CEREBRAL WHITE MATTER MICROSTRUCTURAL CHANGES IN PURE MAXILLOFACIAL TRAUMA AND ITS ASSOCIATED NEUROPSYCHOLOGICAL OUTCOME AMONGST MALAYSIAN

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FACULTY OF DENTISTRY
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CEREBRAL WHITE MATTER MICROSTRUCTURAL CHANGES IN PURE MAXILLOFACIAL TRAUMA AND ITS ASSOCIATED NEUROPSYCHOLOGICAL OUTCOME AMONGST MALAYSIAN

ABSTRACT

Purpose: The aim of the present study was to establish cerebral white matter (WM) microstructural changes in pure maxillofacial (MF) trauma injuries and the associated neurocognitive deficits in an effort to improve the prognostic values of Diffusion Tensor Imaging (DTI) parameters in mild traumatic brain injury (mTBI) care. **Materials and Methods**: A prospective review of 21 patients with pure MF was included in the study along with 21 healthy control participants. Magnetic resonance imaging (MRI) and structural DTI were performed on all patients using a 3T MRI (within 24 hours from the time of trauma). The DTI values were registered to the ICBM DTI-81 white matter atlas. Fractional anisotropy (FA), mean diffusivity (MD) and radial diffusivity (RD) values were automatically calculated for 50 white matter tracts. Comprehensive neuropsychological evaluation was done using the Screening – Neuropsychological Assessment Battery (SNAB) within the same admission. After 6 months in average (chronic phase), patients were subjected for a repeat of DTI scan and neuropsychological evaluation. Descriptive statistics were used for the demographic data, and a paired *t* – test and repeated measure analysis of variance were used to establish the intergroup differences and susceptibility. **Results**: The included patients were relatively young adults, with a mean age of 29 ± 8.1 years and 13.0 ± 1.2 years of education. Of the 21 patients, 5 (24%) had MF injuries involving the soft tissue, 2 (9%) had MF injury on upper third region, 12 (57%) had injuries at middle third and 2 (10%) were injured on lower third. Of the 21 patients with MF injuries, none had intracranial abnormalities found on the admission CT scan. Executive function and attention were significantly altered across the time points, with patients with MF injury doing poorly at

baseline with signs of a slowed recovery 6 months later. Wider variety of WM tracts injury responses were noted with radiological evidence of reactive astrogliosis, vasogenic and cytotoxic edema in the acute phase and subsequent demyelination and degeneration of WM tracts over time. The pathogenic processes were strongly correlated with the neuropsychological deficits seen in MF patient group. **Conclusion**: The unique DTI parameters (both at acute and follow up) enable better prognostication of neuropsychological outcomes in patients with MF injuries.

Keywords: maxillofacial injury; diffusion tensor imaging; microstructural changes; traumatic brain injury; neuropsychology

MENGENALPASTI PERUBAHAN MIKROSTRUKTUR JARINGAN PUTIH SEREBRUM INDIVIDU YANG MENGALAMI KECEDERAAN TRAUMA MAKSILOFASIAL TULEN DAN KESAN NEUROPSIKOLOGIKALNYA DI KALANGAN RAKYAT MALAYSIA

ABSTRAK

Tujuan: Objektif kajian ini adalah untuk mengenalpasti perubahan mikrostruktur pada jaringan putih serebrum (WM) dalam kecederaan trauma maksilofasial tulen (MF) dan defisit neurokognitif dalam usaha untuk meningkatkan nilai ramalan parameter *Diffusion Tensor Imaging* (DTI) dalam rawatan kecederaan otak trauma ringan (mTBI). **Kaedah dan Bahan:** Kajian prospektif 21 pesakit dengan kecederaan MF tulen telah disertakan di dalam kajian ini bersama-sama dengan 21 orang peserta kawalan yang sihat. Imbasan otak *Magnetic Imaging Resonance* (MRI) dan DTI telah dilakukan ke atas semua peserta kajian menggunakan 3T MRI (dalam masa 24 jam dari kejadian trauma). Nilai DTI telah didaftarkan pada *atlas* jaringan putih ICBM DTI-8. Nilai-nilai *fractional anisotropy* (FA), *mean diffusivity* (MD) dan *radial diffusivity* (RD) telah dikira secara automatik untuk 50 saluran jaringan putih. Penilaian neuropsikologikal komprehensif telah dilakukan ke atas perserta kajian dengan menggunakan *Screening – Neuropsychological Assessment Battery* (SNAB). Secara purata, selepas 6 bulan (fasa kronik), pesakit telah mengulangi imbasan DTI dan penilaian neuropsikologikal. Statistik deskriptif digunakan untuk data demografik manakala *paired t -test* dan *repeated measure analysis of variance* telah digunakan untuk menunjukkan perbezaan antara kumpulan dan kecenderungannya. **Keputusan:** Peserta kajian kebanyakkannya orang muda, dengan purata umur 29 ± 8.1 tahun dan 13.0 ± 1.2 tahun pendidikan. Daripada 21 pesakit, 5 (24%) mengalami kecederaan MF melibatkan tisu lembut, 2 (9%) mempunyai kecederaan MF pada bahagian satu per tiga atas, 12 (57%) mempunyai kecederaan di pertengahan ketiga dan 2 (10%) kecederaan di

bahagian satu per tigabawah. Di kalangan 21 pesakit yang mengalami kecederaan MF, tiada keabnormalan intrakranial dikesan pada imbasan CT penilaian awal. Fungsi eksekutif dan perhatian mempunyai perubahan yang ketara, di mana pesakit yang mengalami kecederaan MF didapati kurang memuaskan pada penilaian awal dan terdapat tanda-tanda pemulihan yang perlahan 6 bulan kemudian. Kepelbagaian respons kecederaan saluran WM diperhatikan dengan bukti radiologikal astrogliosis reaktif, vasogenik dan edema sitotoksik dalam fasa akut dan *demyelination* dan degenerasi saluran WM mengikut tempoh. Proses-proses patogenik berkaitan kukuh dengan defisit neuropsikologikal yang dilihat dalam kumpulan pesakit dengan kecederaan MF. **Kesimpulan:** Keunikan parameter DTI (akut dan susulan) membantu menghasilkan ramalan yang lebih baik terhadap kesan neuropsikologikal pesakit yang mengalami kecederaan MF.

Kata kunci: kecederaan maksilofasial, pengimejan diffusi tensor, perubahan mikrostruktur, kecederaan trauma otak, neuropsikologi

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LIST OF SYMBOLS AND ABBREVIATIONS

FA	:	Fractional anisotropy
MD	:	Medial diffusivity
RD	:	Radial diffusivity
GCS	:	Glasgow Coma Scale
MRI	:	Magnetic resonance imaging
mTBI	:	Mild traumatic brain injury
MVA	:	Motor vehicle accident
ROI	:	Region of interest
SNAB	:	Screening – Neuropsychological Assessment Battery
UMMC	:	University Malaya Medical Center
LOC	:	Loss of consciousness
PTA	:	Post traumatic amnesia
WM	:	White matter
TBSS	:	Tract Based Spatial Statistics
FLAIR	:	Fluid Attenuated Inversion Recovery
CT	:	Computed Tomography
DWI	:	Diffusion Weighted Imaging

LIST OF APPENDICES

CHAPTER 1: INTRODUCTION

1.1 Background

Relative to its population, Malaysia has one of the highest traffic fatality risks in the world since 1996 (Abdul Manan & Várhelyi, 2012). The statistics of annual incidence of motor vehicle accidents (MVA) in Malaysia provided by the Malaysian Institute of Road Safety Research (MIROS) showed that in 2015, there were 489,606 incidences with 18,258 casualties and 6706 deaths (Nordin et al., 2015). Head trauma is by far the commonest reason for Computed Tomography (CT) scan to be performed at any time in a day. Many studies from developed countries have focused on identifying clinical variables that can predict positive CT findings and the need for neurosurgical intervention. In Malaysia however, CT scan is not readily available in many rural hospitals. The limited availability of this scan has caused a high rate of non-recordings and inaccuracy in diagnosing TBIs in subjects with MF traumatic injuries in hospitals all over the country (Abdul Latip et al., 2004).

A review of the literature indicates that the frequency of neurologic injury associated with MF fractures is as high as 76% (Puljula et al., 2012). While most patients with minor head injury demonstrate immediate recovery, a proportion deteriorates and necessitates intervention for better outcomes. Yet, the relationship between TBI and MF fractures has not been firmly established within a large population. MF fractures or injuries many at times masks any accompanying TBI (Nordin et al., 2015). A timely detection may lead to improved results as proper and prompt treatment of TBI is crucial in boosting the outcome of head injury (Isik et al., 2012). Traumatic brain injury (TBI) resulting from MVAs is a significant public health problem because it often results in negative long-term or permanent physical, cognitive, behavioural as well as emotional changes (Rajandram, Syed Omar, Rashdi, & Abdul Jabar, 2014). Although many of

these patients make a good recovery, morbidity including transient or persistent distortion, loss of function and psychosocial problems do exist.

The lack of a unified consensus about what constitutes an injury to face or brain is an inherent problem in studies of TBI. Advance neuroimaging studies involving DTI, a technique that is sensitive to the changes in white matter microstructure and fiber tract integrity amongst patients with TBI have reported significant microscopic changes in white matter tracts (Veeramuthu et al., 2015). Microstructural injuries are beyond the capabilities of conventional imaging techniques (CT and MRI), and can be easily missed in patients who present with MF injuries (Grossman, Inglese, & Bammer, 2010). This could pose a practical challenge to both neurosurgeons and maxillofacial surgeons in terms for diagnostic accuracy, prognosis, and patient management. Computed tomography (CT) or conventional T1- and T2-weighted magnetic resonance imaging (MRI) are poor at characterizing this injury and therefore provide limited information on incidence, extent, severity and temporal profile of axonal injury. Fluid attenuated inversion recovery (FLAIR) imaging offers some additional diagnostic information, but definitive diagnosis of traumatic axonal injury (TAI) is only possible on autopsy (Armstrong, Mierzwa, Marion, & Sullivan, 2016). In this review, we focus primarily on MRI and, most particularly, on DTI findings in mTBI. Diffusion tensor imaging (DTI) allows in vivo quantification of white matter microstructural alterations following TBI hence it provides information regarding the degree and directionality of tissue water diffusion non-invasively (Shenton et al., 2012).

Among the neuropsychological alterations that are commonly reported in patients with mTBI include impairment in attention, memory, language, visuospatial and executive functions which predispose this subset of patient with long term neuropsychological sequelae (Gomez-Anson et al., 2015). In previous studies, the lack of radiological evidence of brain injury in mTBI has led clinicians typically to diagnose

mTBI on the basis of clinical and cognitive symptoms, which are generally based on self-report, and are non-specific as they overlap with other diagnoses (Shenton et al., 2012). Persistent symptoms, however, may be the result of more subtle white matter alterations that are beneath the threshold or beyond the capability of spontaneous recovery from mTBI. Although brain injuries are quite heterogeneous, it is generally accepted that the most common pathophysiological change persisting in the chronic phase is due to disruption of axons as either the direct, or more typically indirect, effect of mechanical trauma, and it has been implicated as a key factor related to persistent cognitive problems following TBI (Armstrong et al., 2016).

This study planned to investigate the 'cushion effect' of pure MF trauma and its relationship with microstructural brain damage as seen in DTI. Hence, we investigated the integrity of the white matter tracts by comparing DTI metrics (FA, MD and RD) values acutely after trauma and over time. The results of DTI taken several hours (hyper – acute state) after the trauma are compared with changes after 6 months (during the follow-up) and it's correlation with the neurocognitive performance is assessed.

1.2 Research Objectives

The objectives of the study were:

- To identify the incidences of intracranial abnormalities or lesions in patients with pure maxillofacial (MF) injuries.
- To identify whether different subtypes and location of MF fractures predispose patient to traumatic axonal injury (TAI) via diffusion tensor imaging.
- To evaluate neuropsychological changes in patients with MF injury acutely and during follow up at 6 months' post trauma.
- To identify whether the neurocognitive changes were associated with structural changes observed through diffusion tensor imaging.

1.3 Research Questions

The research questions were as following:

- What is the incidence of intracranial abnormalities or lesions in patients with pure maxillofacial injuries?
- Do certain maxillofacial fractures subtypes and its location predispose patients to traumatic axonal injury observed through diffusion tensor imaging?
- Are there any neuropsychological changes in patients with pure maxillofacial injury acutely and during 6 months of follow up? Are these changes associated with the any of the structural changes observed through the diffusion tensor imaging?

1.4 Conceptual Framework

A number of studies suggested that the severity of white matter damage detected by DTI correlates with behavioural and cognitive measures of impairment in mTBI (Veeramuthu et al., 2015; Wozniak et al., 2007). TAI is thought to represent one of the more common injuries observed in the aftermath of mTBI (Shenton et al., 2012). These subtle alterations of brain tracts or fiber pathways have been visualized using diffusion tensor imaging (DTI), which enables better visualization of the extent of early microstructural changes post-mTBI (Assaf & Pasternak, 2008). A variety of metrics can be generated through DTI scans, including fractional anisotropy (FA), mean diffusivity (MD) and radial diffusivity (RD). The values characterized by these DTI metrics detected as early as few days after neuro trauma to weeks as well as months after the initial insult enables clinicians to differentiate edemas either from vasogenic or cytotoxic origin (Grossman et al., 2010). These findings are crucial in predicting long – term neurological outcome including neuropsychological performances (NP).

We aimed to clarify these longitudinal DTI changes using a whole brain white matter measurement strategy with Tract Based Spatial Statistics (TBSS) in mTBI and control groups. From the TBSS white matter skeleton of comparison across the subjects, we identified significant tract changes and correlated these regions with neuropsychological performances both at admission and 6 months post-injury in MF patients with mTBI. We also examined the relationship between anatomical correlates of the tracts and cognition in an effort to improve the prognostic values of DTI parameters in mTBI care.

CHAPTER 2: LITERATURE REVIEW

2.1 Prevalence of Road Traffic related Traumatic Brain Injury

The incidence of maxillofacial (MF) trauma due to road traffic accident (RTA) continues to be a major cause of morbidity and mortality worldwide. In fact, traffic accidents have been reported as the ninth most common cause of death, according to the World Health Organization (WHO) and the total number of annual traffic accident fatalities is estimated to be approximately 1.3 million (Garg et al., 2015). MF trauma may mask traumatic brain injuries (TBI) prompting for intensive care treatment. It is an undeniable truth that returning to work in the UK is problematic following TBI. Approximately 1 million people in the UK sustain TBI each year and up to 150,000 incur mild or moderate injury resulting in cognitive and psychological problems, such as impaired insight, executive dysfunction, anxiety and fatigue that interfere with activities of daily living including work (Ilvesmaki et al., 2014).

Similarly in Malaysia, it was reported that more than half of the total traffic fatalities in Malaysia are motorcycle fatalities (Nordin et al., 2015). The study determined that the majority of the motorcycle fatalities (90 %) occur during the evening and on weekends, and most of these motorcycles were privately owned. In addition, approximately 35% of the motorcycle drivers do not have an appropriate driver's license. To date, there were no specific analyses done which categorizes road traffic crash casualties based on the severity of TBI incurred. The increase in population and motorisation led to a consequent increase in the number of road traffic accidents. From 414,421 MVA incidences in 2010, the number increased to a total of 489,606 MVA incidences in 2015. The number of injuries which can be serious or slight however stated a decreased value from 21,397 incidences in 2010 to 11,552 incidences in 2015. Although statistics do show a decreasing trend for casualties who sustained serious or

slight injury, a proper data to record the severity TBI for all the casualties should be done for a proper assessment of head trauma injuries. In persons under 45 years of age, TBI is the leading cause of death and disability, with an overall mortality rate of 25 per 100,000 (Ahmed, Sadullah, & Shukri Yahya, 2016).

