12-1-2020

Association between White Matter Hyperintensities, Cortical Thinning, and Clinical Outcomes in Mild Traumatic Brain Injury

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ASSOCIATION BETWEEN WHITE MATTER HYPERINTENSITIES, CORTICAL THINNING, AND CLINICAL OUTCOMES IN MILD TRAUMATIC BRAIN INJURY

By

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Bachelor of Science – Physics
Northern Arizona University
July 2017

A thesis submitted in partial fulfillment
of the requirements for the

Master of Science – Health Physics

Department of Health Physics and Diagnostic Sciences
School of Integrated Health Sciences
The Graduate College

University of Nevada, Las Vegas
December 2020

UNLV | GRADUATE COLLEGE

Thesis Approval

The Graduate College
The University of Nevada, Las Vegas

November 11, 2020

This thesis prepared by

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entitled

Association between White Matter Hyperintensities, Cortical Thinning, and Clinical Outcomes in Mild Traumatic Brain Injury

is approved in partial fulfillment of the requirements for the degree of

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Abstract

Traumatic Brain Injury (TBI) is a global health challenge, with over 4.6 million confirmed cases annually in North America alone. Mild traumatic brain injuries (mTBIs) are the most common and make up approximately 81% of all TBI diagnoses worldwide [1]. Studies indicate that 10–15% of patients suffer from trauma induced symptoms (i.e. headache, loss of balance, cognitive impairments, fatigue, and mental health/affective disorders) as far as 1 year post injury [2]. Prediction and management of these post-traumatic sequalae is complicated by a lack of symptom associated neuroimaging findings. In spite of a "prominent distribution" of frontotemporal WMHs in pediatric subjects with mTBI, a 2016 study (N=72) by *Bigler et al*. found no association between unique changes in cortical thickness and WMHs after statistical correction for multiple comparisons. This retrospective study will investigate the associations between cortical thinning, white matter hyperintensities, and clinical outcomes in a large (N=147) and neurodevelopmentally diverse (18-40 years-old) group of subjects diagnosed with mTBI. Regional (Frontal Lobe, Temporal Lobe, Occipital Lobe, Parietal Lobe, and Cerebellum) volumetric and WMH data was obtained for all 147 patients. Assessment of image finding correlation showed that white matter hyperintensities did not consistently coincide with cortical thinning as defined by the NeuroQuant normative percentile values. Interval-censored analysis revealed statistically significant associations between positive WM status and longevity of post-concussive cognitive deficits ($p<0.024$).

Acknowledgements

I would like to express my sincere gratitude to each of my committee members for their guidance and contribution to this project. Their time, perspective, and counsel have made my research experience here at UNLV more meaningful than I could have ever imagined. Thank you Dr. Madsen and Dr. Pluth for your assistance, patience, and support during the changing of my original thesis project. Special thanks also to Dr. Cheryl Vanier for educating me on interval censored statistical analysis and coding in R. I would especially like to thank Dr. Travis Snyder. You have completely transformed my perspective on how science can be done and how life can be lived.

Cheers to a successful project, and many more to come!

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I. Introduction

Mild Traumatic Brain Injury (mTBI)

Traumatic brain injury (TBI) is a multifaceted and widespread condition known to affect at least 2% of the US population. Broadly defined as an alteration in brain function or brain pathology caused by an external force, TBIs are clinically described as either mild, moderate, or severe [3, 4]. Mild traumatic brain injury (mTBI), also referred to as a concussion, is the most common type of acute brain injury, making up approximately 81% of all TBI diagnoses worldwide [4]. In recent years, mTBI has been branded a "silent epidemic" by experts due to persisting cognitive, behavioral, and motor deficits experienced by 10-15% of concussed individuals [5]. mTBIs can occur in a number of ways, and the extent to which mechanism of injury modifies image findings and symptomatology is not known. Studies on mTBI commonly include patients with a history of motor vehicle collisions [1, 6], sports injuries [6-8], and even combat related blast injuries [9, 10] . The precise structural/functional changes that cause an mTBI are not yet known, but it is known that any deposition of mechanical force in the brain may damage neurons, and disrupt the patency of neurological structures [11].

There is a decided lack of evidence-based diagnostic criteria for mTBI. This is due to minimal interdisciplinary consensus on how to define, identify, or categorize traumatic brain injuries in a quantitative capacity [2]. A recent survey found that in the United States, less than half of level I trauma centers adhere to a standardized protocol for the evaluation or treatment of mTBI [12]. At present, mTBIs are clinically described as the aggregate of post-concussive somatic and neuropsychological symptoms. Somatic symptoms refer to any non-psychological functional complications induced by brain

trauma, such as headaches, fatigue, dizziness/difficulty balancing, and abnormal sleep patterns. Neuropsychological (sometimes referred to as neurobehavioral) sequelae include cognitive deficits and anxiety/mood disorders. Post-traumatic cognitive impairment, anxiety, and depression are particularly well described clinically and experimentally [2, 13-17]. Cognitive deficits following mTBI are common and may even occur without any posttraumatic amnesia or loss of consciousness. In this context, cognitive deficits include any combination of impaired attention, working memory and/or executive decision-making skills. Persistent post-concussive cognitive deficits are frequently accompanied by increased anxiety, irritability, or depressive tendencies in human subjects [14, 18, 19]. Nearly 100% of all mTBI patients report some degree of neuropsychological impairment 0-3 months post-mTBI, with a small percentage exhibiting persistent injury related complaints beyond 12 months post injury [14]. The mechanism by which these brain related sequalae are related to mild traumatic brain injury remains poorly understood [13, 17, 20].

Not all mTBI patients present with image findings that are detectable via conventional imaging sequences and radiological interpretation. Even studies utilizing more sophisticated imaging modalities have yielded minimal consensus on pathologic image findings in mTBI. The absence of objective image findings limits clinical evaluation to neuropsychological testing. There is great interest in establishing a more quantitative taxonomy of TBI, particularly through non-invasive methods like advanced medical imaging, which allows for acquisition of characteristic and quantitative data.

Diffuse Axonal Injury in mTBI

Head trauma is known to cause diffuse shearing (tearing) of axons as the brain shifts and rotates inside the skull. Axons are very thin, sometimes even thinner than a human hair, and can range in length from a few millimeters to over a meter along the spinal cord [6]. From a functional perspective, the axon serves as a neurological impulse highway, transferring electrical signals from the neural cell body to a synapse, where they are converted into chemical signals called neurotransmitters [21]. A visual representation of a neuron is shown in the figure below.

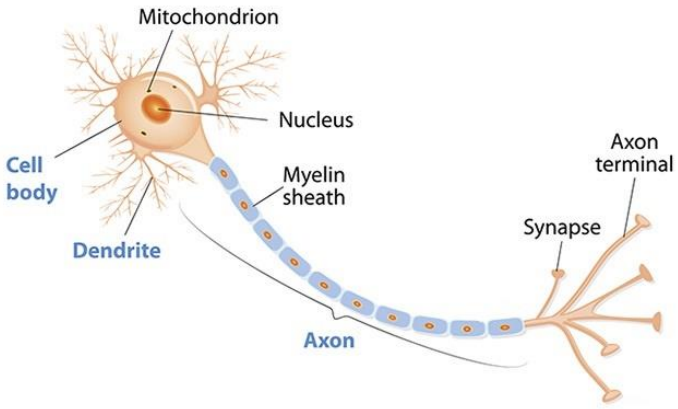

Figure 1: Anatomy of a nueron. Open access image courtesy of The University of Sydney School of Medicine

The longer the axon, the more vulnerable it is to rotational or lateral shearing, and as such trauma associated axonal injuries are commonly described in the white matter tracts of the corpus collosum, the largest, most well-defined tract in the brain connecting the two

hemispheres [5, 10, 22]. Clinically, this damage is referred to as diffuse axonal injury (DAI). DAI is most commonly described on imaging in moderate/severe TBI but is known to occur across the full spectrum of traumatic brain injuries [22]. Animal studies show that DAI are important pathological features of brain injury and are important modulators of symptomological outcomes [23, 24]. Image manifestation of DAI varies proportionately with TBI severity and may appear as; hemorrhagic sites in CT or MRI scans, increased signal on diffusion weighted sequences, or as white matter hyperintensities (non-hemorrhagic shearing) (WMHs) on FLAIR/T2 weighted MRIs or even on Diffusion Tensor Imaging in the form of low fractional anisotropy (FA) values. These modalities differ in terms of what they measure and how they work but are all highly sensitive to structural changes in white matter. Fluid-attenuated inversion recovery (FLAIR) imaging, a post-processed T2 MRI sequence set to null fluid signals, is commonly used in mTBI injury assessment. Figure 2 contains two representative images of a WMH on both the FLAIR and conventional T2 sequences.

