# CAREER STAGE MODERATES THE RELATIONSHIP BETWEEN MENTAL HEALTH SEVERITY AND WHITE MATTER INTEGRITY IN SPECIAL OPERATIONS FORCES COMBAT SOLDIERS

by

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## ABSTRACT

Special Operations Forces (SOF) combat Soldiers are exposed to mild traumatic brain injury (mTBI) risk during training and combat operations. Service members who have sustained an mTBI may also experience various mental health issues. Neurophysiological changes from mTBI outlast clinical recovery including decreased structural integrity of white matter (WM) tracts in the brain. Therefore, using clinical tests to predict WM integrity could aid in assessing neurotrauma in SOF combat Soldiers. The purpose of this study was to determine how mTBI and career stage moderate the association between mental health symptom severity and WM tract integrity in SOF combat Soldiers. We reconstructed 40 WM tracts for 66 SOF Soldiers. Significant interaction effects of career stage were found in the corpus callosum, significant main effects of depression and anxiety symptom severity were found in the frontal aslant tract, a significant main effect of PTSD symptom severity was found in the uncinate fasciculus, and a significant main effect of later career stage was found in the superior longitudinal fasciculus and the corpus callosum.

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# CHAPTER I

## INTRODUCTION

Mild traumatic brain injuries (mTBI) are a serious global public health issue. Military personnel are particularly susceptible to sustaining concussions, a form of mTBI.[1,2] According to the Department of Defense (DOD), over 440,000 active Service Members were diagnosed with a concussion from 2000-2021;[3] however, the suspected incidence rate may be much higher due to underreporting whether intentionally or unintentionally.[4] Traumatic brain injury is defined as the result from a blow or jolt to the head that disrupts the normal function of the brain.[19] Concussions can occur directly, due to a traumatic blow to the head, or indirectly due to forces elsewhere in the body that lead to a change in cranial acceleration.[5] Often, Service Members who have sustained an mTBI also experience concomitant mental health issues such as Posttraumatic Stress Disorder (PTSD) and depression[6] which can increase neurophysiological symptoms and delay recovery.

In standard mTBI clinical management, return to activity decisions are made based on symptom resolution.[5] However, some neurophysiological changes caused by mTBI outlast clinical recovery including decreased structural integrity of white matter tracts in the brain.[48] Axonal damage results in impaired ability to transport information, thus leading to chronic symptoms and recalcitrant cognitive impairments that last beyond return to activity clearance.[7] Diffusion tensor imaging (DTI) is an advanced magnetic resonance imaging (MRI) technique which can be used for white matter tract integrity assessment in individuals who have sustained an mTBI.

Axonal injury occurring after mTBI cannot be detected by conventional computed tomography (CT) and MRI. Diffusion tensor imaging can identify these axonal disruptions by

measuring water diffusion rates to indirectly assess white matter tract integrity. There are four DTI scalar parameters that quantify diffusion: 1) fractional anisotropy (FA), 2) mean diffusivity (MD), 3) axial diffusivity (AD), and 4) radial diffusivity (RD). Restricted diffusion along an axis is described by FA while MD quantifies overall diffusion rates within a voxel or tract.[7] Axonal degeneration results in lower FA and higher MD.[49] This neuroimaging technique has been used in the military to evaluate tract abnormalities following both acute concussions as well as chronic blast exposure.[8] Posttraumatic Stress Disorder is a persistent symptom commonly experienced in military populations[7] and DTI has been used to assess how mTBI and PTSD affect white matter in Service Members. However, there is not a consistent pattern in the literature regarding which tracts are affected by these injuries.[7,9] Although there is a high prevalence of other mental health issues that affect Soldiers such as anxiety and depression,[9] the literature has been focused on PTSD. Pathological mental health can alter tissue structure in the brain and modify diffusion patterns,[9] thus more studies utilizing DTI are necessary to understand how anxiety and depression affect white matter. About 1 in 4 active Service Members suffer from a mental health disorder and these disorders are leading causes of death in the US military population.[10] Using DTI to quantify abnormalities in white matter caused by both mTBI and mental health disorders in military populations is critical to the wellbeing of Service Members.

Few studies have examined the relationship between mental health issues and white matter tract integrity in Service Members with mTBI history. The detrimental effects of mTBI overlap with mental health issues such as anxiety, depression, and PTSD which complicates the overall recovery process.[11] With this fact in mind, more research is necessary to establish a combined approach to successfully manage cognitive and emotional symptoms. Davenport et al. observed that in military veterans, PTSD disrupts the association between mTBI and lower white

matter integrity that was previously detected in civilian populations.[12] Results revealed that an interaction between lifetime PTSD and deployment mTBI decreased fractional anisotropy (FA) globally as well as in 10 regions of interest (ROI) out of the 20 ROIs studied.[12] In light of this study, more research is needed to determine the association between other mental health issues that affect Service Members and mTBI on white matter integrity. Specifically, this research should study more tract paths that have the potential to be affected. Once a consensus is reached in the literature regarding affected white matter tracts, clinicians can use DTI to objectively diagnose mTBI which is currently diagnosed based on symptoms alone. If specific damaged ROIs can be identified, treatment for both mTBI and mental health disorders has the potential to become more individualized and targeted to specific deficits arising from axonal damage in certain tracts.

Therefore, the overall goal of this study was to determine the effects of mTBI history on the relationship between anxiety, depression, and PTSD and white matter tract integrity in combat Soldiers. To accomplish this goal, specific aims will be followed. The first specific aim was to determine how various mental health disorders are associated with FA and mean diffusivity (MD) in white matter tracts. The second specific aim was to determine how mTBI history moderates these effects on FA and MD. This exploratory study examined FA and MD in 40 white matter tracts to assess group differences associated with common mental health disorders and mTBI affecting Service Members.

**Research Questions**

1. What is the relationship between high anxiety/depression/PTSD and white matter tract integrity in Service Members (SM) as assessed by fractional anisotropy (FA) and mean diffusivity (MD)?

2. How does concussion history moderate the effects of mental health on FA and MD?

**Research Hypotheses**

1. Higher percentile scores on mental health questionnaires will result in decreased integrity of white matter tracts in SM.

2. SM with mTBI history will exhibit lower FA and higher MD in tracts affected by mental health issues.

**Clinical Significance**

This study provides no immediate clinical relevance. The study's main purpose is to contribute to DTI findings to identify a pattern of affected white matter tracts after concussion. Once a pattern of specific functional outcomes is identified, these data can help clinicians in the future. The potential implications of this study include furthering the understanding of how mTBI affects axonal microstructure in the brain in order to improve concussion treatment and diagnosis. Revealing which white matter tracts have been compromised for each patient can individualize and improve treatment for mTBI patients in the future. The information found in this study will be submitted to a scientific journal for peer-review to share our findings with other researchers and inform clinical care for mTBI.

# CHAPTER II

# LITERATURE REVIEW

## Introduction

Traumatic brain injuries are the result of a blow to the head that causes altered brain functioning such as dizziness, confusion, trouble concentrating, and headaches. There are multiple severity classifications for TBI – mild, moderate, and severe – with concussion falling into the mild category. The Glasgow Coma Scale is used to determine the severity of the injury by assessing three behavioral responses: eye opening, verbal response, and motor response.[27] Post-concussive syndrome (PCS) is a medical problem that persists after head injury. PCS symptoms include headache, dizziness, sleep problems, and psychological symptoms such as depression, irritability, and anxiety.

Along with depression and anxiety, PTSD is a concomitant mental health issue in military populations with mTBI. The consequences of these mental health disorders are far-reaching, impacting family members as well as SM.[22] While the etiology of these mental health issues is still being studied, it is known that axonal injury in WM is possible in populations with depression, anxiety, and PTSD. Traumatic brain injuries can also cause WM damage, complicating recovery from mTBI as well as coexistent mental health problems. Because WM damage can be quantified by DTI, it has been suggested as a biomarker to predict mTBI and related mental health disorders. This literature review encompasses metrics in military service members and veterans with mTBI and/or any of the mental health issues listed above. This

document provides an overview of the literature discussing research methods and resulting DTI metrics found in the studies.

Literature was reviewed for mental health, traumatic brain injury, diffusion tensor imaging, and white matter tract integrity in military and veteran populations using database searches including PubMed, SportDiscus, CINAHL, Scopus, Web of Science, Embase, ProQuest, and PsycINFO. Specific key words and phrases were used such as white matter, integrity, patterns, concussion, traumatic brain injury, soldiers, military, mental health, PTSD, and diffusion tensor imaging (see Appendix A). After removing duplicates found across different databases, 86 studies underwent title and abstract screenings, 51 studies were retained for full text screenings, and 22 relevant articles were identified (see Figure 1). Included studies needed to discuss WM and mTBI in military populations and use DTI as a measurement tool with FA or MD as an outcome metric.

## Background

### *Traumatic Brain Injury*

Traumatic brain injuries have the potential to cause neurological damage, leading to decreased axonal integrity and psychiatric issues. According to the Centers for Disease Control and Prevention, there were approximately 223,050 TBI-related hospitalizations in 2018 and 60,611 TBI-related deaths in 2019.[47] Concussion, a mild form of TBI, accounts for around 80% of TBI cases.[29] Many of these cases go untreated and unreported, thus the total number of mTBIs is expected to be higher than what is reported each year.[29]

Service Members are particularly susceptible to mTBIs, especially due to blast exposure. Blast traumatic brain injury is the second most common injury from blast.[27] There were 13,634 Service Members diagnosed with TBI in 2016, 86% of those cases categorized as mTBI.[27] Blast

exposure complicates TBI because repeated exposure to low-level blasts can lead to long-term impacts on the brain. There are four main modes of blast injury: primary, secondary, tertiary, and quaternary. Primary injury occurs from blast wave pressure. Secondary injury occurs due to objects thrown by the blast waves. Tertiary injury comes from acceleration of the body and ultimately the head and quaternary injuries come from direct effects of the explosion such as chemical burns. Service Members may be exposed to multiple mechanisms of injury while experiencing blast, complicating brain injury etiology.