2.2 Definition and Classification of Traumatic Brain Injury

The general consensus on the definition of TBI is an alteration of brain function, caused by an external force which includes the manifestation of at least one of the following clinical signs: i) loss of consciousness (LOC) or decreased consciousness, ii) loss of memory immediately before and after injury / post traumatic amnesia (PTA), iii) alteration of mental status (confused, disorientated), iv) neurological deficits and v) intracranial lesions (Hohlrieder et al., 2004). Glasgow Coma Scale (GCS) is a good marker for determining potential brain injury, clinical conditions and prognosis of the patients following trauma. In the current understandings, the risk of brain injury increases as the GCS decrease (Puljula et al., 2012). However, this does not mean that there is no risk of brain injury in patients with MF trauma who documented a high GCS scores within the range of 13 – 15.

TBI can be classified as missile and non-missile. The latter can further be subdivided as focal and diffuse damage, which often overlaps:

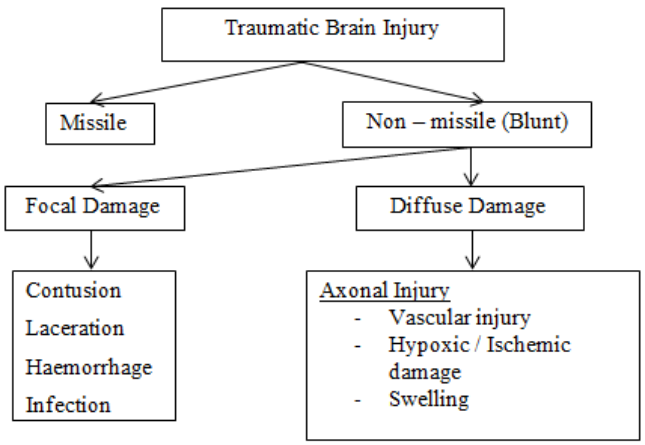

Figure 2.1: Classification of Traumatic Brain

Focal damage includes contusions, which are usually superficial bruises of the brain, affecting the cortex and in more severe cases also the underlying white matter. Contusions often have a triangular shape, with a wide base on the surface of the crest of a gyrus as opposed to ischaemic damage, which tends to be more severe and at the depths of the sulci. They are classified as i) indirect ('contre-coup'), frequently seen in the anterior and inferior surfaces of the frontal and temporal lobes, and ii) direct ('coup') contusions seen at the site of severe impact on the surface of any region of the brain (Kinnunen et al., 2011). Lacerations occur when the damage is severe enough to cause tearing of the meninges. Bleeding is common after TBI. Intracranial haemorrhage may develop over a period of time, which may extend into the subarachnoid space causing subarachnoid haemorrhage (SAH); other causes of SAH include skull fracture with tearing and/or dissection of arteries such as the vertebral arteries. Extradural haematoma (EDH) is usually associated with skull fracture and torn meningeal arteries, whereas subdural haematoma (SDH) results from the tearing of the bridging veins in particular those related to the superior sagittal sinus. Focal infection is frequently a complication of skull fracture and contamination with bacteria (Manson et al., 2009).

Diffuse damage includes traumatic axonal injury (TAI), vascular injury and hypoxia/ischemia. TAI can be focal, multi-focal or diffuse. In focal and multifocal axonal injury the damaged axons are seen in one or few locations in the supratentorial parts of the brain, mainly in the corpus callosum and internal capsule. TAI is usually associated with rapid angular (rotational) acceleration and deceleration of the brain. Diffuse vascular injury results from shear stress and traction of parenchymal blood vessels resulting in petechial haemorrhages. On the other hand, diffuse hypoxic ischaemic damage sometimes accompanies TBI, especially in patients with raised intracranial pressure (over 30 mmHg) and severe long-lasting hypotension (Hohlrieder et al., 2004).

TAI can be caused by immediate (primary) axotomy which occurs at the time of injury or delayed (secondary) axotomy which evolves over a few minutes or hours after impact. In the majority of cases of head injury, secondary axotomy is the major mechanism (Main et al., 2017). The focal damage to the axonal cytoskeleton is followed by formation of axonal swellings and varicosities proximal to the site of injury. These swellings contain accumulated material which cannot be transported due to disruption of axoplasmic flow. Therefore, the axonal swelling usually occurs sometime after head trauma and indicates some period of survival.

2.3 Aetiologies of Head Injury

It has been proposed that the face protects the brain from injury the way an airbag protects the chest in a motor vehicle crash. Lee et al. reported that MF fractures are associated with a decreased risk of a TBI; conversely Davidoff et al. found MF fractures to be highly associated with TBI. Similarly, study done by Keenan et al. demonstrated MF fractures does not help to prevent TBI, instead the risk of intracranial injury was increased almost 10-fold, and the risk for all brain injuries including concussion was doubled. The result of the study done is more in agreement with Davidoff et al who reported a 50% incidence of MF fractures having positive signs of brain injury.

The skull is composed of three principle bony structures: cranial vault, cranial base, facial skeleton. The rigid cranial vault protects the brain from external injury. The brain rests on cranial base, which also has various vessels and nerves entering and exiting, through various foramina. This constitutes ‘‘neurocranium.’’ The facial skeleton which is connected with the cranial vault and cranial base can be divided into three parts, the upper third of facial skeleton being the part of cranial vault and comprising of frontal bone, the middle third comprising of central midfacial bone: the maxilla, the nasoethmoid, and bilateral zygoma bones, and the lower third comprising of rigid bone—mandible, with its condylar articulation to base of skull. This constitutes with the

oral cavity and other associated soft tissues, ‘‘viscerocranium’’(Dube, Rao, & Tanwar, 2014).

It is now generally agreed that a major cause of brain injury is tissue deformation induced by accelerations imparted to the whole head. When the head is strucked, the skull is accelerated; the brain shows inertia and suffers strains of different types. An identical sequence of injury is seen when the moving head hits a rigid object and abruptly decelerates. These are also known as acceleration and deceleration injuries of brain (Ji, Wang, Song, Chen, & Wang, 2012). The injuries to the head resulting from impacts in the maxillofacial region fall into four groups, namely:

- Open frontal fractures and penetrating wounds, with varying degrees of local cerebral damage.
- Internal compound fractures of the anterior cranial fossa.
- Closed brain injuries resulting from impact-induced acceleration or deceleration.
- Secondary complications, of which the chiefs are:
  - i) Intracranial hemorrhage
  - ii) Cerebral edema and other types of brain swelling
  - iii) Cerebral hypoxia
  - iv) Cerebrospinal fluid leakage
  - v) Intracranial infections
  - vi) Carotid cavernous fistula
  - vii) Post traumatic epilepsy.

Since the interest for this study would be a mild Glasgow Coma Scale (13 – 15) documented on a MVA victims, closed brain injuries that showed no pathological changes in the CT scan was ideally selected to be the samples for the research. A close relationship between MF fracture and intracranial injury has been reported in many

articles. But very few reported on relationship of MF trauma and TAI using advance non-invasive neuroimaging technique. Indications of TBI generally are the presence of emesis, vomiting, loss of consciousness, or a low GCS score are important findings for suspicion of an intracranial injury. However, in patients with MF trauma, injury to the brain may present without observing any of the above mentioned findings (Zelken et al., 2014).

Previous studies on mechanism of injuries of the brain states that, at the moment of impact, a diffuse neuronal lesion is inflicted on the brain, which is responsible for the immediate clinical picture of brain injury. Chang et al. stated that during the first collision in accidents, part of the impact energy is absorbed by the facial soft tissues and skeleton, and part of the energy is transmitted into the intracranium. Thus, the force of the impact is a pertinent factor in determining the severity of the MF fracture and head injury. The severity of intracranial injury can be caused by direct impact or indirect force transmitted through the facial skeleton (Chang, Lombard, & Greher, 2011). Most high energy direct impacts to the central region of the facial skeleton create severe central MF fractures that involve the nasal, lacrimal, vomer, maxillary, ethmoidal, and frontal bones. In these central MF fractures, the maxilla is not only important for functional, physiological, and esthetic reasons but together with other bones of the central area, it forms a structure capable of absorbing considerable impact energy, thus protecting the brain from direct collision. The tri-planar arrangement of the facial bones in the horizontal, sagittal and coronal planes may act as an effective cushion against violent forces to the cranium. The compressible air-filled energy-absorbing facial bones serve as a decelerating cushion to protect intracranial structures located behind them (Pappachan & Alexander, 2012).

Nevertheless, with all these high impact force absorbing capabilities which the facial skeleton has, it is undeniable that a harmful unknown force could be somehow

transmitted to the neurocranium or the brain. This could cause TAI which lead to a variety of neuropsychological problems. Axons as we all know are arranged together to form fibers and it travels along its designated tracts to its respective destinations in the brain. It carries vital information in the form of impulses and ensures the human mind and body responses accordingly depending on the need or certain reflexes (Tang et al., 2012).

2.4 Relationship of mTBI with Neuropsychiatric Disorders

The head is often subjected to forces arising from impact or trauma to the MF region ranging from low to high velocity motor-vehicle collisions. The commonly accepted theory in head injury is that the brain is protected by a 'cushioning' layer which contains the cerebrospinal fluid (CSF) to absorb some of the forces of impact. Similarly, study done by Lee et al reported that MF fractures are associated with decreased risk of TBI due to the 'cushioning' effect. Conversely, Davidoff et al. published conflicting results which showed MF fractures to be highly associated with TBI (Macciocchi, Seel, & Thompson, 2013).

Most often patients with mTBI following a MF injury are often not seen by a neuropsychologist and no proper brain assessment are made to evaluate their neuropsychological functional level. Widespread axonal injury disrupts the brain's normal transmission of information and can result in substantial changes in a person's wakefulness. For some unfortunate individual, complications or sequelae of TAI will only show much later after the trauma and it might give a negative impact in their life and environment as it may impair their usual habits and behavioural (Kinnunen et al., 2011).

The primary injury force (direct physical impact or rotational acceleration/deceleration) gives rise to either a focal or diffuse injury which initiates

secondary systemic complications or cellular injury mechanisms leading to cell death, axonal injury, and impaired synaptic plasticity contributing to the cognitive dysfunction observed following a TBI (Ji et al., 2012). The extent of cell death and axonal injury correlate strongly with neurological outcome following brain injury. TBI induced impairments in synaptic plasticity characterized by impaired long-term potentiation (LTP) and enhanced long-term depression (LTD), two well-known molecular mechanisms controlling memory formation; also contribute to cognitive dysfunction particularly in mild TBI where no overt cell loss is detected despite chronic cognitive deficits being observed (Walker & Tesco, 2013).

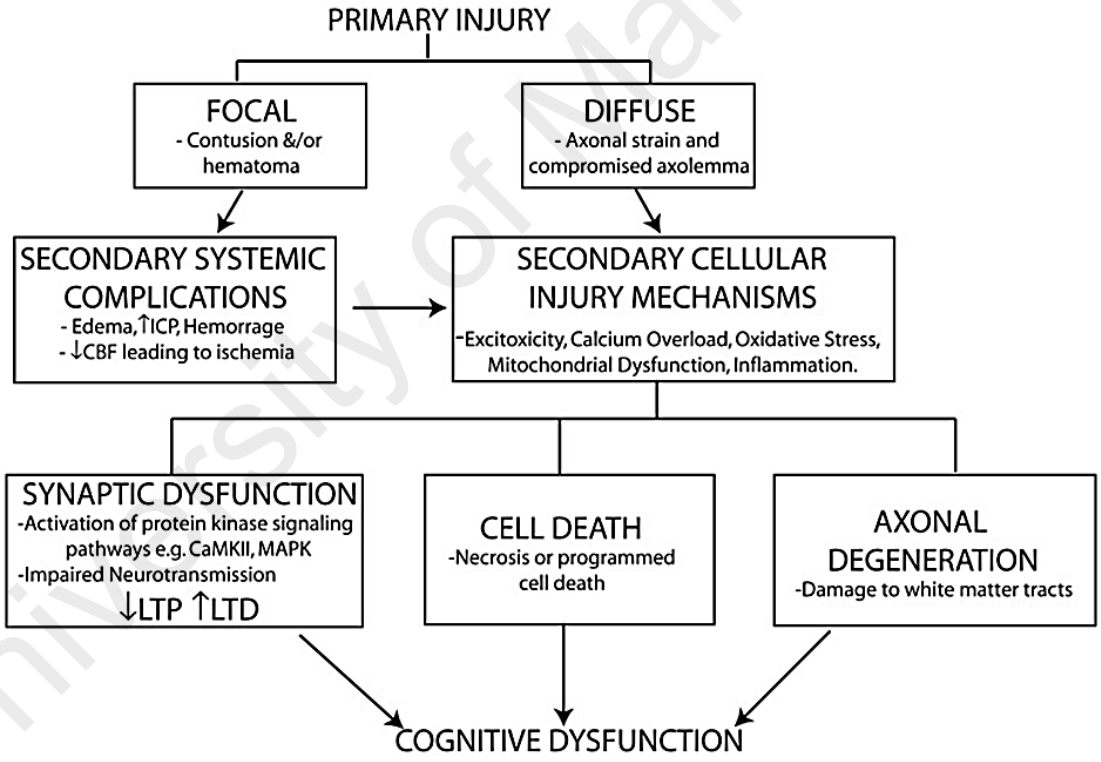

Figure 2.2: Mechanism of mTBI leading to neuropsychiatric disorder

The neuropsychiatric disturbances associated with TBI are numerous. A new classification of the neuropsychiatric sequelae of TBI according to their phenomenology was proposed by Vani and Constantine (2000) is described in Table 2.1.

Table 2.1. Neuropsychiatric sequelae of traumatic brain injury (TBI)
1. Cognitive deficits 2. Mood disorders a) Major depression b) Mania 3. Anxiety disorders 4. Psychosis 5. Apathy 6. Behaviour or dyscontrol disorder a) Major variant b) Minor variant 7. Other a) Sleep disturbances b) Headache

What follows is a discussion of neuropsychiatric disorders. TBI is associated with a plethora of cognitive deficits, some of which are more common than others. They include impairment of visuospatial, attention, memory, language, and executive function. Loss of memory may be for both verbal and nonverbal skills. Disturbances of executive functioning include poor planning, organizing, sequencing, and set-shifting, with impaired judgment and impulse control. The cognitive deficits are caused by the cumulative effects of focal and diffuse brain damage (Gomez-Anson et al., 2015). Cognitive outcome depends on a number of factors, such as degree of diffuse axonal injury, duration of LOC and PTA, clinical evidence of brain stem dysfunction at the time of injury, and presence and size of focal hemispheric injury. Researchers have suggested that cognitive deficits can be divided into four groups according to when they occur in relation to the phases of the TBI. The first two phases will show symptoms such as agitation, confusion, disorientation, and alteration in psychomotor activity. This period is associated with inability to recall events, sequence time, and learn new information which usually last from few days to 1 month and latter, followed by a rapid recovery phase usually from 6 to 24 months. However, the fourth phase is characterized by permanent cognitive sequelae, and includes problems with speed of information-processing, attention and vigilance, short- and long-term memory deficits, verbal and

nonverbal deficits, and problems with executive functions and mental inflexibility. This phase has also been described as "dementia due to head trauma" (Rao & Lyketsos, 2000).

