mobility disability affects the individual's ability to lead autonomous lifestyles. For example, only 24.8% of those with a mobility disability are employed[1]. Ambulation is one task that may seem automatic to most people but becomes increasingly more difficult for older adults due to the natural decline of many of the body's systems. Yogev-Seligmann and colleagues[18] best describe this phenomenon as a "manifest in part by an individual's awareness of destination, the ability to appropriately control the limb movements that produce gait, and the ability to navigate within often complex environs to successfully reach the desired location" (pp. 329). Mobility disability is defined in many different ways in the scientific community. For example the CDC[1] defines mobility disability as having serious difficulty walking or climbing stairs, others define it as the inability to complete the 400MW. Regardless of the formal definition presented, this type of disability makes it extremely challenging to accomplish the tasks necessary to be self-sufficient in their environment[1]. This may include walking long or short distances, or basic self-care. Nagi[19] defines disability as the inability to perform the tasks that are expected of the individual within their cultural norms. This model does not identify differences in the definitions of mental or physical limitations, but rather disability in general. The model has four different domains including bodily functions, activities and functions of daily living, environmental factors, and social or personal factors[19]. Verbrugge and Jette[20] also developed a model which helps to understand the impact of disease on disablement, called the Disablement Process Model. It has been thought that the influence of three variables ultimately leads to disablement: predisposing risk factors, intraindividual factors, and extraindividual factors[20]. These variables may positively or negatively change an individual's life, but disability is only achieved if all three of these phenomena make a negative impact in that individual's life. Risk factors may be age, gender, a specific genetic makeup, or lifestyle. The intraindividual and extraindividual factors influence whether or not the afflicted individual sees functional limitations in his or her life. Extraindividual variables include anything outside of yourself that supports the individual and their ability to cope with the disease. This can include medication, family, or therapy programs. Typically, these variables have a positive impact on the individual and lessen the influence of the disease including the functional limitations it may bring. Intraindividual factors may be positive or negative as they come from any emotions, behaviors, or attributes within the individual. This can include cognitive or behavior changes, mental illnesses, amotivation, or increased motivation. Ultimately, the final stage of the model is disability[20].

Health Conditions that Influence Mobility Disability

Health conditions that may influence mobility include injury, obesity, musculoskeletal disorders, cancer, cardiorespiratory issues, general pain, or metabolic disease[1]. Most diseases and disorders lead to fatigue and discomfort, which can in turn affect one's ability to ambulate effectively. Musculoskeletal diseases, such as arthritis or osteoporosis, affect the major structures necessary for proper movement. The cardiovascular and pulmonary systems are two other bodily structures that are required for proper ambulation. Any diseases that disrupt the cardiorespiratory system can inhibit the body's ability to distribute oxygen to working muscles or cause excessive dyspnea with exertion making mobility extremely difficult. Metabolic diseases, such as diabetes, can also put individuals at risk for mobility disability[1]. If this disorder is not properly controlled, it can lead to lower extremity limb loss or vision problems thereby affecting mobility[1]. Although most risk factors leading to mobility disability are accounted for by health problems, such as the ones listed above, there are other outside risk factors that can also increase one's risk of mobility disability. As described by the Disablement Process Model other risk factors, unrelated to health, such as socioeconomic status (SES) are also associated with mobility impairment. Koster and colleagues[21] argue that SES can contribute to understanding markers of disability, while Shumway-Cook and colleagues[22] argue that mobility disability is worsened due to low SES and the lack of healthcare in that particular population. Koster and colleagues[21] went a step further to determine what, if any, psychosocial factors cause this increased decline in mobility in lower SES people. They reported a statistically significant increased risk of mobility disability in low SES individuals with adverse life events (OR = 1.52), situational long-term difficulties (OR = 1.84), poor coping strategies (OR = 1.47-2.18), and a low locus of control (OR = 3.33)[21].

More research needs to be conducted in order to further solidify these factors; however, it is an excellent starting point in attempting to make appropriate health recommendations for low SES individuals. Satariano and colleagues[23] also determined women are more likely to develop a functional limitation, this is thought to be because of weaker bone composition and less efficient musculoskeletal make up thereby making them more susceptible to mobility disability. Leveille and colleagues[24] also found a higher prevalence of women diagnosed with mobility disability, 22% at the age of 70 years, compared to men, 15%. These epidemiologists also found the rate at which women were getting diagnosed was much greater than men, with 81% of women and 57% diagnosed by 90 years old[24]. It is currently unclear why the prevalence is higher in women than men. Identification of risk factors are key in prevention of mobility issues, but it is also important to determine individual's with ambulatory impairments.

Assessing Mobility Disability: 400-meter walk test

Although numerous measures exist to assess mobility disability in older adults such as the 6-minute walk test[25], 4m corridor walk[26], and the Short Physical Performance Battery (SPPB)[5], few measures have been validated to identify mobility disability. Recent research suggests that the 400m walk test (400MW) is the most reliable, valid, and accessible[5,27]. Newman and colleagues[27] first established the validity of the 400MW in a 5-year cohort study of participants aged 70-79 years old. Originally called the long-distance corridor walk, this test consisted of 10 laps around on a 40m track[27]. Participants were instructed to walk as quickly and safely as possible and walking performance was timed. Researchers assessed systolic blood pressure, diastolic blood pressure, and heart rate on 2,324 people who completed the 400m walk[27]. Myocardial oxygen consumption was calculated by determining the product of SBP and HR and is an indicator of heart health. The average total walk time was 5 minutes and 20 seconds, but times were significantly slower for those in the older age group, women, black participants, and those with subclinical disease markers[27]. The researchers did not clearly identify the cause of slower walk times in women and black individuals; however, many comorbidities can affect walking time due to the impending health deficits on the cardiovascular, pulmonary, and metabolic systems[27]. These comorbidities often cause more stress on the organs and tissues in the body, forcing the heart to work harder at similar workloads when compared to apparently healthy adults. Newman and colleagues[27] concluded a decline in walking ability, or an increased total 400m walk time, was an early marker for disease. The results also indicated that each extra minute on their total walk time was associated with a 52% higher rate of being categorized as having some sort of adverse health event later in life[27]. Furthermore, slower walk time and longer rest time was associated with higher risk for mortality, cardiovascular disease, mobility limitation, and disability. After age and sex adjustments mobility disability was 2.85 times more likely to occur later in life in those who had not completed the 400m walk[27].

Thus, the 400MW has been found to be an important measure of mobility disability and numerous studies have used this test to examine factors related to mobility disability. For example, in prospective cohort study with a follow up of 21 months, researchers examined factors that are related to the occurrence of mobility disability, defined as whether the participant could complete the 400MW[28]. Of the 62 participants that initially completed the 400m walk test, 21 were no longer able to follow up and were subsequently categorized with having a mobility disability[28]. The authors concluded that the strongest predictor of mobility disability at follow-up was the time to complete the course at baseline[28].

In light of the importance of mobility, studies have tested interventions designed to prevent mobility disability. A large-scale randomized trial, the Lifestyle Interventions and Independence for Elders (LIFE), tested whether a structured exercise program could reduce the risk of mobility disability in adults aged 70 to 89 years at high risk for mobility disability[5]. Mobility disability was the primary outcome and defined as the ability to complete the 400MW[5]. Participants (n = 1,635) were randomized to either the physical activity group or a health education group[5]. In the exercise condition, participants engaged in 150 min/wk of walking with strength, flexibility, and balance training and the health education program taught participants about successful aging[5]. The health education group started out weekly for the first 26 weeks, then were held bimonthly[5]. Patients were assessed every 6 months at the clinic, and again after an average of 2.6 years follow up. Pahor and colleagues[5] found the physical activity intervention to be protective against major mobility disability with a 0.82 hazard ratio. This means those that exercise are 18% less likely to suffer from mobility disability compared to those who do not participate in regular exercise. All of the studies discussed above found similar results regarding the strong predictive power of the 400MW and mobility disability as well as the protective effects of exercise[5,27,28].