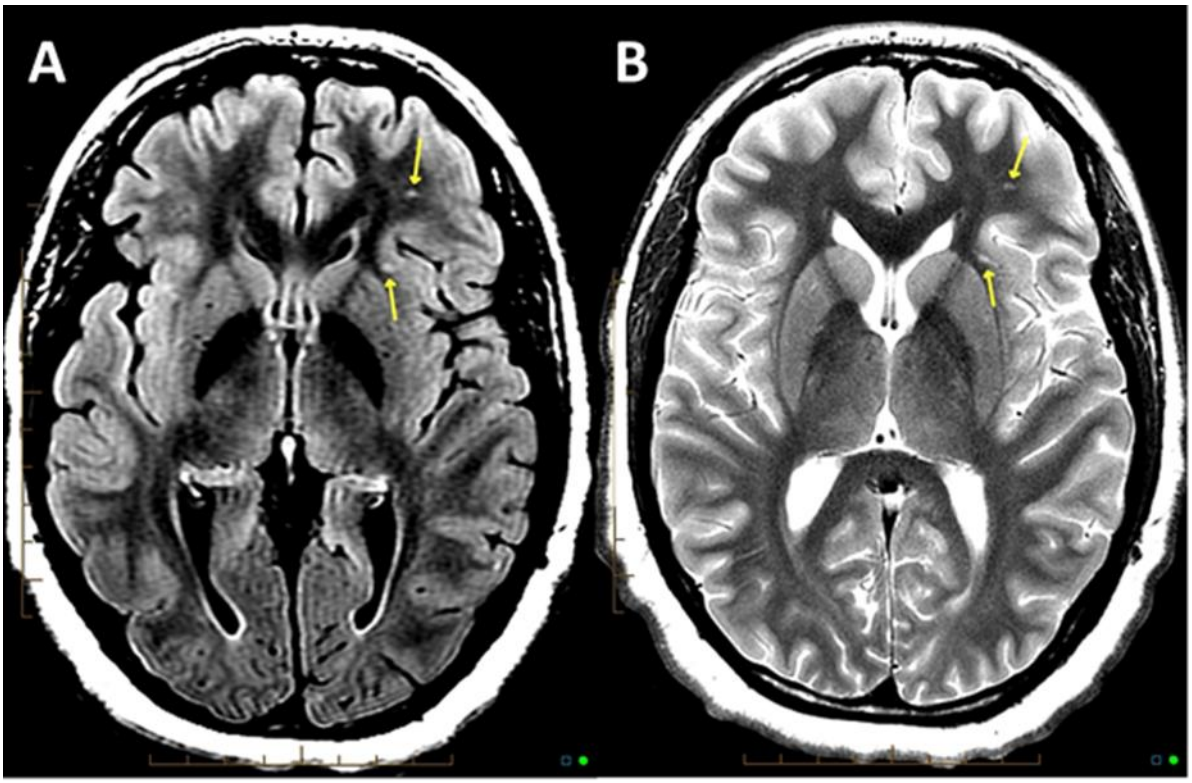

Figure 2: FLAIR (1A) and conventional T2 MRI (1B) showing two subcortical WMHs at grey-white matter junction in the left anterior frontal lobe of a 22 year old female diagnosed with mTBI.

In addition to its clinical utility, FLAIR has proven especially useful in the expansion of TBI classification and taxonomy, revealing quantitative neuroimaging findings predicting unfavorable recovery in ~30% of a large (N=135) and diverse patient population diagnosed with mTBI [27]. Many studies have sought to characterize the relationship between white matter lesions and clinical outcomes following mTBI, and have limited conclusions on the association between WMH and post-concussive symptoms [6, 11, 18, 25]. *Shetty et al.* reported that while white matter abnormalities occurred at a higher rates in mTBI patients than in controls, direct comparison was limited by differences in

imaging technology, and recommended follow up investigation [25]. *Chung et al.* noted that since non-hemorrhagic DAIs frequently occur concomitantly with hemorrhagic lesions (HDAI), it is difficult to determine the specific contribution of non-hemorrhagic DAIs (manifesting as WMHs) to clinical outcomes [11]. To study the specific relationship between non-hemorrhagic WMHs and mTBI, all patients with image evidence or clinical history of hemorrhaging were excluded from analysis.

Recent studies indicate that DAI is a major pathologic event across the full spectrum of TBI including concussion [15, 23, 26], and correlates with persistent cognitive and verbal memory impairments after mTBI [26, 27]. Advances in diffusion tensor imaging and post processing methods have identified large injury prone WM tracts reaching through cortical regions of the brain, namely the corona radiata (CR) and cerebral peduncle (CP) [28]. Diffusion Tensor Imaging studies focusing on non-hemorrhagic DAI are inconclusive with regard to their impact on clinical outcomes, with some studies finding a positive correlation between white matter changes and patient symptomology [29], and others finding no apparent correlation [11, 30]. This study will not consider the impact of WMH or cortical volume loss alone, but will instead focus on the impact of WMH in relation to cortical regional volume to see how two subtle imaging findings may be used in conjunction to predict symptom presentation following mTBI.

Cortical thinning in mTBI

By definition TBIs damages brain tissue. If the neuronal damage is sufficient to induce neuronal apoptosis, this damage may manifest as decreased regional brain volume. Some studies have hypothesized that atrophy of the cerebral cortex, frequently referred to

'cortical thinning', could serve as a quantitative biomarker in mTBI clinical assessment. Most of these studies have shown trauma associated patterns of cortical thinning, though these patterns are variable between studies [31-33]. Two pediatric studies have described regional and whole-brain atrophy in the sub-acute (0-4 months) phase post-mTBI when compared to age and sex matched controls [8, 34]. The 2008 study by *Merkley et al.* also reported a relationship between cortical thinning and reported deficits in working memory [34]. These pediatric studies indicate that cortical thinning may be a temporal pathologic feature in mTBI and could serve as a complimentary measure in mTBI diagnosis/assessment. Like WMH formation, cortical thinning is known to be an age associated phenomenon and is often seen alongside WMH development in elderly people [35]. To minimize a possible age-related bias in the findings, I have preferentially selected subjects between 18 and 40 years old, for whom cortical atrophy is unlikely to be age-related.

The precise mechanism by which mTBI influences cortical atrophy remains unclear, with current studies yielding significant regional variability and inconsistent results between chronic and acute mTBI patient populations in the level of cortical atrophy described [33, 36]. It is thought that regional variability of cortical atrophy may be due to mechanism of brain injury, since different kinds of force deposition yield different and distinct damage patterns [37]. This is substantiated by the fact that inter-patient regional variability of cortical atrophy is reduced among patient populations with the same mechanism of injury [33, 38]. There is some variability in patient demographics, however it is worth mentioning that 78% of patients in this dataset were injured in motor vehicle collisions (MVCs). From a clinical perspective this may be seen as convenient, since MVCs are among the leading causes of mTBI worldwide [1]. However, this does introduce variability

in terms of injury mechanics. No conclusions on the association between traumatic force vectors and cortical thinning can be made from this data. Several studies have shown a positive correlation between regional cortical thinning and severity of cognitive and behavioral symptoms in cases of moderate and severe TBI [34, 39, 40]. While this association does not necessarily suggest a causal relationship, each of these studies recommended further inquiry into cortical thinning as a potentially pathological event in mTBI. The continued investigation of functionally relevant changes in regional brain volume could lead to improved diagnosis and treatment of mTBI patients.

Preliminary Findings

Cortical volume and asymmetry in the 5 major lobes of the brain of 250 mTBI patients were compared to age and gender matched controls in the Neuroquant normative database. Correlation between symptom longevity and normative volumetric percentiles was tested using a semi-parametric interval-censored survival analysis, shown in the table 1 below.