Mood depression in medical literature can be divided into major depression and mania. Major depression occurs in approximately 25% of patients with TBI. Feelings of loss, demoralization, and discouragement seen soon after injury are often followed by symptoms of persistent dysphoria. Fatigue, irritability, suicidal thoughts, anhedonia, disinterest, and insomnia are seen in a substantial number of patients 6–24 months or even longer after TBI. Psychological impairments in excess of the severity of injury and poor cooperation with rehabilitation are strong indicators of a persistent depressive disorder. Mania after TBI is less common than depression but much more common than in the general population. It is seen in about 9% of patients. Changes in mood, sleep, and activation may manifest as irritability, euphoria, insomnia, agitation, aggression, impulsivity, and even violent behaviour (Rao & Lyketsos, 2000).

Besides these, variants of anxiety disorders are commonly seen in TBI patients, including generalized anxiety disorder, panic disorder, phobic disorders, posttraumatic stress disorder, and obsessive–compulsive disorder. TBI patients often experience generalized "free-floating" anxiety associated with persistent worry, tension, and fearfulness. Psychotic symptoms following TBI often manifest as frank delusions, hallucinations, and illogical thinking. They may also be associated with symptoms of agitation, ideas of reference, grimacing, silly giggling, and expression of odd ideas, regression, and impulsive aggressiveness. The psychotic features may be acute or chronic, transient or persistent, and may or may not be associated with mood disturbances.

Apathy refers to a syndrome of disinterest, disengagement, inertia, lack of motivation, and absence of emotional responsively. The negative affect and cognitive

deficits seen in patients with depression are not seen in patients with apathy. Besides these, behaviour dyscontrol disorder - minor variant or post-concussion syndrome (PCS), is the most commonly diagnosed entity following TBI. The syndrome is poorly defined and has been a source of controversy for a number of years. It refers to a cluster of signs and symptoms that often follows mild TBI but can occur with injury of any severity. The final possible sequelae would be TBI patients presenting with a variety of other symptoms, such as sleep disturbances or headaches. Careful evaluation of these patients should be done to ascertain if they are just isolated symptoms or if they are part of a syndrome (Rao & Lyketsos, 2000).

2.5 Neuroimaging of Mild Traumatic Brain Injury

Mild traumatic brain injury (mTBI) constitutes approximately 75–85% of all brain trauma cases. The difficulty in accurately diagnosing mTBI relates to the frequent lack of CT scan evidence to support the diagnosis, which often leads clinicians to diagnose mTBI based on clinical or cognitive symptoms. In studies done by Veeramuthu et al. proved that injuries without any intracranial lesions in mTBI patients increases the risk of short and long-term neurocognitive derangement compared to mTBI patients having positive findings of intracranial lesions. The study was conducted using an advance imaging technique known as Diffusion Tensor Imaging (DTI). The presence of mTBIs usually results from impact or trauma to the brain and can lead to a variety of neuropsychology problems (Veeramuthu et al., 2016).

To date there are very few studies done to identify damage occurring at the axonal level within the white matter of the brain using Diffusion Tensor Imaging (DTI-MR). Traumatic axonal injury (TAI) is shearing and stretching of the nerve cells at the cellular level. It occurs when the brain quickly moves back and forth inside the skull during a MF trauma, tearing and damaging the nerve axons. Usually in the mild form of

impact, identifying any positive evident of TAI in the CT scan images is almost impossible. The structural mapping of neuron networks during health and disease states is essential for understanding brain function. DTI is a recently developed MRI technique that can measure macroscopic axonal organization in nervous system tissues.

The detection of TAI can be done by histological or by using advanced imaging technique. The most widely used and most reliable histological method is the detection of Amyloid Precursor Protein (APP) immunohistochemistry. It is important to emphasize that axonal injury cannot only be caused by trauma but by different mechanisms such as ischemia, hypoglycaemia, inflammation, haemorrhage, drugs, alcohol and even ageing. Therefore, APP immunohistochemistry should be considered to be a sensitive, but not specific marker of axonal injury. On the other hand, diffusion tensor (DT) imaging is a magnetic resonance (MR) imaging technique that is widely used nowadays for the detection of axonal injuries in the brain. In mTBI research, white matter integrity assessment by DTI has been the centre of attention for the last decade (Mori & Zhang, 2006). The success of DTI is deeply rooted in the powerful concept that during their random, diffusion-driven displacements molecules probe tissue structure at a microscopic scale well beyond the usual image resolution. As diffusion is truly a three dimensional process, molecular mobility in tissues may be anisotropic, as in brain white matter. With DTI, diffusion anisotropy effects can be fully extracted, characterized, and exploited, providing even more exquisite details on tissue microstructure (Rijken et al., 2015).

In mTBI, the identification of diffuse damage to the axons in the brain should follow a detailed imaging examination of many parts of the brain which are more susceptible to axonal injury. These include the frontal parasagittal white matter, parietal lobe (including deep white matter), anterior corpus callosum, posterior corpus callosum, basal ganglia (to include the internal capsule), cerebellum (to include middle cerebellar

peduncle) and pons (to include dorsolateral rostral brainstem)(Roberts, Mathias, & Rose, 2016).

White matter fiber tracts traditionally have been classified as follows: Association fibers interconnect cortical areas in each hemisphere. Fibers of this type typically identified on DTI include cingulum, superior and inferior occipitofrontal fasciculi, uncinate fasciculus, superior longitudinal (arcuate) fasciculus, and inferior longitudinal (occipitotemporal) fasciculus. Projection fibers interconnect cortical areas with deep nuclei, brain stem, cerebellum, and spinal cord. There are both efferent (corticofugal) and afferent (corticopetal) projection fibers. Fibers of this type typically identified on DTI include the corticospinal, corticobulbar, and corticopontine tracts, as well as the geniculocalcarine tracts (optic radiations). Commissural fibers interconnect similar cortical areas between opposite hemispheres. Fibers of this type typically identified on DTI include corpus callosum and anterior commissure. Other tracts that are occasionally, but not consistently, identified on directional DTI include optic tract, fornix, tapetum, and many fibers of the brain stem and cerebellum (Duckworth & Stevens, 2010). In this study, we focused on the major tracts that are consistently identified in our practice as depicted in Figure 2.3.

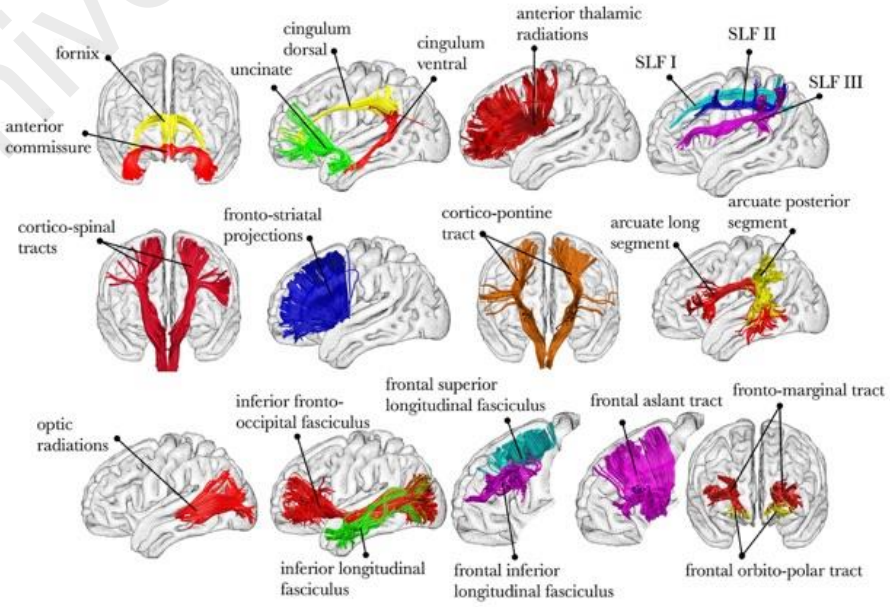

Figure 2.3: Cerebral white matter tracts atlases

Diffusion tensor imaging (DTI) is a development of MRI that provides objective measures of directional water diffusion in space (e.g., fractional anisotropy), which in white matter regions is essentially determined by the integrity of axonal membranes and myelin sheaths (Mori & Zhang, 2006). DTI has been used to detect white matter changes both in the acute and chronic stages of TBI. DTI abnormalities appear to be graded according to the initial severity of TBI and are negatively correlated with neuropsychological performance. By applying the appropriate magnetic field gradients, MR imaging may be sensitized to the random, thermally driven motion (diffusion) of water molecules in the direction of the field gradient. Diffusion is anisotropic (directionally dependent) in white matter fiber tracts, as axonal membranes and myelin sheaths present barriers to the motion of water molecules in directions not parallel to their own orientation. The direction of maximum diffusivity has been shown to coincide with the white matter fiber tract orientation. This information is contained in the diffusion tensor, a mathematic model of diffusion in three-dimensional space (Jang, 2011). In general, a tensor is a rather abstract mathematic entity having specific properties that enable complex physical phenomena to be quantified. In the present context, the tensor is simply a matrix of numbers derived from diffusion measurements in several different directions, from which one can estimate the diffusivity in any arbitrary direction or determine the direction of maximum diffusivity. The overall effect observed in a diffusion MRI image voxel of several mm^3 reflects, on a statistical basis, the displacement distribution of the water molecules present within this voxel. The observation of this displacement distribution may thus provide unique clues to the structure and geometric organization of tissues (Yuh et al., 2014).

DTI measures the movement or diffusion of water molecules within the white matter of the brain, which is normally greatest parallel to nerve fibers (Assaf & Pasternak, 2008). In myelinated axons, the main components (myelin, axonal membrane,

microtubules, and neurofilaments) are all orientated longitudinally, which facilitates diffusion parallel to the length of the axon while hindering diffusion perpendicular to the length of the axon (Beaulieu, 2002). Brain damage that affects the orientation of axons and/or the surrounding myelin sheaths may alter the direction of the diffusion, while also increasing the total amount of diffusion because there are fewer intact structures constraining this movement (Roberts et al., 2016).

Several measures have been developed to capture these changes; some focus on the direction of the diffusion (anisotropy), the most common of which is fractional anisotropy (FA), and others on the amount/rate of diffusion, including the apparent diffusion coefficient (ADC) and mean diffusivity (MD). Specifically, FA measures uniformity in the relative amount of diffusion in different directions, with values ranging between 0 (diffusion is the same in all directions) and 1 (diffusion only occurs only along a single orientation); when FA is large, it is generally assumed that the major direction of diffusion is parallel to the major axon in the voxel (Mueller, Lim, Hemmy, & Camchong, 2015). ADC, on the other hand, measures the amount of diffusion, which is usually averaged over three orthogonal directions (X, Y, Z axes). MD is very similar to the ADC and measures the average of the diffusivity values across the three axes/directions. Indeed, ADC and MD values are similar when obtained from the same scanner, with the two terms often being used interchangeably in the literature. Higher FA and lower ADC/MD values are generally interpreted to indicate white matter integrity, reflecting more consistent ordering of axons, greater myelination, and denser axons (Beaulieu, 2002).

Other metrics include the axial diffusivity (AD), which is the magnitude of diffusion along the fiber orientation within the tract, and radial diffusivity (RD), which is the mean rate of diffusion orthogonal to the fiber orientation. An FA value of zero indicates that the diffusion is uniform in all directions, whereas values approaching unity indicate

that the diffusion is exclusively along a single axis. Healthy, organized, and myelinated white matter tracts tend to have lower ADC values and higher FA values from the myelin sheath, the axolemma, neurofilaments, microtubules, and other longitudinally oriented microstructural elements compared with injured or poorly developed tracts. Generally, with damage to a white matter tract, one expects the ADC/MD to increase due to fewer microstructural elements hindering diffusion and the FA to decrease because fewer longitudinally oriented microstructural elements hindering diffusion orthogonal to the tract (Assaf & Pasternak, 2008).

2.6 Neuropsychological Assessment Battery (NAB) - Screening Module

Neuropsychology is the study of brain-behaviour relationship with the development of a science of human behaviour based on the function of human brain. Clinical neuropsychology is the application of empirically established facts concerning brain-behaviour relationships to clinical problems and neurological assessment, which is sensitive to the condition of the brain. The association of pure MF injury (without concomitant brain injury) and neuropsychological sequel is quite controversial. The objective of this study is to identify whether pure maxillofacial fracture patterns predispose patients to TAI affecting the neurocognitive function. Evaluation of neuropsychological changes in patients with MF injury associated with microstructural changes observed through DTI was done using standardized Neuropsychological Assessment Battery (NAB) - Screening Module.

Assessment process typically includes identifying specific areas of the brain, that have been damaged and demonstrating the relative severity of the patient's cognitive and emotional impairments. Since the issue of causation is often important, it is essential that a variety of confounding or extraneous factors be ruled out so that the relationship between a specific event (e.g., accident, trauma, or fall) and the patient's

neuropsychological impairments may be made as unequivocally clear as possible. Hence, primary goals of all neuropsychological evaluations are, first, to determine an individual's cognitive and behavioural strengths and weaknesses then to interpret the findings from a diagnostic viewpoint, and finally, to recommend viable treatment and rehabilitation resolutions. Neuropsychological procedures also provide a complement to other medical evaluations when used in conjunction with quantitative or functional neuroimaging. This enhances the understanding of pathological disturbances of the brain (Veeramuthu et al., 2015).

There are two distinct strategies of approaching neuropsychological assessment, one is the comprehensive battery approach (also known as the fixed approach), and the other is flexible approach, utilizing a qualitative, hypothesis-testing strategy. Each of these approaches has different strengths and weaknesses. There are number of standardized neuropsychological batteries to evaluate individuals suspected of having brain dysfunction or damage. The important neuropsychological test battery used for this study is Neuropsychological Assessment Battery (NAB). This was designed by Stern and White in 2003 to assess the major five cognitive areas (called "modules") of functioning, i.e., Attention, Language, Memory, Spatial, and Executive functions. A sixth module called the screening module is composed of two or more of the same or abbreviated tests in the other five modules so chosen as to test both high and low ability levels. The battery was developed for flexible use. Each module (including the screening module) can stand alone and norms are provided for individual tests as well.

The Screening – Neuropsychological Assessment Battery (S – NAB) is a comprehensive, modular battery of neuropsychological tests developed for the assessment of a wide array of cognitive skills and functions in adults, aged 18 to 97 years, with known or suspected disorders of the central nervous system. The screening module alone was administered for this study because patients may not be able to

tolerate a lengthier examination. Besides, screening module would be used as an assessment tool to determine whether additional and more in-depth follow-up are necessary. The S - NAB is a comprehensive, co-normed (across all tests) neuropsychological test battery that consists of 12 individual tests designed to assess cognitive functioning across five domains: Attention, Language, Memory, Spatial, and Executive Functioning. The normative sample is large and the coverage of neuropsychological abilities assessed is broad.