Gait Speed

Although mobility disability is often defined as whether one can complete the 400MW, this approach creates a dichotomous variable that limits the usefulness of the test. Gait speed during the 400MW has also been used to examine physical functioning in older adults (e.g., Pahor and colleagues, 2014). Gait speed has been found to be useful for researchers and clinicians because it can help identify those with a current disability, it could be used as a diagnostic test for disability, and it could be used to help assess changes in an individual over time[29]. Walking at 0.67 m/sec (1.5 mph) requires roughly 2 METs of energy expenditure, which is roughly the energy level required for basic self-care[29]. Basic self-care may include actions like getting dressed, carrying groceries, or using the restroom. Those who have a gait speed of less than 0.67 m/sec are more likely to suffer from mobility disability and not be able to take care of themselves[29]. The Task Force of the International Academy on Nutrition and Aging has defined a seriously abnormal ambulatory speed to be less than 0.6 m/s, mildly abnormal is between 0.6 - 1.0 m/s, 1.0 - 1.4 m/s is considered normal, and 1.4 m/s or higher puts the individual in a superior category for walking[29].

Impact of Exercise on Gait Speed

After researchers developed normal ranges for gait speed, questions arose about the impact of exercise on gait speed. One study conducted in 2011 examined the impact of physical activity and weight loss on mobility in overweight and obese, sedentary older adults aged 60-79 years old with past cardiac issue[6]. Participants were randomized into a weight loss and physical activity (WL and PA) intervention, physical activity (PA), or a successful aging intervention group[6]. Those in the WL and PA group were asked to participate in 48 sessions of intensive PA that lasted 90 minutes three days a week, along with caloric restrictions for the 18-month period[6]. The PA group was asked to reach 150 min/wk or more or PA at a moderate intensity, with 3 group exercise sessions a month[6]. Lastly, the successful aging group attended a total of 18 sessions and learned about healthy aging, disease, nutrition, and mental health[6]. As the months progressed, the interventionists became less involved in all three groups in order to focus more on autonomy. In order to assess mobility, the researcher's used 400m walk time at baseline, 6 months, 12 months, and 18 months. At 6 months, there was statistical significance (P = 0.002) in both the WL and PA group as well as the PA only group, however, this trend did not continue at the end of the 18-month study for the PA only group[6]. This study found moderate intensity aerobic exercise intervention did improve mobility in older, sedentary, cardiovascular impaired adults when combined with caloric restriction and weight loss[6]. The authors of this study rationalized weight loss as an essential aspect in creating long term improvements in mobility[6].

The LIFE study, discussed earlier in this paper, also sought out to determine if aerobic exercise would improve mobility. The study was conducted on sedentary older adults, aged 70-89 years, who were at risk for mobility disability based on the SPBB[5]. Ultimately, the PA intervention significantly reduced mobility disability compared to the health education group (P = 0.03)[5]. This intervention also improved 400MWT by approximately 16 seconds in the sample population[5]. Pahor and colleagues[5] concluded structured PA as a feasible and effective intervention to decrease mobility disability in vulnerable populations. Both of these studies effectively showed the positive impact an aerobic intervention has on mobility in functionally limited older adults.

Cognition's Impact Gait Speed

Since gait speed has been found to be an instrumental predictor of mobility disability it is important to understand the risk factors impacting one's rate of ambulation. Sauvaget and colleagues[2] also found gait speed to be a major predictor for mobility disability in a sample of 1,358 Japanese men and women with dementia. However, the authors of this study defined mobility disability as the inability to perform regular and instrumental activities of daily living rather than one's ability to complete the 400MW[2]. Effective gait requires many higher order commands from the brain. Sauvaget and colleagues[2] found a similar relationship and concluded dementia to be a strong predictor of functional disability, even when adjusted for age, sex, and history of stroke, with an odds ratio of 14. This is to say those with dementia are 14 times more likely to have a mobility disability as defined by the inability to do certain activities necessary for daily living.

One study looked at aging in 1,478 healthy adults (M age = 79 years) over a 5-year time span and determined how it affects cognition and gait[30]. It is known that aging naturally leads to a decline in almost all cognitive and bodily functions, but large decrements in functioning are typically due to disease or impairment[30]. These participants were evaluated every 15 months on gait speed via the 25m walk, as well as several measures of global cognition: processing speed, short term memory, EF, verbal fluency, and sustained attention[30]. Over the five years of the study, cognition and gait both declined[30]. Although this was an expected outcome, it is important to emphasize what normal aging looks like so there is some sort of baseline for individuals who experience any ailments that could affect this process. Abnormal aging, in this case, includes any older adults who suffer critical cognitive decline or mobility disability. Over the 5 years researchers found faster gait speed at baseline was associated with less cognitive decline[30]. Studies like these have helped direct researcher's attention toward declining cognition and how it greatly affects mobility.

In particular, Hajaar and colleagues[31] found a relationship between gait speed and executive function (EF). The study concluded there was a cluster phenomenon between individuals with slow gait, low EF, and depression[31]. This particular sample (N=765) consisted of healthy older adults, who completed the short physical performance battery and used a 4m course to assess gait speed[31]. Participants also completed the TMT-A and TMT-B to identify the level of EF. After further analysis the researchers found the phenotype does exist for individuals who have depression, low EF, and slow gait speed, but this phenotype does not exist if memory is switched out for EF in the cluster[31]. Hajjar and colleagues have identified a clear relationship between EF and gait speed, rather than any other feature of cognition, that needs to be further evaluated[31].

Executive Function

EF is defined as a higher order of processing used to form abstract ideas, create flexibility in thought, and generate the ability to reason[32]. Royall and colleagues[33] emphasizes that EF is a regulatory function because it controls the execution of complex activities. EF could be described as the area of the brain that makes human beings so special from other mammals. EF requires the integration of many different parts of the prefrontal cortex, making proper neuron firing and circuitry in order for it to work effectively[32]. EF has been found to be particularly vulnerable to age-associated decline and associated impaired activities of daily living[18]. Age-related atrophy of the brain and deterioration of the neurons due to a decrease in dopaminergic activity in the prefrontal cortex can lead to an impaired EF response[18]. Individuals with dementia have difficulty making and executing short- and long-term goals due to impairments in the following: planning, reasoning, organization, follow through, social appropriateness, judgment, and problem solving [33]. Although some age-related decline is normal, the magnitude varies depending on the individual's risk factors. Due to the pathology of dementia, some researchers believe EF impairment is a primary feature of dementia and the diagnosis[33]. It is clear that EF is imperative for normal human behavior in society, as well as for an individual to live an autonomous life.

EF controls many different actions performed on a daily basis therefore making it an essential function for autonomy. Furthermore, numerous complex and interrelated functions are involved EF. In light of the importance of EF, researchers have described working models of EF to guide research and assessment. Miyake[34] reviewed the literature and proposed a 3-factor working model of EF, which included: shifting between tasks, updating, and the inhibition of responses[34]. Task shifting involves the ability to first disengage from an irrelevant task and focus on the important task set at hand[34]. An example of this may be seen when someone is watching television and a baby begins to cry. One must be able to shift their attention from the show they are watching to the crying child. Miyake and colleagues[34] found engagement may not be the only role in shifting, but also the inability to perform a new task in the face of distractions. Distractions can be extremely devastating for individuals with an impaired cognition in day to day life for activities such as driving or having a fluid conversation. On a neurological level, researchers believe shifting occurs between different lobes of the brain requiring the proper, efficient firing of neurons[34]. It is the inability of these neurons to fire appropriately that is a trademark of dementia.