Traumatic brain injuries often result in axonal damage. This type of injury to the brain does not result in bleeding but does include cell death or damage. Axons are the vessels through which electrical signals travel in the brain. Injury to these vessels decreases signaling in the brain, jeopardizing normal function of the brain. Symptoms remain the primary way that mTBI is diagnosed, however there are many biomarkers being explored as more objective ways to diagnose mTBI. White matter damage is one potential biomarker that could be used clinically to improve mTBI diagnosis and treatment.[42]

*Common Mental Health Disorders*

Over the past decade, mental health concerns among Service Members have emerged in the media with depression and PTSD as the two most publicized issues.[22] The effects of these issues can be exacerbated by mTBI and affect family members as well. PTSD is a psychiatric and biological disorder that occurs in people who witnessed a traumatic event and is usually characterized by disturbing thoughts and feelings related to the event. Combat-related PTSD ranges from 2-17% of US veterans, with 10-20% of cases resulting in debilitating symptoms for Service Members.[22] The Posttraumatic Stress Disorder Checklist for Diagnostic and Statistical Manual of Mental Disorders – 5 (PCL-5) is a validated diagnostic tool for PTSD. It includes 20

questions assessing symptoms related to reexperiencing traumatic events and answer choices are "Not at all," "A little bit," "Moderately," "Quite a bit," and "Extremely." Scores range from 0-80 with a score of 31 or higher indicating probable PTSD diagnosis.[23] Damage to WM microstructures impacts recovery and could be implicated in the etiology of PTSD which is still being studied.

The military environment contributes to Major Depressive Disorder (MDD) with an 11.4% minimum of Service Members in military clinics receiving a depression diagnosis. MDD presents through a variety of symptoms such as depressed mood, lack of motivation and concentration, changes in sleep or eating habits, feelings of worthlessness, or thoughts of suicide. The Patient Health Questionnaire – 9 (PHQ-9) objectifies depression severity through nine questions that address the usual symptoms of depression. Each question addresses feelings in the past two weeks with four answer choices possible, "Not at all," "Several days," "More than half the days," and "Nearly every day." Scores range from 0-27 with a score of 5 representing mild depression and 20 representing severe depression.[24] Because depression decreases mood, this disorder affects everyday life making it difficult to execute assigned tasks.

Although Generalized Anxiety Disorder (GAD) is not as publicized as PTSD and MDD, anxiety is associated with past-year deployment and traumatic events within the previous year.[25] Anxiety is characterized by psychological responses such as nervousness and worry, as well as physiological reactions such as increased heart rate and tension. These symptoms are in response to everyday, nonthreatening events that are interpreted as threatening. The GAD-7 is a questionnaire that assesses anxiety severity. Each question addresses feelings in the past two weeks with four answer choices possible, "Not at all," "Several days," "More than half the

days," and "Nearly every day." Scores range from 0-27 with a score of 10 as a cut-point for identifying cases of GAD.[26]

*Diffusion Tensor Imaging*

Diffusion tensor imaging is a noninvasive neuroimaging technique based on magnetic resonance imaging (MRI) that quantifies diffusion in white matter tracts. DTI is increasing in popularity because it can detect axonal injury whereas conventional MRI detects macroscopic brain structures. DTI is based on water's ability to self-diffuse and undergo Brownian motion, which is the random movement of particles in a particular medium.[7,13] Within each voxel in the brain, a three-dimensional "tensor" is generated to describe the shape of the water diffusion within the voxel.[7] These tensors provide the diffusion trajectory necessary to recreate WM tracts. The complete random motion of water in all directions is termed isotropic diffusion and the tensor will be spherical in shape. When movement is restricted in certain directions the diffusion becomes anisotropic and the tensor is ellipsoidal in shape. White matter tracts in the brain are characterized by axons covered in lipids that restrict diffusion, ideally leading to anisotropic movement.[13] Cerebrospinal fluid (CSF) provides an example of isotropic movement in the brain because diffusion is not restricted in any direction.

DTI uses strong magnetic gradients in noncollinear directions to produce eigenvectors ($\varepsilon_1$, $\varepsilon_2$, $\varepsilon_3$) and eigenvalues ($\lambda_1$, $\lambda_2$, $\lambda_3$) that represent the tensor images characterizing the diffusion of water. This technique can measure areas surrounding water molecules allowing for WM tracts to be observed *in vivo*.[7] The four scalar parameters used to quantify the diffusion tensor are fractional anisotropy (FA), mean diffusivity (MD), axial diffusivity (AD), and radial diffusivity (RD), are represented by eigenvalues. FA describes the uniformity of water's diffusion rate on a scale of 0-1. An FA of 0 indicates that water is unrestricted, diffusing equally

in all directions, such as CSF in the ventricles. An FA of 1 indicates that the flow of water is in one specific direction, such as when restriction is provided by axons in WM of the brain. FA represents the shape of the diffusion tensor, whereas the size of the tensor is represented by MD.[7] MD provides an average measure of diffusion rate within each voxel and is usually inversely related to FA.[7] The predominant diffusion direction in each voxel determines MD, meaning that tracts where fibers are crossed could be misrepresented by this measurement.[45] AD refers to diffusion along the principal axis ($\lambda_1$) and RD refers to diffusion along the two minor axes ($\lambda_2$ and $\lambda_3$). Tractography is one analytical technique for DTI which recreates WM fiber architecture based on these diffusion metrics. Using the information gathered from diffusion properties in WM, axonal tracts can be recreated and axonal microstructural properties assessed.

## Studies Assessing White Matter Integrity in Service Members

### *DTI Metrics for mTBI in SM/Veterans*

Concussion and other mTBIs have been researched for centuries, however using DTI as a measurement tool has been implemented only in the last decade. Civilians receive much more attention in this area than do SM and veterans. One of the first studies utilizing DTI to study mTBI found that there was no WM injury for veterans with mTBI despite their residual symptoms and difficulty during verbal memory tasks.[28] However, just one year later, MacDonald et al. found that DTI scans for US military personnel with mTBI were abnormal when their traditional MRI scans were normal.[8] They also found that these axonal injuries, particularly in the middle cerebellar peduncles, cingulum bundle, and right orbitofrontal WM, persisted on DTI scans 6-12 months later.[8] Another study found that veterans with mTBI history displayed lower WM symmetry between hemispheres.[30] A positive association between the number of WM clusters with decreased FA and physical PCS symptoms was determined by Miller et al.[35] While

these studies laid the groundwork, current research is aimed at using the four DTI metrics to determine where WM abnormalities reside in the brain and what other factors, such as age or mental health, influence WM integrity post-mTBI.

Some studies focused on certain areas of the brain while others studied 20 or more WM tracts scattered throughout the brain. MacDonald et al. manually traced regions of interest (ROI) in the cerebellum only, but found a significant decrease in relative anisotropy in the middle cerebellar peduncle for US military personnel with mTBI compared to controls with no mTBI.[31] Delano-Wood et al. looked only at three tracts in the brainstem, the medial lemniscus-central tegmentum tract, corticospinal tract (CST), and the pontine tegmentum (PT). No difference in FA was found between controls and mTBI groups for any brainstem tracts, however associations between LOC duration and PCS were found for certain tracts. LOC duration was associated with decreased FA in the CST while increased PCS was associated with decreased FA in the PT.[32]

Two studies found in the literature review focused on blast exposure. Blast exposure as well as mTBI resulting from blast exposure, is associated with diffuse, global patterns of lower WM integrity.[33] There is also a positive relationship between the number of mTBI events and the number of voxels with lowered FA.[33] However, Davenport et al. did not find any voxels where a majority of the SM in the mTBI group had low FA, suggesting a large amount of spatial heterogeneity across individuals.[33] Ivanov et al. did find certain tracts for which blast exposure was associated with decreased FA. The CC, CST, internal capsule, and cingulum – particularly the right cingulum – were affected by blast exposure.[34] Blast exposure and WM damage have a dose-response relationship in SM and veterans.[34]

While many studies report a heterogenous distribution of voxels or ROIs with abnormal DTI metrics, some have found specific tracts or areas of WM that are consistently affected in

their study population. Petrie et al. compared FA between war veterans with and without mTBI history. The mTBI group had lower FA in the right genu of the CC.[36] Yeh et al. compared the four DTI metrics between active duty US military personnel diagnosed with mTBI and healthy military controls. The mTBI group had significantly lower FA in the WM regions of the left anterior limb of internal capsule, posterior limb of internal capsule, anterior corona radiata, superior corona radiata, external capsule, superior fronto-occipital fasciculus (SFOF), thalamus, globus pallidus, putamen, fornix, superior longitudinal fasciculus (SLF), uncinate fasciculus (UF), sagittal stratum (including the inferior longitudinal fasciculus), and brainstem.[37] Yeh et al. also studied whole brain FA and found low FA clusters in the dorsal component of the left SLF near the posterior part of the superior frontal and parietal lobes, the ventrolateral component of the right SLF near the superior temporal lobe, the anterior parts of the bilateral IFOF, the inferior longitudinal fasciculus (ILF) at the temporo-occipital junction, and the UF near the lateral aspects of the orbito-frontal lobes.[37] McClelland et al. found WM abnormalities mostly in the CC, brainstem, and cerebellum.[15] But it was emphasized that there was a heterogenous distribution of clusters with increased and decreased FA,[15] meaning that parsing out which ROIs have increased or decreased FA is important. Global FA could even out to be nonsignificant while certain WM tracts were significant by themselves.

One study found in the literature review assessed return to work for combat veterans with mTBI. There was a significant increase in FA, decrease in MD, and decrease in RD in the posterior limb of internal capsule in those veterans who returned to work.[15] The ability to return to work was essentially associated with DTI metrics trending in the opposite way that usually occurs with WM damage from mTBI injury. The internal capsule was most likely affected because of the important traversing fibers it contains that provide motor information to the

typically dominant right side of the body. Fine motor movements were needed for the veterans who returned to work, thus utilizing the internal capsule.[15]

Main et al. aimed to determine which fiber tracts best predict mTBI status for each of the four DTI metrics. They studied 20 tracts and determined that the left cingulum was an optimal classifier for FA measures.[38] The left inferior fronto-occipital fasciculus (IFOF) was an optimal classifier for MD, RD, AD.[38] The left SLF-temporal tract was identified as a secondary classifier for MD.[38] All of these affected tracts are at least in part responsible for memory, executive function, and semantics. This study's goal is one that continues to be worked towards in research on mTBI. Using Main et al.'s study and future studies that contribute to this effort could lead to an objective way for mTBI to be clinically diagnosed.

*DTI Metrics for PTSD*

Most of the research conducted on PTSD and WM is done in conjunction with mTBI. This cooccurrence of mTBI and PTSD requires special consideration because both issues affect WM microstructures.[45] Research has shown that there is overlap in affected regions, completely different WM regions affected by each disorder, and even that mTBI and PTSD effect WM in opposite ways.

