EXPLORING GROUP DIFFERENCES IN WHITE MATTER HEALTH IN OLDER ADULT FALLERS AND NON-FALLERS WITH MCI

BY

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LIST OF ABBREVIATIONS

AD	Alzheimer's Disease
ADCC	Alzheimer's Disease Core Center
ALS	Amyotrophic Lateral Sclerosis
BET	Brain Extraction Tool
CSF	Cerebral Spinal Fluid
CT	Computed Tomography
DICOM	Digital Imaging and Communications in Medicine
DTI	Diffusion Tensor Imaging
EPI	Echo-planar Imaging
FA	Fractional Anisotropy
FES	Falls Efficacy Scale
FSL	The FMRIB Software Library
MA	Movement Alone Group
MAC	Memory Assessment Clinic
MCI	Mild Cognitive Impairment
MD	Mean Diffusivity
MG	Movement Group
MPRAGE	Magnetization Prepared Rapid Gradient Echo
MR	Magnetic Resonance
MRI	Magnetic Resonance Imaging

MS	Multiple Sclerosis
NAWM	Normal Appearing White Matter
NC	No Contact Group
NDI	Neurite Density Index
NIA	National Institute on Aging
NIFTI	Network Interface to File Transfer in the Internet
NODDI	Neurite Orientation and Dispersion Imaging
ODI	Orientation Dispersion Index
PWD	Person With Dementia
RD	Radial Diffusivity
SG	Social Group
SPPB	Short Physical Performance Battery
TE	Echo Time
TI	Inversion Time
TR	Repetition Time
US	United States
WFSM	Wake Forest School of Medicine
WM	White Matter
WMH	White Matter Health

ABSTRACT

Older individuals with MCI experience increased fall risk. However, the precise mechanism behind this increased fall risk remains unknown. Current literature suggests that increased fall risk may be the result of impaired balance and gait. Abnormalities in microstructural integrity of white matter may contribute to impaired balance and gait. This is the first study to utilize the NODDI technique to explore group differences in white matter health in older adult with MCI who were classified as fallers and non-fallers. Baseline data from 56 participants within the ongoing IMOVE study was used to explore group differences. NODDI derived NDI and ODI values were calculated from diffusion data from 39 participants.

To assess group differences in gait parameters and cognition data amongst fallers and non-fallers, a Student's t-test was performed for continuous variables and a Fisher's exact test for binomial data on 56 participants. To test for group differences in NODDI parameters in fallers and non-fallers and the association of these parameters with gait variability, an exploratory whole-brain voxelwise analysis was performed using SPM12. Compared to non-fallers, fallers had significantly lower BMI and gait variability during normal walking conditions. Significant positive associations were found between NDI values and gait variability in the superior longitudinal fasciculus, uncinate fasciculus, fronto-occipital fasciculus and inferior longitudinal fasciculus. Significant negative associations were found between ODI values and gait variability in the inferior longitudinal fasciculus, fronto-occipital fasciculus and cingulum. This study shows that subclinical changes in white matter tracts involved in executive functioning play a role in increased fall risk in people with early-stage dementia.

CHAPTER 1

INTRODUCTION

Cognition and mobility impact the quality of life of older adults

There is an increasing number of individuals 65+ years of age within the US population. Although one of the main goals of public health is prolonging life, extending life should also involve preserving one's quality of life (QoL). Cognition and mobility are two important factors that determine the QoL in older adults. Declines in cognition and mobility often coexist with increasing age, and these declines are common among individuals with mild cognitive impairment (MCI). MCI is the transitional state between normal aging and early dementia.[1] Compromised cognition and mobility lead to the loss of independence, which can substantially affect QoL.[2] Cognitive impairment is an independent risk factor for falls in older adults.[3] Individuals with mild cognitive impairment experience an even greater impact of cognitive and motor decline on QoL, as a result of their increased fall risk.

Individuals with MCI and dementia have an increased fall risk

Globally, falls are an important public health concern[4] and can significantly impact the health of older adults with MCI. Fall risk is doubled among older adults with cognitive impairment.[5] In fact, fallers with cognitive impairment are five times more likely to be admitted to institutional care than individuals with cognitive impairment who do not fall.[6] Falls that result in injuries are more prevalent in older adults with dementia, with more than a threefold increase in hip fracture compared to older adults without dementia.[7] Hip fractures are a serious consequence of falls, with few people returning to their previous

level of function. In addition, having low cognitive function increases the risk of not regaining function after hip fracture. [8]

Falls not only impact the health of older adults, but their QoL as well. Even when an individual has no previous fall history or when no physical injury occurs after a fall,[9] approximately a third of older adults develop a fear of falling that leads to self-imposed restrictions in mobility, reduced activity, depression, social isolation, and subsequent increased fall risk .[10,11,12] Apart from indirect cost and care giver burden, the direct medical cost of falls is becoming unsustainable for the US health care system.[13] As the prevalence of falls among individuals with MCI continues to rise with increasing age[14,15,16,17], research examining predictors of increased fall risk is lacking.

Little is known about why there is an increased fall risk among older adults with MCI

Despite the growing prevalence of falls among individuals with MCI with increasing age, the mechanisms underlying increased fall risk in individuals with cognitive impairment are poorly understood. While researchers are studying the impact of falls in individuals with dementia, minimal research is being done to assess the underlying factors that contribute to fall risk in individuals with MCI and dementia.

Researchers hypothesize that impairment in cognitive abilities can limit attentional resource allocation that can compromise gait and postural stability. In particular, cognitive impairment limits performance in divided attention tasks, which refers to the ability to carry out more than one task at the same. Divided attention plays an integral role in walking,[18] and is often used as tool for examining clinical implications for fall risk. Also, impairments in executive function are associated with dementia as well as increased fall risk.[19] Executive functioning is a set of cognitive processes that enable the identification

of goals, mental planning, behavior organization, and planning actions to achieve these goals.[20] Inhibition of executive function can lead to poor self-awareness, planning, and goal setting. These characteristics often manifest as careless walking, poor decision making, and loss of inner drive to move, which can lead to an increased fall risk.

Increased fall risk is also linked to multiple factors besides cognition, such as medications, impaired gait and balance, alcohol consumption, obesity status, and sleep disturbances.[21,22] Among these risk factors, a growing body of literature supports an association between cognition, gait and balance performance, and falls in older adults with MCI[23, 24, 25, 26,27] such that the increased fall risk amongst older individuals with MCI may result from impaired balance and gait. A better understanding of the relationship between cognition and falls may lead to the discovery of novel interventions and preventive measures to help reduce fall risk and dementia, but most importantly improve the QoL for older adults with MCI and dementia.