Region	Symptom	SE	z Value	p Value
Cerebellum (Norm %)	Headache	2.44	-0.1	0.893
	Balance	4	-0.1	0.902
	Cognitive	5.14	-0.2	0.832
	Anxiety	7.91	-1.4	0.165
Frontal Lobe (Norm %)	Headache	0.28	-0.8	0.432
	Balance	0.3	-0.856	0.3923
	Cognitive	0.26	-0.7	0.499
	Anxiety	2.24	-0.4	0.723
Occipital Lobe (Norm %)	Headache	0.28	-1.8	*0.071*
	Balance	0.27	-1.7	*0.086*
	Cognitive	**0.28**	**-2.7**	**0.008**
	Anxiety	3.22	-0.5	0.001
Parietal Lobe (Norm %)	Headache	0.36	-1.9	*0.063*
	Balance	0.31	-0.7	0.494
	Cognitive	0.3	-0.478	0.6326
	Anxiety	**0.47**	**-23.7**	**0**
Temporal Lobe (Norm %)	Headache	0.25	-1.7	*0.084*
	Balance	0.31	-1.9	*0.063*
	Cognitive	0.22	0.3	0.776
	Anxiety	1.21	-0.4	0.662

Table 1: Association between imaging findings and symptom outcome. Statistically significant associations between norm percentile and symptom longevity are bold.

Patients in the bottom tenth percentile in occipital or parietal volumes exhibited cognitive deficits ($p=0.008$) and anxiety ($p<0.001$) lasting longer than patients showing higher occipital or parietal percentile volumes. Based on this preliminary analysis, occipital and parietal lobe volume appear to associate with persistent anxiety and cognitive deficits in mTBI subjects. I hypothesize that WMHs and cortical atrophy may co-associate and independently correlate with unfavorable clinical outcomes in a cohort of subjects (18-40 years-old) diagnosed with mTBI. To test my hypothesis I will assess the statistical association between the two image findings, and between each image finding and symptom incidence/longevity.

II. Background

White Matter and the Cerebral Cortex

White matter (WM) lies beneath the gray matter cortex in an area known as the medulla and is composed principally of myelin coated nerve fibers referred to as axons. These axons connect the neurons of the brain, ultimately allowing the brain to function as an advanced electrical circuit. The circuit is complete with electrical insulation called 'myelin' that coats axons and gives white matter its characteristic color. White matter is essential for normal cognitive function and psychological normalcy [18, 41]. Myelin is essential for high-speed transmission of electrical impulses, and damage to it can impair conduction and consequently, sensory, motor, and cognitive functions. Bundles of white matter neurons, referred to as "tracts", connect the functional regions of the brain.

The cerebral cortex is historically defined as the outermost 2-3 mm of neural tissue. Comprised primarily of dense gray matter, the cortex contains 10-14 billion neurons and makes up 40% of the brain's total mass [4]. This region gives the brain its 'wrinkly' appearance, consisting of peaks called gyri, and valleys called sulci where approximately two thirds of the cortical surface area is buried. The thickness of the cortex is not uniform but is thicker over gyri and thinner over sulci [32]. Divided lengthways into two cerebral hemispheres by the corpus callosum, the cerebral cortex is typically described in terms of five regions: frontal, parietal, temporal, occipital, and cerebellar [8, 32, 42]. Advancements in neuroscience have shown that most brain functions rely on complex information highways spanning many different regions of the brain, with the lobes of the brain responsible for varying functions [35].

The frontal lobe is positioned anterior to the parietal lobe, directly behind the forehead. The neurons in the frontal lobe are different from those in other cortical regions in that they produce a critical neurotransmitter called dopamine. Attention span, short-term memory, planning, and motivation are all cognitive processes known to rely on dopaminergic pathways. As such, the frontal lobe is considered the primary modulator of executive functions such as emotional regulation, decision making, task prioritization, and reward motivated behavior [43]. Neuropsychological issues relating to frontal lobe trauma have been extensively documented in the literature [8, 35, 43]. One of the earliest recorded examples of neuropsychological changes following frontal lobe trauma dates back to 1848 when railyard worker Thomas Gage attempted unsuccessfully to set off a controlled explosion. A spark from an iron tamping rod prematurely ignited the blasting powder, resulting in the penetration of his frontal lobe by a 3-foot-long, 14-pound metal spike. The iron rod obliterated much of his left frontal lobe, but incredibly, his wounds were non-fatal. Gage regained all cognitive and motor skills and within a year and returned to work on the railroad. However, his physician, friends, and family noted dramatic changes to his personality, describing him as more primal, fitful, and irreverent [44]. While obviously an extreme and antiquated case, recent studies also indicate that less severe damage to the frontal lobe may be accompanied by personality changes, behavioral disinhibition, and generally uncharacteristic behavior [8, 35, 43].

Posterior to the frontal lobe is the parietal lobe. The parietal lobe is a hub of tactile processing, receiving signals that in turn stimulate the sensations of touch, temperature, and pain. The parietal lobe is also the primary source of visuospatial processing, which affects general spatial awareness as well as reading, writing, and mathematic ability [15,

35]. Trauma to the parietal lobe may result in a series of cognitive changes known as Gerstmann's Syndrome, characterized by diminished perception of language, difficulty writing, difficulty with mathematics, and left-right confusion [45]. The impact of mTBI on parietal lobe volumetrics or functionality is not well understood, though it is reasonable to assume that post-concussive cognitive deficits may be due in part to damage and functional alternation of the parietal lobe.

The temporal lobe, located anteroinferior to the frontal lobe, is heavily involved in the processing of auditory signals, language recognition and visual memory (particularly of facial features) [32, 35]. Moderate to severe damage to the temporal lobe is known to inhibit recollection of visual stimuli. Neuropsychological tests have confirmed that patients with inhibited visual memory do not have reduced perception of visual stimuli and can describe faces and objects in real time. One possible explanation for this phenomenon is that that post-traumatic modification of visual memory results from interruption or modification of signal processing in the temporal lobe [46].

The occipital lobe is the most posterior region of the cerebral cortex and serves as the major visual processing center of the brain [35]. The occipital lobe is unique in that physiologists have been able to successfully and repeatedly map function sub-regions of the occipital lobe using electrode stimulation and functional MR imaging (fMRI) [47]. Apart from its comparatively robust functional characterization and importance in visual processing, the occipital lobe is of particular interest in mTBI due to it's position at the rear of the skull. Many mTBIs can be described as 'coup contrecoup' injuries, meaning that damage occurs both at and directly opposite the site of original insult. For example,

motor vehicle collisions, frequently result in whiplash damage to the occipital lobe [4]. The term 'whiplash' is often used interchangeably with 'coup contrecoup' but may also refer to injuries of the cervical vertebrae and paraspinal muscles. When examined via perfusion imaging, patients reporting "whiplash" due to front-end collisions exhibited significantly reduced blood flow to the occipital and temporal lobe when compared to non-trauma control groups [48].

The cerebellum, an important processor of signals traveling via the spinal cord, contains the cortex which regulates the processes of balance and proprioception [32]. While not responsible for the initiation of movement, the cerebellum does utilize sensory feedback from the peripheral nervous system to fine tune the precision, timing, and coordination of motor functions [49]. Damage to the cerebellum is most frequently accompanied by persistent lack of equilibrium, manifesting clinically as difficulty walking and/or balancing. Subjects will often try to compensate for this lack of balance with an ungainly stride and/or a widened stance [50].

Symptomatology of mTBI

Although exact percentages vary depending on the author, 10-15% of mTBI patients experience severe post-concussion symptoms lasting months or even years post injury [1, 51]. The aggregate of these symptoms is often referred to as post-concussion syndrome (PCS) [5]. Diagnostic criteria for PCS is defined in the International Classification of Diseases (ICD)-10 manual, as well as the Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV [52]. However, both definitions suffer from a lack of measurable diagnostic criteria, relying primarily on assessment of self-reported symptoms and details

relating to injury. Many studies attempting to establish a more robust taxonomy of PCS are inconclusive, citing inconsistent coincidence of symptoms, lack of quantitative biomarkers, and minimal consensus on how persistent non-specific symptoms relate to trauma. The subjective definition of post-concussion syndrome, the low specificity of PCS symptomatology, and the significant symptomatic overlap with more thoroughly documented neurological and psychiatric conditions render the term PCS of minimal utility in both clinical and research environments [53-55].