The second part of EF, updating, requires manipulating information given to you in your environment[34]. This is most often seen when doing more complex math equations that require one to remember the previous total while continuing to further manipulate the number. This requires constant updating since we are always being presented with new information that needs to be evaluated and stored accordingly. Lastly, inhibition, which in this context means resisting a dominant or automatic response to some stimulus[34]. An example of good inhibitory control is after being bit by a mosquito; the victim is able to avoid scratching that itch. Miyake found moderate correlations between each of the components, but the pattern of results suggests that the components are orthogonal[34]. Although Miyake and colleagues[34] present compelling evidence for a 3-component model of EF, not all researchers agree, and EF assessments vary widely across studies and there is currently no gold standard[33]. However, despite the multitude of methods for assessing EF, it is clear that EF is a critical part of autonomous living. Recent evidence suggests that EF also plays an important role in mobility.

Relationship Between EF and Mobility

Reviews

Although the body of literature has much heterogeneity in terms of study designs and findings, there is evidence of a reciprocal relationship between EF and mobility disability. A meta-analysis identified any articles that discussed gait, walking, executive function, and depression[35]. The investigators further confined their search by only including studies with participants over the age of 65, and excluded case studies or those with samples who had impaired cognitive function[35]. It is important to emphasize the researchers in this study did not confine their sample to any specific cognitive status. Ultimately, they were left with 15 studies for the review. A relationship between depression, executive function, and gait disruption was found in 80% of these studies[35]. Although the magnitude of this relationship was not established, the relationship can still bring about clinical value because these factors can lead to increased risk of falls and poor quality of life[35]. One study in the meta-analysis was a prospective cohort study which looked at whether EF at baseline would predict maintenance of physical performance over a 12-month period[36]. Here, researchers hypothesized those with higher EF scores at baseline would have better physical performance later in life regardless of physical activity level. Participants were asked to perform the timed up and go test to evaluate physical performance, and several measures of EF, including TMTB-A, DSST, Stroop test, verbal fluency, and digits test[36]. Researchers concluded that baseline performance on the tests examining EF were associated with lower fall risk ($p = 0.02$), higher gait speed ($p < 0.001$), greater amount of PA ($p = 0.008$) at baseline as well[36]. Significant residual correlation was also seen between EF and these domains at the one year follow up[36]. These results confirm a direct relationship between executive function and physical performance (i.e. gait speed) in aging older adults.

Another study in the meta-analysis sampled 2,276 healthy functioning older adults over a course of 5 years using a 6m course and the DSST[37]. Analyses found a decline in DSST score and gait speed over the 5-year period, this decline is normal in the older adults aged 70-79 years old[37]. Analyses also found a small baseline difference in gait speed, 0.3m/s, was associated with two times increased risk of decline in EF[37]. The DSST challenges the working memory part of EF. Holzter and colleagues[3] also used DSST to examine EF, along with the Weschler adult intelligence test, and the free and cued selective reminding test. These assessments are utilized more so for global cognition and working memory, respectively. The researchers tested a large sample (N = 751) of healthy older adults at baseline and a seven year follow up for changes in cognition and gait speed over a 15m course[3]. Ultimately, they found protective effects of EF meaning those with a higher EF score at baseline were more likely to see less decline in gait speed at follow up[3]. Researchers determined an average decline in gait speed for the cohort to be 2.87cm/sec per year, and this was a statistically significant change. These results are similar to those of Inzitari and colleagues[37] such that changes in EF over some period of time predicted physical performance. Holtzer and colleagues[3] went even further as to say the protective effect of even one standard deviation, in the positive direction, for a participant's cognitive score could ultimately safeguard the individual's decline in gait speed by 0.46 cm/sec per year.

Although all of the studies presented in the Patience et al.[35] review thus far have had significant findings regarding the relationship between EF and gait speed, none of them have looked specifically at a population with MCI. McGough[38] was the only study to look at how performance on standard physical therapy tests of mobility was associated with EF assessments in sedentary older adults with MCI (N = 201). Due to the abnormal breakdown of neural tissue in this population, their EF scores are at a further disadvantage compared to those with without MCI[38]. In this cross-sectional study, participants were asked to perform the time up and go, a test of gait speed on an 8m course, the TMTB, and the Stroop test[38]. After adjusting for covariates, including age, sex, depressive symptoms, and BMI, researchers found gait speed was associated with the TMTB ($B = -0.267$; $p < 0.001$) and with the Stroop Interference ($B = -0.214$; $p = 0.004$)[38]. Slower rate of ambulation was associated with a lower score on both tests of EF. It is important to note, causation remains unclear for individuals with MCI due to the cross-sectional nature of the study.

Cohort Studies

In order to further assess the relationship between cognition and gait, the Mayo Clinic Study of Aging took 1,478 healthy older adults through assessments of cognition and gait speed[30]. The cognitive tests associated with EF included TMT-B and DSST. Gait speed was assessed over 25 feet at a normal pace. Participants were reevaluated every 15 months for 4.1 years, allowing the investigators to assess changes cross sectionally and longitudinally[30]. Cross sectionally and after controlling for potential confounders, researchers determined for every 1 m/s increase in gait speed, there was also a 0.467 z-score increase in EF[30]. This data shows gait speed was associated with higher EF as well, as was predicted. Longitudinally, using mixed models examining baseline gait as a predictor of cognitive decline, there was a similar increase with a 0.112 increase in z-score for EF with every 1 m/s increase in gait speed[30]. Over the course of the study, 320 participants were diagnosed with MCI or dementia, however, when these individuals were excluded from the analysis the relationship between faster gait speed and improved cognition remained[30]. For both normally cognitive functioning and cognitively impaired older adults faster gait speed was associated with improved EF. Further analysis showed baseline cognition did not predict future changes in gait speed[30]. The results of this study are in line with other literature that there is a relationship between gait and EF, however, cognitive abilities do not appear to be predictive of future gait speed.

Dual Tasking Studies

Dual tasking is one's ability to do multiple tasks at once. The basic premise is that detriments in walking performance that occur when engaging in a simultaneous cognitive task provides insight into that relationship. Moreover, systematically testing different dual tasks can further elucidate that relationship. One paper which summarized the findings of several dual tasking studies, determined that reliance on EF increases as the walking task becomes more challenging[18]. This may include things such as obstacles in the path of locomotion or having to navigate varying terrain. When dual tasking studies have been conducted on healthy adults, healthy older adults, and older adults with neurological disorders researchers found each population having progressively worse gait[18]. Specifically, in the older adult population with neurological disorders, swing time variability increased, and gait speed decreased across four different tasks: usual walking, simple task, complex task, and serial 7's[18]. The results of this study imply that engaging in challenging cognitive activity can impact gait speed. In other words, the dual tasks may compete for EF resources and thus result in compromised performance. Some researchers believe it is due to the poor prioritization between competing areas of the brain that control motor demands and cognitive demands[18].

In one of the largest cohort studies conducted on gait and cognition, researchers sought to determine the contribution of several elements of cognition on gait speed during dual tasking in a massive longitudinal study of 4,431 adults aged 50 years and older[39]. Gait was analyzed in three separate conditions including a single task, a cognitive task, and a motor task[39]. During the motor task, the participant was asked to walk at a normal speed while carrying a very full glass of water, while the cognitive task required the participant to recite alternating letters of the alphabet[39]. The same cognitive measures were assessed here as in the previously mentioned Mielke[30] study[39] (e.g., TMT-B and DSST). Immediate recall and processing speed were significant predictors of gait speed in the cognitive and motor tasks even when controlling for age, gender, body mass index, education, depression, medications, and comorbidity[39]. Whereas gait has traditionally been viewed as an overlearned, automatic process, Dual tasking studies suggest that it may require significant cognitive effort such that engaging in cognitive tasks can negatively impact gait in older adults. Thus, the decline of cognitive resources associated with aging may ultimately impair gait and mobility in older adults.