Individuals with MCI experience impaired gait while performing dual tasks

Many falls occur when older adults walk and try to perform another cognitive task, such as talking.[25] This phenomenon is referred to as dual task walking. The dual task paradigm assesses the relationship between cognition, gait performance, and fall risk. The dual task paradigm consists of the subject performing a demanding divided attention task while walking. Divided attention tasks include counting down from one hundred by seven or reciting letters of the alphabet.

Past studies revealed that the inability to maintain conversation while walking was predicative of future falls in individuals with MCI. [28,29] In addition, individuals with a

history of falls had more significant changes in walking, such as increases in gait variability while performing the dual task compared to non-fallers.[24] The magnitude of the change in an individual's gait performance during the dual and single task conditions is called dual task cost. Dual task cost may reflect inefficient cortical control.[21] Studies across various populations show that dual task cost affects gait and influences the performance of secondary tasks in heathy older adults as well as older adults with neurological disorders.[28]

Impaired gait is common in individuals with MCI under dual task conditions and is characterized as a decrease in gait speed [30,31,32] and stride length [33], and an increase in stride time [30,34], step length variability [35], step width variability [35], double support time variability [32], as well as stride time variability. [3,30,32]

Stride time variability shows test–to–retest reliability in distinguishing healthy adults from cognitively impaired adults under dual tasking conditions. Stride time variability, which is calculated out of the mean and standard deviation of stride time, reflects the change in time elapsed between the first two contacts of two consecutive footfalls of the same foot over a number of gait cycles.[36] It is often expressed as a Coefficient of Variation (CoV), which determines the variability within a participant by utilizing the mean and standard deviation of stride time. Low stride-to-stride variability indicates that the automatic stepping mechanism is functioning properly. However, loss of this automatic motor control may lead to higher stride time variability. Additionally, a recent study shows that high stride time variability predicts future falls in community-dwelling older persons even when gait velocity fails to distinguish between those who fell and those who had not.[21]

Abnormalities in white matter may contribute to impaired gait in individuals with MCI

As the brain ages it becomes susceptible to structural and functional changes that include changes to higher level structures of motor control.[37] Many regions of the brain that involve motor control connect to one another by white matter tracts. Changes in cerebral white matter tracts are common with age and indicate that there is damage to white matter tracts that could be responsible for the processing of sensory information as well as motor control.[38] Many studies suggest that changes in white matter integrity are associated with impaired balance, gait, mobility, and reduced executive functioning.[39,40,41,42] In addition, changes in white matter integrity increase with age[43] even in the absence of a neurological disease. However, individuals with MCI exhibit greater reductions in white matter integrity compared to healthy controls.[44]

The use of imaging techniques such as CT and MRI enable the detection of changes in white matter health. Increases in brightness in T2 FLAIR MRI called white matter hyperintensities (WMH) reflect damage in the white matter tracts. In recent years interest in visible WMH and the area that surrounds them, which is commonly referred to as normal appearing white matter (NAWM) continues to grow. Longitudinal studies show that WMH often span from existing WMH, and that the damage can spread to NAWM.[45,46] Abnormalities in NAWM are associated with impaired gait[47,48,49], suggesting that NAWM may also play a role in increased fall risk amongst individuals with MCI. However, its role remains unknown due to limited research. The study of NAWM requires the use non-conventional MRI approaches.

DTI can provide insight into white matter connectivity and microstructural integrity of NAWM.

Conventional MRI, such as T2 FLAIR MRI is able to detect macrostructural changes in the integrity of white matter that often appear as WMH. However, conventional MRI lacks sensitivity to detect the smaller and earlier microstructural changes to the integrity of NAWM. Diffusion tensor imaging (DTI) is a magnetic resonance imaging technique that provides a way to assess the early changes in the microstructural integrity of white mater within the brain by utilizing the diffusion of water within tissue. Previous studies based on diffusion show the presence of white matter damage in earlier stages of the AD.[49,50]

The diffusion of water molecules can change based on the tissue type, integrity, and presence of barriers.[51] Studies suggest that changes in the structural integrity of white matter can be characterized by loss of myelination, axonal degeneration, atrophy, and increased membrane permeability.[49] Currently, it is unknown what factors influence the change in the structural integrity of white matter. Studies show that changes in the integrity of white matter with age may be attributed to vascular-related risk factors, such as diabetes, hypertension, and smoking.[52]

By using change in diffusion properties, DTI can provide measures that serve as useful surrogates of tissue microstructure. The most commonly used DTI measures include mean diffusivity (MD), a measure for the absolute magnitude of diffusion, and fractional anisotropy (FA), a measure of the directionality of diffusion. In addition, it can provide information to draw conclusions about axial diffusivity (AD), a measure of diffusion parallel to fibers, and radial diffusivity (RD), a measure of perpendicular diffusion.[53]

Reduced microstructural integrity is characterized by decreased FA and increased MD and RD.

While DTI can provide enhanced sensitivity relative to T2 FLAIR imaging to microstructural changes in white mater, it has limitations. Changes in FA, MD, and RD values derived from DTI may reflect changes in many aspects of the neurons such as reduction in neurite density and increase in neurite orientation dispersion. Further, DTI is insensitive to microstructural nuances within a particular voxel, such as regions in which WM tracts intersect, fan, or bend.[54] Therefore, DTI derived values lack specificity for characterizing early subtle changes in the microstructural features of white mater within individuals with MCI.[55]

NODDI can provide additional information on the microstructural features of NAWM

Neurite orientation dispersion and density imaging (NODDI) can provide more specific markers of tissue microstructure than conventional DTI.[56] NODDI is a diffusion MRI technique that utilizes a model based on the differences in the diffusion of water within the intracellular, extracellular, and cerebral spinal fluid (CSF) compartments within the brain.