While some studies have found that PTSD is not associated with WM alterations[35] or FA,[36] multiple studies have used various diffusion metrics to point to specific WM changes in the brain. Lepage et al. showed that there is a positive association between PTSD symptom severity and number of clusters with reduced FA, specifically in civilians and veterans with mTBI history.[16] Significantly lower FA in mTBI+PTSD groups compared to controls was found in left pre- and post-central gyral tracts[39] and the right UF.[40] Santhanam et al. also found that mTBI+PTSD participants had significantly increased MD and RD in bilateral UF and

significantly increased RD in the left anterior thalamic radiation (ATR).[40] PTSD severity alone positively correlated with RD values and inversely correlated with FA values for bilateral UF.[40] PTSD severity also positively correlated with MD values in left UF specifically.[40] These tracts represent parts of the limbic system, illustrating that the limbic system is implicated in PTSD. The default mode network is another region that may reinforce PTSD symptoms when it is damaged because of its implications in network coordination during goal-oriented behavior.[41] In addition, the fronto-striatal and fronto-limbic pathways have been proposed as associated with PTSD severity due to reduced FA in these regions.[37] Lastly, hippocampal-striatum connectivity is another area of the brain that has compromised WM integrity in SM and veterans with mTBI and PTSD.[42] More diffusion was documented in WM fibers connecting the hippocampus and striatum, suggesting a structural etiology for PTSD.[42] Based on these findings, Rangaprakash et al. suggest hippocampal-striatum connectivity as a potential biomarker for PTSD/mTBI.[42]

Other studies have identified specific tracts that are affected by mTBI and PTSD in participants or PTSD alone. Bazarian et al. observed that DTI changes in the caudate nucleus and inferior cerebellar peduncle were associated with PTSD and mTBI.[43] But, after adjusting for multiple comparisons no specific region had a significant association with PTSD.[43] In this study, DTI metrics were observed but only the 1$^{st}$, 50$^{th}$, and 99$^{th}$ percentile scores were recorded. PTSD was found to be associated with more regions having higher 1$^{st}$ percentile values of MD.[43] Bolzenius et al. studied US SM with mTBI and PTSD, mTBI only, PTSD only, and military controls with orthopedic injury. The PTSD group had increased RD in the right anterior internal capsule, right posterior internal capsule, and right retrolenticular internal capsule (compared to mTBI and mTBI+PTSD groups).[44] The PTSD group also had increased RD in the right retrolenticular internal capsule compared to orthopedic injury control group.[44]

One study in the reviewed literature focused on generalized fractional anisotropy (GFA) and reported DTI metrics that trended in the direction opposite to what many other studies reported. Recently deployed SM with mTBI, PTSD, both mTBI and PTSD, or neither underwent DTI scanning in Davenport et al.'s study. PTSD was associated with higher GFA in 9 of 20 ROIs studied, generalized to the right hemisphere: bilateral ATR, right CST, right IFOF, bilateral cingulum, right ILF, right UF, and right SLF.[45] PTSD was found to be associated with lower MD in the right CST.[45] Davenport et al. detected no effects of PTSD on FA but they did report that PTSD was associated with increased global FA, indicating that there might be additional voxels outside of the 20 ROIs studied where FA is higher.[45] This study suggests that areas with complex WM configurations house the diffusion abnormalities seen on DTI and these abnormalities cannot be modeled by a single tensor, thus rendering FA as an unhelpful metric.[45]

Davenport et al. also studied the interaction between mTBI and PTSD, finding that it led to increased FA.[12] PTSD disrupts the association between mTBI and WM integrity.[12] The interaction between deployment mTBI and lifetime PTSD in this study had significant effects on global FA, global GFA, number of voxels with high FA, number of voxels with high GFA, mean FA, and mean GFA in bilateral IFOF, bilateral SLF, bilateral ILF, right uncinate, and right hippocampal cingulum.[12] This study reported that mTBI alone and PTSD alone tend to lower FA, but when these issues are combined they tend to increase FA.[12]

PTSD severity is a spectrum,[42] suggesting a potential dose-response relationship between symptom severity and WM damage. The relevant literature calls for an approach that assesses PTSD alone as well as mTBI+PTSD within the same study design to determine how each disorder damages WM alone, and then how they combine to affect WM. Much remains to be

learned about the etiology of PTSD and how it affects WM both with and without coexisting mTBI diagnosis.

*DTI Metrics for Depression*

While many studies have been dedicated to studying PTSD in SM and veterans, very few have analyzed Major Depressive Disorder (MDD) which plagues Soldiers both during and after deployment. Most studies look at depression as a comorbidity after mTBI diagnosis. Depression symptoms, as well as sleep and cognitive impairments, following mTBI are related to WM damage in the brain.[14] However, depression severity has also been associated with PTSD which complicates parsing out which WM tracts are affected by MDD alone.[15,16] While Ware et al. found that there was no significant association between DTI and clinical diagnosis of depression,[15] Raikes et al. found that there was a negative correlation between FA and depression severity in mTBI patients.[14] In addition to lower FA, increasing depression symptoms are positively associated with MD and AD observed bilaterally in the anterior and posterior internal capsule, anterior and superior corona radiata, fornix, and fronto-occipital fasiculi.[14] These tracts are responsible for episodic memory, information processing, executive function, emotion regulation, and connecting deep brain structures like the thalamus.[14] Increased diffusion in these tracts, and therefore decreased signaling, could lead to symptoms of depression such as decreased motivation, lethargy, sadness, and decreased concentration.

Within mTBI populations, diagnosis of MDD has been found to be associated with increased LOC as well as WM damage in the ATR and UF.[17,18] In a review study by Asken et al., it was reported that the UF was consistently affected and usually had lower FA.[7] The UF is responsible for parts of memory, particularly emotional memories, and naming objects and faces.[46]

All the studies mentioned above include an element of mTBI when assessing WM tracts for damage. No study in the literature review analyzed WM damage from MDD aside from mTBI/concussion. It is crucial to know how MDD itself affects microstructures in order to best treat the issue. It is also imperative to determine if the presence of mTBI exacerbates the WM damage from MDD or if entirely separate tracts are affected. Depression severity is a continuum, implying that there is a potential dose-response relationship between WM damage and severity that could help diagnosis and treatment of MDD if a consensus is reached in the literature.

*DTI Metrics for Anxiety*

Although some studies have gathered psychometric data regarding anxiety, I was unable to find a study that looked at diffusion metrics specifically for anxiety. This study aims to fill this gap and contribute to understanding how various mental health disorders can affect microstructures in the brain.

**Findings from Review Studies**

Three review articles were included in this literature review. All three studies discussed the absence of agreement regarding which WM tracts are affected by mTBI, calling for more specificity and replicable patterns before DTI data can be meaningfully used in clinics.[7,20,21] Narayana found that FA tended to decrease and MD tended to increase in the majority of the studies included in the review.[20] The CC, SLF, corona radiata, and the ATR were consistently identified as damaged WM tracts post-mTBI.[20] Narayana suggested that DTI could be used for individual analysis, improving clinical management of mTBI.[20] It was also suggested that future studies explicitly label the hemisphere of affected tracts in their results, thus increasing the specificity to make DTI serviceable in clinics.[20] Cogan's review agreed with Narayana, finding that the CC and SLF were consistently reported as damaged after mTBI.[21] Cogan also expressed

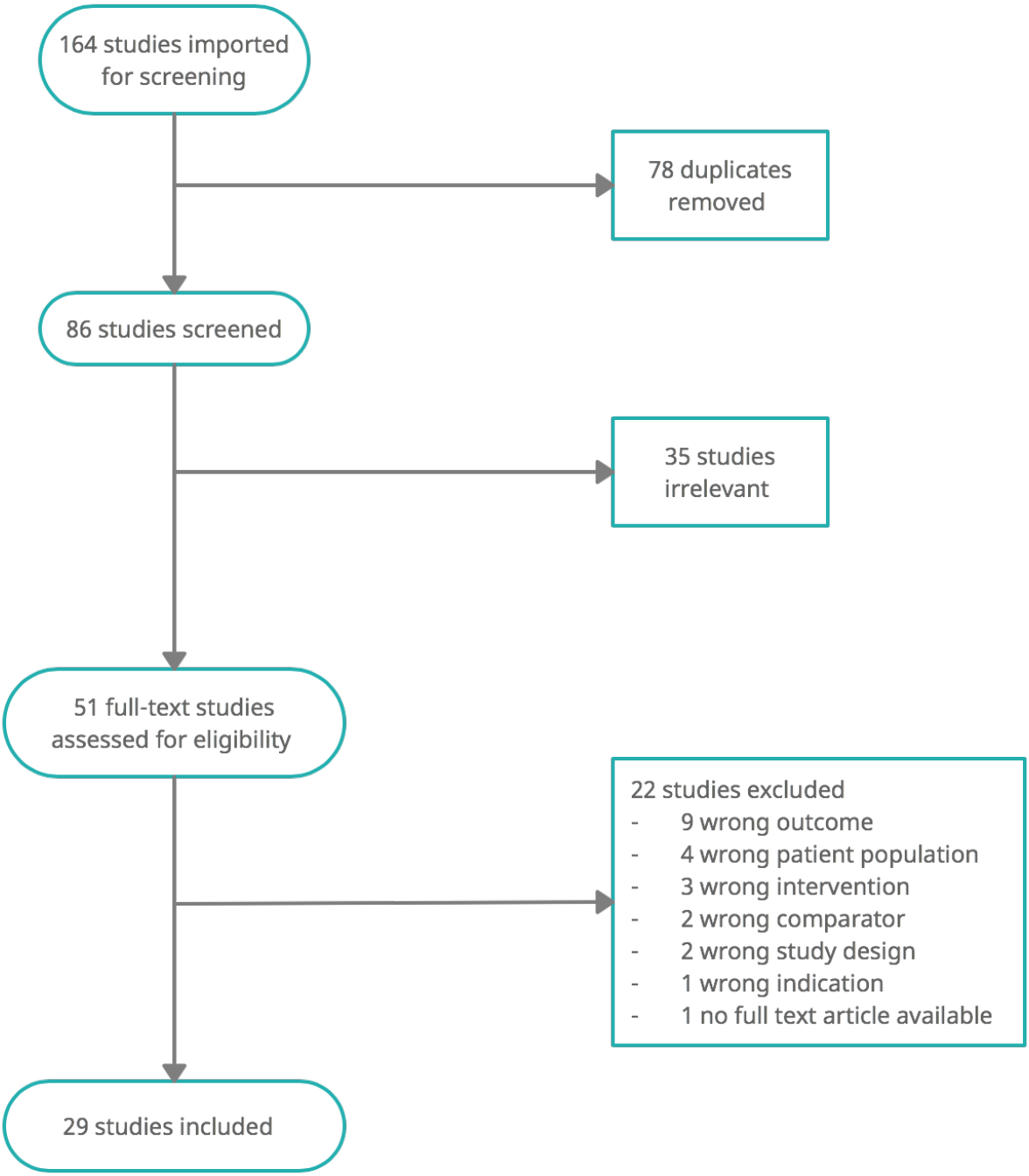
that MDD diagnosis is associated with increased LOC and a greater number of voxels with decreased FA.[21] Asken et al. concluded that the UF generally had lower FA in patients with MDD, adding a specific tract to Cogan's conclusion.[7] Both Asken et al. and Cogan examined studies that included data regarding how PTSD and mTBI affected WM tracts, but both reviews did not find a significant correlation between WM damage (specifically assessed by FA) and PTSD severity.[7,21]

**Conclusions**

The results from studies presented in this review show that both mTBI and psychiatric disorders damage WM in the brain. DTI has been shown to be a useful measurement tool for assessing axonal injuries. Across studies, FA trended in the same way for mTBI history, but when PTSD was incorporated results became more varied. Additional studies are needed to determine the interaction between mTBI and mental health disorders, specifically PTSD and its effects on mTBI damage. More research is also needed to determine how anxiety affects WM, specifically measured by FA and MD as outcome metrics.