Importantly, dual tasks studies have also been conducted in samples with diagnosed cognitive deficits beyond normal aging, such as MCI. Researchers saw the same effect with dual tasking in individuals with MCI[40]. Investigators evaluated global cognition, working memory, EF, and attention in order to see any associations with gait velocity during dual tasks: counting backwards, and naming animals[40]. There was a significant decrease in walking speed from the original after pace of 0.85 m/s during the single task, to a 0.65 m/s speed during the verbal task and 0.63 m/s during the counting task[40]. Ble and colleagues[41] examined the effect of EF on walking speed on a 4m course and a 7m obstacle course with 926 healthy adults. In this dual tasking study, the participants were asked to walk at a usual pace on the 4m course and fast pace on the 7m obstacle course. This study is unlike other dual tasking studies such that it challenges one's EF with a motor task, rather than a cognitive task[41]. However, challenging the subject with obstacles in the course still tests the participant's cognitive resources. These researchers evaluated EF using trail making test (TMT) A and B, a well-established and validated method of cognitive assessment[41]. TMT-A consists of circles numbered 1-25, by which the test taker must make a line connecting each circle in standard numerical order[42]. TMT-B is similar to TMT-A, however, the 24 circles consist of the numbers 1-12 and letters A-L[42]. The participant must then connect the circles, so they read "1-A-2-B-3-C" and so on[42]. Although there are many other assessments used for EF, this is one of the most commonly used. The investigators found a significant positive relationship between a higher TMT score and a faster gait speed in the 7m obstacle walk. This same relationship was found in other studies of dual tasking in participants with and without MCI. The TMT-B was also utilized in these other studies to assess the EF of participants at baseline. Even when adjustments were made for confounders, Montero-Odasso and colleagues[40] found similar results to Ble and colleagues, such that TMT-B was found to be inversely associated with gait velocity in all three conditions of the study: single task, dual verbal task, and dual motor task[40]. This means that those with a higher TMT-B score were more likely to have a slower gait during the single walking task, verbal task, and counting task. With every 100 second increase in TMT-B time, there was a corresponding 4 cm/s decrease in ambulation speed, which was deemed to be clinically significant[40]. This study reaffirms the relationship between EF and gait speed as seen in many other studies.

Some investigators broke gait speed down further and looked at the effects of dual tasking on cadence and stride length, as well as velocity. Although not conducted specifically on individuals with MCI, Holtzer and colleagues (2012) used all of these components of ambulation to determine the relationship between gait and attention, memory, and language. 671 adults (M age = 79 years) were asked to walk at a normal pace and while reciting every other letter of the alphabet[3]. Participants with any abnormal scores on the MMSE were screened out, which resulted in a cognitively healthy sample. A decline in gait speed in individuals with MCI, may lead clinicians to believe that individuals with further impaired cognition might also see larger deficits in ambulatory performance. Due to the mounting evidence surrounding the association between gait speed and EF, shown by dual tasking, this study chose to look at EF as the independent variable and gait speed as the dependent variable.

Exercise as a Treatment for Dementia

To examine the relationship between modes of exercise and cognitive functioning, Northey and colleagues[43] conducted a meta-analytic review of 39 studies. Eligibility criteria for the review included samples of adults over 50 years of age, who did not exemplify other neurological diseases other than MCI. The studies included in the analyses included any mode of exercise program, a control group with no alternative exercise treatment, at least one outcome of cognition, was a randomized controlled trial, and was peer reviewed. Meta-analyses revealed that across all modes of exercise and measures of cognition, the standardized mean difference (SMD) effect size of exercise on cognition was .29 (95% CI 0.17 to 0.41; $p<0.01$)[43]. Moderator analyses also revealed those studies that included both resistance and aerobic training and occurred 5-7 days a week were the most beneficial for cognitive functioning[43]. Medium duration (45-60 minutes) and long duration (>60 minutes) had a small effect size of 0.33, intensity of program did not yield a significant effect size (averaging 0.1-0.17), and length of intervention was most successful if between 13 and 26 weeks (SMD = 0.28)[43]. This meta-analysis concluded all modes of physical exercise interventions can be effective for improving cognition in healthy older adults and those with MCI[43].

Another meta-analysis identified studies with a combination of terms about cognitive impairment, and cognitive or physical interventions[44]. These studies could be combined interventions or dual tasks, but the sample must include those with MCI/dementia, be a randomized controlled trial, and have a passive control group[44]. Cohort studies, case reports, and abstracts were not included. After the search was completed, ten studies were identified that looked at the protective effects of exercise on cognition with an intervention involving both exercise and cognitive training[44]. All of these studies looked at individuals with MCI, unlike the studies described above that used subjects without any known cognitive impairment, and still found the effects of the intervention to be beneficial for the participants (SMD = 0.75[0.42;1.08], $p < 0.01$)[44]. This is a very important conclusion so clinicians can improve the prevention and treatment for individuals with impaired cognition.

The current standard of care for individuals with dementia is thought to be social and intellectual stimulation, as well as an overall healthy diet and physical activity. Some studies utilize health education as a standard of care in order to incorporate these types of stimulation[45]. One study conducted a 16-week aerobic exercise intervention with stepping protocol on individuals with MCI[45]. The stepping protocol was done on a 10cm step to ensure participant safety and incorporated upper extremity movements that mimicked ADLs, like teeth brushing[45]. Although these researchers utilized the MoCA to assess cognitive function at baseline and follow up, there were similar results to the previous studies which used other methods for the assessment of cognitive function[45]. The intervention group in this study also had significantly greater improvements in memory, EF, attention, language, and visual-spatial ability[45]. The effect size was larger in this study compared to the 26-week intervention from the Northey et al.[43] study, likely due to the greater sample size of 120 participants[45]. Although both studies were quite different in nature, regarding intervention type and duration, they had similar results. From these studies we can conclude an aerobic exercise intervention will have a positive impact on cognition in older adults with MCI and could potentially be developed as a new standard of care. Since the studies above identified a strong positive relationship between aerobic exercise and cognition, it is reasonable to believe there is some sort of relationship between the 400m walk and EF. In order for this information to be more definitive more studies need to be conducted.

Changes in Gait & Changes in EF

Liu-Ambrose and colleagues[9] conducted a 12-month randomized controlled trial on 135 healthy women (M age = 69 years). The two exercise interventions were held once to twice weekly for resistance training, and twice weekly for the balance and tone intervention[9]. This is significantly less than the desired frequency of exercise in several of the other studies reported (5-7 days/wk). The resistance training group completed a 60 minute high intensity class, while the balance and tone group were asked to do stretching, range of motion, kegals, balance, and relaxation[9]. Gait speed was measured as walking at usual pace on a 4m course[9]. Cognition was measured using TMT A & B, verbal digits forward and backward tests, and the Stroop Test[9]. These tests covered the three aspects of EF used in Miekle's model. Ultimately, researchers found improved selective attention and conflict resolution were associated with faster gait speed[9]. Usual gait speed was increased by a mean of 0.22m/s by the end of the intervention and was found to be statistically significant ($p < 0.001$)[9]. When adding the change score for selective attention and conflict resolution was added to the linear regression model researchers found an R-square change of 7.5%[9]. This shows that the processes of EF account for about 7.5% of the changes seen in gait speed from baseline to 12 month follow up[9]. Although there are other factors influencing the changes in gait speed, changes in EF appear to have a significant impact.

Summary

The evidence consistently suggests that aerobic exercise can improve mobility and gait speed in older adults. It is also clear a relationship exists between cognition and gait, in healthy individuals, as well as those who are neurologically compromised. The literature suggests that cognitive resources are involved with gait, and there is also literature that shows these cognitive resources are compromised when dual-tasking. Areas of cognition that have been found to be most related to gait include mental tracking, inhibitory control, verbal fluency, and working memory. One study found changes in EF are associated with improved gait speed[9]. However, this was done in a 12 month resistance training intervention conducted on a sample of only women.

The majority of these studies have been conducted on healthy older adults, rather than those with MCI. Any changes in EF that are related to gait speed have only been found in a study with resistance training as an intervention, opposed to an aerobic exercise intervention which has shown to improve mobility and gait speed. Many of the studies in this paper have extremely varied methods of identifying mobility, as well as different standards of mental status including normally functioning, dementia, MCI, and AD.