The spectrum of cognitive symptoms in MF trauma patients can span various domains, including executive function, language, attention, memory and visuospatial skills. These symptoms may be attributable to the degradation of projection fibers associated with the underlying neurodegenerative process or even disruption of axonal transport contributing to further axonal loss via axonal swelling and disconnection. The primary purpose of this study is to find microstructural alterations which correlate with the impairments across these cognitive domains in MF trauma patients using diffusion tensor imaging (DTI).

CHAPTER 3: METHODOLOGY

3.1 Overview

A prospective study was designed to assess the incidence of intracranial white matter abnormalities in patients who sustained pure maxillofacial fractures during a period of 2 years between January 2016 and January 2018. The study population comprised the patients reporting to the emergency department of Universiti Malaya Medical Centre (UMMC). A case proforma to record the details of each patient including the age, sex, aetiology of injury, type and number of bones fractured in the facial skeleton, types of associated head injury if present was designed and used for each patient. The findings of the computed tomography were also included. The Glasgow Coma Scale (GCS) was used to assess the neurologic status of each of the patients. The patients were then divided into two groups: Group A including patients with MF injury alone and Group B including those as healthy control participants.

3.2 Participants and Study Samples

The study samples was derived from the population of all motor vehicle accident (MVA) victims brought to the Accident & Emergency Department of University Malaya Medical Centre, Kuala Lumpur for the evaluation and management of MF injuries from January 2016 till January 2018. To be included in the study sample, MVA victims had to be referred to the Oral and Maxillofacial Surgery (OMFS) Department. Patients were excluded as study subjects if they had incomplete hospital records or refused to participate.

3.3 Sample Size and Selection of Sample

Our sample consisted of 21 MVA patients with no sign of brain injury. The diagnostic evaluation included a history and physical examination, which was uniformly

accomplished within 24 hours of the patient's admission to the Accident & Emergency Department of UMMC. Our definition of mTBI for the recruitment of the subjects for this study was acute non-penetrating head injury exhibiting: (1) no signs of loss of consciousness (LOC), (2) no post traumatic amnesia (PTA), (3) no transient neurological deficit or post traumatic seizures and (4) presented with Glasgow Coma Scale (GCS) of 13 – 15 upon acute clinical examination. Twenty one (21) aged - matched healthy control participants, with no previous history of head injury, or central nervous system pathology were also recruited in this study. The flow of the study is presented in Figure 3.1.

3.3.1 Inclusion Criterias

The inclusion criterias of subjects being recruited in this study are:

1. Age between 18 – 55 years old
2. Sex (male or female)
3. Mechanism of injury: Motor vehicle traffic accident
4. Glasgow Coma Scale (GCS) upon arrival in Emergency Department should be 13 – 15 (Mild)
7. No other known pre-morbidity (e.g. no psychiatric disorders, hypertension, diabetes)
8. Nationality (Citizen of Malaysia)

3.3.2 Exclusion Criterias

The exclusion criterias are:

1. Age below 18 and/or more than 55 year old
2. Known central nervous system pathology
3. Pre-existing neurologic and psychiatric condition
4. Presence of alcohol and drug abuse

5. Subjects with known non-MRI compatible devices ;e.g. pacemakers, aneurysm clips, heart valve replacements, neuro-stimulators, cochlear implants, metal fragments in the eye, metal foreign bodies, magnetic dental implants and drug infusion pumps
6. Other major trauma that requires urgent surgical intervention under general anaesthesia
7. Previous history of head injury.

3.4 Sources of Data

All subjects' data that were eligible to be recruited in this study were collected using a standardized trauma proforma and was assessed by a single assessor. These data were collected from various hospital sources, including the medical record, trauma registry, health system outpatient database and emergency department database. Among the details tabulated in the proforma were:

(a) Demographic Data – This includes age, ethnicity, gender and level of education. Age was grouped in 4 categories; i) 18 – 29 years, ii) 30 – 39 years, iii) 40 – 49 years, iv) 50 – 55 years. Ethnicity was categorized as i) Malay, ii) Chinese, iii) Indian, iv) Others. Level of education were classified into i) Junior High School, ii) High School, iii) Diploma, iv) Degree.

(b) Trauma Details – This includes date, time of injury, Glasgow Coma Scale (GCS) on admission, presence of retrograde amnesia and loss of consciousness, mechanism of injury, clinical and radiographic investigations and findings and last but not least types and pattern of maxillofacial injuries sustained during trauma. Mechanism of MVA were categorized into i) motorcycle vs motorcycle, ii) motorcycle vs car, iii) car vs car, iv) motorcycle skidded and v) others. Pattern of maxillofacial injuries were divided into hard and soft tissue injuries.

The former was further subdivided based on location in the facial region namely i) upper third, ii) middle third and iii) lower third.

3.5 Study Protocol

The subjects were first examined in the Accident and Emergency Department by the investigators to ensure all criteria is fulfilled. Informed consent was obtained from all subjects. The subject must agree to undergo the diffusion tensor imaging (DTI – MRI)) that lasts about 30 - 40 minutes per session as well as the neuropsychological assessment once they were much stable and comfortable. The healthy control participants were subjected to the same protocols as the patients upon admission (DTI – MRI and neuropsychological assessment).

All subjects meeting criteria for the study underwent computed tomography (CT) scans of the brain using Siemens Somatom Sensation 16 CT scanner (Siemen, AG, Berlin, Germany). The subjects were admitted into the Oral Maxillofacial Surgery ward prior to the procedure to reduce the necessities for transportation and travelling to the hospital, unless they are to be admitted directly from the Accident and Emergency Department depending on the plan from respective team (if the injury includes other region of the body). At the time of image acquisition, it's imperative that the patients were stable to undergo the scan. Any soft tissue wounds were addressed, and if required, temporary wiring for fractures immobilization was fixed. The primary support of airway, breathing and circulation were ensured to be of optimal state. The subjects were able to breathe spontaneously without any airway assistance, with optimum SPO2 of > 95% under room air. The subjects were accompanied by the investigators to the MRI room and throughout the procedure. The subjects were allowed to be discharged thereafter, when no further surgical or medical intervention were required.

The Neuropsychological Assessment Battery – Screening Module (S-NAB) was used for the purpose of neuropsychological evaluation in this study. Five main domains of neurocognitive were evaluated namely – memory, attention, language, spatial reasoning and executive functioning. Magnetic resonance imaging (MRI) and neuropsychological assessments were repeated again at six months post trauma. The healthy control participants were subjected to the same protocols as the patients upon admission (i.e. MRI and neuropsychological assessment).

3.6 Data Analysis Strategies

1. Demographic and clinical characteristics of the study patients and healthy control group.
2. Differences of the diffusion metrics, intergroup and intragroup cerebral white matter microstructural changes over time.
3. Differences of maxillofacial fracture patterns based on location with DTI parameters.
4. Assessment of neuropsychological performance (NP) over time.
5. Associations between DTI parameters and neuropsychological performance.

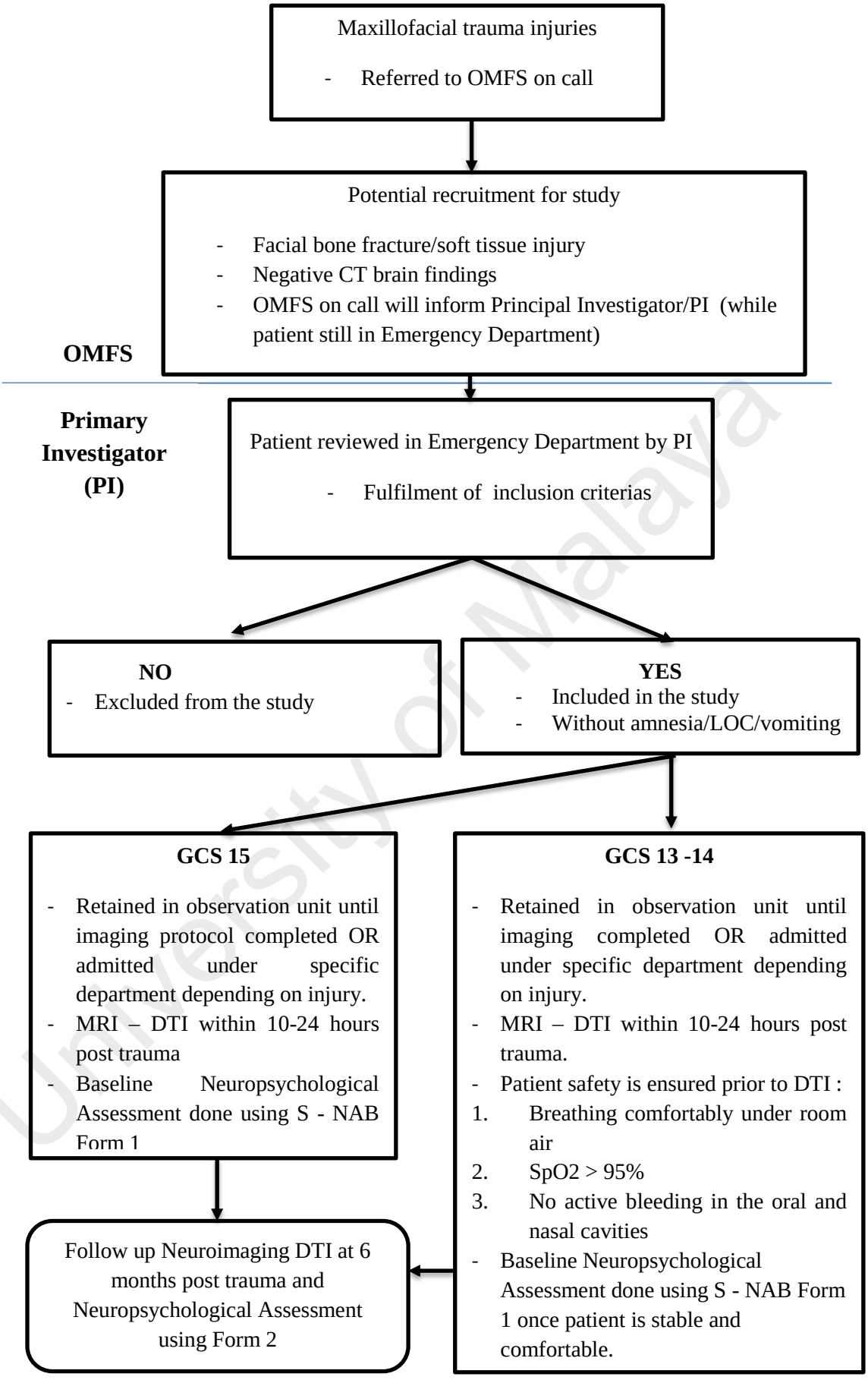

Figure 3.1: Study Protocol in Detail

3.7 MRI Acquisition

All consented subjects will be imaged on a 3T MRI scanner (Signa HDx, General Electric, USA) using an 8 channel head coil. The imaging protocol includes: (a) axial T1-weighted 3D fast spoiled gradient echo (FSPGR), TR = minimum 6.7 ms, TE = minimum 1.9 ms, FOV = 31 mm, matrix = 256 x 256, slice thickness = 1.2 mm, slice overlap =0.6 mm with image scan time of 3 min 48 s, (b) axial T2 weighted fast spin echo (FSE), TR = 4240ms, TE = 102ms, FOV = 24mm, matrix = 512 x 384, thickness = 5mm, spacing = 1.5mm with image scan time of 2mins 30s, (c) coronal gradient echo (GRE), TR = 655 ms, TE = 20ms, flip angle 15^0, bandwidth 31.25, FOV = 24 cm, matrix = 320 x 256, thickness = 5.0mm and spacing = 1.5mm with image scan time of 2mins 7s. The DTI sequence was obtained using these parameters: TR = 13 000 ms, TE = 81.2 ms, FOV = 24 mm, matrix = 128 x 128, slice thickness = 3.0 mm, 32 directions, diffusion-weighted factor, b = 700 s/mm^2 with image scan time of 7 min 22 s.

3.8 Diffusion Tensor Imaging Analysis - Region of Interest (ROI) Analysis

The image processing pipeline consists of pre-processing, image registration, and analysis. In brief, FSL software package (v 5.0.6 University of Oxford, UK) will be used for eddy current correction, skull stripping, and diffusion tensor fitting. DTI-TK (v 2.3.1 University of Pennsylvania, USA) is used to register the DTI data set of each individual subject to match the International Consortium of Brain Mapping (ICBM) DTI-81 atlas. This atlas defines 50 separate white matter tracts in MNI152 space compatible with the FMRIB58_FA target volume used in the previous TBSS registration. The binary intersection of the ICBM atlas and the TBSS mean skeletonization mask was used to obtain mean values of fractional anisotropy (FA), mean diffusivity (MD), radial diffusivity (RD) and axial diffusivity (AD) of the 50

separate skeletonized tracts. ICBM-labels as follow are the list of 50 tracts used by the ICBM JHU white matter atlas shown in Table 3.1.

Table 3.1: White Matter Tracts of Interest Selected for Study

		ICBM White Matter Atlas
1	MCP	Middle cerebellar peduncle
2	PCT	Pontine crossing tract (a part of MCP)
3	GCC	Genu of corpus callosum
4	BCC	Body of corpus callosum
5	SCC	Splenium of corpus callosum
6	FX	Fornix (column and body of fornix)
7	CST-R	Corticospinal tract right
8	CST-L	Corticospinal tract left
9	ML-R	Medial lemniscus right
10	ML-L	Medial lemniscus left
11	ICP-R	Inferior cerebellar peduncle right
12	ICP-L	Inferior cerebellar peduncle left
13	SCP-R	Superior cerebellar peduncle right
14	SCP-L	Superior cerebellar peduncle left
15	CP-R	Cerebral peduncle right
16	CP-L	Cerebral peduncle left
17	ALIC-R	Anterior limb of internal capsule right
18	ALIC-L	Anterior limb of internal capsule left
19	PLIC-R	Posterior limb of internal capsule right
20	PLIC-L	Posterior limb of internal capsule left
21	RLIC-R	Retrolenticular part of internal capsule right
22	RLIC-L	Retrolenticular part of internal capsule left
23	ACR-R	Anterior corona radiata right
24	ACR-L	Anterior corona radiata left
25	SCR-R	Superior corona radiata right
26	SCR-L	Superior corona radiata left
27	PCR-R	Posterior corona radiata right
28	PCR-L	Posterior corona radiata left
29	PTR-R	Posterior thalamic radiation (include optic radiation) right
30	PTR-L	Posterior thalamic radiation (include optic radiation) left
31	SS-R	Sagittal stratum right
32	SS-L	Sagittal stratum left
33	EC-R	External capsule right
34	EC-L	External capsule left
35	CGC-R	Cingulum (cingulate gyrus) right
36	CGC-L	Cingulum (cingulate gyrus) left
37	CGH-R	Cingulum (hippocampus) right
38	CGH-L	Cingulum (hippocampus) left
39	FX/ST-R	Fornix (cres) / Stria terminalis right
40	FX/ST-L	Fornix (cres) / Stria terminalis left

41	SLF-R	Superior longitudinal fasciculus right
42	SLF-L	Superior longitudinal fasciculus left
43	SFO-R	Superior fronto-occipital fasciculus (could be a part of anterior internal capsule) right
44	SFO-L	Superior fronto-occipital fasciculus (could be a part of anterior internal capsule) left
45	IFO-R	Inferior fronto-occipital fasciculus right
46	IFO-L	Inferior fronto-occipital fasciculus left
47	UNC-R	Uncinate fasciculus right
48	UNC-L	Uncinate fasciculus left
49	TAP-R	Tapatum right
50	TAP-L	Tapatum left

3.9 Neurocognitive Assessment

The neurocognitive assessments of the patients were performed using the screening module of Neuropsychological Assessment Battery (S-NAB) Form 1 at admission and S-NAB Form 2 at follow -up by the investigator. The assessments were only performed upon the patient's full GCS recovery with no signs of significant physical or emotional duress. The S-NAB comprises a comprehensive set of neuropsychological tests assessing 5 main neurocognitive domains, with demographically corrected norms for adults between the ages of 18 to 97 years. Five main cognitive domains being assessed are attention, memory, language, visuospatial and executive functions. This battery consists of 12 individual tests across the five domains aforementioned. From these 12 tests, a total of 16 T scores are derived, 14 of which contribute toward five separate Screening Index (domain- specific) scores and one Total Screening Index score. The same subsets were repeated at 6 months by the investigator using the S – NAB Form 2 (Veeramuthu et al., 2016) (Table 3.2).