**Figures**

Figure 2.1: Literature Review Article Selection



**Tables**

Table 2.1: Overview of Published Studies Included in the Literature Review that Addressed PTSD

| Author(s) | Publication Year | Study Design | Study Population | Sample Size (N) | Outcome Measures | General Results |
|---|---|---|---|---|---|---|
| Lepage et al. | 2018 | Cross-sectional | Military and Civilian | 35 mTBI, 22 mTBI+PTSD, 37 HC | Regions with abnormal FA | mTBI+PTSD group had a greater number of abnormally low FA clusters; increased clusters with low FA associated with PTSD severity |
| Rashid et al. | 2017 | Cross-sectional | US Service Members | 33 HC, 6 mTBI, 9 PTSD, 20 mTBI+PTSD | Average FA | Significantly lower average FA in mTBI and mTBI+PTSD groups in the pre- and post-central gyral tracts |
| Rangaprakash et al. | 2017 | Cross-sectional | US Army Soldiers | 17 PTSD, 42 PCS+PTSD, 28 HC | Connectivity strength and variance | Compromised WM integrity in hippocampal-striatum connectivity only in PCS+PTSD group |
| Bazarian et al. | 2013 | Nested cohort study | Veterans | 9 PTSD+mTBI, 6 PTSD, 21 mTBI, 16 HC | FA, MD | PTSD severity associated with higher 1st percentile MD values and severity of BE events; BE associated with lower 1st percentile FA values |
| Santhanam et al. | 2019 | Cross-sectional | SM/Veterans | 34 mTBI+PTSD, 35 mTBI | FA, MD, RD | mTBI+PTSD group had significantly lower FA in the right UF and significantly higher MD and RD in bilateral UF; PTSD severity positively correlated with RD values and inversely correlated with FA values for bilateral UF |
| Main et al. | 2017 | Cross-sectional | Veterans | 15 mTBI, 57 mTBI+PTSD, 21 PTSD, 15 HC | FA, RD, MD, AD | Left cingulum is the optimal classifier for FA; Left IFOF is the optimal classifier for MD, RD, AD |

| | | | | | | |
|---|---|---|---|---|---|---|
| Bolzenius et al. | 2018 | Cross-sectional | US SM | 27 mTBI, 16 PTSD, 42 mTBI+PTSD, 43 controls with orthopedic injury | FA, RD, MD, AD | PTSD group had higher RD in right anterior internal capsule, right posterior internal capsule, and right retrolenticular internal capsule (compared to mTBI and mTBI+PTSD group); PTSD group had higher RD in right retrolenticular internal capsule (compared to orthopedic injury group) |
| Davenport et al. | 2015 | Cross-sectional | Recently deployed SM | 18 mTBI, 45 mTBI+PTSD, 31 PTSD, 38 HC | FA, MD, GFA | PTSD associated with higher GFA in 9 of 20 ROIs (mostly where fibers converge); PTSD associated with lower MD in right CST |
| Yeh et al. | 2014 | Cross-sectional | Active Duty US Military Personnel | 37 mTBI (among them 10 had issues with PTSD, depression, or anxiety) 14 HC | Whole-brain voxel-wise analysis of FA, RD, AD | PTSD severity associated with reduced FA in fronto-striatal and fronto-limbic fibers |
| Davenport et al. | 2016 | Cross-sectional | Veterans | 124 recent veterans with varying mTBI and PTSD studies | FA, MD, GFA | History of PTSD alters the relationship between mTBI and WM damage; mTBI alone and PTSD alone tend to lower FA but combined issues results in increased FA |
| Miller et al. | 2016 | Cross-sectional | Veterans | 37 no TBI, 29 mTBI-LOC, 24 mTBI+LOC, 14 HC | Number of clusters with abnormal FA | PTSD severity associated with PCS severity, but not with WM alterations |
| Petrie et al. | 2014 | Nested case-control | SM | 11 mTBI, 11 HC | PTSD symptom severity and FA | mTBI related WM changes disrupt function of DMN which could reinforce PTSD symptoms |

Table 2.2: Overview of Published Studies Included in the Literature Review that Addressed Depression

| Author(s) | Publication Year | Study Design | Study Population | Sample Size (N) | Outcome Measures | General Results |
|---|---|---|---|---|---|---|
| Matthews et al. | 2011 | Cross-sectional | Veterans | 11 MDD, 11 w/o MDD | FA | MDD group had lower FA in SLF; decreased FA in SLF associated with increased depression symptoms |
| Raikes et al. | 2018 | Cross-sectional | Veterans and Civilians | 34 within a year of mTBI, 18 no mTBI Hx | FA, MD, RD | FA demonstrated a negative correlation with depression symptoms and MD and RD demonstrated positive correlation with depression symptoms in mTBI group; correlations observed in bilateral internal capsule, corona radiata, fornix, and SFOF |
| Ware et al. | 2016 | Retrospective cohort study | Combat Veterans | 57 mTBI | FA, MD, RD, AD | No significant associations between DTI and metrics and clinical diagnosis of MDD |
| Vakhtin et al. | 2021 | Cross-sectional | Veterans | 171 mTBI, 115 HC | FA, MD, RD, AD | Decreased WM integrity in ATR and UF associated with MDD |

# CHAPTER III

# METHODS

## Participants

This cross-sectional study utilized data that were collected from 2019-2022 at the University of North Carolina at Chapel Hill. Participants were 66 male Special Operations Forces (SOF) combat Soldiers. Exclusion criteria included moderate or severe TBI and contraindications to MRI (e.g. shrapnel). All participants completed verbal consent, multimodal MRI, and a battery of psychometric tests including the PCL-5, PHQ-9, and GAD-7. Participants also self-reported mTBI diagnosis and lifetime mTBI occurrence.

## Clinical Assessment

Participants completed the Posttraumatic Stress Disorder Checklist for Diagnostic and Statistical Manual of Mental Disorders – 5 (PCL-5) to assess PTSD symptom severity, the Patient Health Questionnaire – 9 (PHQ-9) to assess depression symptom severity, and the GAD-7 to assess anxiety symptom severity. The PCL-5 is a validated diagnostic tool for PTSD assessing symptoms related to reexperiencing traumatic events. There are 20 questions with answer choices “Not at all,” “A little bit,” “Moderately,” “Quite a bit,” and “Extremely.” Scores range from 0-80 with a higher score indicating more severe PTSD symptoms. The PHQ-9 addresses symptoms of depression to objectify depression severity. Depression symptoms addressed include lack of energy and motivation, decreased mood, trouble sleeping, reduced appetite, trouble concentrating, and feelings of worthlessness. Each question addresses feelings in the past two weeks with four answer choices possible, “Not at all,” “Several days,” “More than half the days,” and “Nearly every day.” Scores range from 0-27 with a higher score

indicating more severe depressive symptoms. The GAD-7 is a questionnaire that assesses anxiety severity. Similar to the PHQ-9, each question addresses feelings in the past two weeks with four answer choices possible, "Not at all," "Several days," "More than half the days," and "Nearly every day." Scores range from 0-27 with a higher score indicating more severe anxiety symptoms. No clinical diagnoses were made as a result of the tests. Participant's answers were scored and categorized based pre-existing categories. For the PHQ-9, scores 0-4 were "minimal" (n = 36), scores 5-9 were "mild" (n = 20), and scores 10-16 were "moderate" (n = 6).[50] For the GAD-7, scores 0-4 were "minimal" (n = 48), scores 5-9 were "mild" (n = 11), and scores 10-17 were "moderate" (n = 4).[51] The PCL-5 has a clinical cutoff score of 31, so participants 0-31 were given the category "below" (n = 55) and participants above 31 were given the category "above" (n = 2).[52]

**Image Acquisition**

All participants were imaged at the University of North Carolina at Chapel Hill Biomedical Research Imaging Center. MRI data were obtained on a 3T Biograph mMR or 3T MAGNETOM Prisma (Siemens, Erlangen, Germany). Each participant underwent the following scan sequences: T1 Magnetization-Prepared Rapid Gradient-Echo (MPRAGE) (TI = 900ms, TR = 1900ms, TE = 2.26ms, 0.5 x 0.5 x 1mm, flip angle=9°, FOV = 256mm$^3$, 192 slices) and diffusion-weighted imaging (DWI) (Echo-planar imaging, TR = 9400 ms, TE = 94.0 ms, b = 1000 s/mm$^2$, 2.0x2.0x2.0 mm, FOV = 256mm$^3$ , 66 slices, 62 diffusion directions).

Brain surfaces and subcortical regions were reconstructed from T1-weighted images using recon-all (FreeSurfer 7.2.0). Diffusion pre-processing followed the pipeline in the FMRIB Software Library (FSL 6.0.5), including eddy-current corrections, computing head motion during the scan, skull-stripping, and computing anatomical priors for WM pathways. BEDPOSTX was

used to fit a ball-and-stick model to the diffusion images in order to estimate probability distributions of diffusion within each voxel. Automated probabilistic reconstruction of white matter pathways was applied using Tracts Constrained by Underlying Anatomy (TRACULA). TRACULA uses global probabilistic tractography with anatomical neighborhood priors derived from a set of manually annotated training subjects. Pathways are reconstructed according to the fiber orientation vectors from the diffusion MRI data as well as the anatomical neighborhood priors from the T1 data. Four diffusion metrics, fractional anisotropy, mean diffusivity, axial diffusivity, and radial diffusivity, were computed for 40 white matter tracts for each participant.

**Statistical Analysis**

Data were analyzed using SAS statistical software. Linear regressions were performed with the DTI outcomes FA and MD as separate dependent variables. The mental health issues and their categories served as independent variables as well as two interaction effects, mTBI history and career stage. The interaction effects were binary with mTBI being reported as "yes" if a Soldier had experienced an mTBI or "no" if not. Career stage was categorized as either "baseline" for Soldiers who were tested right after they completed their training pipeline or "in-career" for Soldiers who had served in their organization for some time.