Interval-Censored Statistics

Interval censoring is a form of survival analysis used to analyze incomplete or temporally non-uniform datasets. More broadly interval censoring is a technique that can be used when a variable (or multiple variables) of interest are known to change at a point during an interval of time, but cannot be localized to any single discrete time point. This method is defined arithmetically by the formula below:

$$T \equiv I = (L, R]$$

In the above equation take 'T' to be the survival time of some variable of interest, defined by the interval 'I'.

In this study I am assessing the "survival time" of the previously described seven post-concussive symptoms. When T is interval-censored we use I = (L, R] to define the interval measuring time T. In this formula () is used to indicate an open interval while [] means the interval is closed. For example, the interval (96, 209] defines the set of all numbers

between 96 and 209 excluding 96 and including 209.) Our limit "L" is the number of days post injury that symptoms were reported. The limit "R" is defined as the number days post injury that improvement or resolution of a previously documented symptom was reported. Additional censoring can be provided in cases where either $L = 0$ or $R = \infty$. These intervals are described as left and right censored, respectively.

III. Materials and Methods

Subjects

All data was obtained from a database of 400 mTBI patients following IRB approval. All subjects were diagnosed with mTBI by the same board-certified neurologist specializing in head trauma and received neurological consultation/imaging no more than 6 months post-concussion. Demographic data was obtained from clinical reports and input into a deidentified patient data sheet prior to analysis. Exclusion criteria were extensive and included: history of demyelinating disease, cerebrovascular accident, head trauma, chronic epilepsy, brain surgery, cerebral contusions, hemorrhagic diffuse axonal injury (DAI), intracranial hemorrhaging, cerebral vascular malformations, cavernoma, or brain tumors. Studies suggest that clinical outcomes following mTBI are likely age dependent [25, 56], and that fully neuro-developed adults report higher symptom severity scores than their younger counter parts [25]. Similarly, WMH formation is an age associated phenomenon. To increase sensitivity of this analysis, all patients over the age of 40 were removed from the dataset, and remaining subjects were separated into over/under 30-year-old subgroups. The age cutoff was set at 30 for two main reasons: to account for the completion of neurodevelopment and to maintain statistical power. The 2008 study "Microstructural maturation of the human brain from childhood to adulthood" describes two important frontotemporal connections (the cingulum and the uncinate fasciculus) which by age 25 years have still not reached full developmental maturity [57]. This suggests that neurodevelopment between the frontal and temporal lobes may not fully complete until after 25 years of age. The cutoff of 30 provides consideration for neurodevelopment while also retaining more statistically comparable samples sizes (Cohen's d: 0.45 vs 0.88) than a cutoff of 25. After exclusions, 147 mTBI patients

remained for subsequent analysis. Patient demographics of white matter subgroups are defined in table 2.

	0 WMH	1 WMH	>1 WMH
No. Subjects	88 (59.9%)	25 (17.0%)	34 (23.1%)
Age (Mean, SD) [Min, Max]	(28.6, 7.5) [19-40]	(29.9, 5.61) [20,40]	(31.0, 6.98) [18-39]
Sex (Female)	28 (32.94%)	13 (38.24%)	18 (52.94%)

Table 2: Patient demographics of 147 subjects diagnosed with mTBI, sorted based on WM subgroups (0 WMH: Patients with zero WMHs, 1 WMH: Patients with a single WMH, >1 WMH: Patients with multiple WMHs)

Most of the patients in this cohort were involved in motor vehicle collisions. A breakdown of common causes of injury in this civilian mTBI cohort is provided in table 3.

	0 WMH		1 WMH		>1 WMH	
Sex (Female)	28	32.94%	13	38.24%	18	52.94%
Cause of Injury (Assault)	4	4.71%	2	8%	1	0.43%
Cause of Injury (Fall)	1	1.18%	1	4%	2	5.89%
Cause of Injury (MVC)	77	83.53%	22	88%	29	85.29%
Cause of Injury (Falling Object)	1	1.18%	0	0	2	5.89%
Cause of Injury (Unknown)	4	4.71%	0	0	0	0

Table 3: Injury demographics of 147 subjects diagnosed with mTBI, sorted into WMH subgroups

Subjects in this mTBI cohort are non-combatant, non-athlete civilians all of whom were receiving consultation due to ongoing litigation relating to their injury and the severity of their symptoms. One recent meta-analysis found litigation to have a 'moderate effect' on clinical outcomes in TBI patients [58]. However two focused review articles found minimal effect on cognitive deficits and headaches in litigants versus non litigants [59] with many patients continuing to report post-traumatic headaches well after litigation resolution [60].

Symptomatology

Symptom longevity is calculated from the date of injury to the time when improvement or resolution (both referred to as 'improvements' hereafter) were reported during a visit to the physician. Developments in post-concussive symptomological outcomes were noted at each neurological consultation/follow-up. Studies examining symptom incidence and outcomes following mTBI frequently deploy the term "symptom" to mean any self-reported somatic/neuropsychiatric change experienced after a concussion [5, 9, 61, 62]. Incidence and resolution of seven common post-concussive symptoms were obtained via a retrospective neurological consultation review. In accordance with recent literature, seven symptoms were selected for consideration in this study: headaches, balance issues, cognitive deficits, fatigue, anxiety, depression, and emotional lability. [8,12,29].

Headaches were self-reported and assessed qualitatively by the neurologist and documented in clinical reports. Balance issues were broadly defined as reduced steadiness when walking, sitting, standing or resting. Common patient descriptions of balance deficit

included ‘unsteadiness on the feet’, ‘feeling of falling’ and ‘coordination problems’. Balance issues were assessed by the neurologist using a standard confirmatory physical exam called the Romberg test for balance. For the purpose of this study, cognitive deficits were defined as any impairment in attention, learning, memory, speaking, or frontal executive functions [15]. Self-reported cognitive deficits were clinically assessed via AO Mental Status Test, designating an alert and oriented score from 1-4 for each patient. Neuropsychological symptoms including anxiety, depression and emotional lability were diagnosed in accordance with DSMV diagnostic criteria. [13] Patient cognitive status was assessed via AO Mental Status Test and were assigned an alert and oriented score from times 1 to times 4. Patients describing anxiety and/or depression were evaluated via the Beck index and provided scores from 0 to 63. Patients who reported loss of consciousness (LOC) were evaluated and assigned scores via the protocol defined in the Glasgow Coma Scale.

Imaging

Patients underwent an MRI protocol with either a 3.0 Tesla Signa HDxt MR system or a 3.0 Tesla Siemens system, both equipped with an 8-channel head coil. On the GE magnet, slice thickness of 4.0 mm with 4.5 mm gap was performed, on the Siemens, a 2.2 mm thickness with a 2.2 mm gap was performed. T2 FLAIR images were used for quantification of white matter lesions using Inteleviewer DICOM viewer. WMH were distinguished from fluid filled foci (dilated perivascular spaces) by dual confirmation on T2 and FLAIR imaging sequences. Lesions were counted and then categorized by their cortical region. Volumetric analysis was performed utilizing 1.2 mm GE thickness and 0.9 mm Siemens T1 weighted imaging as per NeuroQuant technical specifications.

NeuroQuant volumetric software

NeuroQuant is an FDA approved neurovolumetric software which obtains regional brain volumes from ultra-thin (~1 mm slice thickness) MRI images via an automated voxel intensity analysis. In addition to providing raw volumetric output, NeuroQuant also compares regional volumetrics to their normative database and provides normative percentile values accounting for subject age, sex, and intracranial volume (ICV). NeuroQuant has been used in both research and clinical environments to aid in the diagnosis of brain injury and neurodegenerative disease. An example of a NeuroQuant processed MRI is provided in the figure below.