Purpose & Hypotheses

The purposes of this study were to examine the influence of an exercise intervention on gait speed in patients with mild cognitive impairment and to examine the relative association of changes in executive functioning on changes in gait speed from baseline to follow-up. Therefore, we hypothesize that the aerobic exercise group would experience significantly greater improvements in gait speed as compared to the stretching and balance group. We also hypothesized improvements in EF would be associated with improvements in gait speed.

METHODS

Overview

The data for the present study came from the Piedmont Aging, Cognition, and Exercise 2 trial (PACE-2). The purpose of PACE-2 was to examine the effects of aerobic exercise on cognition and disease-related biomarkers for older adults with prediabetes *and* mild cognitive impairment. PACE-2 randomly assigned 29 older adults to either a moderate to high intensity aerobic exercise condition (AX) or a low intensity stretching and balance exercise condition (SB). Both conditions involved exercise for 4 days per week, 45-60 minutes each session, and lasted for 6-months.

Recruitment and Screening

Participants for this study included men and women aged 50-89 years old. They were drawn from a diverse racial background and were only considered if neurologists and psychiatrists conceded a diagnosis of MCI. Participants also had to meet the criteria for prediabetes, such that they had a hemoglobin A1c of between 5.7% and 6.4%. Participants were also required to be able to speak and understand English, as well as give informed consent. Exclusion criteria included any significant neurological disease that may affect cognition, significant medical illness or organ failure (liver disease, kidney disease, uncontrolled HTN, CVD, or chronic lung disease), current use of any antipsychotics, use of cognition enhancing medication, use of hypoglycemic agents or insulin, and musculoskeletal impairment that could interfere with study participation.

Chosen participants were contacted via phone by the study coordinator who explained the nature of study and procedures. If the subjects expressed interest, they were asked to meet with the study coordinator in person so any questions can be answered, and the informed consent could be obtained. Potential participants then underwent clinical evaluation and cognitive screening to ensure they met the inclusion criteria. To avoid any confusion or potential coercion, during both meetings the coordinator stressed that involvement is voluntary, subjects can withdraw at any time, and withdrawal would not affect any of their medical care or benefits.

Screening consisted of two separate visits whereby researchers collected basic health information, determined A1c, a resting EKG, several cognitive tests, and a full blood panel workup. Diagnosis of MCI included a medical history, blood chemistry analysis, and formal testing of memory impairment and dementia. Once the participants were screened, they were randomly allocated to two different study arms.

Interventions

Aerobic Exercise (AX). The aerobic exercise study arm was conducted in a laboratory at Wake Forest School of Medicine and consisted of walking/running on a treadmill, using an elliptical trainer, or spinning on a stationary cycle. Per the American College of Sports Medicine, subjects were asked to reach 70-80% of their heart rate reserve (HRR) for 45-60 minutes at least 4 days a week. Each session consisted of a 5 minute warmup and 5 minute cool down to allow for safe increase and decrease of heart rate. Participants wore a heart rate monitor for the entire session to ensure they were exercising in a safe range and at the targeted intensity. Researchers logged resting heart rate (HR), exercise duration, mean HR, type of activity, velocity, and total distance.

Stretching & Balance (SB). The SB group required the participants to do a series of stretching and balance activities. These exercises were the same frequency and duration, with warmup and cool down, as the AX program. Each stretch was held for 20-

30 seconds and repeated 5-10 times. HR range was set to be at an intensity below 35% of their HRR. Logs were similar to those of the other program arm as well.

Measures

Gait speed. Gait speed was assessed using the 400 meter walk test (400MWT). Before and after the walk assessors determined the time to completion, heart rate, blood pressure, and oxygen saturation. Participants were asked to complete the walk as quickly, and safely, as possible without any running or jogging. After completion of the walk, their total walk time was divided from the 400 meters to get each individual's gait speed in meters per second.

Executive Function. Participants were also tested on level of EF with many different forms of evaluation. The Trail Making Test (TMT-A & TMT-B) was used to assess inhibition and processing speed. TMT-A consists of 25 randomly numbered circles (1-25) and participants are asked to connect these dots in ascending order as quickly as possible[42]. Participants are asked to do the same thing for TMT-B except the circles only consist of numbers 1-13 and include letters A through L[42]. They are then instructed to connect the circles alternating and in ascending order for both the numbers and letters of the alphabet. These tests are scored based on time to completion. Whereas TMT-A reflects processing speed TMT-B is thought to reflect processing speed and the cognitive cost of inhibition. TMT B-A involves subtracting TMT-A from TMT-B and reflects inhibition only.

The letter word fluency test was used to assess cognitive flexibility. Participants are asked to generate as many words as possible in one minute that begin with a different letter of the alphabet, three separate times[46]. They are then asked to do the same thing, but the words must also belong to a specific semantic category[46]. The total numbers of words they come up with in all the trials constitutes their score.

Analytic Plan

Between group differences in demographics, gait speed, and EF at baseline were all assessed with independent t-tests and chi-squared tests to ensure groups were equal at baseline. In order to test the hypotheses, we first examined the distributions of normality. To do this, we used histogram plots and the Kolmorgorov Smirnoff test. After further analysis we determined the data was not normal. Since the data was not normally distributed, we used a Mann-Whitney U test to examine between group differences in changes in gait speed. To test hypothesis B, that there would be associations between improvements in gait speed and improvement in EF, we used Spearman correlations to examine the bivariate relationships and multiple regression analyses to examine multivariate relationships.

RESULTS

Of the 71 subjects who participated in the study 37 were assigned to the AX group and 34 to the SB group, 66% of the participants recruited were female. The average age for the group was 65±8.4 years, the aerobic exercise group averaged 64±8.8 years while the stretching and balance group averaged 66±8.1 years. The AX group consisted of African American (24%), Caucasian (65%), Hispanic (8%), and other (5%), however, the SB group only had African Americans (24%) and Caucasians (77%). Table

1 also shows group characteristics in education, blood pressure, BMI, and MMSE scores. Independent samples t-tests and Chi squared tests revealed no statistically significant differences between groups ($p > 0.05$).

Inspection of the distribution of the gait speed at follow up and changes in gait speed and a Kolmogorov-Smirnov test indicated that the data were not normally distributed. Therefore, we used a non-parametric Mann-Whitney U test to examine between group differences in changes in gait speed. Table 2 shows baseline measures between both intervention groups for gait speed, TMT-A, TMT-B, TMT B-A, and verbal fluency. A Mann-Whitney U test revealed no significance between group differences in EF measures or gait speed ($p=0.29$). Mean (SD) gait speed at baseline was 1.42 (0.19) m/s and 1.41 (0.21) m/s for the AX and SB groups respectively. At follow up, gait speed in the AX group averaged to 1.4 m/s and the SB group had a mean of 1.38 m/s.

Since Gait speed was not normally distributed, we used nonparametric Spearman correlations to examine bivariate relationships among gait speed and EF. Table 4 shows the correlations between gait speed, TMT-A, TMT-B, TMT B-A, and verbal fluency. None of these variables were found to be significantly correlated. However, at follow up TMT-A ($r = -0.29$), TMT-B ($r = -0.43$), and TMT B-A ($r = -0.31$) were all significantly related to gait speed ($p <0.05$; Table V). Follow up verbal fluency was not related to gait speed. Correlations among baseline to 6-month changes in measures of cognition and gait speed were statistically significant (Table VI).

We used a stepwise multiple regression analysis to examine the multivariate relationships among demographic variables, cognition, and changes in gait speed. We inspected scatterplots to confirm linear relationships among variables, normal distribution of the standardized residuals, and homoscedasticity. Although several predictor variables were correlated (e.g., measures of cognition), coefficients were below 0.7 and thus multicollinearity was not an issue. The model first included demographic variables (race, sex, age, and BMI) and treatment condition followed by measures of cognition at each time point as well as baseline to 6-months changes in a forward stepwise procedure. The final model included the demographic variables, treatment condition, and TMT-B and accounted for 27.8% of the variance in gait speed ($R^2_{adj} = 0.278$; $p < 0.01$). TMT-B was the only variable in the regression analysis that was statistically significant ($B = -0.003$; $p < 0.01$). All other variables were excluded from this linear regression analysis as they were not statistically significant.