While DTI derived values provide composite information about a single voxel, the NODDI model divides each voxel into 3 compartments, which can help distinguish between features of microstructural change. The two main NODDI derived parameters based on these three compartments include neurite density index (NDI) and orientation dispersion index (ODI), which contribute to FA. In addition, fraction of free water F_{iso} is

another parameter derived from NODDI. The NDI values provide information about the volume fraction of neurites within the intraneurite space. The ODI values provide information that reflects changes in the orientation of fibers within the extracellular space of white mater. NDI and ODI have been found to be highly correlated with histological measures, indicating that the NODDI model allows for accurate estimation of neurite density.[57] The F_{iso} values represent the volume fraction of water that diffuses freely like CSF.[55] Compromised microstructural integrity in white matter can be reflected by an increase in ODI values and a decrease in NDI values.[56] Studies have shown that NDI values are more sensitive to changes in white matter than FA values derived from DTI in individuals with AD and MCI.[55,58] Despite these findings, no study has used NODDI to assess the relationship between NAWM and mobility performance in individuals with MCI.

Brain regions associated with NAWM changes and mobility performance remain unclear

While the relationship between cognition and mobility is well established, the relationship may reflect changes to white matter in shared brain regions and networks that age and neurodegeneration commonly affect. Little is known about the relationship between the structural regions of the brain that are involved in age-related mobility performance and cognitive decline in the elderly.[59] This may be due partially to limitations in imaging modalities, as individuals are imaged in the supine position, and are immobile while in the scanner. Also, the association between cognitive and age-related mobility performance can be complex. Decline in age-related mobility performance is multifactorial, and may have contributors in multiple domains of the body, as mentioned

previously. Furthermore, aging affects multiple domains simultaneously; older adults rarely have isolated impairments.[60]

More recent neuroimaging methods, such as DTI and NODDI, have begun to reveal brain structures, regions, and functional networks that are involved in mobility, which will provide additional support for the assessment of white matter health in individuals with increased fall risk. Several studies have investigated white matter integrity related to gait impairment. Impaired mobility in older adults was associated with decreased FA and AD values in the inferior and superior cerebellar peduncles.[61] White matter tracts within the inferior and superior cerebellar peduncles allow the cerebellum to communicate with various regions of the brain, and are critical components in maintaining balance and coordination during voluntary movement.[61]

The primary motor cortex receives various inputs from many cortical and subcortical regions of the brain such as the thalamus, parietal cortex, and the cerebellum. Also, it is considered as one of the final integrators of motor control. [62] The primary motor cortex is connected to various regions of the brain by projection fibers (thalamic radiation, corticofugal) and association fibers (superior longitudinal and fronto-occipital fasciculi). A study has demonstrated that bilateral lesions in white matter involving the projection fibers in the corona radiata and some long and short association fibers were associated with poorer gait in the general older adult population.[63] For example, lower FA values in white matter tracts associated with the periventricular region of the brain such as the cingulum were associated with lower gait performance. [47,48] The cingulum is a bundle of association fibers that is involved in the communication between different components of the limbic system and aids in attention and decision making while executing movement. In addition,

abnormal white matter in the medial, frontal, parietal subcortical pathways, genu, and splenium of the corpus callosum was associated with gait performance in home bound older adults.[64] These finding suggest that degradation of the microstructural integrity white matter tracts that provide connections to the primary motor cortex, may explain gait impairment in individuals with MCI, and furthermore increased fall risk.

Although studies have found a consistent association between abnormalities in white matter health and mobility performance both in individuals with MCI[65] and healthy older adults, the relationship needs further investigation. Studies in the past vary in rating scales of WMH, measures of mobility performance, imaging techniques, and populations, which can make it difficult to form conclusions on the specifics of the relationship. The assessment of the association of white mater health as it relates to mobility performance in older adults with MCI is under-researched, and rarely considered with other risk factors that contribute to fall risk in mobility research and practice.

The specific brain regions associated with changes in mobility performance and cognitive decline remain unclear in individuals with MCI. It remains unknown if the magnitude or location of white matter change affects the relationship between cognition and mobility performance. It also remains unknown whether there are other factors that mediate increased white matter damage. To date no study has utilized NODDI to assess changes in the white matter health of older adults with MCI.

The objective of this analysis is to use baseline data from participants enrolled in the ongoing IMOVE study to examine group differences in older adult fallers and non-fallers with MCI. These differences may provide more insight into risk factors that contribute to increased fall risk among older adults with MCI. Aim 1 is focused on

describing differences in demographic characteristics in older adult fallers and non-fallers with MCI that are known to be associated with increased fall risk. The hypothesis is that there will be significant group differences in known risk factors associated with falls. Aim 2 is focused on using the NODDI technique to examine the association of white mater integrity with gait variability in brain regions of fallers and non-fallers with MCI, to evaluate whether the integrity of white matter tracts within specific brain regions is associated with gait variability. The hypothesis is that that there will be significant negative associations between NDI values and positive associations between ODI values and gait variability in white matter tracts of older adult fallers and non-fallers with MCI, that are involved in cognition and motor function. As a result, these findings may reveal early changes in brain regions that are associated with increased gait variability that could be used to assess fall risk in older adults with MCI.

CHAPTER 2
METHODS

Study Design

This analysis includes baseline physical function and neuroimaging data from participants in the IMOVE study ("IMOVE: A randomized, controlled trial of Improvisational MOVEment for people with memory loss and their caregivers", R01 AT009444). IMOVE is an ongoing single-blind randomized clinical trial that uses a 2x2 factorial design to assess the separate and combined effects of social engagement and movement on QoL of older adults adjudicated with MCI or early stage dementia and their caregivers. Once the participants are screened and determined eligible for the study, they attend two baseline study visits prior to the intervention. All participants completed IRB-approved, written informed consent prior to any data collection. In addition to informed consent, vital measurements, medical history, list of current medications, and baseline measurements of outcomes were collected during the two baseline visits.

Study participants

In this thesis, analyses were done on baseline data for 56 participants from the IMOVE Study. Participants were recruited from the WFSM Memory Assessment Clinic (MAC), the WFSM Alzheimer's Disease Core Center (ADCC), other neurology clinics, and the community. Participants were determined eligible to participate in the study if they were between 60-85 years old, had a diagnosis of MCI or early stage dementia of predominantly AD, vascular or mixed AD/vascular within 1 year of the study, English speaking, able to undergo an MRI scan, had a study partner who could regularly

accompany them to intervention sessions, and were not enrolled in another interventional study for at least 3 months prior to beginning IMOVE.

Participants were excluded if they were currently symptomatic or had cortical stroke deemed exclusionary by the study physician, had other cause of dementia, such as Lewy body, fronto-temporal or Parkinsonian dementia, diagnosed with amyotrophic lateral sclerosis (ALS) or multiple sclerosis (MS), had any major medical problem that could affect cognitive or brain imaging measures used to determine eligibility or outcomes or severely impact attendance, were currently taking medication that could negatively influence safety during the intervention, had current drug or alcohol use or dependence that would interfere with adherence to study requirements, were unwilling to provide consent or assent for study participation, and planned extensive travel during the study period.