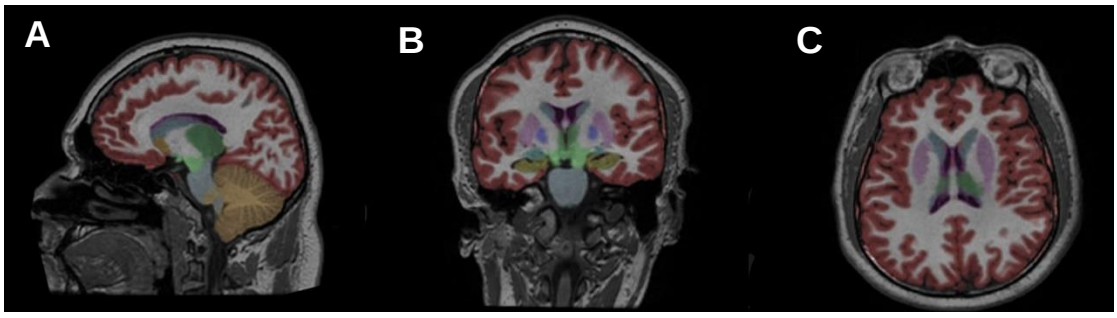

Figure 3: Representative image of a sagittal, coronal, and axial T1 MRI of a 24-year-old male diagnosed with mTBI. Images were processed using NeuroQuant 3.0 (Note: that in the above image slices each neuroanatomical sub-region is defined with a different color).

Statistical Analysis

To prove or disprove my hypothesis, I will need to first examine the correlation between imaging findings for WMHs and cortical thinning. A Spearman rank correlation is well suited to characterize this correlation, as it is a non-parametric correlation test that does not carry any assumptions about the distribution of the data and is considered the most accurate method of rank correlation analysis provided both datasets are at least ordinal. The Spearman correlation does assume that scores on one variable must be monotonically related to the other variable, which essentially means that any correlation (positive or negative) between the two data groups is either entirely nonincreasing or nondecreasing. For good measure, Spearman's Rho and Pearson's correlations will also be determined using excel and used to examine the association between WMHs and cortical atrophy.

A Fisher's exact test was used to assess the independent association between sex, age, cortical atrophy, WMH status and symptom presentation/resolution. Comparisons between defined subgroups were also made using a Fisher's exact test for each symptom-characteristic pair. The Fisher's exact test was chosen over a chi-square test for two reasons; Fisher's exact test does not make any parametric assumptions about the data distribution, and it is more sensitive to datasets with frequently occurring low (near 1) values in each cell. Cortical atrophy positive patients were defined as having any lobular volume in the 1^{st}-25^{th} percentile after NeuroQuant volumetric analysis. White matter status was defined and analyzed in two ways. The first method dichotomization sorted patients into a simple WMH positive or negative group. The second method dichotomization separated patients with a single WMH from those with multiple WMHs.

Independent variable models for sex, age, cortical atrophy and WMH status were estimated separately for each post-concussive symptom. Standard errors (SE) were derived from bootstrapping (100 samples). Differential symptom persistence between stratified subgroups were tested by using the bootstrapped standard errors to form z-scores. Analyses were conducted in R 3.5.1 software with the 'icenReg' package.

Many patients never reported improvement or resolution of symptoms. In such cases, the data will be right-censored, which means that the symptom might improve at some future time, but it had not improved by the date of the last visit to the physician. This analysis assumes that symptom abatement or resolution is equally probable across the interval of time between two appointments expressed by (L, R], where 'L' is the physician visit where the symptom was last reported, and 'R' is the visit where improvement/resolution was reported. This data censoring allows for statistical consideration of variable time between injury and consultation. Data that are both interval-censored and right-censored statistics are relatively common in medical studies, and can account for the uncertainties of this retrospective clinical dataset [30]. Each patient in the analysis will be counted only once for the analysis, with the uncertainty associated with the elapsed time between visits serving as the maximum likelihood estimate of the survival function.

Limitations

All data is obtained retrospectively and is analyzed in the absence of a control group. All findings and results in this analysis will need to be verified using longitudinal follow-up studies with proper control groups and larger sample sizes. Subjects could not be screened for certain comorbidities such as hypertension and pre-existing headaches/migraines

with the clinical data available. Hypertension and migraines are particularly important within the context of WMHs, with which they are both known to associate [63]. Neurological examination and subsequent imaging were obtained at variable times post-injury. For this reason, additional factors known to modify clinical outcomes such as acute pain, memory, and headache could not be completely considered or corrected for statistically [64]. To account for the lack of true volumetric controls, NeuroQuant normative percentile values were used to characterize normalcy of cortical volume. These values are generated by comparison of subject brain volumes to a proprietary normative database, therefore providing some insight into normalcy of volumetric findings. No such normative database exists for WMHs. Symptoms described in this study may be nonspecific and can be caused/influenced by factors that are non-trauma related [16, 64]. There is an inescapable ascertainment bias, in that patients who are more symptomatic are more likely to likely to seek clinical consultation and imaging. The data analyzed in this study should not be used to estimate the incidence of mTBI associated symptoms or image findings.

IV. Results

Statistical association of Cortical Atrophy and WMH

	Pearson's Correlation	*Spearman's Rho*
Frontal (Both)	-0.18	-0.10
Frontal (L)	-0.17	-0.12
Frontal (R)	-0.15	-0.24
Parietal (Both)	0.04	0.04
Parietal (L)	0.01	0.00
Parietal (R)	0.08	0.02
Occipital (Both)	-0.17	-0.04
Occipital (L)	0.09	0.04
Occipital (R)	-0.13	-0.14

Table 4: Statistical association between number of regional WMHs and NeuroQuant normative percentile. Values closer to ± 1.00 indicate a stronger correlation (N=59) No temporal or cerebellar WMH were present in any subjects.

The Pearson's correlation and Spearman's Rho test values in table 4 demonstrate minimal correlation between regional or lateral-regional white matter burden and NeuroQuant normative percentile. This indicates minimal co-association between our quantitative image findings, suggesting independent mechanisms for the induction of WMH formation and cortical atrophy or that associated cortical atrophy was so regional that it was overshadowed by the large volume of the entire lobe. Whether or not one, or both, of these imaging findings may be related to trauma is difficult to definitively determine without a control group. However, these image findings may still impact symptom presentation/longevity in mTBI even if they are not traumatically induced. This notion is substantiated by our preliminary findings showing an association between occipital/parietal volume and longevity of cognitive/anxiety clinical outcomes.

Headaches, balance issues, and cognitive deficits were the most commonly reported symptoms in all subgroups, and also the most likely to improve or resolve. Conversely, emotional lability and fatigue were the two least commonly reported and also the least likely to improve or resolve. Interval censored analysis revealed statistically significant positive associations between WM status and longevity of post-concussive cognitive deficits ($p<0.024$). Positive WM status is also nearly significant predictor of post-concussive headache longevity. These correlations are reported in table 6, and also shown in figures 4 and 5.

Prevalence of Symptom Presentation & Improvement in WM Subgroups

	0 WMH		1 WMH		>1 WMH	
	Incidence	*Improvement*	*Incidence*	*Improvement*	*Incidence*	*Improvement*
Headache	83 (94%)	31 (37.4%)	24 (96%)	9 (37.5%)	32 (94.1%)	6 (18.7%)
Balance	57 (64.8%)	17 (29.8%)	21 (84%)	6 (28.6%)	26 (76.5%)	4 (15.4%)
Cognitive	67 (76.1%)	27 (40.3%)	23 (92%)	9 (39.1%)	29 (85.3%)	4 (13.8%)
Fatigue	10 (11.4%)	1 (10.0%)	5 (20.0%)	1 (20.0%)	10 (29.4%)	0 (0%)
Anxiety	24 (27.3%)	4 (16.7%)	10 (40.0%)	1 (10.0%)	14 (41.2%)	0 (0%)
Depression	20 (22.7%)	3 (15.0%)	8 (32.0%)	1 (12.5%)	13 (38.2%)	0 (0%)
Emo. Lability	13 (14.8%)	1 (7.69%)	6 (24.0%)	0 (0%)	10 (29.4%)	0 (0%)

Table 5: Incidence and resolution of symptoms by number of patients in analyzed patient population, or the % of the patient population (Note: the % patient population under incidence is relative to the total "n" for each subgroup, % patient population for improvement is relative to number of incidences).

Interval Censored Symptom Survival Statistics for All Subgroups

	Symptom	SE	z-value	p-value
Sex	Headache	0.42	0.5	0.921
(Male/Female)	Balance	0.53	-0.9	0.711
	Cognitive	0.49	-1.6	0.361
	Anxiety	2.10	0.4	0.898
	Depression	1.98	-0.1	0.993
Age	Headache	0.46	-1.1	0.115
(<30y/≥30)	Balance	0.49	-1.9	0.238
	Cognitive	0.39	-2.1	0.092
Cortical Atrophy	Headache	0.80	1.1	0.194
(With/Without)	Balance	0.94	-2.4	0.267
	Cognitive	0.81	-1.3	0.143
WM Status	Headache	0.84	-1.3	0.090
(With/Without)	Balance	1.08	-2.9	0.119
	Cognitive	0.76	2	**<0.024**
WM Status	Headache	0.65	-1.2	0.283
(1/>1)	Balance	0.71	-1.0	0.215
	Cognitive	0.85	-0.7	0.194

Table 6: Statistics for survival functions comparing symptom longevity among dichotomized patient subgroups. Bootstrapped standard errors (SE), z value, and p-values are all reported.