DISCUSSION

The purpose of this study was to examine the association of an exercise intervention on gait speed in patients with MCI, as well as to examine the relationships among EF and gait speed. There was no significant increase found for gait speed from baseline to follow up for either of the treatment arms. Although no bivariate relationships were found among EF and gait at baseline, all EF measures at follow up were significantly related to gait speed. Multiple regression analyses that included sex, age, treatment group and measure of EF significantly predicted changes in gait speed. Additionally, TMT-B at follow up was the only independent variable to significantly predict changes in gait speed.

The hypothesis that the AX treatment would result in greater improvements in gait speed as compared to the SB treatment was not supported in this study. This may have been due to a ceiling effect on gait speed. That is, the average gait speed for older adults is 1.0 - 1.4 m/s, anything greater than 1.4 m/s puts the individual in a superior category for walking[29]. The average speed of ambulation for the sample in this study was about 1.41 m/s at baseline for both intervention groups. Since the sample's baseline gait speed was already considered very fast for their particular age group, it was likely difficult for these subjects to increase their gait speed even more even in the aerobic exercise group. Many systems influence gait speed in addition to aerobic capacity, such as muscle strength and biomechanical factors (e.g., stride length, gait initiation, stride frequency[53]). It is possible that in this sample of high functioning adults, interventions should target these other systems to improve and/or maintain gait speed.

The hypothesis that EF would be related gait speed was also not supported in the present study. This finding is in contrast to a 16-week aerobic exercise intervention where the intervention group had significantly greater improvements in memory, EF, attention, language, and visual-spatial ability[45]. The results of this study also contrasted large meta-analyses that revealed all modes of exercise and measures of cognition produced at least a small effect size of 0.29 (95% CI 0.17 to 0.41; $p<0.01$)[43]. Studies that held interventions 5-7 days a week and the length of intervention between 13 and 26 weeks were the most beneficial for cognitive functioning[43]. The PACE-2 study intervention lasted 24 weeks and participants exercised on at least days per week, and the results still differed. Lastly, Montero-Odasso and colleagues[40] found similar results to Ble and colleagues, such that TMT-B was found to be inversely associated with gait velocity[40]. With every 100 second increase in TMT-B time, there was a corresponding 4 cm/s decrease in ambulation speed[40]. It is possible that the changes in EF and changes in gait speed were too small to detect significant relationships.

However, the pattern of bivariate relationships among EF and gait speed are interesting. At baseline, measures of EF and gait speed were not related. But at follow up, EF and gait speed were moderately correlated. Moreover, the multivariate model indicated that TMT-B at follow up was significantly related to gait speed. Although purely speculative, it is possible that the manner in which participants process multisensory gait information changed over the course of the interventions. This could be explained by the central capacity sharing model and greater structural interference in older adults caused by increased activation of the frontal lobe[53]. There is an age-related increase in neural activation, this leads to more interference when attempting difficult tasks that require both cognitive and motor awareness due to reduced residual capacity in shared brain regions[53]. Exercise could improve mind/body awareness improving neural activation and potentially decreasing structural interference. Perhaps gait speed was associated with TMT-B due to the enhanced cognitive and motor awareness gained throughout the 6-month training program in this study. That is, gait is considered an overlearned, automatic process requiring few attentional resources. This may be particularly true in sedentary adults with high levels of physical functioning (i.e., gait) such as the sample in the present study. In other words, it is possible that participants simply did not pay much attention to their physical functioning prior to the start of the intervention. However, it is possible after 6-months of the physical activity intervention participants paid more attention to their physical functioning and thus EF measures were more related to gait.

Previous research supports the relationship between TMT-B and physical functioning. TMT-B has been found to make a large contribution to an individual's performance of IADLs, especially when compared to verbal fluency and TMT-A[51]. These findings suggest different aspects of EF may play a role in IADLs because they are more challenging than basic self-care tasks[51.] Slower gait speed can predict a decline in instrumental activities of daily living (IADL)[50]. IADLs are the skills required for independent living, tasks such as home management, health maintenance, etc. Patel and colleagues[52] speculated that cognitive tasks may impact walking speed during dual tasking due to the diversion of attention to the task at hand. This shows a cognitive task has a considerable cost during ambulation.

Analyses also showed no relationship between verbal fluency, TMT-A, or delta trails and gait speed. Verbal fluency tests the updating aspect of executive functioning. Previous studies have found relationships between verbal fluency and either gait or physical performance[30,35,40,44]. One study with 309 older adults with cognitive impairment also found an association between verbal fluency and gait speed[47]. This cross-sectional study measured gait speed over 2.4 meters and used the ACE-III test to assess global cognition[47]. This assessment consists of a series of tests which included six different domains of cognitive functioning. The researchers on this study looked at executive function, via verbal fluency, by adjusting for four other cognitive domains: attention, memory, language, and visuospatial[47]. The association between gait speed and these cognitive domains were attenuated in this analysis, while the relationship between EF and visuospatial ability withstood the adjustment[47]. The authors of this study found an indirect relationship of EF with visuospatial tasks (e.g. constructional praxis)[47]. The lack of visuospatial testing could be why verbal fluency alone was not significantly related to gait speed in this study. Although the majority of studies found an association between these variables, some research found data that challenged this notion. It is also possible verbal fluency is an easily learned task that participants get better as time goes on, or with repeated trials.

Finally, a study conducted on several different language and EF assessments sought out to find if verbal fluency was a better indicator of lingual ability or EF. The subjects in this study were administered the controlled oral word association test (FAS), animal fluency, Boston naming test, vocabulary from the Wechsler Adult Intelligence Scale, Wisconsin card-sorting test, and TMT-B[49]. They found FAS and animal fluency to be high correlated to language, rather than EF[49]. Although this does not necessarily exclude this test as a measure of EF it may suggest verbal fluency as a more critical component for language rather than EF[49]. Since this assessment was not a solid representation of EF, it may not be a good indicator of EF for our study. These results may explain why verbal fluency was not as highly correlated to gait speed in this study as initially thought after evaluating previous literature.

There were several limitations to this study. First, the PACE-2 study was designed to test the effects of physical activity on EF in older adults at risk for dementia and was powered as such. With only 71 participants, it is unknown whether a larger sample size would have produced the statistical power to detect treatment effects and other relationships among variables. Second, only 2 measures of EF were included in this study. We were thus unable to examine a more complete assessment of EF that included each of the proposed subcomponents of EF. Lastly, the intervention was only 6-months long. It is possible that a longer intervention would have conferred effects on gait speed as well as allowed for relationships among EF and gait speed to emerge.

Further research is needed to examine the impact of physical activity on mobility with patients in cognitive impairment as well as to determine the relationships among cognitive functioning and mobility. The dose response relationship among physical activity and mobility in patients with cognitive impairment is largely unknown. Longer term interventions are needed to determine whether mobility can be preserved in this population. The most efficient and sustainable mode of physical activity needed to improve and/or maintain mobility has not yet been determined. The current study contrasted a high intensity aerobic training program to a stretching, balance, range of motion condition, but it may be useful to investigate the effects of moderate intensity programs or resistance training. Further consideration should also be taken when choosing measures of EF to assess, as each test evaluates different aspects of EF.

If exercise continues to show improvements in EF, which leads to decreased mobility disability in individuals with MCI, appropriate interventions could be implemented to better the lives of this population. The improvement of mobility disability could change the lives of individuals with MCI by allowing for a more autonomous and safe life. The potential to improve gait speed with an exercise intervention in those with MCI could decrease the rate of falls thereby improving overall health and safety of the individual while in their homes or out in the community. Improved stride and gait speed can potentially ameliorate the already challenging lives of individuals suffering from MCI.