Assessment of gait and falls

Gait speed and variability were assessed during single, fast, and dual task conditions using the GAITRite Mat. During the single task trials participants were instructed to walk over the 4m gait mat 4 times at usual pace and 4 times at a fast pace. During the usual pace participants were instructed to walk over the mat 4 times at a pace that feel comfortable to them, as if they were walking to the mail box or window shopping. During the fast pace participants were instructed to walk over the mat 4 times at a fast pace, as if they were hurrying to get out of the rain but not running. During dual task conditions participants were instructed to walk over the mat 4 times at usual pace while performing a cognitive task, which was reciting every other letter of the alphabet starting with B. No instructions on whether to prioritize the cognitive or the gait task. Gait speed was expressed as centimeters/second (cm/s). Stride time was considered equivalent to gait cycle time and

both were defined as the time elapsed between the first two contacts of two consecutive footfalls of the same foot and was measured in seconds.[66]

The coefficient of variation (CoV) was calculated by taking the quotient of the average stride time standard deviation (STD) of the right and left foot, and the average gait cycle time of the right and left foot. **See Figure 1.**

Figure 1. Formula used for calculating CoV.

$$\mathbf{CoV=}\ \frac{\text{average (stride time STD of R\&L foot)}}{\text{average(gait cycle time of R\&L foot)}}\ \mathbf{X\ 100\%}$$

Abbreviations: CoV, Coefficient of Variation, STD, Standard Deviation

A fall was defined as an event when the participant made complete contact with the ground. Self-reported retrospective fall history was determined by asking the participant if they had fallen within the past twelve months. Global mobility was assessed by the short physical performance battery (SPPB) a quick test of global mobility that can be used to predict future disability risk. The scores range from 0 (Worst Performance) -12 (Best Performance). The expanded short physical performance battery (eSPPB), is similar to the SPPB, but increases difficulty of the standing balance task by asking participants to hold posture for 30 seconds instead of 10 seconds, adds a one-leg stand, and adds a narrow walk. The resulting score is normally distributed, continuous, and shows greater sensitivity to higher levels of physical functioning[67].

The falls efficacy scale international (FES) was used to assess fear of falling. The scores range from 16-24, with higher scores indicting greater risk of falling. Fallers were

defined as individuals who self-reported a fall in the previous year. Non-fallers were defined as individuals with no self-reported falls in the previous year.

Adjudication of Cognitive Status

Participants had a comprehensive cognitive evaluation that included a neuropsychological test battery, functional status questionnaires, and a history and physical by a board-certified geriatrician. Participants who didn't have imaging or blood work to rule out reversible causes of cognitive impairment receive standard blood assays and an MRI (or CT scan if MRI is contraindicated). After reviewing all data and undergoing consensus, dementia experts assigned a diagnosis of AD, other forms of dementia, MCI, or normal cognition using Alzheimer's Association/NIA criteria. The panel of dementia experts included at least one; neurologist, geriatrician, and neuropsychologist who all specialize in assessing and treating older adults with cognitive impairment.

Imaging acquisition and data processing

A 3T MR Scanner (Siemens MAGNETOM Skyra) using a 32–channel head coil was used to perform scans on research participants. T1-weighted anatomical images collected in the sagittal plane were acquired by using 3D volumetric MPRAGE sequence (Voxel size=1.0 x1.0 x 1.0mm; repetition time [TR]=2300.0ms; echo time [TE]=2.98ms; inversion time TI=900ms; Flip angle=9 degrees; phase encode direction = anterior to posterior; slice thickness=1.00m; 192 slice)]. NODDI images collected in the axial plane were acquired using a 2D single-shot EPI sequence (Voxel size= 2.0 x 2.0 x 2.0 mm; [TR]=3500ms; [TE]=108.20ms; Flip angle=90 degrees; phase encode direction = anterior to posterior; slice thickness= 2.00m; 80 slices; 131 diffusion directions).

The diffusion data were processed using the following procedure:

1) Images were converted from Digital Imaging and Communications in Medicine (DICOM) to Neuroimaging Informatics Technology Initiative (NIFTI).
2) Images were corrected for susceptibility induced distortions using FSL TOPUP.
3) Residual motion and image distortion as a result of eddy currents were corrected using EDDY in FSL toolbox.
4) Non-brain tissue was extracted by using the Brain Extraction Tool (BET) in FSL.
5) AMICO software[68] was utilized to fit the NODDI model and calculate NODDI parameters in native space.
6) Images were then warped to common MNI space.

Statistical analysis

To assess group differences between fallers and non-fallers in demographic and gait parameters, a Student's t-test was performed for continuous variables and a Fisher's exact test for binomial data using SAS software version 9.4 implemented in SAS Enterprise Guide 7.1 (SAS Institute, Inc., Cary, NC, USA). The analysis of demographic data included a total of 56 participants, while the analysis of gait parameters included 47 participants, with 8 participants being removed due to missing gait data. Data for one participant in the Faller group was excluded because gait variability in all three walking conditions was greater than 3 standard deviations from the mean. To assess group differences in NODDI parameters between fallers and non-fallers, a voxelwise student t-test was performed and corrected for family wise error using SPM12 software. A total of 39 participants were included in the analysis with 16 participants being excluded due to missing gait variability and or scan data, and 1 participant being excluded due to gait data

being considered an outlier. To assess the association between NODDI parameters and gait variability between brain regions of faller and non-fallers, an exploratory voxelwise multiple linear regression model was used and was corrected for family wise error using SPM 12.

CHAPTER 3

RESULTS

Demographics

A total of 56 participants were included in this analysis. Of these participants, 21 (37.5%) reported falls at baseline. Refer to **Table I** for a summary of the demographic statistics based on reported fall history at baseline. There were no significant differences in gender, age, Type II diabetic status, or medication use between fallers and non-fallers at baseline. Of note, BMI was significantly lower in fallers than non-fallers (t=1.12, p=<.001) and total SPPB Scores approached, but did not reach a statistically significant difference (t=1.81, p=0.08).

Table I. Summary of demographic and other baseline characteristics of the participants by reported history of falls.