**Tables**

Table 3.1: Diffusion Tensor Imaging Acquisition Parameters

| Sequence Parameter | BIOGRAPH Scanner |
|---|---|
| Orientation | Transversal |
| Phase Encoding Direction | Anterior to Posterior |
| Bandwidth | 1562 Hz/Px |
| Number of Directions | 62 |
| b-value | 1000 s/mm$^2$ |
| TR | 9400 ms |
| TE | 94.0 ms |
| Slice Thickness | 2.0 mm |
| Number of Slices | 66 |
| Field of View | 256 mm |
| Voxel Size | 2.0x2.0x2.0 mm |
| Acquisition Time | 10:20 |

# CHAPTER IV

# MANUSCRIPT

## Introduction

Mild traumatic brain injuries (mTBI) are a serious global public health issue. Military personnel are particularly susceptible to sustaining concussions, a form of mTBI.[1,2] According to the Department of Defense, over 440,000 active Service Members were diagnosed with a concussion from 2000-2021,[3] however the suspected incidence rate may be much higher due to underreporting whether intentionally or unintentionally.[4] Traumatic brain injury is defined as the result from a blow or jolt to the head that disrupts the normal function of the brain.[19] Soldiers also sustain occupational blast exposure that may cause neurological damage without acute symptoms. Special Operations Forces (SOF) Soldiers are exposed to these risks during training and combat. Thus, Soldiers further into their career are likely to have sustained greater blast exposure. Often, Service Members who have sustained an mTBI also experience concomitant mental health issues such as Posttraumatic Stress Disorder (PTSD) and depression[6] which can increase neurophysiological symptoms and delay recovery.

Some neurophysiological changes caused by mTBI outlast clinical recovery including decreased structural integrity of white matter (WM) tracts in the brain.[8] Axonal damage results in impaired ability to transport information, thus leading to chronic symptoms and recalcitrant cognitive impairments that last beyond return to activity clearance.[7] Diffusion tensor imaging (DTI) is an advanced magnetic resonance imaging (MRI) technique which indirectly assesses WM tract integrity by measuring water diffusion rates. There are four DTI scalar parameters that

quantify diffusion: fractional anisotropy (FA), mean diffusivity (MD), axial diffusivity (AD), and radial diffusivity (RD). Restricted diffusion along an axis is described by FA while MD quantifies overall diffusion rates within a voxel or tract.[7] Axonal degeneration results in lower FA and higher MD.[49] This neuroimaging technique has been used in the military to evaluate tract abnormalities following both acute concussions as well as chronic blast exposure.[8]

About 1 in 4 active Service Members suffer from a mental health disorder and these disorders are leading causes of death in the US military population.[10] Using DTI to quantify abnormalities in white matter caused by both mTBI and mental health disorders in military populations is critical to the wellbeing of Service Members. However, few studies have examined the relationship between mental health issues and WM tract integrity in Service Members with mTBI history. The detrimental effects of mTBI overlap with mental health issues such as anxiety, depression, and PTSD which complicates the overall recovery process.[11] Once a consensus is reached in the literature regarding affected WM tracts, clinicians can use DTI to objectively diagnose mTBI or WM damage.

Therefore, the overall goal of this study is to determine the effects of mTBI history on the relationship between anxiety, depression, and PTSD and WM tract integrity in combat Soldiers. To accomplish this goal, specific aims will be followed. The first specific aim is to determine how various mental health disorders are associated with FA and MD in white matter tracts. The second specific aim is to determine how mTBI history and career stage moderates these effects on FA and MD. This exploratory study will examine FA and MD in 40 white matter tracts to assess group differences associated with common mental health disorders and mTBI affecting Service Members.

## Methods

### *Study Design*

This cross-sectional study utilized data that were collected from 2019-2022 at the University of North Carolina at Chapel Hill. Participants were 66 male Special Operations Forces (SOF) combat Soldiers. Exclusion criteria included moderate or severe TBI and contraindications to MRI (e.g. shrapnel). All participants completed verbal consent, multimodal MRI, and a battery of psychometric tests including the PCL-5, PHQ-9, and GAD-7. Participants also self-reported mTBI diagnosis and lifetime mTBI occurrence.

### *Clinical Assessment*

Participants completed the Posttraumatic Stress Disorder Checklist for Diagnostic and Statistical Manual of Mental Disorders – 5 (PCL-5) to assess PTSD symptom severity, the Patient Health Questionnaire – 9 (PHQ-9) to assess depression symptom severity, and the GAD-7 to assess anxiety symptom severity. The PCL-5 is a validated diagnostic tool for PTSD assessing symptoms related to reexperiencing traumatic events. There are 20 questions with answer choices "Not at all," "A little bit," "Moderately," "Quite a bit," and "Extremely." Scores range from 0-80 with a higher score indicating more severe PTSD symptoms. The PHQ-9 addresses symptoms of depression to objectify depression severity. Depression symptoms addressed include lack of energy and motivation, decreased mood, trouble sleeping, reduced appetite, trouble concentrating, and feelings of worthlessness. Each question addresses feelings in the past two weeks with four answer choices possible, "Not at all," "Several days," "More than half the days," and "Nearly every day." Scores range from 0-27 with a higher score indicating more severe depressive symptoms. The GAD-7 is a questionnaire that assesses anxiety severity. Similar to the PHQ-9, each question addresses feelings in the past two weeks with four

answer choices possible, “Not at all,” “Several days,” “More than half the days,” and “Nearly every day.” Scores range from 0-27 with a higher score indicating more severe anxiety symptoms. No clinical diagnoses were made as a result of the tests. Participant’s answers were scored and categorized based pre-existing categories. For the PHQ-9, scores 0-4 were “minimal” (n = 36), scores 5-9 were “mild” (n = 20), and scores 10-16 were “moderate” (n = 6).[50] For the GAD-7, scores 0-4 were “minimal” (n = 48), scores 5-9 were “mild” (n = 11), and scores 10-17 were “moderate” (n = 4).[51] The PCL-5 has a clinical cutoff score of 31, so participants 0-31 were given the category “below” (n = 55) and participants above 31 were given the category “above” (n = 2).[52]

*Procedures*

All participants completed the aforementioned mental health assessments and were also imaged at the University of North Carolina at Chapel Hill Biomedical Research Imaging Center. MRI data were obtained on a 3T Biograph mMR or 3T MAGNETOM Prisma (Siemens, Erlangen, Germany). Each participant underwent the following scan sequences: T1 Magnetization-Prepared Rapid Gradient-Echo (MPRAGE) (TI = 900ms, TR = 1900ms, TE = 2.26ms, 0.5 x 0.5 x 1mm, flip angle=9°, FOV = 256$mm^3$, 192 slices) and diffusion-weighted imaging (DWI) (Echo-planar imaging, TR = 9400 ms, TE = 94.0 ms, b = 1000 s/$mm^2$, 2.0x2.0x2.0 mm, FOV = 256$mm^3$ , 66 slices, 62 diffusion directions).

*Data Reduction*

Brain surfaces and subcortical regions were reconstructed from T1-weighted images using recon-all (FreeSurfer 7.2.0). Diffusion pre-processing followed the pipeline in the FMRIB Software Library (FSL 6.0.5), including eddy-current corrections, computing head motion during the scan, skull-stripping, and computing anatomical priors for WM pathways. BEDPOSTX was

used to fit a ball-and-stick model to the diffusion images in order to estimate probability distributions of diffusion within each voxel. Automated probabilistic reconstruction of white matter pathways was applied using Tracts Constrained by Underlying Anatomy (TRACULA). TRACULA uses global probabilistic tractography with anatomical neighborhood priors derived from a set of manually annotated training subjects. Pathways are reconstructed according to the fiber orientation vectors from the diffusion MRI data as well as the anatomical neighborhood priors from the T1 data. Four diffusion metrics, fractional anisotropy, mean diffusivity, axial diffusivity, and radial diffusivity, were computed for 40 white matter tracts for each participant.

*Statistical Analysis*

Data were analyzed using SAS statistical software. Linear regressions were performed with the DTI outcomes FA and MD as dependent variables. The mental health issues and their categories served as independent variables as well as two interaction effects, mTBI history and career stage. The interaction effects were binary with mTBI being reported as "yes" if a Soldier had experienced an mTBI or "no" if not. Career stage was categorized as either "baseline" for Soldiers who were tested right after they completed their training pipeline or "in-career" for Soldiers who had served in their organization for some time.

**Results**

Models including all predictors were significant for 6 different tracts: CCBODYPM, RHSLF1, RHUF, LHUF, CCBODYC, and RHFAT. The CCBODYPM and CCBODYC had a significant interaction effect of career stage on the relationship between GAD-7 score and average MD. The overall $p$ values were 0.0241 and 0.0373 while the interaction effect $p$ values were 0.0457 and 0.0107, respectively. Career stage predicted that the relationship between MD and anxiety symptom severity. When anxiety symptom severity was lower, baseline career stage

showed better WM integrity than in-career. However, at greater anxiety symptom severity, baseline career had poorer WM integrity compared to in-career soldiers. There were no interaction effects or main effects of mTBI for any of the 40 tracts analyzed.

The RHFAT was significantly affected by depression symptom severity ($p_{overall} = 0.0046$, $p_{PHQ9} = 0.0006$). The RHFAT was also significantly affected by anxiety symptom severity ($p_{overall} = 0.0267$, $p_{GAD7} = 0.0022$). The UF was significantly affected by PTSD symptom severity in both the right hemisphere ($p_{overall} = 0.0097$, $p_{PCL5} = 0.0150$) and left hemisphere ($p_{overall} = 0.0172$, $p_{PCL5} = 0.0046$). The WM of these tracts was negatively affected by increased mental health symptom severity.

Two tracts were significantly affected by career stage, the RHSLF1 ($p_{overall} = 0.0305$, $p_{career} = 0.0223$) and the CCBODYPM ($p_{overall} = 0.0419$, $p_{career} = 0.0430$). In-career stage was associated with poorer WM integrity, specifically lower FA, in the RHSLF1 and CCBODYPM.

**Discussion**

In a sample of 63 SOF combat Soldiers, a significant interaction effect of career stage was found in the corpus callosum, specifically in the central and premotor portion. Career stage predicts the relationship between MD and anxiety symptom severity. When anxiety symptom severity is lower, baseline career stage shows better WM integrity than their in-career counterparts. However, once anxiety symptom severity is greater, baseline career has poorer WM integrity compared to in-career Soldiers. Poorer WM integrity is reflected by increased average MD. The relationship between WM integrity and anxiety symptom severity changes based on a Soldier's career stage (Figures 4.1 and 4.2). This finding was the opposite of what we hypothesized which was that Soldiers further into their career would have poorer WM integrity compared to baseline counterparts because of blast exposure or general wear and tear. This

interaction effect was only significant in those Soldiers with anxiety symptom severity so the underlying cause may be linked to anxiety itself. The corpus callosum connects the hemispheres of the brain and allows information to be transmitted between them. The central portion of the corpus callosum has specific roles in inhibiting actions due to the presence of many inhibitory neurons.[53] The premotor portion of the corpus callosum helps to coordinate the hemispheres while planning motor movements with the motor cortex.[53] If these tracts are deteriorated, communication and coordination between the brain's hemispheres may be weakened.