Table 3.2: List of S – NAB Subtests, Domains Assessed, Standard Score Range and Its Clinical Interpretation (Veeramuthu et al., 2015).

List of S – NAB Module Tests:	Domains Assessed
Screening Orientation	Orientation
Screening Digits Forward	Attention
Screening Digits Backward	Attention / Working Memory
Screening Numbering and Letters	Attention
Screening Shape and Learning Immediate Recognition	Memory
Screening Story Immediate Recall	Memory
Screening Delayed Shape Learning Delayed Recall	Memory
Screening Story Learning Delayed Recall	Memory
Screening Auditory Comprehension (3 subsets)	Language
Screening Naming	Language
Mazes	Executive Function
Screening Word Generation	Executive Function / Verbal
Screening Design Construction	Visuospatial
Screening Visual Discrimination	Visuospatial
Score Clinical Interpretation	**Standard Score Range**
Very Superior	130 – 155
Superior	115 – 129
Above Average	107 – 114
Average	92 – 106
Below Average	85 – 91
Mildly Impaired	77 – 84
Mildly to Moderately Impaired	70 – 76
Moderately – Impaired	62 – 69
Moderately to Severely Impaired	55 – 61
Severely Impaired	45 – 54

3.10 Statistical Analysis

All statistical analyses for the purpose of this study were conducted using the SPSS statistical software, version 23.0. The demographic and clinical characteristics of all study subjects (mTBI vs. healthy controls) were analysed using descriptive statistics. An independent-samples *t*-test was used to establish whether mean values of FA, MD, and RD of selected WM tracts were significantly different between healthy control and mTBI groups during the acute phase (or baseline exam). The same test was also used to investigate whether patients (at admission) performed differently from healthy control participants on the neuropsychological assessment. The patients were classified on the basis of GCS score as mild TBI. A paired *t* – test was used thereafter to observe how

WM tracts changed over time in chronic phase. TBSS skeletonized image of the significant changes observed over time were processed to better visualize any significant changes. Based on the Kolmogrov-Smirnov test, the normality of the distributions for all the tracts of interest was assessed and ascertain. Lastly, Pearson correlation coefficient was used to examine the association between the WM region of interest and neuropsychological performance (NP) over different phases. A *p*-value less or equal to 0.05 was considered to be significant; 95% confidence interval of the estimated parameters was also computed wherever applicable.

CHAPTER 4: RESULTS

4.1 Demographic Data

The demographic characteristic of the study patients and healthy controls are presented in Table 4.1. Overall, 21 subjects who met the inclusion criterias were recruited in the research study and had undergone the acute evaluation of neurocognitive function and MRI-DTI imaging protocol. However, at 6 months post trauma, only 13 subjects participated in their follow – up neuropsychological evaluation and brain imaging. The patients in this study were on average young adult (mean age = 29 years, SD = 8.09) and males predominantly involved as subjects (80.95%). A majority of subjects had GCS of 15 on admission (71.43%).

No statistical difference was found between the groups (pure maxillofacial trauma vs control) with an exception of average years spent on acquiring formal education. The healthy control group were slightly more educated (mean = 15.3 years, SD = 2.8). The average time for full GCS recovery taken by patients during the acute phase was 6 hours (SD = 1.32). Meanwhile, the average duration of time taken to repeat MRI –DTI scan during the chronic phase was 6.25 months (SD = 1.42). Out of the 21 patients, 7 failed to turn up for the follow –up assessment due to loss of interest and 1 patient was dropped during post scan processing because she was wearing orthodontic braces but neuropsychological assessment was done. All healthy controls had no significant neurological findings. A detailed summary of the patients' demographic characteristics and clinical features is presented in Table 4.1.

Table 4.1: Demographic and Clinical Characteristics of Maxillofacial (MF) trauma Patients with Mild Traumatic brain Injury (mTBI).

Characteristic	MF with mTBI (N = 21)		Control Subjects (N = 21)	
	Mean	SD	Mean	SD
Age (years)	29	8.09	30	8.69
Age Category (%)				
Between 18 – 29	66.67		56.25	
Between 30 – 39	28.57		25.00	
Between 40 – 49	0.00		18.75	
Between 50 – 55	4.76		0.00	
Educations (years)	13.0	1.22	15.3	2.80
Gender (% of Male)	80.95		75.00	
Ethnicity (%)				
Malay	66.67		68.75	
Chinese	9.52		6.25	
Indian	19.05		25.00	
Others	4.76		0.00	
Right Handedness (%)	90.48		75.00	
Average Time Taken:				
To Full GCS recovery (hour/s)	6	1.32	n/a	n/a
To Repeat MR Scan (month/s)	6.25	1.42	6.09	0.16
GCS (%)				
GCS 15	71.43		75.00	
GCS 14	23.81		18.75	
GCS 13	4.76		6.25	

Abbreviation: GCS, Glasgow Coma Scale; SD, standard deviation

4.2 Mechanism of Injury

As depicted in Figure 4.1, the mechanisms of MVA identified in this study are skidded motorcycle which contributed the highest percentage (47.6%) followed by motorcycle colliding with another motorcycle (29%), motorcycle colliding with car (0.1%), skidded car (0.1%). and lastly motorcycle colliding with lorry (0.05%).

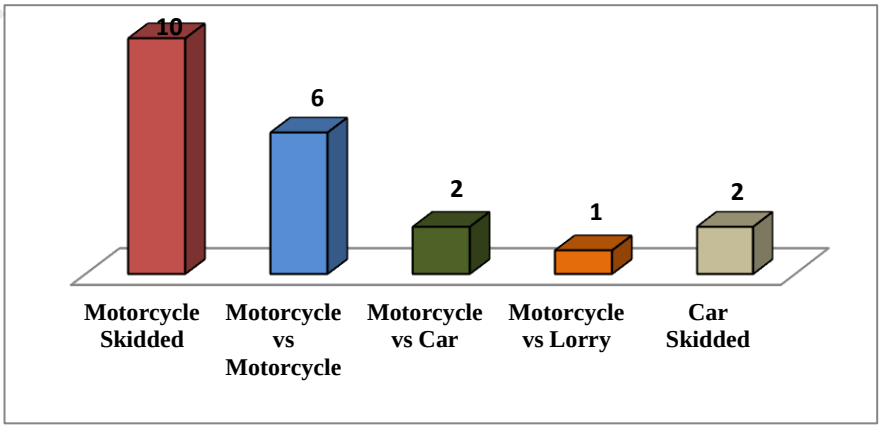

Figure 4.1: Mechanism of Injury Sustained by MF Injury Patients

4.3 Maxillofacial Region of Trauma

Maxillofacial injuries based on constitution and location of the fractures was identified during clinical examination and recorded as depicted in Figure 4.2 and Table 4.2. Based on constitution, hard tissue comprised of the majority of injuries with 76% in comparison with soft tissue injuries (24%). On the other hand, based on location of the facial bone fractures where we have divided facial skeleton into the upper, middle and lower third, the highest incidence of injury was seen in the middle third (57%), followed by lower third (10%) and upper third with 9%.

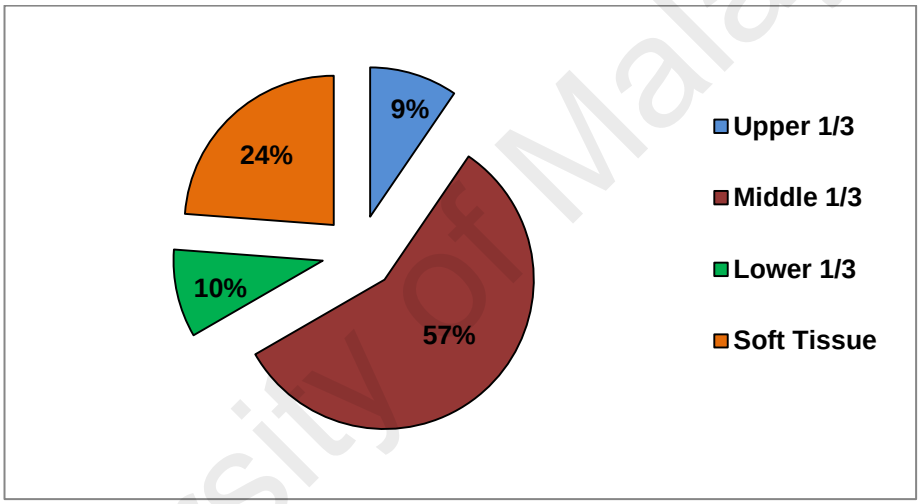

Figure 4.2: Maxillofacial Region of Trauma among the MF Patients

Table 4.2: Distribution of Maxillofacial Fracture Patterns Based on Anatomical Location

Region	Anatomical location	Frequency (%)
Hard Tissue:		
Upper Third	2	9.0
Middle Third	12	57.0
Lower Third	2	10.0
Soft Tissue Injury	5	24.0

4.4 GCS Distribution among the Subjects

Majority of the subjects (n = 15, 71.43%) had full GCS (E4 V5 M6) recorded at the time of admission to the Emergency Department. 5 of the subjects sustained GCS score of 14 (E3 V4 M6) and 1 had score of 13 (E3 V4 M6) (see Figure 4.3). However, there we no loss of consciousness or retrograde amnesia seen in all the patients selected as subjects in this study. Failure to attain a full GCS score was because most of the injuries were sustained within the facial region especially around the periorbital aspects. The swelling and hematoma around the periorbital region contributed the inability for spontaneously eyes opening during examination.

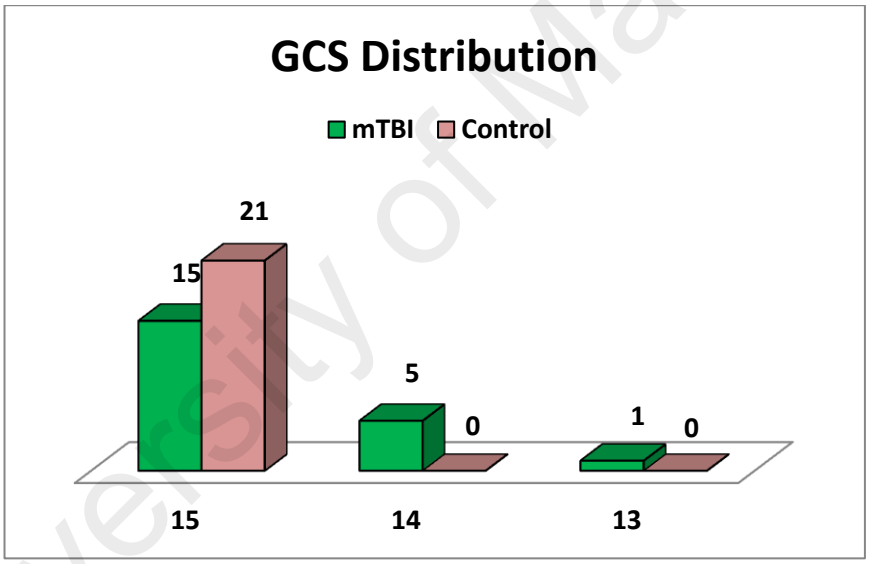

Figure 4.3: Glasgow Coma Scale Score among the MF Patients.

4.5 Analysis of Fractional Anisotrophy (FA) changes in Patients with Pure MF Injury (Acute) and Baseline Scans of Healthy Control

Table 4.3 presents mean FA values of both patients and healthy control participants during the acute phase. Based on the Kolmogorov-Smirnov test, the distributions for FA at baseline were approximately normal with p-value less than 0.05. Thus, the parametric test using Independent *t-test* was used to compare the mean difference between patient and control group. At baseline, patient group showed significantly lower FA values in

24 white matter tracts when compared to the control group. The significant white matter tracts were middle cerebellar peduncle (MCP; $t_{(39)}$ = -13.9, p = <0.001), pontine crossing tract (PCT; $t_{(39)}$ = -5.3, p = <0.001) , body of corpus callosum (BCC; $t_{(39)}$ = -3.7, p = 0.001), corticospinal tract right (CST-R; $t_{(39)}$ = 3.6, p = 0.001), inferior cerebellar peduncle right (ICP – R; $t_{(39)}$ = -26.6, p = <0.001), inferior cerebellar peduncle (ICP – L; $t_{(39)}$ = -16.6, p = <0.001), superior cerebellar peduncle left (SCP – L; $t_{(39)}$ = -2.5, p = 0.017), anterior limb of internal capsule right (CP – L; $t_{(39)}$ = -2.2, p = 0.032), posterior limb of internal capsule left (PLIC – L; $t_{(39)}$ = -2.2, p = 0.032), retrolenticular part of internal capsule right (RLIC – R; $t_{(39)}$ = -3.4, p = 0.001), anterior corona radiata left (ACR – L; $t_{(39)}$ = -4.7, p = <0.001), superior corona radiata right (SCR – R; $t_{(39)}$ = -3.1, p = 0.003), superior corona radiata left (SCR – L; $t_{(39)}$ = -4.6, p = <0.001), posterior corona radiata left (PCR – L; $t_{(39)}$ = -6.6, p = <0.001), sagittal stratum right (SS – R; $t_{(39)}$ = -2.2, p = 0.030), cingulum right (CGC – R; $t_{(39)}$ = -3.8, p = <0.001), cingulum hippocampus left (CGH – L; $t_{(39)}$ = -6.0, p = <0.001), fornix (FX/ST – R; $t_{(39)}$ = -3.6, p = 0.001), fornix left (FX/ST – L; $t_{(39)}$ = -5.3, p = <0.001), superior longitudinal fasciculus right (SLF – R; $t_{(39)}$ = -4.7, p = <0.001), superior fronto – occipital fasciculus right (SFO – R; $t_{(39)}$ = -3.2, p = 0.003), superior fronto – occipital fasciculus left (SFO – L; $t_{(39)}$ = -5.2, p = <0.001), inferior fronto – occipital fasciculus right (IFO – R; $t_{(39)}$ = -2.9, p = 0.005) and tapatum left (TAP – L; $t_{(39)}$ = -18.9, p = <0.001).