Participant Demographics			
	Non-Fallers (n=35)	**Fallers (n=21)**	**P-value**
Gender, female, n (%)	21(60)	11(52.38)	0.58
Age, y, mean(SD)	73.47(6.21)	78.58(5.60)	0.64
Race			0.71
White, n(%)	31(88.57)	18(85.71)	
Black, n(%)	4(11.43)	3(14.29)	
Education, y, mean (SD)	15.71(3.30)	14.90(2.61)	0.26
BMI, kg/m^2, mean(SD)	28.69(9.79)	26.68(3.68)	**<.001**
Type II Diabetes, n(%)	5(14.29)	2 (9.52)	0.60
Hypertensive, n(%)	19(54.29)	10(47.62)	0.63
Diagnosis of Depression	8(22.86)	9(42.86)	0.12
Anti-Diabetic medication, n(%)	3(8.82)	1(4.76)	0.57
Anti-Hypertensive medication, n(%)	20(58.82)	12(57.4)	0.90
Cognitive Medication, n(%)	13(38.24)	11(52.38)	0.30
Anti-depressant Medication, n(%)	11(32.5)	11(52.38)	0.14
eSPPB, mean(SD)	1.81 (0.56)	1.59(0.44)	0.25
SPPB total, mean(SD)	9.35(2.14)	8.29(2.10)	0.08
Falls Efficacy Score, mean(SD)	25.41(9.44)	26.38(7.06)	0.17

Abbreviations: BMI, Body Mass Index; eSPPB, Expanded Short Physical Performance Battery; SPPB, Short Physical Performance Battery

Examining differences in gait parameters by reported fall history at baseline

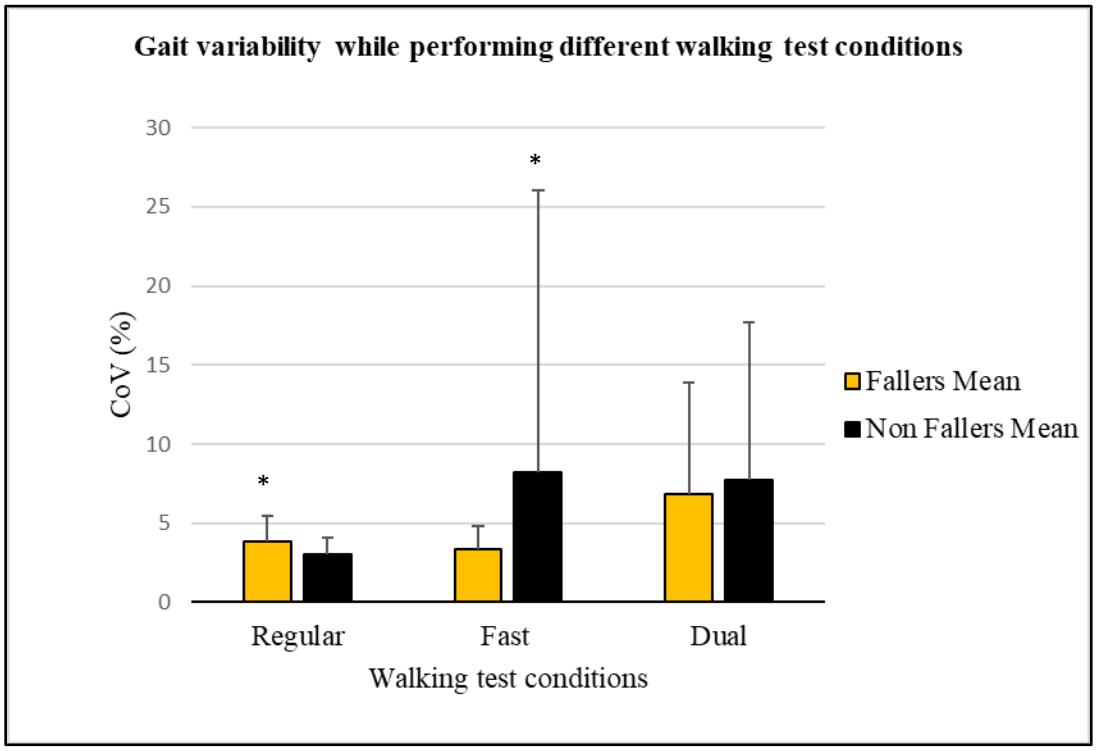
A total of 47 participants were included in the analysis of gait parameters by reported fall history. The overall gait speed was not significantly different between the fallers and non-fallers for normal, fast paced, or dual task walking conditions ($p > 0.4$). Participants who reported fall history had significantly higher CoV during normal walking conditions ($t=-1.99$, $p=0.03$), and significantly lower CoV during fast walking conditions ($t=1.16$, $p<.001$). While CoV during dual task conditions was higher among non-fallers, it was not a significant difference ($t=0.26$, $p=0.09$). Refer to **Table II** and **Figure 2** for a summary of differences in gait parameters based on falls reported at baseline.

Table II. Groups differences in gait parameters based on falls reported at baseline.

Gait Parameters			
	Non Fallers (N=29)	**Fallers (N=18)**	**P-value**
Gait Velocity normal (cm/s), mean(SD)	101.38(18.84)	98.4 (15.79)	0.48
Gait Velocity fast (cm/s), mean(SD)	134.8(25.47)	125.8 (25.4)	>0.9
Gait Velocity dual (cm/s),mean(SD)	92.21 (23.71)	86.27(20.8)	0.50
CoV (normal), mean(SD)	3.07% (1.04)	3.85% (1.65)	**0.03**
CoV (fast), mean(SD)	8.21% (17.8)	3.32% (1.53)	**<0.001**
CoV (Dual), mean(SD)	7.73% (10.0)	6.86% (7.00)	0.09

Abbreviations: CoV, Coefficient of Variation

Figure 2. Mean gait variability during normal walking conditions was significantly higher in older adult fallers with MCI, while during fast walking conditions mean gait variability was significantly lower in older adult fallers with MCI.



Examining differences in NODDI parmameters by reported fall history at baseline

A total of 39 participants, 16 fallers and 23 non-fallers, were included in the voxelwise analysis of between group differences in NODDI parameters. There were no overall significant between group differences in NDI (peak t= 3.44, p=0.997) and ODI values (peak t=4.67, p=0.478) when corrected for multiple comparisons using family wise error.