In a sample of 62 SOF combat Soldiers, depression symptom severity was found to be significantly associated with lower WM integrity in the frontal aslant tract of the right hemisphere (Figure 4.3). Increased PHQ-9 score was significantly associated with lower average FA values. In a sample of 63 SOF combat Soldiers, anxiety symptom severity was found to be significantly associated with lower WM integrity in the frontal aslant tract of the right hemisphere (Figure 4.4). Increased GAD-7 score was significantly associated with lower average FA values. The frontal aslant tract plays a role in executive function as well as inhibiting behavior.[52] The right hemisphere is also specialized for controlling actions.[52] If this tract has decreased integrity, there is potential for difficulty controlling cognitive processes and motor actions.

In a sample of 57 SOF combat Soldiers, PTSD symptom severity was found to be significantly associated with lower WM integrity in the uncinate fasciculus of the left and right hemispheres (Figures 4.5 and 4.6). Increased PCL-5 score was significantly associated with lower average FA values in both hemispheres. The uncinate fasciculus plays a role in action, object naming, and semantic processing which helps to encode words and their meanings.[46]

Decreased WM integrity in this tract could lead to impaired ability to process commands and subsequently execute them.

In a sample of 57 SOF combat Soldiers, advanced career stage was found to be significantly associated with lower WM integrity in the SLF1 of the right hemisphere and the premotor portion of the corpus callosum (Figures 4.7 and 4.8). Soldiers further into their career with PTSD symptoms had significantly lower FA in the RHSLF1 than their baseline counterparts. The premotor portion of the corpus callosum plays a role in planning motor patterns and communicating with the motor cortex to allow those movements to happen.[53] The superior longitudinal fasciculus plays a role in executing the movements that the CCBODYPM helps to plan as well as provides a sense of proprioception.[54]

We did not observe any mTBI interaction effects on the relationship between mental health symptoms and WM integrity. This finding points to repetitive head trauma as more influential on WM for Soldiers than acute mild traumatic brain injuries. These Soldiers are particularly susceptible to blast exposure in training and combat which may be why Soldiers further into their career had poorer WM integrity in some tracts than their baseline counterparts.

All the tracts identified in this study have a direct role in executing actions and movement patterns.[46,52-54] Although these tracts were identified to have lower WM integrity in this study, we do not know if significantly lower WM integrity necessarily causes decreased ability to execute actions. It has been shown that decreased WM integrity, specifically increased MD and decreased FA, leads to poorer performance in simple motor tasks such as walking, chair to stand, finger-tapping tests, and hand pronation-supination.[51] However, how much of a decrease in FA or increase in MD is needed to influence performance is unknown. In addition, the actions these Soldiers are performing are much more complex and require more tract communication in the

brain than the actions performed in the Zhai 2020 study. It could be speculated that because simple tasks had poorer performance, complex tasks must be all the more affected by lower WM integrity. However, the population used in the study was vastly different due to civilian status, age, and baseline motor abilities, meaning that SOF Soldiers might not experience performance deficits in the same way that the general population experiences them. Research in specific military populations is crucial to understand the link between decreased WM integrity and possible performance deficits.

*Implications*

The long-term goal for this field would be to use a simple questionnaire and infer what is going on in a Soldier's brain, thus eliminating the need to perform DTI scans on every Soldier. As it stands right now, the field is far from this important goal. Our study is very exploratory because that is what the field at present needs. More data about WM integrity and what affects it is necessary as well as consensus in the literature. While this study aims to add to the small amount of existing information about Soldier's brain composition, there are a few practical implications to be taken away. Firstly, Soldiers should undergo baseline testing when beginning their careers. Not only will this testing provide more data with which to study the connection between experiences and WM integrity, but it will also allow for observation across Soldier's careers. Secondly, Soldiers should be monitored throughout their career. Again, by undergoing testing more data will be provided to the larger literature. Since the Soldiers will have baseline measurements, their in-career measurements can be compared with baseline to determine how status progresses, declines, or is maintained over time. Lastly, this population is elite and may need specialized tests and assessments. Assessments for the general population may not be able to detect subtle changes in the symptoms or abilities of these elite Soldiers. Additionally, while a

difference of a few percentiles may not important for the general population, this difference is large for a SOF Soldier. More specialized and rigorous testing may need to be developed to fully study this elite population.

*Future Directions*

The exploratory data in this study calls for a longitudinal approach to studying these Soldiers in order to understand how WM and performance change over time. Assessing Soldiers throughout their careers will bring the necessary data to establish a link between clinical questionnaires and structural issues in the brain. Another link that must be pursued in a military setting is the link between decreased WM integrity and performance outcomes. Once it is determined what symptoms are associated with lower WM integrity and the performance outcomes of various levels of decreased WM integrity, diagnosis and treatment of WM issues can become available. In the meantime, more rigorous and specialized tests should be developed for military personnel specifically SOF Soldiers in order to ascertain subtle changes in their symptoms and performance.

*Limitations*

This study was cross-sectional meaning that we cannot determine causation – only association – between mental health symptom severity and WM integrity. The sample size in this study was small and variable as we explored different mental health outcomes. This variable sample resulted from the pragmatic nature of our data collection and the election of some combat Soldiers not to fully complete assessments. We also had a lack of severe symptoms in mental health issues, which is a great outcome for the study population but did limit our ability to study how our imaging results would be affected by those most debilitated by severe mental health outcomes. One Soldier fell into the moderately-severe category for depression symptom severity

and two Soldiers fell into this same category for anxiety symptom severity. These Soldier's scores were barely above the moderate cut-off and the Soldiers were placed into the moderate category so as not to be in a category alone. While we were able to find significant relationships by analyzing minimal, mild, and moderate symptoms, more significant relationships may be found when Soldiers with severe symptoms are included in the study. We also did not correct for multiple comparisons because each tract was assessed separately with the respective independent and dependent variables. Lastly, this study does not include data for females.

**Conclusions**

This study found an association between higher depression symptom severity and lower WM integrity in the RHFAT. We also observed an association between higher anxiety symptom severity and lower WM integrity in the RHFAT. Higher PTSD symptom severity was associated with lower WM integrity in the UF of the left and right hemispheres. Soldiers further into their career were found to have lower WM integrity in the RHSLF1 and CCBODYPM when PTSD was present and baseline stage Soldiers were found to have poorer WM integrity in the LHUF when anxiety symptoms were present. Career stage also moderated the relationship between anxiety symptom severity and WM integrity in the premotor and central portions of the corpus callosum. All the affected tracts have a role to play in executing movements.

Our findings contribute to the growing body of knowledge about WM integrity in various populations. Longitudinal research should be pursued to ascertain how Soldier's brain change over time. Gathering more data of this nature will allow us to eventually diagnose structural brain abnormalities without having to perform scans on every Soldier. Longitudinal research will also allow us to explore how poorer WM contributes to performance deficits.

## Figures

Figure 4.1: Interaction plot for the CCBODYPM with a significant interaction effect of career stage.

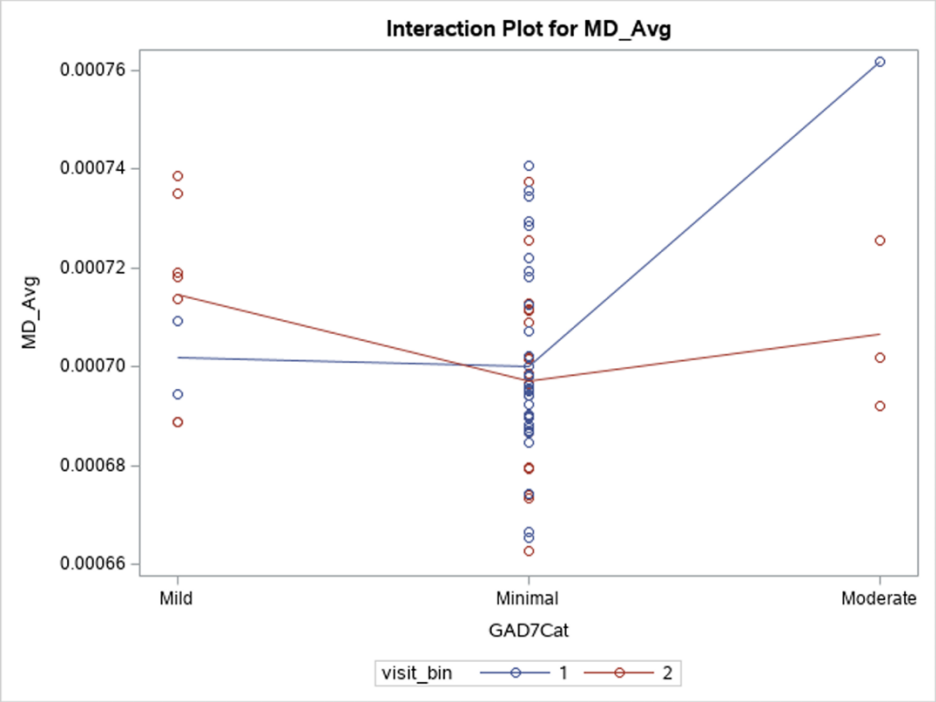


Figure 4.2: Interaction plot for the CCBODYC with a significant interaction effect of career stage.

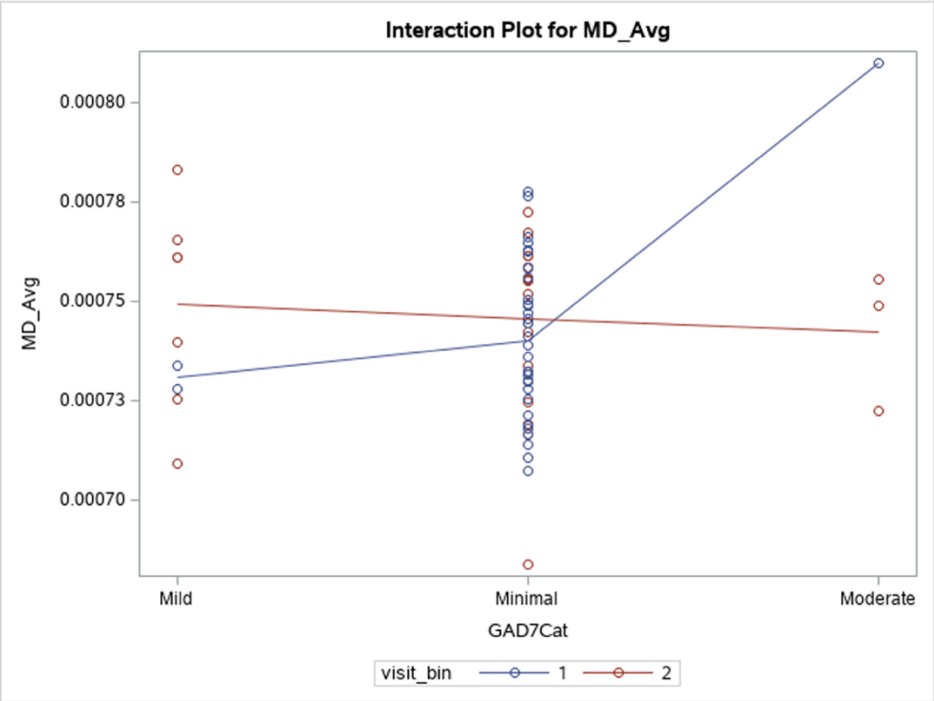



Figure 4.3: Interaction plot for the RHFAT with a significant main effect of PHQ-9 score on average FA.