There were 4 white matter tracts found to have significantly higher FA values when compared to the control group. Among those were left corticospinal tract (CST – L; $t_{(39)}$ = 2.7, p = 0.010), right superior cerebellar peduncle (SCP – R; $t_{(39)}$ = 2.5, p = 0.016), left retrolenticular part of internal capsule (RLIC – L; $t_{(39)}$ = 2.5, p = 0.019) and left uncinate fasciculus (UNC – L; $t_{(39)}$ = 7.9, p = <0.001). Table below shows the result of the study.

Table 4.3: Differences of Fractional Anisotrophy (FA) between Patients with Pure MF Injury (Acute) and Baseline Scans of Healthy Controls

DTI metrics vs Tracts	*Group*	*n*	*Mean*	*SD*	*p - value*
MCP	mTBI	20	0.50	0.023	<0.001
	Control	21	0.61	0.027	
PCT	mTBI	20	0.48	0.072	<0.001
	Control	21	0.58	0.045	
GCC	mTBI	20	0.73	0.026	0.054
	Control	21	0.75	0.030	
BCC	mTBI	20	0.64	0.040	0.001
	Control	21	0.68	0.026	
SCC	mTBI	20	0.81	0.021	0.050
	Control	21	0.82	0.021	
FX	mTBI	20	0.48	0.065	0.099
	Control	21	0.52	0.073	
CST - R	mTBI	20	0.70	0.039	0.001
	Control	21	0.65	0.042	
CST - L	mTBI	20	0.68	0.052	0.010
	Control	21	0.64	0.048	
ML – R	mTBI	20	0.66	0.063	0.126
	Control	21	0.63	0.049	
ML - L	mTBI	20	0.65	0.065	0.362
	Control	21	0.63	0.036	
ICP – R	mTBI	20	0.28	0.039	<0.001
	Control	21	0.56	0.027	
ICP – L	mTBI	20	0.40	0.034	<0.001
	Control	21	0.57	0.031	
SCP – R	mTBI	20	0.68	0.034	0.016
	Control	21	0.66	0.023	
SCP – L	mTBI	20	0.66	0.043	0.017
	Control	21	0.69	0.034	
CP – R	mTBI	20	0.72	0.029	0.216
	Control	21	0.73	0.020	
CP - L	mTBI	20	0.71	0.021	0.034
	Control	21	0.72	0.032	
ALIC – R	mTBI	20	0.61	0.033	0.109
	Control	21	0.62	0.026	
ALIC – L	mTBI	20	0.60	0.034	0.032
	Control	21	0.62	0.025	
PLIC – R	mTBI	20	0.71	0.023	0.941
	Control	21	0.71	0.029	

PLIC – L	mTBI	20	0.68	0.019	0.032
	control	21	0.70	0.031	
RLIC – R	mTBI	20	0.57	0.029	0.001
	Control	21	0.59	0.022	
RLIC – L	mTBI	20	0.58	0.018	0.019
	Control	21	0.56	0.031	
ACR – R	mTBI	20	0.51	0.034	0.953
	Control	21	0.50	0.033	
ACR – L	mTBI	20	0.49	0.027	<0.001
	control	21	0.54	0.034	
SCR – R	mTBI	20	0.52	0.032	0.003
	Control	21	0.55	0.026	
SCR – L	mTBI	20	0.51	0.025	<0.001
	Control	21	0.55	0.025	
PCR – R	mTBI	20	0.51	0.024	0.772
	Control	21	0.51	0.025	
PCR - L	mTBI	20	0.48	0.027	<0.001
	Control	21	0.54	0.027	
PTR – R	mTBI	20	0.61	0.041	0.145
	Control	21	0.62	0.030	
PTR – L	mTBI	20	0.63	0.026	0.281
	Control	21	0.64	0.041	
SS – R	mTBI	20	0.54	0.038	0.030
	Control	21	0.56	0.027	
SS – L	mTBI	20	0.55	0.029	0.607
	Control	21	0.55	0.034	
EC – R	mTBI	20	0.46	0.023	0.843
	Control	21	0.47	0.021	
EC - L	mTBI	20	0.48	0.022	0.852
	Control	21	0.48	0.017	
CGC – R	mTBI	20	0.54	0.042	<0.001
	Control	21	0.58	0.032	
CGC – L	mTBI	20	0.57	0.041	0.318
	Control	21	0.55	0.037	
CGH –R	mTBI	20	0.51	0.052	0.218
	Control	21	0.53	0.051	
CGH – L	mTBI	20	0.46	0.053	<0.001
	Control	21	0.57	0.057	
FX/ST – R	mTBI	20	0.51	0.042	0.001
	Control	21	0.55	0.027	
FX/ST – L	mTBI	20	0.50	0.032	<0.001
	Control	21	0.55	0.025	

SLF – R	mTBI	20	0.49	0.029	<0.001
	Control	21	0.53	0.026	
SLF – L	mTBI	20	0.51	0.027	0.818
	Control	21	0.50	0.026	
SFO – F	mTBI	20	0.49	0.042	0.003
	Control	21	0.52	0.035	
SFO – L	mTBI	20	0.48	0.053	<0.001
	Control	21	0.55	0.036	
IFO – R	mTBI	20	0.50	0.036	0.005
	Control	21	0.53	0.029	
IFP – L	mTBI	20	0.49	0.032	0.097
	Control	21	0.51	0.030	
UNC – R	mTBI	20	0.60	0.050	0.435
	Control	21	0.59	0.058	
UNC – L	mTBI	20	0.61	0.060	<0.001
	Control	21	0.49	0.037	
TAP – R	mTBI	20	0.63	0.037	0.643
	Control	21	0.63	0.045	
TAP - L	mTBI	20	0.59	0.046	<0.001
	Control	21	0.82	0.027	

SD=standard deviation, DTI=diffusion tensor imaging, mTBI=mild traumatic brain injury

4.6 Analysis of Medial Diffusivity (MD) changes in Patients with Pure MF Injury (Acute) and Baseline Scans of Healthy Control

MD values were found to be significantly higher in 17 white matter tracts when compared to control group. Based on the Kolmogorov-Smirnov test, the distributions for medial diffusivity changes (MD) at baseline were approximately normal with p-value less than 0.05. Thus the parametric test using Independent *t test* was used to compare the mean difference between case and control group. The significant white matter tracts were pontine crossing tract (PCT; $t_{(25)}$ = 4.08, p = <0.001), splenium of corpus callosum (SCC; $t_{(39)}$ = 2.84, p = 0.007), corticospinal tract left (CST – L; $t_{(39)}$ = 2.58, p = 0.014) , anterior limb of internal capsule (ALIC – R; $t_{(39)}$ = 2.80, p = 0.008), posterior limb of internal capsule right (PLIC – R; $t_{(39)}$ = 2.23, p = 0.032), superior

corona radiata right (SCR – R; $t_{(39)}$ = 4.10, p = <0.001), posterior corona radiata right (PCR – R; $t_{(39)}$ = 2.24, p = 0.032), external capsule right (EC – R; $t_{(39)}$ = 2.69, p = 0.011), cingulum right (CGC – R; $t_{(39)}$ = 2.10, p = 0.001), cingulum left (CGC – L; $t_{(39)}$ = 3.52, p = 0.001), cingulum right (CGH – R; $t_{(39)}$ = 3.79, p = 0.001) , cingulum left (CGH – L; $t_{(39)}$ = 3.03, p = 0.004) , superior longitudinal fasciculus right (SLF – R; $t_{(39)}$ = 4.43, p = <0.001), superior longitudinal fasciculus left (SLF – L; $t_{(39)}$ = 4.80, p = <0.001), superior fronto-occipital fasciculus (SFO – R; $t_{(39)}$ = 3.60, p = 0.001), inferior fronto – occipital fasciculus right (IFO – R; $t_{(39)}$ = 3.05, p = 0.004) and inferior fronto – occipital fasciculus left (IFO – L; $t_{(39)}$ = -5.05, p = <0.001).

There were 5 white matter tracts found to have significantly lower MD values when compared to the control group. Among those were uncinate fasciculus left (UNC – L; $t_{(39)}$ = 11.02, p = <0.001), fornix (FX/ST – L; $t_{(39)}$ = -2.87, p = 0.007), external capsule left (EC – L; $t_{(39)}$ = -3.72, p = 0.001), anterior limb of internal capsule left (ALIC – L; $t_{(39)}$ = -2.09, p = 0.044) and superior cerebellar peduncle right (SCP – R; $t_{(39)}$ = -5.58, p = <0.001). Table below shows the result of the study.

Table 4.4: Differences of Medial Diffusivity (MD) Between Patients with Pure MF Injury (Acute) and Baseline scans of Healthy Controls.

DTI metrics vs Tracts	*Group*	*n*	*Mean*	*SD*	*p - value*
MCP	mTBI	20	0.72	0.03	0.056
	Control	21	0.70	0.04	
PCT	mTBI	20	0.90	0.14	<0.001
	Control	21	0.76	0.06	
GCC	mTBI	20	0.80	0.03	0.359
	Control	21	0.81	0.03	
BCC	mTBI	20	0.88	0.04	0.360
	Control	21	0.87	0.02	
SCC	mTBI	20	0.76	0.04	0.007
	Control	21	0.73	0.03	
FX	mTBI	20	1.49	0.27	0.904
	Control	21	1.48	0.29	
CST-R	mTBI	20	0.79	0.08	0.170
	Control	21	0.76	0.06	

CST-L	mTBI	20	0.81	0.09	
	Control	21	0.76	0.05	0.014
ML-R	mTBI	20	0.76	0.07	
	Control	21	0.75	0.05	0.842
ML-L	mTBI	20	0.78	0.05	
	Control	21	0.75	0.07	0.181
ICP-R	mTBI	20	0.74	0.09	
	Control	21	0.75	0.05	0.661
ICP-L	mTBI	20	0.76	0.04	
	Control	21	0.77	0.05	0.413
SCP-R	mTBI	20	0.77	0.05	
	Control	21	0.85	0.06	<0.001
SCP-L	mTBI	20	0.84	0.05	
	Control	21	0.86	0.05	0.181
CP-R	mTBI	20	0.82	0.03	
	Control	21	0.83	0.03	0.368
CP-L	mTBI	20	0.83	0.03	
	Control	21	0.83	0.04	0.791
ALIC-R	mTBI	20	0.80	0.03	
	Control	21	0.77	0.02	0.008
ALIC-L	mTBI	20	0.79	0.02	
	Control	21	0.80	0.02	0.044
PLIC-R	mTBI	20	0.79	0.03	
	Control	21	0.77	0.03	0.032
PLIC-L	mTBI	20	0.80	0.02	
	control	21	0.79	0.03	0.522
RLIC-R	mTBI	20	0.84	0.04	
	Control	21	0.83	0.03	0.136
RLIC-L	mTBI	20	0.85	0.03	
	Control	21	0.83	0.04	0.054
ACR-R	mTBI	20	0.80	0.02	
	Control	21	0.80	0.03	0.494
ACR-L	mTBI	20	0.81	0.03	
	control	21	0.81	0.03	0.922
SCR-R	mTBI	20	0.78	0.02	
	Control	21	0.75	0.02	<0.001
SCR-L	mTBI	20	0.79	0.02	
	Control	21	0.78	0.02	0.708
PCR-R	mTBI	20	0.83	0.04	
	Control	21	0.81	0.02	0.032
PCR-L	mTBI	20	0.84	0.04	
	Control	21	0.82	0.03	0.177
PTR-R	mTBI	20	0.86	0.07	
	Control	21	0.84	0.04	0.126

PTR-L	mTBI	20	0.87 0.84	0.04 0.07	0.100
	Control	21			
SS-R	mTBI	20	0.89 0.87	0.04 0.03	0.217
	Control	21			
SS-L	mTBI	20	0.89 0.88	0.03 0.04	0.208
	Control	21			
EC-R	mTBI	20	0.84 0.82	0.03 0.02	0.011
	Control	21			
EC-L	mTBI	20	0.83 0.86	0.02 0.03	0.001
	Control	21			
CGC-R	mTBI	20	0.78 0.76	0.03 0.03	0.042
	Control	21			
CGC-L	mTBI	20	0.78 0.75	0.03 0.03	0.001
	Control	21			
CGH-R	mTBI	20	0.82 0.74	0.08 0.05	0.001
	Control	21			
CGH-L	mTBI	20	0.83 0.76	0.09 0.06	0.004
	Control	21			
FX/ST-R	mTBI	20	0.84 0.84	0.05 0.03	0.829
	Control	21			
FX/ST-L	mTBI	20	0.85 0.87	0.03 0.03	0.007
	Control	21			
SLF-R	mTBI	20	0.79 0.76	0.03 0.02	<0.001
	Control	21			
SLF-L	mTBI	20	0.79 0.79	0.03 0.03	0.802
	Control	21			
SFO-R	mTBI	20	0.77 0.73	0.03 0.02	<0.001
	Control	21			
SFO-L	mTBI	20	0.77 0.75	0.04 0.04	0.200
	Control	21			
IFO-R	mTBI	20	0.87 0.83	0.03 0.03	0.001
	Control	21			
IFO-L	mTBI	20	0.84 0.86	0.04 0.04	0.100
	Control	21			
UNC-R	mTBI	20	0.85 0.79	0.05 0.08	0.004
	Control	21			
UNC-L	mTBI	20	0.80 0.90	0.07 0.06	<0.001
	Control	21			
TAP-R	mTBI	20	0.89 0.88	0.07 0.07	0.904
	Control	21			
TAP-L	mTBI	20	0.90 0.72	0.06 0.04	<0.001
	Control	21			

SD=standard deviation, DTI=diffusion tensor imaging, mTBI=mild traumatic brain injury

4.7 Analysis of Radial Diffusivity (RD) changes in Patients with Pure MF Injury (Acute) and Baseline Scans of Healthy Controls.

RD values were found to be significantly higher in 26 white matter tracts when compared to control group. Based on the Kolmogorov-Smirnov test, the distributions for radial diffusivity changes (RD) at baseline were approximately normal with p-value less than 0.05. Thus the parametric test using Independent *t test* was used to compare the mean difference between case and control group. Among these significant tracts were middle cerebellar peduncle (MCP; $t_{(39)} = 8.99$, $p = 0.000$), pontine crossing tract (PCT; $t_{(26)} = 5.11$, $p = 0.000$), body of corpus callosum (BCC; $t_{(32)} = 5.22$, $p = 0.006$), splenium of corpus callosum (SCC; $t_{(39)} = 8.99$, $p = 0.000$), inferior cerebellar peduncle right (ICP – R; $t_{(39)} = 6.69$, $p = 0.000$), inferior cerebellar peduncle left (ICP – L; $t_{(39)} = 5.87$, $p = 0.000$), anterior limb of internal capsule right (ALIC – R; $t_{(39)} = 2.31$, $p = 0.027$), posterior limb of internal capsule left (PLIC – L; $t_{(39)} = 2.09$, $p = 0.045$), retrolenticular of internal capsule right (RLIC – R; $t_{(39)} = 3.11$, $p = 0.003$), anterior corona radiata left (ACR – L; $t_{(39)} = 2.97$, $p = 0.005$), superior corona radiata right (SCR – R; $t_{(39)} = 3.99$, $p = 0.000$), superior corona radiata left (SCR – L; $t_{(39)} = 3.35$, $p = 0.002$), posterior corona radiata right (PCR – R; $t_{(39)} = 2.13$, $p = 0.039$), posterior corona radiata left (PCR – L; $t_{(39)} = 3.85$, $p = 0.000$), sagittal stratum (SS – R; $t_{(39)} = 2.37$, $p = 0.023$), external capsule right (EC – R; $t_{(39)} = 2.28$, $p = 0.006$), cingulum right (CGC – R; $t_{(39)} = 4.05$, $p = 0.000$), cingulum hippocampus (CGH – R; $t_{(39)} = 4.01$, $p = 0.000$), cingulum hippocampus left (CGH – L; $t_{(39)} = 6.07$, $p = 0.000$), fornix right (FX/ST – R; $t_{(39)} = 2.69$, $p = 0.010$), fornix left (FX/ST – L; $t_{(39)} = 2.37$, $p = 0.027$), superior longitudinal fasciculus right (SLF – R; $t_{(39)} = 4.97$, $p = 0.000$), superior fronto – occipital fasciculus right (SFO – R; $t_{(39)} = 5.07$, $p = 0.000$), superior fronto – occipital fasciculus left (SFO – L; $t_{(39)} = 4.22$, $p = 0.000$), inferior fronto – occipital fasciculus right (IFO – R; $t_{(39)} = 3.87$, $p = 0.000$), tapatum left (TAP – L; $t_{(39)} = 19.88$, $p = 0.000$).