TABLES

Table I. Sample demographic characteristics.

		Aerobic X	SB	Total	P value
Total (n)		34	37	71	
% Female		59.5	73.5	66.2	0.214
Age		64.1 (8.8)	66 (8.1)	65.1 (8.4)	0.332
Race	African American	8 (23.5%)	8 (23.5%)	16 (22.5%)	0.175
	Caucasian	24 (64.9%)	26 (76.5%)	50 (70.4%)	
	Hispanic	3 (8.1%)		3 (4.2%)	
	Other	2 (5.4%)		2 (2.8%)	
Education (years)		14.9 (2.6)	15.1 (2.5)	15.0 (2.5)	0.747
Blood Pressure (mmHg)	Systolic	133.7 (16.6)	128.7 (13.1)	131.3 (15.1)	0.159
	Diastolic	75.5 (9.4)	75.1 (9.7)	75.3 (9.5)	0.877
BMI (kg/m^2)		31.7 (5.2)	29.4 (1.8)	30.8 (5.1)	0.122
MMSE		28.4 (1.8)	28.5 (4.8)	28.5 (1.7)	0.755

Table II. Baseline gait speed and measures of EF for both intervention groups.

	Aerobic X	SB	P value
Gait Speed (m/sec)	1.42 (0.19)	1.41 (0.21)	0.53
TMT (A) (sec)	86.43 (26.94)	87.71 (26.54)	0.92
TMT (B) (sec)	126.76 (46.38)	129.35 (48.58)	0.84
TMT (B-A) (sec)	40.32 (34.64)	41.65 (43.12)	0.89
Verbal Fluency	50.65 (13.33)	51.44 (15.1)	0.80

Table III. Baseline to 6-month changes in Gait speed across treatment conditions

	Aerobic Exercise N= 28			SB Exercise N= 29					
	Baseline M (SD)	6-mo M (SD)	Mean Rank	Baseline M (SD)	6-mo M (SD)	Mean Rank	Mann-Whitney U	Z	P
Gait Speed (m/sec)	1.43 (0.19)	1.40 (0.34)	31.36	1.41 (0.22)	1.29 (0.23)	26.72	472.0	1.05	0.29

Table IV. Spearman correlations of gait speed and executive function variables at baseline.

	Gait Speed (m/sec)	**TMT A (sec)**	**TMT B (sec)**	**TMT B-A (sec)**	**Verbal Fluency (#)**
Gait Speed (m/sec)	1.00	-0.169	-0.194	-0.084	0.235
TMT A (sec)	-0.169	1.00	0.684*	0.073	-0.218
TMT B (sec)	-0.194	0.684*	1.00	1.00	-0.341*
TMT B-A (sec)	-0.084	0.073	0.732*	1.00	-0.311*
Verbal Fluency (#)	0.235	-0.218	-0.341*	-0.311*	1.00

Table V. Spearman correlation matrix for gait speed and executive function measures at follow up.

	Gait Speed F/U (m/sec)	TMT A F/U (sec)	TMT B F/U (sec)	TMT B-A F/U (sec)	Verbal Fluency F/U (#)
Gait Speed F/U (m/sec)	1.00	-0.399*	-0.551*	-0.337*	0.374*
TMT A F/U (sec)	-0.399*	1.00	0.537*	-0.060	-0.379*
TMT B F/U (sec)	-0.551*	0.537*	1.00	0.750*	-0.498*
TMT B-A F/U (sec)	-0.337*	-0.060	0.750*	1.00	-0.327*
Verbal Fluency F/U (#)	0.374*	-0.379*	-0.498*	-0.327*	1.00

Note: * = $p<0.05$.

Table VI. Spearman correlations for the changes in gait speed and executive function variables between baseline and follow up.

	Δ Gait Speed (m/sec)	**Δ TMT A (sec)**	**Δ TMT B (sec)**	**Δ TMT B-A (sec)**	**Δ Verbal Fluency (#)**
Δ Gait Speed (m/sec)	1.00	0.066	0.011	0.102	-0.014
Δ TMT A (sec)	0.066	1.00	0.208	0.524*	0.542*
Δ TMT B (sec)	0.011	0.208	1.00	-0.654*	-0.654*
Δ TMT B-A (sec)	0.102	0.524*	-0.654*	1.00	0.015
Δ Verbal Fluency (#)	-0.014	-0.218	-0.154	0.015	1.00

Note: * = p<0.05.

Table VII. Regression analysis with dependent variable 400MW and independent variables treatment condition, age, sex, race, BMI and measures of Executive Functioning.

	Unstandardized Coefficients		Standardized Coefficients	t	Sig.
Model*#	B	Std. Error	Beta		
Treatment Condition	-0.038	0.063	-0.048	-0.402	0.689
Age	0.009	0.004	0.241	1.916	0.061
Sex	0.023	0.063	0.042	0.372	0.712
Race	-0.045	0.044	-0.123	-1.037	0.305
BMI	-0.003	0.006	-0.053	-0.451	0.654
TMT B (F/U)	-0.003	0.001	-0.600	--5.030	<0.001

Note: * = $R^2_{adj} = 0.278$; $p < 0.01$; # = race, sex, treatment condition, age, TMT-A, TMT-B, TMT B-A, and Verbal Fluency at each time point and changes in these variables were included in the model.

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Research Interests

Investigating the effects of exercise interventions on cognition, mobility, and corresponding biomarkers in individuals with neurological disorders.

Education

Master of Science:
Wake Forest University, Winston Salem, NC
Anticipated graduation May 2020

Major: Health and Exercise Science
GPA: 3.48 Total credits: 36

Bachelor of Science:
University of Wyoming, Laramie, WY
Graduated May 2018

Major: Kinesiology	Minor: Psychology	
GPA: 3.796	Kinesiology GPA: 3.863	Total credits: 135
GRE Quantitative: 151	GRE Verbal: 151	Analytical: 4.0

Certifications and Training

- ACSM Clinical Exercise Physiologist
- AHA Basic Life Support
- GXT Administration
- EDC Data Entry
- DEXA Operation
- EKG Interpretation
- CITI Training

Research Experience

2018 – Present RESEARCH ASSISTANT, Jeff Katula, Ph.D., Wake Forest University, Winston Salem, NC

Research assistant for nationwide study, EXERT, involving the effects of aerobic exercise on physiological and psychological symptoms in individual's with mild cognitive impairment.

- Entered field data into EDC online computer system
- Assisted in exercise related questions on conference calls for YMCA trainers
- Communicated important information and trainer questions to principle investigators on the study

2018 – Present RESEARCH ASSISTANT, Jeff Katula, Ph.D., Wake Forest University, Winston Salem, NC

Research assistant for nationwide study, POINTER, involving the effects of aerobic exercise on cognition in individuals at risk for Alzheimer's disease.

- Recruited mock participants for training protocol videos
- Participated in training video to help assist group discussion and flow of conversation
- Attended initial study session to take notes on group dynamic and trainer's ability to effectively communicate information/instruct participants

2015 – 2018

RESEARCH ASSISTANT, Cynthia Hartung, Ph.D., Laboratory for the study of the effects of exercise on ADHD students, University of Wyoming, Laramie, WY

Volunteer position as a research assistant in a lab that focused on the positive and negative effects of vigorous intensity exercise on the hyperactivity and attention deficit symptoms in college students with ADHD

- Attended weekly meetings to discuss previous research conducted on children and adolescents with ADHD
- Facilitated in the writing of testing protocols in IRB proposal
- Ran and analyzed DEXA scans on participants of the study to determine bone density and body fat percentage
- Administered health questionnaires during intake sessions and gathered information such as waist circumference, hand grip strength, blood pressure, heart rate, and data from Queen's College Step test
- Ran online cognitive tests
- Created surveys, health questionnaires, and cognitive tests for participants
- Oversaw sprint interval training sessions with subjects while gathering heart rate and rate of perceived exertion throughout the test

Professional Activities

2020 - current

DIRECT SUPPORT PROFESSIONAL, Community Entry Services, Jackson, WY

Assist individuals with physical, behavioral, and intellectual disabilities so they can be more independent in the community.