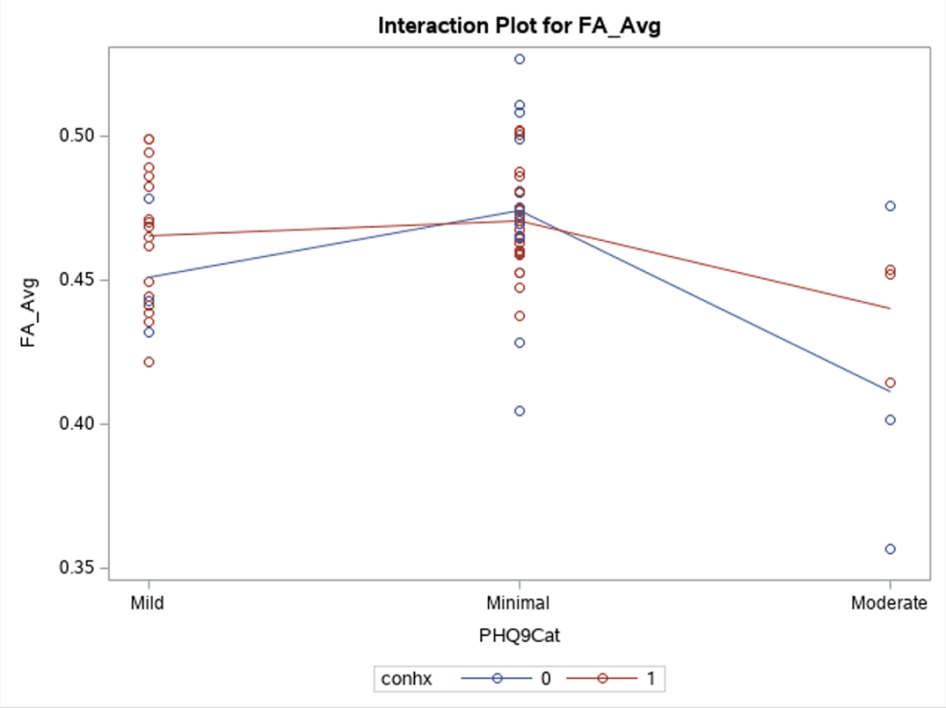


Figure 4.4: Interaction plot for the RHFAT with a significant main effect of GAD-7 score on average FA.

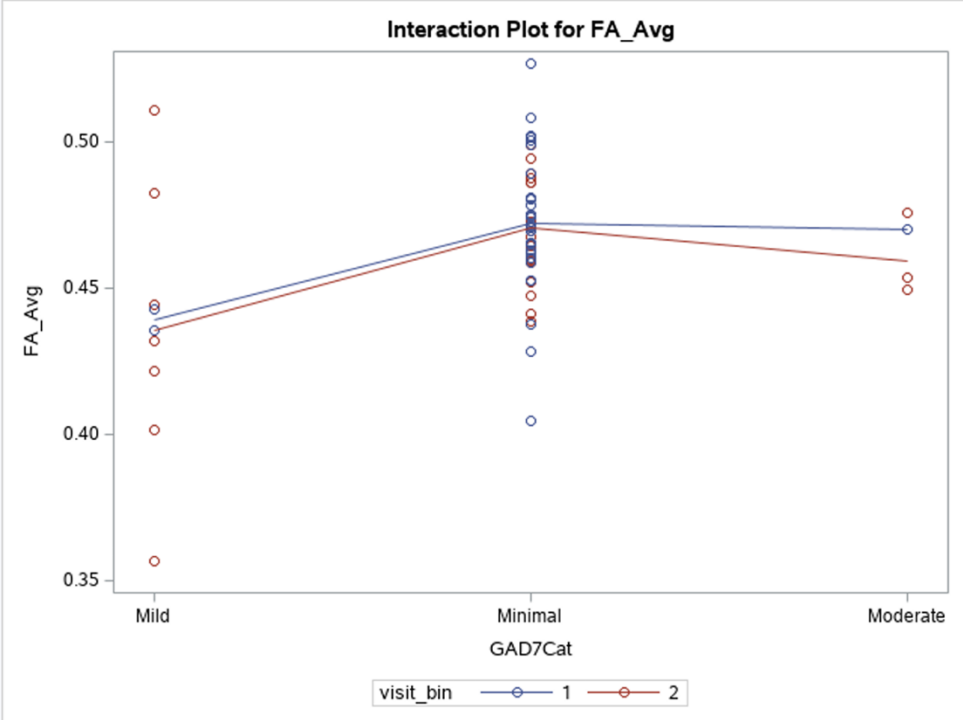



Figure 4.5: Interaction plot for the LHUF with a significant main effect of PCL-5 score on average FA.

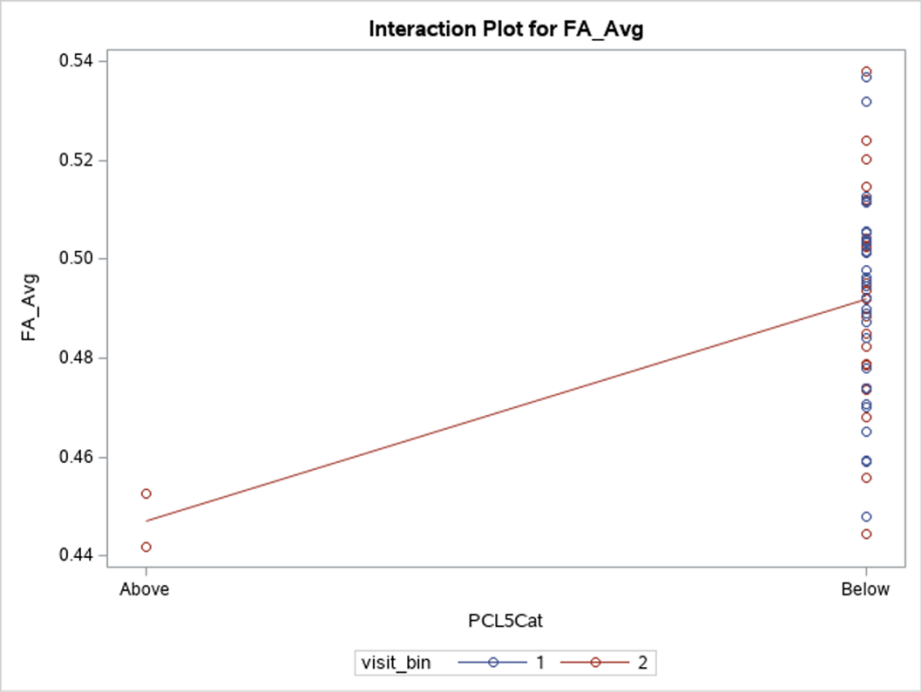


Figure 4.6: Interaction plot for the RHUF with a significant main effect of PCL-5 score on average FA.

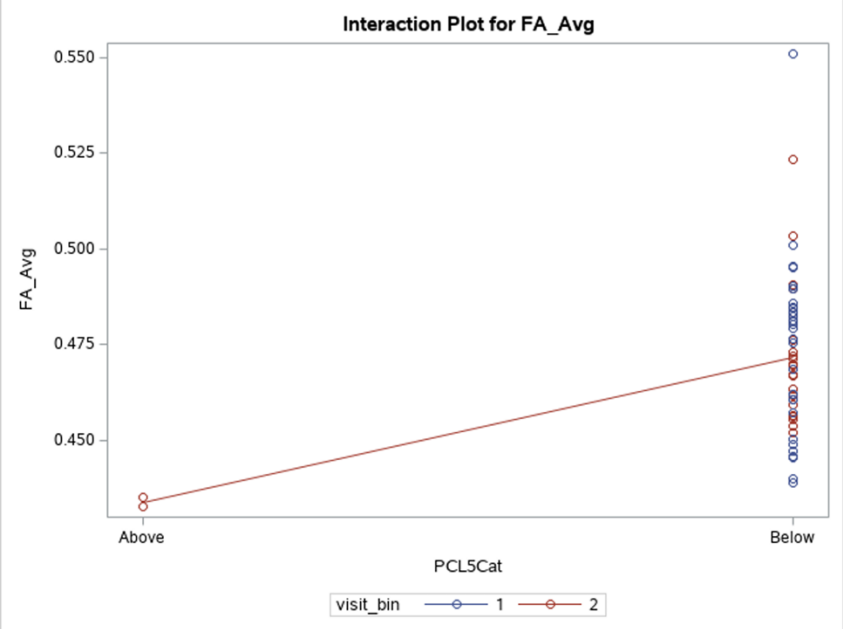



Figure 4.7: Interaction plot for the RHSLF1 with a significant main effect of career stage (visit_bin) on average FA.