There were 2 white matter tracts showed lower RD values when compared to control group namely external capsule left (EC – L; $t_{(39)}$ = 2.28, p = 0.006) and uncinate fasciculus left (UNC – L; $t_{(39)}$ = 11.02, p = 0.000) although they were found to be statistically non – significant.

Table 4.5: Difference of Radial Diffusivity (RD) Between Patients with Pure MF Injury (Acute) and Baseline scans of Healthy Controls.

DTI metric vs Tracts	*group*	*n*	*Mean*	*SD*	*p - value*
MCP	mTBI	20	0.51	0.02	0.000
	Control	21	0.42	0.04	
PCT	mTBI	20	0.68	0.14	0.000
	Control	21	0.50	0.06	
GCC	mTBI	20	0.37	0.03	0.410
	Control	21	0.36	0.04	
BCC	mTBI	20	0.49	0.05	0.006
	Control	21	0.45	0.03	
SCC	mTBI	20	0.27	0.04	0.047
	Control	21	0.25	0.04	
FX	mTBI	20	1.10	0.27	0.615
	Control	21	1.05	0.30	
CST-R	mTBI	20	0.40	0.07	0.063
	Control	21	0.44	0.06	
CST-L	mTBI	20	0.43	0.09	0.305
	Control	21	0.45	0.06	
ML-R	mTBI	20	0.42	0.08	0.313
	Control	21	0.44	0.06	
ML-L	mTBI	20	0.44	0.05	0.888
	Control	21	0.44	0.06	
ICP-R	mTBI	20	0.63	0.09	0.000
	Control	21	0.49	0.04	
ICP-L	mTBI	20	0.58	0.05	0.000
	Control	21	0.49	0.04	
SCP-R	mTBI	20	0.41	0.04	0.000
	Control	21	0.48	0.04	
SCP-L	mTBI	20	0.46	0.06	0.429
	Control	21	0.45	0.05	
CP-R	mTBI	20	0.41	0.04	0.711
	Control	21	0.40	0.03	
CP-L	mTBI	20	0.42	0.03	0.329
	Control	21	0.41	0.05	

ALIC-R	mTBI	20	0.48	0.03	
	Control	21	0.46	0.03	0.027
ALIC-L	mTBI	20	0.48	0.03	
	Control	21	0.47	0.03	0.460
PLIC-R	mTBI	20	0.39	0.03	
	Control	21	0.38	0.04	0.379
PLIC-L	mTBI	20	0.43	0.02	
	Control	21	0.41	0.04	0.045
RLIC-R	mTBI	20	0.55	0.04	
	Control	21	0.51	0.03	0.003
RLIC-L	mTBI	20	0.54	0.03	
	Control	21	0.54	0.05	0.556
ACR-R	mTBI	20	0.56	0.03	
	Control	21	0.56	0.04	0.947
ACR-L	mTBI	20	0.57	0.03	
	Control	21	0.54	0.04	0.005
SCR-R	mTBI	20	0.53	0.03	
	Control	21	0.50	0.03	0.000
SCR-L	mTBI	20	0.55	0.02	
	Control	21	0.52	0.03	0.002
PCR-R	mTBI	20	0.58	0.03	
	Control	21	0.56	0.03	0.039
PCR-L	mTBI	20	0.60	0.04	
	Control	21	0.55	0.04	0.000
PTR-R	mTBI	20	0.52	0.07	
	Control	21	0.49	0.04	0.112
PTR-L	mTBI	20	0.50	0.04	
	Control	21	0.48	0.07	0.128
SS-R	mTBI	20	0.60	0.05	
	Control	21	0.57	0.04	0.023
SS-L	mTBI	20	0.59	0.03	
	Control	21	0.58	0.05	0.633
EC-R	mTBI	20	0.61	0.03	
	Control	21	0.59	0.02	0.022
EC-L	mTBI	20	0.59	0.02	
	Control	21	0.61	0.02	0.006
CGC-R	mTBI	20	0.53	0.04	
	Control	21	0.48	0.03	0.000
CGC-L	mTBI	20	0.50	0.04	
	Control	21	0.49	0.04	0.310
CGH-R	mTBI	20	0.59	0.08	
	Control	21	0.51	0.05	0.000
CGH-L	mTBI	20	0.63	0.08	
	Control	21	0.49	0.06	0.000

FX/ST-R	mTBI	20	0.60 0.56	0.05 0.04	0.010
	Control	21			
FX/ST-L	mTBI	20	0.60 0.58	0.03 0.03	0.027
	Control	21			
SLF-R	mTBI	20	0.57 0.52	0.04 0.03	0.000
	Control	21			
SLF-L	mTBI	20	0.55 0.55	0.04 0.03	0.806
	Control	21			
SFO-R	mTBI	20	0.55 0.49	0.03 0.03	0.000
	Control	21			
SFO-L	mTBI	20	0.55 0.49	0.05 0.04	0.000
	Control	21			
IFO-R	mTBI	20	0.61 0.56	0.04 0.03	0.000
	Control	21			
IFO-L	mTBI	20	0.59 0.59	0.04 0.04	0.888
	Control	21			
UNC-R	mTBI	20	0.52 0.48	0.06 0.08	0.135
	Control	21			
UNC-L	mTBI	20	0.47 0.63	0.08 0.06	0.000
	Control	21			
TAP-R	mTBI	20	0.52 0.52	0.06 0.07	0.714
	Control	21			
TAP-L	mTBI	20	0.55 0.25	0.06 0.04	0.000
	Control	21			

SD=standard deviation, DTI=diffusion tensor imaging, mTBI=mild traumatic brain injury

4.8 Paired t-test Analysis of FA, MD and RD Changes (Acute vs. Chronic) in Tracts of Interest

The paired t-test results (FA, MD and RD) of the patients' WM pathway changes as observed at 6 months (chronic phase) against the baseline (acute phase) values are presented in Table 4.6(a), 4.6(b) and 4.6(c). Various differences were seen in all DTI parameters, with greater alterations noted in the FA values across regions. From the test, 3 bundles of tracts showed significant difference with *p*-value less than 0.05. The significant tracts were the left cerebral peduncle (CP – L), left posterior limb of internal capsule (PLIC – L) and left external capsule (EC – L). The mean for baseline FA was

significantly lower compared to the mean of chronic phase for all the significant tracts. Specifically, FA of the left cerebral peduncle (CP – L; $t\ (10) = -2.7$, $p = 0.021$), left posterior limb of internal capsule (PLIC – L; $t\ (10) = -2.7$, $p = 0.023$) and left external capsule (EC – L; $t\ (10) = -2.5$, $p = 0.032$) were significantly lower in the acute phase.

Mean difference of MD in MF patient group at baseline vs post trauma (chronic phase) showed 6 tracts with significant difference with *p*-value less than 0.05. The significant tracts were among body of corpus callosum (BCC), left anterior limb of internal capsule (ALIC – L), left superior corona radiata (SCR – L), left sagittal stratum (SS – L), left superior fronto – occipital fasciculus (SFO – L), and left inferior fronto – occipital fasciculus (IFO – L). The mean for chronic phase was significantly lower compared to the mean of baseline acute phase for all the significant tracts. Among the tracts which showed significant difference were BCC [$t_{(10)} = 2.6$, $p = 0.026$], ALIC – L [$t_{(10)} = 2.6$, $p = 0.028$], SCR – L [$t_{(10)} = 3.8$, $p = 0.003$], SS – L [$t_{(10)} = 3.9$, $p = 0.003$], SFO – L [$t_{(10)} = 3.0$, $p = 0.014$] and IFO – L [$t_{(10)} = 3.5$, $p = 0.006$].

Finally, Table 4.6(c) shows the mean difference of radial diffusivity (RD) changes in the MF patients at baseline against post trauma 6 months follow – up (chronic phase). Based on parametric test using *t-test*, 6 tracts showed significant difference with *p*-value less than 0.05. The significant tracts were among left cerebral peduncle (CP – L; $t_{(10)} = 2.9$, $p = 0.016$), left posterior limb of internal capsule (PLIC – L; $t_{(10)} = 3.0$, $p = 0.014$), left superior corona radiata (SCR – L; $t_{(10)} = 3.3$, $p = 0.008$), left external capsule (EC – L; $t_{(10)} = 4.0$, $p = 0.003$), left superior fronto – occipital fasciculus (SFO – L; $t_{(10)} = 2.5$, $p = 0.034$) and left inferior fronto – occipital fasciculus (IFO –L; $t_{(10)} = 3.0$, $p = 0.013$). The mean for chronic phase was significantly lower compared to the mean of acute phase for all the significant pairs.

Table 4.6(a): Paired *t* – test Analysis of Fractional Anisotrophy (FA) Changes (Acute vs. Chronic) in Tracts of Interest

Acute vs Chronic Phase	Mean difference	95% Confidence Interval of the Difference		t	df	p-value
		Lower	Upper			
MCP	0.007	-0.007	0.021	1.1	10	0.287
PCT	-0.016	-0.068	0.035	-0.7	10	0.496
GCC	-0.005	-0.019	0.009	-0.8	10	0.432
BCC	0.004	-0.014	0.021	0.5	10	0.629
SCC	-0.003	-0.016	0.011	-0.4	10	0.669
FX	0.008	-0.014	0.030	0.8	10	0.441
CST-R	-0.017	-0.049	0.015	-1.2	10	0.274
CST-L	-0.019	-0.048	0.009	-1.5	10	0.155
ML-R	-0.010	-0.056	0.036	-0.5	10	0.641
ML-L	-0.013	-0.068	0.042	-0.5	10	0.605
ICP-R	-0.010	-0.048	0.029	-0.6	10	0.586
ICP-L	0.005	-0.012	0.021	0.6	10	0.554
SCP-R	0.009	-0.011	0.029	1.0	10	0.323
SCP-L	-0.016	-0.038	0.005	-1.7	10	0.125
CP-R	-0.001	-0.020	0.018	-0.1	10	0.908
CP-L	-0.010	-0.017	-0.002	-2.7	10	0.021
ALIC-R	-0.001	-0.015	0.013	-0.2	10	0.866
ALIC-L	-0.009	-0.028	0.010	-1.0	10	0.320
PLIC-R	0.007	-0.005	0.019	1.3	10	0.214
PLIC-L	-0.016	-0.029	-0.003	-2.7	10	0.023
RLIC-R	0.001	-0.019	0.021	0.1	10	0.923
RLIC-L	-0.010	-0.022	0.002	-1.9	10	0.087
ACR-R	-0.003	-0.016	0.010	-0.5	10	0.608
ACR-L	0.000	-0.013	0.013	0.0	10	1.000
SCR-R	0.006	-0.005	0.016	1.2	10	0.262
SCR-L	-0.009	-0.019	0.001	-2.1	10	0.062
PCR-R	0.005	-0.011	0.021	0.7	10	0.489
PCR-L	0.005	-0.009	0.019	0.8	10	0.423
PTR-R	-0.010	-0.023	0.003	-1.7	10	0.128
PTR-L	-0.010	-0.021	0.002	-1.8	10	0.097
SS-R	-0.002	-0.020	0.016	-0.3	10	0.807
SS-L	-0.004	-0.023	0.015	-0.5	10	0.644
EC-R	-0.003	-0.019	0.013	-0.5	10	0.655
EC-L	-0.012	-0.022	-0.001	-2.5	10	0.032
CGC-R	0.018	-0.009	0.033	1.3	10	0.238
CGC-L	-0.004	-0.020	0.013	-0.5	10	0.619

CGH-R	-0.018	-0.088	0.053	-0.6	10	0.591
CGH-L	-0.010	-0.041	0.022	-0.7	10	0.518
FX/ST-R	0.008	-0.023	0.038	0.5	10	0.596
FX/ST-L	-0.001	-0.021	0.019	-0.1	10	0.929
SLF-R	0.002	-0.012	0.015	0.2	10	0.818
SLF-L	-0.004	-0.019	0.011	-0.6	10	0.560
SFO-R	0.003	-0.026	0.032	0.2	10	0.831
SFO-L	-0.022	-0.054	0.009	-1.6	10	0.149
IFO-R	0.004	-0.009	0.017	0.7	10	0.507
IFO-L	-0.008	-0.018	0.002	-1.7	10	0.119
UNC-R	0.003	-0.038	0.044	0.2	10	0.858
UNC-L	-0.005	-0.034	0.024	-0.4	10	0.723
TAP-R	0.005	-0.020	0.030	0.5	10	0.657
TAP-L	-0.006	-0.028	0.016	-0.6	10	0.563

Table 4.6(b): Paired *t* – test Analysis of Medial Diffusivity (MD) Changes (Acute vs. Chronic) in Tracts of Interest

Acute vs Chronic Phase	*Mean*	*95% Confidence Interval of the Difference*		*t*	*df*	*p-value*
		Lower	*Upper*			
MCP	0.015	-0.006	0.035	1.6	10	0.144
PCT	0.043	-0.029	0.115	1.3	10	0.211
GCC	0.007	-0.014	0.029	0.7	10	0.474
BCC	0.017	0.002	0.032	2.6	10	0.026
SCC	0.013	-0.012	0.037	1.2	10	0.276
FX	-0.037	-0.080	0.007	-1.9	10	0.088
CST-R	0.029	-0.032	0.089	1.1	10	0.314
CST-L	0.023	-0.001	0.048	2.1	10	0.058
ML-R	-0.016	-0.053	0.022	-0.9	10	0.382
ML-L	-0.021	-0.074	0.032	-0.9	10	0.398
ICP-R	0.009	-0.097	0.115	0.2	10	0.852
ICP-L	0.003	-0.017	0.023	0.4	10	0.715
SCP-R	-0.021	-0.054	0.012	-1.4	10	0.188
SCP-L	0.032	-0.013	0.077	1.6	10	0.146
CP-R	0.010	-0.022	0.041	0.7	10	0.506
CP-L	0.023	-0.007	0.052	1.7	10	0.115
ALIC-R	0.011	-0.008	0.031	1.3	10	0.226
ALIC-L	0.029	0.004	0.054	2.6	10	0.028
PLIC-R	-0.006	-0.023	0.011	-0.8	10	0.461
PLIC-L	0.031	0.011	0.052	3.4	10	0.007
RLIC-R	-0.008	-0.031	0.015	-0.8	10	0.449