- Assisted clients in their homes, with employment, and involvement in the community
- Helped clients through their physical therapy or give individualized exercise instruction
- Assisted/educated with health and hygiene goals
- Provided guidance in healthy and individualized nutrition
- Facilitated group interaction/confrontation as it arose

2018 – 2020

PROGRAM COORDINATOR, Healthy Exercise and Lifestyle Program, Wake Forest University, Winston Salem, NC

Unpaid position running a three hour exercise program for older adults with chronic disease.

- Coordinated staff in emergency situations
- Managed first year graduate students
- Made appropriate exercise decisions for the health and safety of participants
- Wrote appropriate exercise prescriptions for each individual based on their goals and exercise test results
- 12-lead placement, exercise blood pressure, EKG analysis during graded exercise stress tests
- Lead resistance training, stretching and Silver Sneakers classes
- Monitored vitals, symptoms, and general well-being of adult participants through exercise
- Attended executive meetings and provided solutions to issues that arose in the facility
- Offered reasonable options to bring about more financial success for the facility
- Implemented new policies and procedures to help the facility operate more smoothly – incorporated educational components to announcements for older adults, downsized and modified medical charts of participants so they were more accessible, etc.

2018 – 2020 PROGRAM FACILITATOR, Weight Management, Wake Forest University, Winston Salem, NC

Facilitator and health coach for faculty and staff weight management program.

- Lead group discussion on exercise and physical activity. Discussed why it is important and how to overcome barriers to better incorporate it into their life
- Facilitated group discussion on nutrition, mental health, and sleep and how it can impact weight
- Built progress reports for participants at halfway point and end of program
- Operated DEXA and explained scans to individuals (i.e. fat mass percentages, bone mineral density, etc.)
- Kept in close contact with participants ensuring their success in the program, answering questions and developing exercise programs as necessary
- Lead functional assessments: 6-minute walk test, sit and reach, blood pressure, sit to stand test

2018 – 2020 INSTRUCTOR, Wake Forest University, Winston Salem, NC

Instructor for a 101 class through the health and exercise science department.

- Taught core concepts in health, fitness, and nutrition
- Facilitated learning and group discussion in class
- Modified and adapted learning materials to best fit students and maintain interest through course

Summer 2017 ASSISTANT COACH, Landow Performance, Centennial, CO

Unpaid/intern position assisting in the maintenance of a strength and conditioning facility for individuals in the general population, as well as professional and collegiate athletes

- Maintaining and setting up equipment for weightlifting and speed/agility drilling

- Running youth speed/agility and football camps with over three hundred kids
- Assisting in the conditioning of varsity football athletes at local high schools
- Developed and directed exercise programs for clients
- Coached strength sessions for superior coaches while they were away – these included members of the general population and professional athletes
- Presented research summaries on the long-term athlete development model and how it was utilized in the facility to other interns and coaches
- Attended a presentation on velocity-based speed training by renowned researcher, Brian Mann, and went through training for GymAware equipment
- Determined asymmetries of the body based on a series of movements performed by clients to locate problems in the skeleton or musculature

Summer 2016 PHYSICAL THERAPY AIDE, St. John's Hospital, Jackson, WY

Physical therapy aide for inpatient and outpatient therapists, and therapists working in a nursing home. Also aided occupational therapists working in the hospital

- Conducted rehabilitation modalities with ultrasound machines and electrical muscle stimulation
- Facilitated clients doing exercises in therapy sessions
- Assisted therapists when walking with patients who were just released from surgery and learning to use crutches, walkers, etc.
- Assisted in the rehabilitation process of several stroke and Parkinson's patients
- Aided in two-day therapy program for patients receiving total hip replacements, total knee replacements, and total shoulder replacements
- Studied the use of functional movement analysis in several different settings

2015 – 2016 STUDENT ATHLETIC TRAINER, University of Wyoming Athletics Department, Laramie, WY

Paid position assisting football athletes on and off the field with injury care and prevention

- Hydrating athletes during practice and games
- Taping ankles, wrists, arches, and shoulders before practice and games
- Assisting athletes in treatments such cryotherapy, heating treatments, scar tissue removal, and ultrasound
- Facilitated head trainers in taking athletes through rehabilitative work outs for mobility, flexibility, strength, and return to sport activities
- Ran athletes returning to sport on underwater treadmills
- Prescribed rehabs for four athletes returning to sport who suffered shoulder or knee injuries that required surgery
- Assisted the head athletic trainer on the field during games with athletes who had musculoskeletal injuries or concussions
- Administered baseline concussion tests to student athletes in wrestling, football, swimming, and soccer

Presentations and Posters

Spring 2020 — Wright, H.A. (2020, May). The effect of exercise on executive functioning and gait in patients with mild cognitive impairment (MCI). *Thesis defended at Wake Forest University for the completion of a health and exercise science master's degree.*

Spring 2018 — Wright, H. A., LaCount, P. A., Berchenbriter, J., Gruntmeir, S., Serrano, J. W., Stevens, A. E., Smith, D. T., & Hartung, C. M. (2018, April). Cardiovascular health of college students with and without attention-deficit/hyperactivity disorders (ADHD). *Poster presented at University of Wyoming's College of Health Sciences Grand Rounds and 24th Annual Research Day, Laramie, WY.*

Spring 2018 — LaCount, P. A., Wright, H. A., Berchenbriter, J., Gruntmeir, S., Serrano, J. W., Stevens, A. E., Smith, D. T., & Hartung, C. M. (2018, April). Acute efficacy trial of high-intensity physical exercise for college students with attention-deficit/hyperactivity disorder (ADHD). *Poster presented at University of Wyoming's College of Health Sciences Grand Rounds and 24th Annual Research Day, Laramie, WY.*

Honors

Spring 2018 — OWN IT AWARD

- Award for women who act as mentors and have contributed to research in the science, technology, engineering, or (STEM) mathematics field

2014 – 2018 — HATHAWAY MERIT HONORS

- Scholarship provided by former Wyoming governor to students who met a 3.5 high school GPA and a score of 25 on the ACT

2014 – 2018 — HATHWAY NEED HONORS

- Scholarship provided by former Wyoming governor to students based on financial need calculated from FAFSA results

2014 – 2018 — PELL GRANT

- Grant awarded to low-income undergraduate students pursuing postsecondary education

2014 – 2018 — WYOMING SCHOLARS AWARD

- Scholarship given to students who met a 3.5 high school GPA and 25 ACT score, as well as maintained a 3.0 GPA during full-time, continuous enrollment at the University of Wyoming

2014 – 2018 — ELK'S LODGE SCHOLARSHIP

- Scholarship received based off of exceptional academic performance in high school

Spring 2014 — DAUGHTERS OF THE AMERICAN REVOLUTION

- Scholarship awarded based off of outstanding essay entry and first generation student criteria

2014 – 2018 — UNIVERSITY OF WYOMING DEAN'S OR PRESIDENT'S LIST

- Granted each semester to students who received a GPA of at least 3.4 (Dean’s) or 4.0 (President’s)

Leadership and Volunteer

2019 – 2020 GRADUATE STUDENT REPRESENTATIVE, Wake Forest University, Winston Salem, NC

- Communicated ideas and policy changes to health and exercise science department.
- Helped to improve quality of student environment and promote fellowship among graduate schools.

2013 – 2014 PRESIDENT/FOUNDER OF CLUB, Best Buddies at Jackson Hole High School, Jackson, WY

Founder of internationally recognized club promoting one-to-one friendships between regular education and special education students, and the integration of special education students in to the community

- Communicated with representatives at the international headquarters to determine the need for an official site
- Built mission statement and organized foundation for which the club resided on
- Fought for club to be nationally recognized as the first site in the state of Wyoming

References

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