Associations between NODDI parmeters and gait variability under usual walking conditions

The NDI values of the right inferior logitudinal fasciculus (peak t=7.54, p<0.001) (Figure 3A), the right uncinate fasiculus (peak t=5.86, p=0.014) (Figure 3B), right inferior frontal occipital fasiculus (peak t=5.55, p=0.032) (Figure 3C), and the left cingulum (peak t=5.42, p=0.045) (Figure 3D) were negatively associated with gait variability under normal walking conditions, when corrected for family wise error. There were no positive associations found between NDI values and gait varibility under normal walking conditions. Refer to **Figure 3** for significant white matter tracts where associations between gait variability and NDI values were found under normal walking conditions. The ODI values of the right inferior fronto-occipital fasiculus(peak t= 8.67, p<0.001)(Figure 4A), right inferior longitudinal fasciculus (peak t= 8.48, p=<0.001) (Figure 4B), and the left cingulum (peak t=5.66, p=0.048) (Figure 4C) were positively associated with gait variability under normal walking conditions when corrected for family wise error. There were no negative associations found between ODI values and gait variabilty under normal walking conditions. Refer to **Figure 4** for white matter tracts where significant

associations between gait variablity and ODI values under normal walking conditions were found.

Figure 3. A, **B**, **C**, and **D** are statistical maps showing that lower NDI values are associated with higher gait variability; in **A** (right inferior longitudinal fasciculus), **B** (right uncinate fasciculus), **C** (right inferior fronto-occiptial fasciculus) , **D** (left cingulum) during normal walking conditions. Red-yellow color denotes regions of negative association. $PFWE_{corrected} < 0.05$.

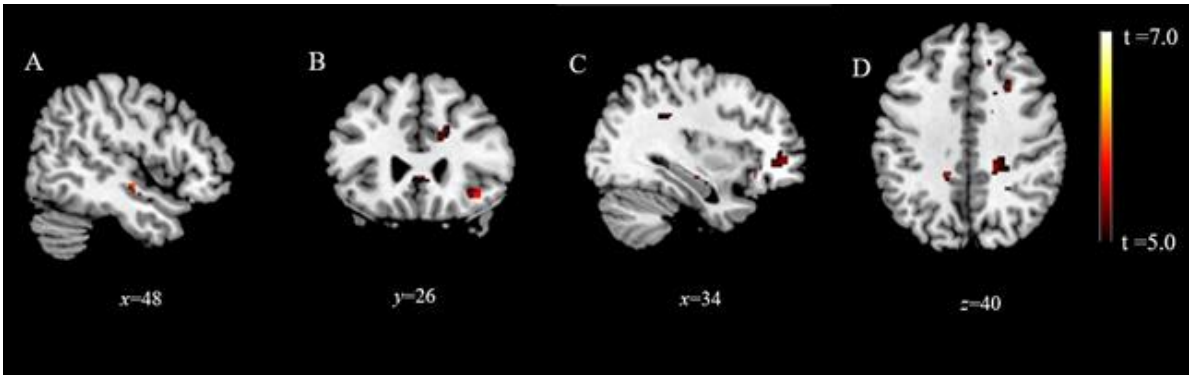
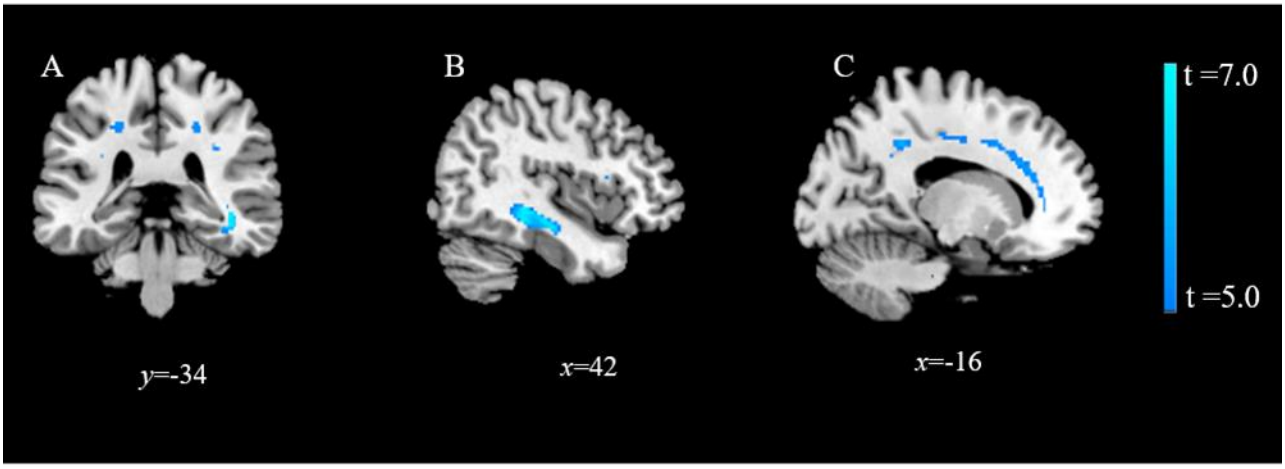


Figure 4. A, **B**, **C**, are statistical maps showing that higher ODI values are associated with higher gait variability; in **A** (right inferior fronto-occipital fasciculus), **B** (right inferior longitudinal fasciculus), **C** (left cingulum) during normal walking conditions. Blue-teal color denotes regions of positive association. P(FWE)corrected <0.05.



Correlations between NODDI parameters and gait variability under dual task walking condtions

There were no associations found between NDI values and gait variability during dual task walking conditions in older adult fallers and non-fallers with MCI or early-stage dementia under dual task walking conditions. In addition, there were no associations found between ODI values and gait variability during dual task walking conditions.

Discussion

Older individuals with MCI experience increased fall risk compared to cognitively healthy older adults. However, the specific mechanism behind this increased fall risk remains unknown. While multiple factors may contribute to fall risk, a growing body of literature suggests that increased fall risk may be a result of impaired balance and gait. Gait impairment can be the result of peripheral nerve, spinal cord, and brain dysufunciton.[69] Microstructural abnormalities in white matter tracts are of particular interest because white matter tracts are involved in the communication between cortical and subcortical region of the brain that are associated with gait. The purpose of this study was to use the NODDI technique to explore the association between NODDI parameters and gait variability in older adult fallers and non-fallers with MCI to determine if microstructural changes in white matter health are related to increased fall risk in older adults with MCI.