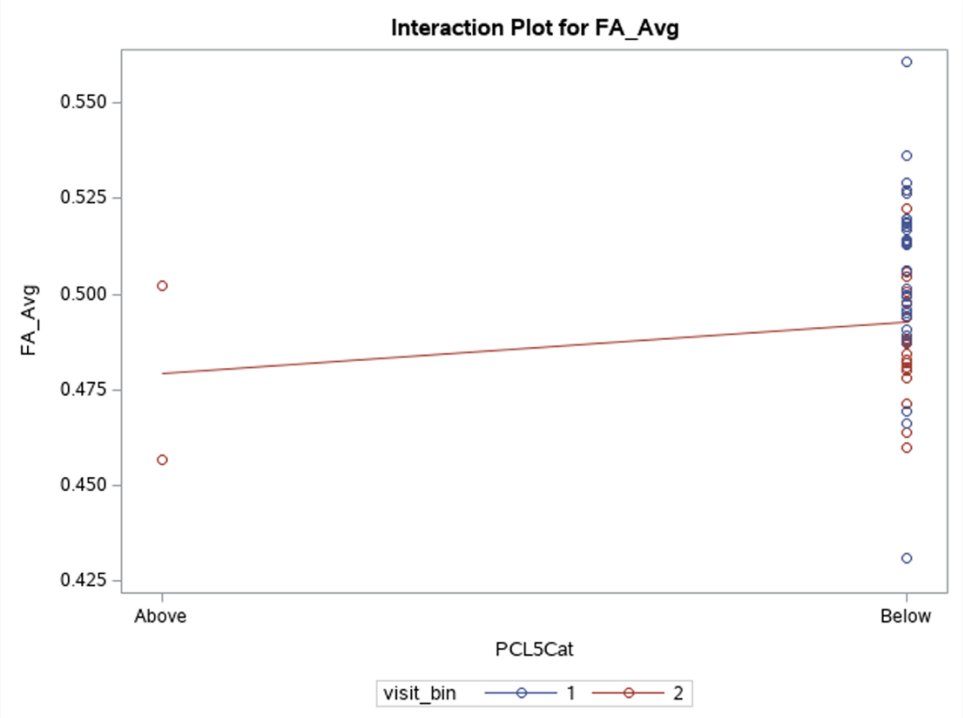
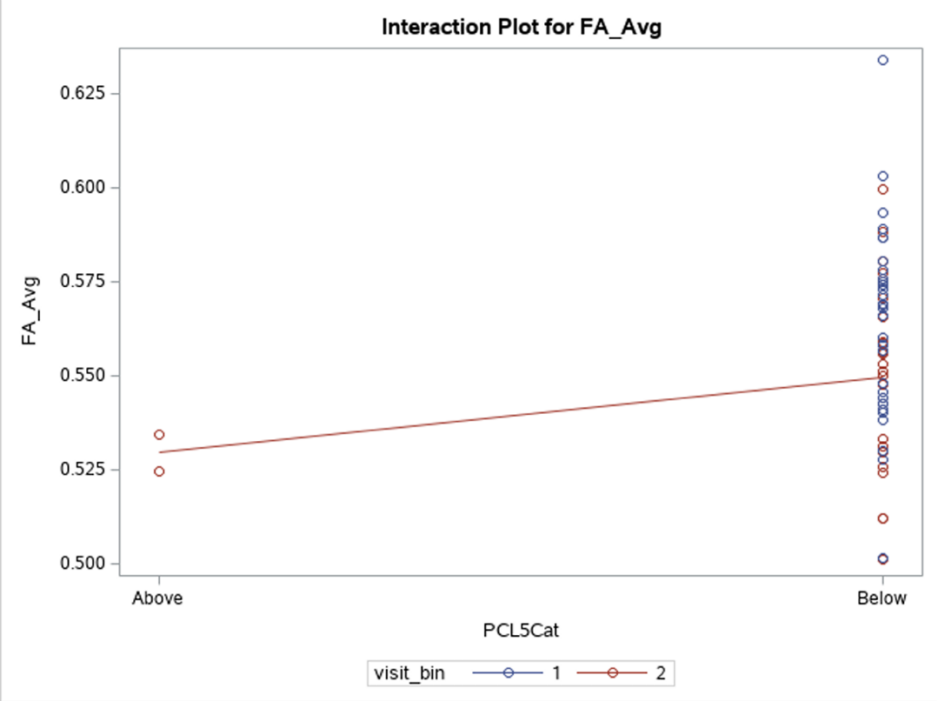


Figure 4.8: Interaction plot for the CCBODYPM with a significant main effect of career stage (visit_bin) on average FA.



# CHAPTER V

# APPENDICES

## Appendix A: White Matter Tract Functions

| Tract (Abbreviation) | Tract (Full Name) | Function |
|---|---|---|
| ACOMM | Anterior commissure | Transfer of visual information (including recall of dreams), auditory information, and olfactory information between hemispheres[55] |
| CCBODYC | Corpus callosum – body – central | Transmits information between hemispheres; inhibitory affects due to presence of inhibitory neurons[53] |
| CCBODYP | Corpus callosum – body – parietal | Relaying somatosensory/tactile information[67] |
| CCBODYPF | Corpus callosum – body – prefrontal | Connects to the prefrontal cortex to relaying signals dealing with planning, personality, motivation, and emotions[67] |
| CCBODYPM | Corpus callosum – body – premotor | Planning motor patterns and communicating with motor cortex[53] |
| CCBODYT | Corpus callosum – body – temporal | Relaying auditory and olfactory information[67] |
| CCGENU | Corpus callosum – genu | Language areas connect here; prefrontal and premotor cortex axons cross here; connects the frontal lobes to harmonize functions[56,66] |
| CCROSTRUM | Corpus callosum – rostrum | Language areas connect here; prefrontal and premotor cortex axons cross here; connects the frontal lobes to harmonize functions[56,66] |
| CCSPLENIUM | Corpus callosum – splenium | Carries fibers connecting the visual areas of the occipital lobe[56,66] |

| | | |
|---|---|---|
| **MCP** | Middle cerebellar peduncle | Connects the cerebellum and prefrontal cortex; relays information for planning and coordination of motor tasks[65] |
| **LHAF** | Arcuate fasciculus – left | Language processing[57] |
| **RHAF** | Arcuate fasciculus – right | Visuospatial processing and some language processing (prosody and semantics)[57] |
| **LHAR** | Acoustic radiation – left | Carries auditory information from thalamus to cortex; language and auditory processing[58] |
| **RHAR** | Acoustic radiation – right | Carries auditory information from thalamus to cortex; language and auditory processing[58] |
| **LHATR** | Anterior thalamic radiations – left | Spatial learning and memory[59] |
| **RHATR** | Anterior thalamic radiations – right | Spatial learning and memory[59] |
| **LHCBD** | Cingulum bundle – dorsal – left | Attention, memory, attenuating emotional responses to pain, implicated in psychiatric diseases[60] |
| **RHCBD** | Cingulum bundle – dorsal – right | Attention, memory, attenuating emotional responses to pain, implicated in psychiatric diseases[60] |
| **LHCBV** | Cingulum bundle – ventral – left | Attention, memory, attenuating emotional responses to pain, implicated in psychiatric diseases[60] |
| **RHCBV** | Cingulum bundle – ventral – right | Attention, memory, attenuating emotional responses to pain, implicated in psychiatric diseases[60] |
| **LHEMC** | Extreme capsule – left | Functions in language because it is connected to Broca's area and Wernicke's area[61] |
| **RHEMC** | Extreme capsule – right | Functions in language because it is connected to Broca's area and Wernicke's area[61] |
| **LHFAT** | Frontal aslant tract – left | Supports speech and language function (specifically verbal fluency, speech initiation, and stuttering), supports executive |

| | | |
|---|---|---|
| | | function (specifically inhibitory control during actions); LH is specialized for speech actions[52] |
| **RHFAT** | Frontal aslant tract – right | Supports speech and language function (specifically verbal fluency, speech initiation, and stuttering), supports executive function (specifically inhibitory control during actions); RH is specialized for controlling general actions of the organism[52] |
| **LHFX** | Fornix – left | Serves as an output tract for the hippocampus; plays a role in memory, specifically inn recalling episodic memories; transmits information from the hippocampus to the mammillary bodies and thalamic anterior nuclei[64] |
| **RHFX** | Fornix – right | Serves as an output tract for the hippocampus; plays a role in memory, specifically inn recalling episodic memories; transmits information from the hippocampus to the mammillary bodies and thalamic anterior nuclei[64] |
| **LHILF** | Inferior longitudinal fasciculus – left | Plays a role in emotions from visual stimuli and a minor role in language, as well as facial recognition[54] |
| **RHILF** | Inferior longitudinal fasciculus – right | Plays a role in emotions from visual stimuli and a minor role in language, as well as facial recognition[54] |
| **LHMLF** | Middle longitudinal fasciculus – left | Plays a role in language and auditory processing, organizes auditory information, and possibly participates in visuospatial functioning and memory[63] |
| **RHMLF** | Middle longitudinal fasciculus – right | Plays a role in language and auditory processing, organizes auditory information, and possibly participates in visuospatial functioning and memory[63] |
| **LHOR** | Optic radiation – left | Carry visual information to visual cortex[62] |
| **RHOR** | Optic radiation - right | Carry visual information to visual cortex[62] |
| **LHSLF1** | Superior longitudinal fasciculus I – left | Plays a role in proprioception and motor movement[54] |
| **RHSLF1** | Superior longitudinal fasciculus I – right | Plays a role in proprioception and motor movement[54] |

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|---|---|---|
| **LHSLF2** | Superior longitudinal fasciculus II – left | Visual-spatial awareness and attention[54] |
| **RHSLF2** | Superior longitudinal fasciculus II – right | Visual-spatial awareness and attention[54] |
| **LHSLF3** | Superior longitudinal fasciculus III – left | Plays a role in somatosensory input, facial and hand fine movements, phonetics, and articulation of language[54] |
| **RHSLF3** | Superior longitudinal fasciculus III – right | Plays a role in somatosensory input, facial and hand fine movements, phonetics, and articulation of language[54] |
| **LHUF** | Uncinate fasciculus – left | Connects the orbitofrontal cortex, involved in face encoding and in processing famous names, to the temporal pole, which is crucial in naming people; action and object naming as well as semantic processing[46] |
| **RHUF** | Uncinate fasciculus – right | Connects the orbitofrontal cortex, involved in face encoding and in processing famous names, to the temporal pole, which is crucial in naming people; action and object naming as well as semantic processing[46] |

**Appendix B: Results from Linear Regressions**

Results for Interaction Effects

| Tract | Dependent Variable | Interaction | Overall P value | GAD7 P value | Interaction Effect P value |
|---|---|---|---|---|---|
| CCBODYC | MD | GAD7Cat*career stage | 0.0373 | 0.0285 | 0.0107 |
| CCBODYPM | MD | GAD7Cat*career stage | 0.0241 | 0.0088 | 0.0457 |

Results for Mental Health Main Effects

| Tract | Dependent Variable | Mental Health Outcome | Overall P value | Mental Health P value |
|---|---|---|---|---|
| RHFAT (frontal aslant tract) | FA | PHQ9 | 0.0046 | 0.0006 |
| RHFAT | FA | GAD7 | 0.0267 | 0.0022 |
| LHUF (uncinate fasciculus) | FA | PCL5 | 0.0172 | 0.0046 |
| RHUF (uncinate fasciculus) | FA | PCL5 | 0.0097 | 0.0150 |

Results for Career Stage Main Effects

| Tract | Dependent Variable | Mental Health Outcome | Overall P value | Career Stage P value |
|---|---|---|---|---|
| RHSLF1 (superior longitudinal fasciculus) | FA | PCL5 | 0.0305 | 0.0223 |
| CCBODYPM | FA | PCL5 | 0.0419 | 0.0430 |

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