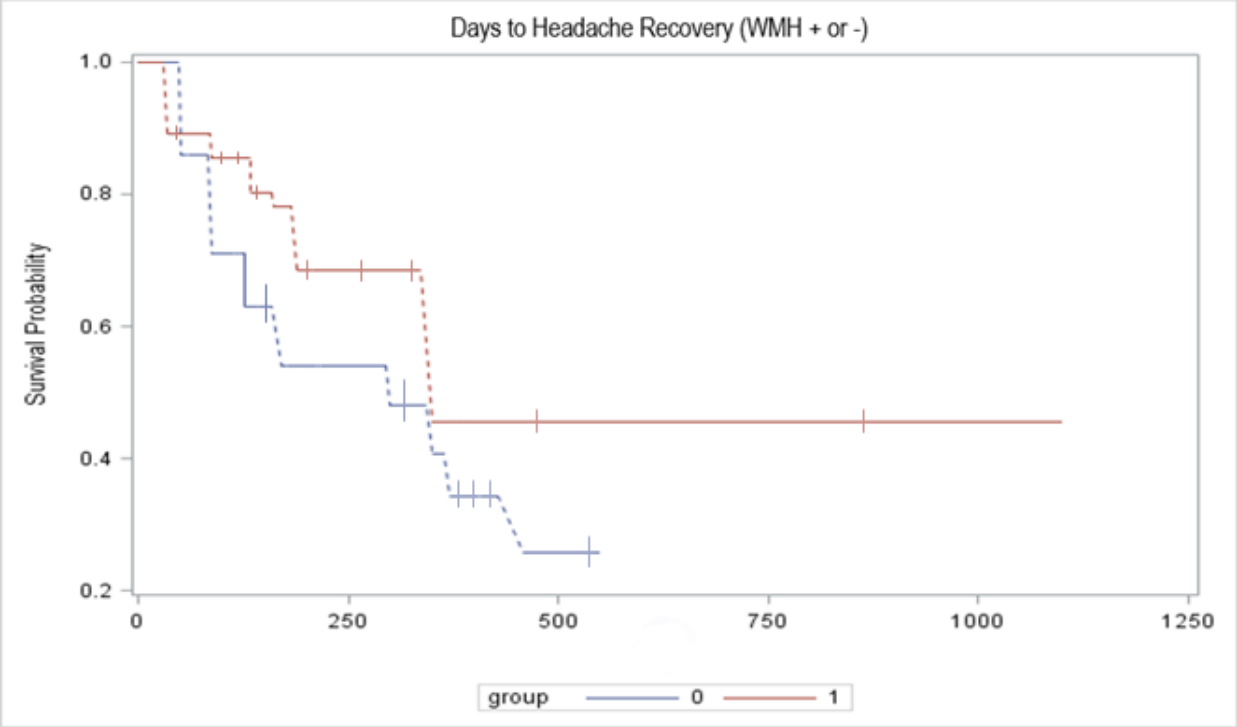

Figure 4: Correlation between WMH status positive (1) or negative (0) and longevity of post concussive headaches (p=0.090). Survival probability (y- axis) in this context is used to indicate proportion of subjects experiencing survival of their headaches after a given number of days (x-axis).

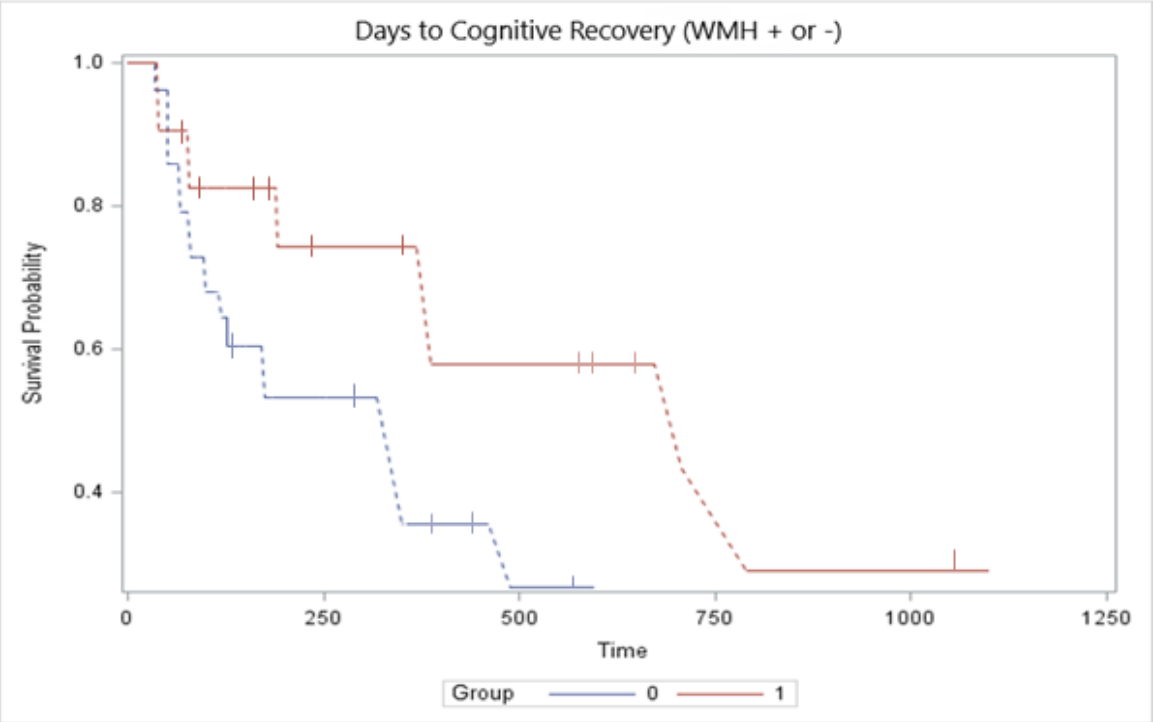

Figure 5: Correlation between WMH status positive (1) or negative (0) and longevity of post concussive cognitive deficits (p=0.024) Survival probability (y- axis) in this context is used to indicate proportion of subjects experiencing survival of cognitive deficits after a given number of days (x-axis).

V. Conclusions & Future Directions

The purpose of this study was to assess how two quantitative image findings (cortical thinning and WMHs) co-associate with one another, and how they might independently correlate with unfavorable clinical outcomes post-concussion. Assessment of image finding correlation shows that white matter hyperintensities do not consistently coincide with cortical thinning, at least as defined by the NeuroQuant normative percentile values used in this analysis (Table 4). Further studies may use other volumetric parameters to examine the relationship between regional white matter burden and changes in volume in the aftermath of a concussion. One significant limitation of this study is the lack of imaging data for multiple timepoints. Some recent studies have indicated that white matter hyperintensities as well as cortical thinning may only be present at certain windows of time post-concussion. A prospective longitudinal study with uniform clinical follow up and imaging may reveal time sensitive associations between imaging findings and clinical outcomes.

There was no statistically significant gender-based differences in symptom longevity observed (Table 6). There were no significant differences in symptom longevity among age dichotomized patient groups. This is consistent with recent studies reporting no significant gender-based differences in clinical symptom presentation or longevity [65]. However, the association between age and longevity of post-concussive cognitive deficits was approaching significance. This is not surprising, since white matter development and structural normalcy are strongly age-dependent even in the absence of trauma. This trend, though not statistically significant merits further investigation and is loosely concordant with findings showing age-dependence on outcomes [25, 56]. It is possible

that the separation of subjects into over/under 30 instead of over/under 25 age groups may be obscuring age related effects and suppressing the significance of this finding. An increase in sample size could allow for movement of the age threshold to over/under 25 while still maintaining adequate statistical power. The small sample size of the WMH sub-grouped data did not lend itself well to statistical analysis, but follow up studies with larger symptomological cohorts could use a matched pair test like the McNemar's Test to identify statistically significant differences in symptom incidence/resolution among WMH and perhaps even cortical atrophy sub-groups.