Results showed that fallers at baseline within the IMOVE study had significantly lower BMI compared to non-fallers, a known risk factor for falls among older adults.[5] Research suggest that there is a u shaped association between BMI and frailty with individuals who have a BMI of less than 18 or greater than 30 at greater risk of frailty. [70] [71] Excessive and low body weight is associated with weakness, impaired balance, and abnormal gait which are all symptoms associated with frailty and can increase fall risk among older adults. The mean BMI for fallers and non-fallers within the IMOVE study fell within the overweight category (25.0-29.9). The lower BMI found among fallers may be the result of unintentional weight loss which has been associated with decline in performance of activities of daily living[72], increase risk of hip fracture in women[73], overall mortality[74], and risk of AD[75]. Differences in known risk factors for falls such as age,

gender, Type II diabetic status and medication use were not found to be significantly different between fallers and non fallers at baseline, suggesting that their maybe similarities in fall risk between the two groups.

Overall, there were no significant differences in gait speed between fallers and non-fallers during the three different walking conditions (usual, fast, dual-task). However, fallers had significantly higher gait variability during usual pace walking conditions and significantly lower gait variability during fast walking conditions. There was no significant difference between fallers and non fallers in gait variability during dual task walking conditions.

The finding that gait variability was significantly lower in fallers compared to non-fallers during fast walking conditions was unexpected because the literature supports the idea that stride time, double support, and step time variability increases with complexity of walking task in individuals with MCI.[30,76] The lower gait variability found during the fast walk condition may be due to methodological challenges associated with using gait variability. First, gait variability can be measured using many different spatio-temporal parameters and it remains unclear which measures of gait variability are of greatest importance when predicting mobility decline. Secondly, there is a lack of consensus about how best to calculate gait variability. Gait variability can be calculated by using the CoV or standard deviation. This matters because the standard deviation is sensitive to the scale of values, while the CoV tends to infinity when the mean is close to zero. As a result, gait variability with low mean values tend to have high coefficient of variance.[77] Lastly, individuals whose mobility is already impaired experience increased gait variability across many spatio-temporal parameters, making it more difficult to determine which parameter

is most indicative of increased fall risk. With this in mind, taking multiple measures of gait variability or using a composite measure of gait variability such as the gait variability index[78] may help to better assess the relationship between gait variability and mobility decline.

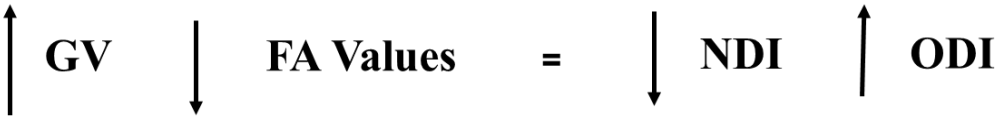
The unexpected finding may also be related to the stratification of the data into groups of fallers and non fallers. The stratification relied on self-report, and assumes that fall events were associated with brain pathology and not accidents, which may not be true for all participants. In addition, individuals assigned to the non fallers group may have fallen, as falls can be underreported when recalled after several months[79]. Stratifying groups based on recurrent falls during the duration of the study may be a more reliable assessment of fall incidence. In addition, in the current sample size of 47 participants; there were 2 observations in non-fallers that may be outliers, because they were considered to be 3 standard deviations away from the mean. However, these individuals were retained for this interim analysis and results may change once a full sample is collected.

No voxelwise differences in ODI or NDI were observed between fallers and non-fallers when compared using a t-test. The lack of significant between-group difference in NDI or ODI could reflect a real trend, or may be because of low power within the study, as some participants couldn't be analyzed due to missing gait parameters and or imaging data. More conclusive evidence may be available at the end of the study.

Since this is the first study to examine associations of NODDI parameters and gait variability, the associations between NODDI parameters and gait variability will be interpreted based on previous studies that used DTI. One of the commonly used parameters of DTI is FA. As described in the introduction, FA is measure of directionality of diffusion

and serves a surrogate measure of tissue microstructure. FA is nonspecific, and changes in FA could be due to axonal degeneration, myelin break down, neuronal density, as well as other tissue microstructure changes. Higher FA values represent better microstructural integrity. NODDI parameters provide additional insight into microstructural integrity. NDI is a measure of neurite density, and ODI provides information about the extent of neurite dispersion. Normal white matter displays higher NDI values and lower ODI values. Therefore, lower NDI values would be anticipated in regions with lower FA, and higher ODI values would be expected to correspond with lower FA values. An illustration of this relationship is displayed below in **Figure 5.**

Figure 5. Illustrates the relationship between gait variability, FA values, and NODDI parameters. Compromised microstructural integrity is associated with increased gait variability and reductions in FA values, which can be further explained by lower NDI values and higher ODI values.



Abbreviations: GV, Gait Variability; FA, Fractional Anisotropy; NDI, Neurite Density Index; ODI, Orientation Dispersion Index

Gait variability was found to be significantly negatively associated with NDI values in the right inferior longitudinal fasciculus, right uncinate fasciculus, right inferior fronto-occipital fasciculus, left cingulum. In addition, there were significant positive associations with ODI values in the right inferior fronto-occipital fasciculus, right inferior longitudinal fasciculus, and left cingulum. All of these white matter tracts are considered to be

association fibers, meaning that that they interconnect various areas of the cortex within the same hemisphere and play important roles in mobility function.

The inferior fronto-occipital fasciculus intermingles with the uncinate fasciculus and connects the temporal lobe to the frontal lobe. It is thought to be involved in semantic processing, which allows for the encoding of the meaning of words. Research has shown that verbal fluency which relies upon semantic memory affects the gait of individuals with MCI while performing dual task.[80] The uncinate fasciculus connects the frontal lobe to the temporal lobe. It is a part of the limbic system, and plays a role in emotion, and formation and retrieval of episodic memory. Studies have shown that the limbic system can be entrained by auditory stimuli and help with gait dysfunction.[81] The inferior longitudinal fasciculus connects the temporal and occipital lobes. It is involved in the processing and modulation of visual cues. It allows individuals to recognize faces and objects. Compromised integrity of the inferior longitudinal fasciculus can lead to visual impairment, which can greatly affect mobility. The cingulum has connections with the prefrontal, parietal lobe, premotor cortex, amygdala, and hypothalamus. It is also central to the default mode network, and is associated with both temporal and spatial gait variability. The cingulum aids in many aspects of movement related functions, such as attention and decision making and has consistently been found to be affected in individuals with AD and MCI.[82,83] Evidence supports the early involvement of the cingulate cortex in the progression of AD. These results support previous DTI studies that have found that FA was lower in older adults with MCI with a history of falls and found significant associations between lower FA and reduced gait performance within several white matter tracts including but not limited to the forceps minor (connects the frontal lobe to the prefrontal

lobe), the uncinate fasciculus (connects the temporal lobe to the frontal lobe), and the inferior longitudinal fasciculus.[65]

Interestingly, all of these association fibers have direct or indirect connections to the frontal executive network which is primarily involved in attention control, executive function, error monitoring, and maintaining a task dependent cognitive state.[84] Previous studies have shown the involvement of executive functioning in mobility and falls[30]. Poorer executive function and attention were associated with higher spatial gait variability in older adults[85]. The negative associations of NDI values with gait variability and positive associations with ODI values found in these association fibers suggest that there may be disruption of connectivity within the executive network. Decreased neurite density and myelin breakdown in these regions may contribute to both cognitive decline as well as gait variability.

Research has shown that older adults with higher cognitive function have larger life space mobility,[86] which is the ability of an individual to move within environments that expand from one's home to the greater community.[87] Often moving further away from home, requires greater cognitive investment. Therefore, executive function may play an important role in the mobility of older adults. Compromised microstructural integrity in regions involved with executive function may explain why individuals with MCI experience increase fall risk. Individuals who are experiencing declines in executive function may have difficulty moving in areas away from their home without assistance, and in return increasing their risk of falls.

A major strength of this study is that it uses the NODDI technique to explore white matter differences in fallers and non-fallers. Review papers suggest that microstructural

integrity rather than brain volume are associated with gait variability.[77] The NODDI technique is thought to be more sensitive to microstructural changes than DTI, and as mentioned earlier, previous studies utilizing DTI have found similar associations between FA values and gait performance in older adults. These findings provide evidence that NODDI may be more sensitive than DTI, and is important for examining associations between microstructural integrity and gait performance. In addition, while the majority of population studies focus on the association of cognitive function with gait speed, gait variability is thought to be a better indicator for fall risk, and this study used gait variability.

Although this study has strengths, there are also limitations. One limitation of the study would be the limited generalizability of the study. The study population is limited to older adults with cognitive impairment. Therefore, a larger sample size of older adults with MCI as well as healthy controls would have been beneficial in ascertaining significant differences in variables that approached significance (e.g., SPPB), increased the power of the study, and made the results more generalizable. In addition, we were unable to account for additional brain pathologies that might affect gait variability, such Aβ deposition. The current analysis is also cross-sectional, so directionality of associations with WM cannot be inferred. The study relies on self-reported fall history in individuals with memory loss, which limits the accuracy of group classification. The physical activity levels of these individuals was also unknown. Lastly the assessment of gait was over a short distance of 4 meters.

Conclusion

It was hypothesized that there would be significant negative associations between NDI values and positive associations between ODI values and gait variability in white

matter tracts of older adult fallers and non-fallers with MCI, that are involved in cognition and motor function. Significant associations were found between NODDI parameters and gait variability in the superior longitudinal fasciculus, uncinate fasciculus, inferior longitudinal fasciculus, the inferior frontal occipital fasciculus and the cingulum. These white matter tracts are essential for maintaining balance, executive function, attention, and decision making. This study shows that earlier changes in white matter tracts involved in executive functioning may play a role in increased fall risk.

Although NODDI may be a sensitive measure, the microstructural integrity of white mater alone may not fully explain the increased fall risk in individuals with MCI. There may be other significant interactions between multiple brain pathologies that may also affect gait performance. Future studies are needed to further elucidate the role of microstructural integrity in relation to other brain pathologies to explain the increased fall risk among older adults with MCI. Future studies should also assess the predictive ability of NODDI derived parameters, in determining incidence of falls and its interplay with other risk factors associated with increased fall risk.

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CURRICULUM VITAE

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SUMMARY

Passionate and motivated graduate student with a solid history of leadership, serving others, and love for science.

EDUCATION

Wake Forest School of Medicine, Winston-Salem, NC
May 2020

Master of Biomedical Sciences in Health Disparities in Neuroscience-related Disorders

Claflin University, Orangeburg, SC
May 2018

Bachelor of Science in Biology with a minor in Chemistry

Honors: Summa Cum Laude, Women's Indoor Track and Field MVP 2017-2018, Coaches Award 2017-2018, Claflin University Outstanding Scholarship and Service Award 2017-2018, Gold Medallion Award 2015-2016

RELATED EXPERIENCE

Concierge, Homestead Hills, Winston-Salem, NC
Feb 2019 – present

Greet visitors, manage incoming and outgoing calls, schedule meetings and make appointments, sorting incoming and outgoing mail, monitors and enforces visitation policies and procedures.

Seasonal Sales Associate, Target, Lexington, SC
Nov 2017-Feb 2018

Operated cash register and processed returns, resolved customer complaints, restocked inventory as needed, helped customers locate products throughout the store, maintained a neat and organized work space.

Tutor, Spartanburg Methodist College, Spartanburg, SC
Jan 2015 - May 2015

Explained complex concepts using easy-to-understand terms, worked with students of all ages, developed action plans based on students' and educators' academic goals.

RESEARCH EXPERIENCE

Graduate Research Assistant, Neuroscience, Wake Forest School of Medicine
Aug 2018 - Present

- Performing research on the IMOVE study, a randomized, controlled trial of improvisational movement for older adults with memory loss and their care givers.
- Interacts with participants regarding the study, conduct phone screenings, perform cognitive and physical performance assessment, works with principal investigator to implement and develop recruitment strategies.

Summer Intern, Cell Biology, University of Virginia School of Medicine

- Performed undergraduate research on the differentiation of neutrophils, and how they can be used to develop and new target for Rheumatoid Arthritis.
- Systematically monitored temperature, cell viability, and other parameters to ensure cell quality. Prepared cell culture media, and harvested cells.

LEADERSHIP ACTIVITIES

Graduate Student Ambassador, *Wake Forest School of Medicine, Winston-Salem, NC*
Jan 2018- present

Assists in student recruitment, lead guided campus tours, and answering questions from prospective graduate students.

Student Athlete Advisory Committee, *Claflin University, Orangeburg, SC*
Aug 2016 - May 2018

Served as a representative of the Cross Country and Track and Field Team for two years, organized student athlete involvement in community outreach, promoted positive image of student athlete to peers, and provided insight on student athlete issues.