The observed correlation between WMH positivity and prolonged cognitive deficits is consistent with publications describing cognitive processes as reliant on complex multi-lobular interactions via white matter tracts [35]. Furthermore, this finding is consistent with the results of a recent study by *Tate et al.* describing worsened cognitive performance among mTBI patients with WMHs when compared to those without [10]. Other studies have demonstrated associations between white matter changes and cognitive deficits [66], but fundamental differences in imaging modalities and scanner specifications prevent direct comparison to this study. Future studies studying white matter and its relationship with cognitive issues in concussion may benefit from the use of an imaging modality that is more sensitive to structural alterations of white matter tracts (i.e. diffusion tensor imaging). Associations between quantitative image findings and neuropsychological symptoms proved difficult to assess using interval censored analysis. This was due to the small number of patients reporting depression, anxiety, and emotional lability. A study with a larger sample size may increase the "n" of these symptomological subsets sufficiently to be analyzed via interval censored analysis. At

present, I am obtaining additional WM measurements from mTBI patients under 40 to add to this existing dataset.

At the beginning of this study, I hypothesized that two trauma related image findings, WMHs and cortical atrophy, may co-associate in a large population of mTBI patients. Correlative assessment using two statistical methodologies demonstrated no such association or trend. This is consistent with the 2016 pediatric population study by *Bigler et al.* which described the association between focal lesions and cortical thinning as idiosyncratic. The second prong of my hypothesis postulated that cortical thinning and white matter status may independently correlate with unfavorable clinical outcomes was mostly disproven, with the exception of the WMH/Cognition association. This finding stands alongside a number of other studies which have described a relationship between white matter integrity and cognition [5, 18, 63, 67]. From the standpoint of statistical methodology, these findings add to the growing body of literature utilizing interval-censored analysis to extract meaning from retrospective datasets. Future studies would benefit strongly from a longitudinal design, with uniform imaging and clinical follow up. Comparison of image findings to a neuroanatomically 'normal" database should be to confirm the validity of my findings. The observed association between a quantitative image finding and post-concussive symptomatology is an exciting development in the quest to establish a more objective method of mTBI diagnosis and management.

Appendix

```
#R Code: WMH/Cortical Association with Symptomatology
#Packages and Setup
setwd("/Users/thkno/Desktop/Thesis2020/Analysis/R/")
raw<-read.delim("raw clinical.txt")
install.packages("icenReg")
library(icenReg)

#Independent variables of interest: Sex, age, cortical atrophy status, WMH status

symptoms<-
c("HA","Balance","Cognitive","Fatigue","Anxiety","Depression","Emotional.Lability")

#Symptom Presentation
#Symptom Presentation (Sex): this section examines the association between sex and
incidence of 7 post concussive symptoms using a Fisher's exact test

for(j in 1:length(symptoms)){
tt<-as.data.frame(cbind(raw$Sex,raw[,j+7]))
ttab<-table(tt[complete.cases(tt),])
temp<-fisher.test(ttab)
```

```
print(c(sum(ttab[1,])-ttab[1,length(ttab[1,])], ttab[1,length(ttab[1,])],sum(ttab[2,])-
ttab[2,length(ttab[2,])],
ttab[2,length(ttab[2,])],temp$estimate,temp$conf.int,temp$p.value))
}
```

#Symptom Presentation (Age): this section examines the association between age and incidence of 7 post concussive symptoms with a dichotomous age variable (greater than/less than or equal to 30) using a Fisher's exact test

```
raw$Age30<-as.data.frame(ifelse(raw$Age<=30,"aLE30","zGT30"))
for(j in 1:length(symptoms)){
tt<-as.data.frame(cbind(raw$Age30,raw[,j+7]))
ttab<-table(tt[complete.cases(tt),])
#print(levels(raw$Age30))
temp<-fisher.test(ttab)
print(c(sum(ttab[1,])-ttab[1,length(ttab[1,])], ttab[1,length(ttab[1,])],sum(ttab[2,])-
ttab[2,length(ttab[2,])],
ttab[2,length(ttab[2,])],temp$estimate,temp$conf.int,temp$p.value))
}
```

#Symptom Presentation (Cortical Atrophy): this section examines the association between cortical atrophy and presentation of 7 post concussive symptoms with a dichotomous cortical atrophy variable (1=positive, 0=negative) using a Fisher's exact test

```
for(j in 1:length(symptoms)){
tt<-as.data.frame(cbind(raw$ATROPHY,raw[,j+7]))
ttab<-table(tt[complete.cases(tt),])
#print(levels(raw$ATROPHY))
temp<-fisher.test(ttab)
print(c(sum(ttab[1,])-ttab[1,length(ttab[1,])], ttab[1,length(ttab[1,])],sum(ttab[2,])-
ttab[2,length(ttab[2,])],
ttab[2,length(ttab[2,])],temp$estimate,temp$conf.int,temp$p.value))
}
```

#Symptom Presentation (WMH): this section examines the association between WM status and incidence of 7 post concussive symptoms with a dichotomous WMH variable (1=positive, 0=negative) using a Fisher's exact test

```
raw$WMH.1.[raw$WMH.1.==""]<-NA
for(j in 1:length(symptoms)){
tt<-as.data.frame(cbind(raw$WMH.1.,raw[,j+7]))
ttab<-table(tt[complete.cases(tt),])
#print(levels(raw$WMH.1.))
temp<-fisher.test(ttab)
print(c(sum(ttab[1,])-ttab[1,length(ttab[1,])], ttab[1,length(ttab[1,])],sum(ttab[2,])-
ttab[2,length(ttab[2,])],
ttab[2,length(ttab[2,])],temp$estimate,temp$conf.int,temp$p.value))
```

```
}
```

#Symptom Longevity

#Model assessment: First I had to decide if my data should be analyzed using a non-parametric, semi-parametric, or parametric model. I made this decision based off sample size, bias assessment, and the general data distribution

```
pdf("Overall symptoms parametric vs nonparametric graphs2.pdf")
for(k in 1:7){
tint<-raw[complete.cases(cbind(raw[,k+17],raw[,k+24])),c(k+17,k+24)]
ha.mod.par<-ic_par(cbind(tint[,1],tint[,2])~1,data=raw)
diag_baseline(ha.mod.par) }
dev.off()
```

#I went with semi-parametric given the small sample size, and large number of right-censored items. All parametric models demonstrated a visually poor fit.
#These loops compare all independent variables of interest, compare them to the 7 symptoms, and return the output from the interval-censored analysis.

```
pdf("Overall symptoms graphs2.pdf")
for(k in 1:7){
temp<-raw[complete.cases(as.data.frame(raw[,c((k+17),(k+24))])),c((k+17),(k+24))]
all.data<-ic_sp(cbind(temp[,1],temp[,2])~1)
plot(all.data,ylab="Proportion of Patients Presenting Symptom",xlab="Days Since
Injury", main=symptoms[k],lwd=2)
}
```

```
dev.off()
```

#Symptom Longevity (Sex): this section examines the association between sex and longevity of 7 post concussive symptoms using a right censored interval censored analysis

```
for.plot<-data.frame(Sex=c("F","M"))
row.names(for.plot)<-c("F","M")
symptoms<-
c("HA","Balance","Cognitive","Fatigue","Anxiety","Depression","Emotional.Lability")
pdf("Sex clinical symptoms graphs.pdf")
for(j in 1:7){
ww<-raw[complete.cases(cbind(raw$Sex,raw[,(j+17)],raw[,(j+24)])),]
temp<-ic_sp(cbind(ww[,(j+17)],ww[,(j+24)])~Sex,data=ww,bs_samples=100)
plot(temp,for.plot,ylab="Proportion of Patients Presenting Symptom",xlab="Days Since
Injury", main=symptoms[j],lwd=2)
print(cbind(symptoms[j],Female=getSCurves(temp,for.plot)$S_curves$'F',Male=getSC
urves(temp,for.plot)$S_curves$'M',getSCurves(temp,for.plot)$'Tbull_ints'))
print(summary(temp))
 }
dev.off()
```

#Symptom Longevity (Age): this section examines the association between age and longevity of 7 post concussive symptoms using a right censored interval censored analysis

```
#For <=30 cut-off (0 for <=30, 1 for >30)
raw$Age30<-as.factor(ifelse(raw$Age<=30,"0","1"))
for.plot<-data.frame(Age30=c("0","1"))
row.names(for.plot)<-c("0","1")
symptoms<-
c("HA","Balance","Cognitive","Fatigue","Anxiety","Depression","Emotional.Lability")
pdf("Age30 clinical symptoms graphs2.pdf")
for(j in 1:7){
ww<-raw[complete.cases(cbind(raw$Age30,raw[,(j+17)],raw[,(j+24)])),]
temp<-ic_sp(cbind(ww[,(j+17)],ww[,(j+24)])~Age30,data=ww,bs_samples=100)
plot(temp,for.plot,ylab="Proportion of Patients Presenting Symptom",xlab="Days Since
Injury", main=symptoms[j],lwd=2)
print(cbind(symptoms[j], "0"=getSCurves(temp,for.plot)$S_curves$'0',
"1"=getSCurves(temp,for.plot)$S_curves$'1',getSCurves(temp,for.plot)$'Tbull_ints'))
print(summary(temp))
 }
dev.off()
```

#Symptom Longevity (Cortical Atrophy): this section examines the association between regional atrophy and longevity of 7 post concussive symptoms using a right

censored interval censored analysis with a with a dichotomous cortical atrophy variable (1=positive, 0=negative)

```
for.plot<-data.frame(ATROPHY=c("0","1"))
row.names(for.plot)<-c("0","1")
symptoms<-
c("HA","Balance","Cognitive","Fatigue","Anxiety","Depression","Emotional.Lability")
pdf("ATROPHY clinical symptoms graphs.pdf")
for(j in 1:7){
ww<-raw[complete.cases(cbind(raw$ATROPHY,raw[,(j+17)],raw[,(j+24)])),]
temp<-
ic_sp(cbind(ww[,(j+17)],ww[,(j+24)])~as.factor(ATROPHY),data=ww,bs_samples=100
)
plot(temp,for.plot,ylab="Proportion of Patients Presenting Symptom",xlab="Days Since
Injury", main=symptoms[j],lwd=2)
print(cbind(symptoms[j], "0 "=getSCurves(temp,for.plot)$S_curves$'0', "1
"=getSCurves(temp,for.plot)$S_curves$'1',getSCurves(temp,for.plot)$'Tbull_ints'))
print(summary(temp))
 }
dev.off()
```

#Symptom Longevity (WMH): this section examines the association between WM positivity/negativity and longevity of 7 post concussive symptoms using a right censored interval censored analysis

```
for.plot<-data.frame(WMH.1.= c("Positive","Negative"))
row.names(for.plot)<-c("Positive","Negative")
symptoms<-
c("HA","Balance","Cognitive","Fatigue","Anxiety","Depression","Emotional.Lability")
pdf("WMH.1. clinical symptoms graphs3.pdf")
for(j in 1:7){
ww<-raw[complete.cases(cbind(raw$ WMH.1.,raw[,(j+17)],raw[,(j+24)])),]
temp<-ic_sp(cbind(ww[,(j+17)],ww[,(j+24)])~ WMH.1.,data=ww,bs_samples=100)
#plot(temp,for.plot,ylab="Proportion of Patients Presenting Symptom",xlab="Days
Since Injury", main=symptoms[j],lwd=2)
print(cbind(symptoms[j], "zPositive"=getSCurves(temp,for.plot)$S_curves$'0',
"Negative"=getSCurves(temp,for.plot)$S_curves$'1',getSCurves(temp,for.plot)$'Tbull_i
nts'))
print(summary(temp))
 }
dev.off()

#Symptom Longevity (WMH): this section examines the association between
multiple/single WMH burden and longevity of 7 post concussive symptoms using a right
censored interval censored analysis

for.plot<-data.frame(WMH.2.= c("Mult","Sing"))
row.names(for.plot)<-c("Mult","Sing")
```

```
symptoms<-
c("HA","Balance","Cognitive","Fatigue","Anxiety","Depression","Emotional.Lability")
pdf("WMH.2. clinical symptoms graphs3.pdf")
for(j in 1:7){
ww<-raw[complete.cases(cbind(raw$ WMH.2.,raw[,(j+17)],raw[,(j+24)])),]
temp<-ic_sp(cbind(ww[,(j+17)],ww[,(j+24)])~ WMH.2.,data=ww,bs_samples=100)
#plot(temp,for.plot,ylab="Proportion of Patients Presenting Symptom",xlab="Days
Since Injury", main=symptoms[j],lwd=2)
print(cbind(symptoms[j], "zMult"=getSCurves(temp,for.plot)$S_curves$'0',
"Sing"=getSCurves(temp,for.plot)$S_curves$'1',getSCurves(temp,for.plot)$'Tbull_ints')
)
print(summary(temp))
 }
dev.off()
```

```
#Graphs for Manuscript
#For sex comparison
for.plot<-data.frame(Sex=c("F","M"))
row.names(for.plot)<-c("F","M")
symptoms<-
c("Headache","Balance","Cognitive","Fatigue","Anxiety","Depression","Emotional
Lability")
pdf("Sex clinical symptoms graphs pub.pdf")
for(j in 1:7){
ww<-raw[complete.cases(cbind(raw$Sex,raw[,(j+17)],raw[,(j+24)])),]
temp<-ic_sp(cbind(ww[,(j+17)],ww[,(j+24)])~Sex,data=ww)
plot(temp,for.plot,ylab="Proportion of Patients Presenting Symptom",xlab="Days Since
Injury", main=symptoms[j],lwd=2,cex.lab=1.3,col=c(17,24))
}
dev.off()

#For atrophy comparison
for.plot<-data.frame(ATROPHY=c("0","1"))
row.names(for.plot)<-c("ATROPHY=0","ATROPHY=1")
pdf("ATROPHY clinical symptoms graphs pub.pdf")
for(j in 1:7){
ww<-raw[complete.cases(cbind(raw$ATROPHY,raw[,(j+17)],raw[,(j+24)])),]
temp<-ic_sp(cbind(ww[,(j+17)],ww[,(j+24)])~as.factor(ATROPHY),data=ww)
```

```
plot(temp,for.plot,ylab="Proportion of Patients Presenting Symptom",xlab="Days Since
Injury", main=symptoms[j],lwd=2,cex.lab=1.3,col=c(17,24))
}
dev.off()

#For age comparison  (0 for <=30, 1 for >30)
raw$Age30<-as.factor(ifelse(raw$Age<=30,"0","1"))
for.plot<-data.frame(Age30=c("0","1"))
row.names(for.plot)<-c("≤30",">30")
pdf("Age30 clinical symptoms graphs pub.pdf")
for(j in 1:7){
ww<-raw[complete.cases(cbind(raw$Age30,raw[,(j+17)],raw[,(j+24)])),]
temp<-ic_sp(cbind(ww[,(j+17)],ww[,(j+24)])~Age30,data=ww)
plot(temp,for.plot,ylab="Proportion of Patients Presenting Symptom",xlab="Days Since
Injury", main=symptoms[j],lwd=2,cex.lab=1.3,col=c(17,24))
}
dev.off()

#For WMH comparison
for.plot<-data.frame(WMH.1.= c("0","1"))
row.names(for.plot)<-c("WMH (-)","WMH (+)")
pdf("MRI clinical symptoms graphs pub2.pdf")
for(j in 1:7){
ww<-raw[complete.cases(cbind(raw$ WMH.1.,raw[,(j+17)],raw[,(j+24)])),]
```

```
temp<-ic_sp(cbind(ww[,(j+17)],ww[,(j+24)])~ WMH.1.,data=ww,bs_samples=100)
plot(temp,for.plot,ylab="Proportion of Patients Presenting Symptom",xlab="Days Since
Injury", main=symptoms[j],lwd=2,cex.lab=1.3,col=c(17,24))
}
dev.off()
```

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Abstracts

Vanier C, Ramachandra V, Knoblauch T, Parikh S, Rodriguez A, Fazzini E, & Snyder T. Comparison of 400 mTBI Subjects Against Tightly Matched Controls Using Automated Volumetric Software. *RSNA Scientific Assembly and Annual Meeting 2020*. 5 December 2020. rsna2020.rsna.org/. Oral Presentation.

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