RLIC-L	0.008	-0.017	0.033	0.7	10	0.515
ACR-R	0.013	-0.010	0.037	1.3	10	0.224
ACR-L	0.011	-0.008	0.029	1.3	10	0.219
SCR-R	0.000	-0.010	0.010	0.0	10	0.984
SCR-L	0.027	0.011	0.043	3.8	10	0.003
PCR-R	-0.008	-0.025	0.009	-1.1	10	0.295
PCR-L	-0.006	-0.034	0.021	-0.5	10	0.614
PTR-R	0.024	-0.019	0.067	1.2	10	0.244
PTR-L	0.008	-0.008	0.024	1.1	10	0.297
SS-R	0.013	-0.010	0.036	1.3	10	0.239
SS-L	0.020	-0.002	0.041	2.1	10	0.067
EC-R	0.005	-0.012	0.022	0.7	10	0.516
EC-L	0.028	0.012	0.045	3.9	10	0.003
CGC-R	-0.004	-0.031	0.023	-0.3	10	0.749
CGC-L	0.005	-0.016	0.026	0.6	10	0.581
CGH-R	-0.006	-0.130	0.118	-0.1	10	0.914
CGH-L	0.011	-0.045	0.068	0.4	10	0.668
FX/ST-R	-0.007	-0.038	0.025	-0.5	10	0.655
FX/ST-L	0.002	-0.028	0.032	0.1	10	0.896
SLF-R	-0.002	-0.012	0.008	-0.5	10	0.610
SLF-L	0.001	-0.018	0.020	0.1	10	0.902
SFO-R	0.007	-0.019	0.033	0.6	10	0.562
SFO-L	0.043	0.011	0.075	3.0	10	0.014
IFO-R	0.007	-0.013	0.027	0.8	10	0.454
IFO-L	0.032	0.012	0.053	3.5	10	0.006
UNC-R	0.012	-0.038	0.062	0.5	10	0.611
UNC-L	0.033	-0.015	0.081	1.5	10	0.156
TAP-R	-0.019	-0.059	0.021	-1.1	10	0.311
TAP-L	0.013	-0.031	0.058	0.7	10	0.524

Table 4.6(c): Paired *t* – test Analysis of Radial Diffusivity (RD) Changes (Acute vs. Chronic) in Tracts of Interest

Acute vs Chronic Phase	*Mean difference*	*95% Confidence Interval of the Difference*		*t*	*df*	*p-value*
		Lower	*Upper*			
MCP	0.013	-0.004	0.029	1.7	10	0.115
PCT	0.042	-0.027	0.112	1.4	10	0.200
GCC	0.008	-0.014	0.030	0.8	10	0.429
BCC	0.005	-0.014	0.025	0.6	10	0.559
SCC	0.007	-0.020	0.034	0.6	10	0.578

FX	-0.033	-0.082	0.016	-1.5	10	0.159
CST-R	0.033	-0.023	0.089	1.3	10	0.217
CST-L	0.028	-0.006	0.062	1.8	10	0.095
ML-R	-0.010	-0.051	0.030	-0.6	10	0.588
ML-L	-0.013	-0.071	0.046	-0.5	10	0.635
ICP-R	0.014	-0.086	0.114	0.3	10	0.768
ICP-L	-0.001	-0.021	0.019	-0.1	10	0.945
SCP-R	-0.018	-0.049	0.014	-1.3	10	0.234
SCP-L	0.034	-0.006	0.074	1.9	10	0.088
CP-R	0.006	-0.024	0.037	0.5	10	0.653
CP-L	0.022	0.005	0.039	2.9	10	0.016
ALIC-R	0.009	-0.011	0.028	1.0	10	0.358
ALIC-L	0.024	-0.001	0.050	2.1	10	0.058
PLIC-R	-0.008	-0.025	0.009	-1.1	10	0.296
PLIC-L	0.029	0.007	0.050	3.0	10	0.014
RLIC-R	-0.004	-0.025	0.016	-0.5	10	0.650
RLIC-L	0.012	-0.010	0.033	1.2	10	0.251
ACR-R	0.011	-0.009	0.030	1.2	10	0.240
ACR-L	0.007	-0.011	0.024	0.9	10	0.407
SCR-R	-0.003	-0.013	0.007	-0.7	10	0.521
SCR-L	0.023	0.007	0.039	3.3	10	0.008
PCR-R	-0.009	-0.027	0.010	-1.1	10	0.314
PCR-L	-0.008	-0.034	0.018	-0.7	10	0.523
PTR-R	0.022	-0.012	0.056	1.5	10	0.175
PTR-L	0.012	-0.004	0.028	1.7	10	0.118
SS-R	0.012	-0.015	0.038	1.0	10	0.353
SS-L	0.019	-0.002	0.041	2.0	10	0.070
EC-R	0.006	-0.012	0.025	0.7	10	0.472
EC-L	0.027	0.012	0.042	4.0	10	0.003
CGC-R	-0.007	-0.036	0.021	-0.6	10	0.586
CGC-L	0.007	-0.014	0.027	0.7	10	0.480
CGH-R	0.000	-0.122	0.121	0.0	10	0.995
CGH-L	0.017	-0.028	0.063	0.9	10	0.414
FX/ST-R	-0.005	-0.044	0.034	-0.3	10	0.789
FX/ST-L	0.004	-0.019	0.027	0.4	10	0.688
SLF-R	-0.002	-0.014	0.010	-0.4	10	0.724
SLF-L	0.003	-0.016	0.023	0.4	10	0.717
SFO-R	0.005	-0.026	0.035	0.3	10	0.746

SFO-L	0.039	0.004	0.074	2.5	10	0.034
IFO-R	0.002	-0.019	0.023	0.2	10	0.835
IFO-L	0.027	0.007	0.046	3.0	10	0.013
UNC-R	0.007	-0.052	0.067	0.3	10	0.791
UNC-L	0.023	-0.025	0.071	1.1	10	0.307
TAP-R	-0.012	-0.049	0.025	-0.7	10	0.488
TAP-L	0.013	-0.027	0.053	0.7	10	0.479

4.9 Neuropsychological Performance

Table 4.7 presents the mean interpretive categories standard score comparison for the domain specific NP among mTBI and healthy control. During the acute phase, MF patients performed poorly across the attention and executive function domains in comparison to the healthy control. The independent samples *t-tests* of both groups and their NPs indicated that the mTBI group was significantly better (p-values > 0.05) on all but one of the neurocognitive domains (executive functions: $t\ (40) = -2.7$, $p = 0.008$).

Meanwhile during the chronic phase, MF patients performed poorly across the language and executive function domains in comparison to the healthy control in exception of memory: $t\ (32) = 2.3$, $p = 0.027$ and visuospatial function: $t\ (32) = -0.8$, $p = 0.032$) where the MF patients outperformed healthy controls.

Table 4.7: Mean of S – NAB Interpretive Categories Score at Acute and Chronic Phase of Both Patients and Controls and Intergroup Differences (Independent t- test) in Domain – Specific Neuropsychological Performance.

Domains	*Group*	*Acute*				*Chronic*			
		n	***Mean ± SD***	***t (df)***	***p-value***	***n***	***Mean ± SD***	***t (df)***	***p-value***
Attention	mTBI	21	83.85 ± 13.45	-2.0(40)	0.050	13	94.54 ±14.15	0.7 (32)	0.461
	Control	21	91.38 ± 10.50			21	91.38 ± 10..50		
Language	mTBI	21	102.81 ± 26.43	0.6(40)	0.514	13	96.85 ± 26.32	-0.05 (32)	0.963
	Control	21	97.29 ± 27.93			21	97.29 ± 27.93		
Memory	mTBI	21	95.00 ± 19.09	0.03(40)	0.977	13	106.23 ± 17.25	2.3 (32)	0.027
	Control	21	94.86 ± 11.44			21	94.86 ± 11.44		

Spatial	mTBI	21	101.62 ± 13.03	1.9(40)	0.061	13	104.23 ± 13.87	2.2 (32)	0.032
	Control	21	94.19 ± 11.97			21	94.19 ± 11.97		
Executive	mTBI	21	79.05 ± 12.17	-2.7(40)	0.008	13	85.38 ± 13.31	-0.8 (32)	0.402
	Control	21	88.95 ± 10.98			21	88.95 ± 10.98		
Overall	mTBI	21	88.67 ± 17.47	-0.4(40)	0.714	13	96.31 ± 21.01	0.9 (32)	0.378
	Control	21	90.43 ± 13.20			21	90.43 ± 13.20		

Abbreviation: S-NAB, Neuropsychological Assessment Battery Screening; SS=standard score; Ctrl=control; SD=standard deviation.

Table 4.8 presents the mean interpretive standard score comparison for the neurocognitive performances among MF patients during acute and chronic phase. Almost all of the domains showed relatively higher mean scores during chronic phase in comparison to the acute phase. Based on parametric test using Independent *t - test*, 3 domains showed a significant differences namely the attention ($t_{(12)}$ = -3.8, p = 0.01), memory ($t_{(12)}$ = -2.1, p = 0.05), executive domains ($t_{(12)}$ = -2.3, p = 0.04) and overall ($t_{(12)}$ = -2.1, p = 0.05).

Table 4.8: Mean Differences of S – Nab Domain Specific Standard Score (SS) among Pure MF Injury Patients (Acute) at Baseline and Follow –up (Chronic).

Domains	*Mean ± SD*	*t (df)*	*p – value*
Attention (Acute)	81.84 ± 14.24	-3.8 (12)	0.01
Attention (Chronic)	94.54 ± 14.15		
Language (Acute)	98.69 ± 28.05	0.2 (12)	0.80
Language (Chronic)	96.84 ± 26.32		
Memory (Acute)	93.92 ± 21.28	-2.1 (12)	0.05
Memory (Chronic)	106.23 ± 17.25		
Spatial (Acute)	100.69 ± 14.48	-0.8 (12)	0.42
Spatial (Chronic)	104.23 ± 13.87		
Executive (Acute)	75.77 ± 12.41	-2.3 (12)	0.04
Executive (Chronic)	85.38 ± 13.31		
Overall (Acute)	85.38 ± 18.97	-2.1 (12)	0.05
Overall (Chronic)	96.31 ± 21.01		

SD=standard deviation

4.10 Association between Diffusion Tensor Imaging Parameters and Neuropsychological Performances.

Longitudinal analysis of WM tract changes against the NP at different intervals among a subset of study patients are presented in Table 4.9. Most of the observed FA associations with neuropsychological status (acute and chronic) represented in negative values. Acute FA (FA_a) negatively correlated with the following baseline neuropsychological indices ($NP_{a)}$: language versus BCC (r = -0.447*;* $p < 0.05$), memory versus ML – L (r = -0.161*;* $p < 0.05$), language versus CGC – R (r = -0.506*;* $p < 0.05$), language versus CGC – L (r = -0.501*;* $p < 0.05$), executive function versus CGH – R (r = 0.489*;* $p < 0.05$), language versus SLF – R(r = - 0.476*;* $p < 0.05$), overall versus TAP – L(r = 0.451*;* $p < 0.05$). FA_a were positively correlated with post trauma neuropsychological indices (NP_c) as follows; attention versus ALIC –R(r = 0.667*;* $p < 0.05$) and attention versus ALIC – L(r = 0.664*;* $p < 0.05$). Chronic FA (FA_c) had 7 associations with NP_a; attention versus GCC (r = 0.588*;* $p < 0.05$), language versus SCC(r = -0.641*;* $p < 0.05$), visuospatial versus CST – L(r = 0.772; $p < 0.01$), attention

versus SCP – L(r = -0.593*; p < 0.05), memory versus SS – R (r = 0.804; p < 0.01), memory versus SLF – L(r = 0.638*; p < 0.05) and visuospatial versus TAP – R(r = 0.589*; p < 0.05). The significantly reduced FA_c had many associations with the NP_c: attention versus GCC (r = 0.877*; p < 0.05), executive versus GCC (r = 0.856*; p < 0.05), overall versus GCC (r = 0.630*; p < 0.05), attention versus FX (r = 0.701*; p < 0.05), executive versus FX (r = 0.634*; p < 0.05), language versus ML – R (r = -0.650*; p < 0.05), language versus SCP – R (r = -0.674*; p < 0.05), executive versus SCP – R (r = -0.668*; p < 0.05), attention versus ALIC – R (r = 0.750, p < 0.01), memory versus ALIC – R (r = 0.662*; p < 0.05), executive versus ALIC – R (r = 0.695*; p < 0.05), attention versus ALIC – L (r = 0.720, p < 0.01), executive versus ALIC – L (r = 0.790, p < 0.01), executive versus PLIC – L(r = 0.613*; p < 0.05), executive versus ACR – R(r = 0.614*; p < 0.05), attention versus ACR – L(r = 0.623*; p < 0.05), memory versus ACR – L(r = 0.633*; p < 0.05), overall versus ACR – L(r = 0.645*; p < 0.05), executive versus ACR – L(r = 0.823; p < 0.01).

MD_a showed few associations with the NP_a namely visuospatial versus SCP – R (r = -0.464*; p < 0.05), executive versus SCP – R (r = -0.502*; p < 0.05), memory versus CP – L (r = -0.573 *; p < 0.01), overall versus CP – L (r = -0.530*; p < 0.05), language versus SLF – R (r = 0.471*; p < 0.05), attention versus SFO – L (r = -0.685; p < 0.01), overall versus SFO – L (r = -0.550*; p < 0.05), attention versus IFO – R (r = -0.548*; p < 0.05) and executive versus UNC – L (r = -0.454*; p < 0.05). The following were the only MD_a values associated with the $NP_{c:}$ visuospatial versus SFO – L (r = -0.769; p < 0.01), visuospatial versus UNC – L (r = -0.650*; p < 0.05) and overall versus UNC – L (r = -0.560*; p < 0.05). Additional associations were subsequently observed between MD_c and NP_a which were as follow: visuospatial versus ACR – L (r = 0.638*; p < 0.05), memory versus SS – R (r = -0.582*; p < 0.05), memory versus FX/ST – R (r = -0.594*; p < 0.05), visuospatial versus SFO – R (r = 0.648*; p < 0.05) and memory versus IFO – R (r = -

0.701*; p* < 0.05). Increased MD_c values were also associated with some domains of the NP_c including attention versus FX (*r* = -0.617*; p* < 0.05), attention versus ACR – L (*r* = -0.640*; p* < 0.05), executive versus EC – R (*r* = -0.588*; p* < 0.05) and language versus IFO – L (*r* = -0.719; *p* < 0.01).

The RD studied was significantly associated with attention, language, memory, executive and visuospatial in both phases of the study. Specifically, RD_a was associated with six NP_a scores: language versus BCC (*r* = 0.481*; p* < 0.05), memory versus FX (*r* = 0.529*; p* < 0.05), memory versus ML – L (*r* = 0.468*; p* < 0.05), language versus CGC – L (*r* = 0.509*; p* < 0.05), language versus SLF – R (*r* = 0.541*; p* < 0.05) and attention versus SFO – L (*r* = -0.574; *p* < 0.01). Additional associations were subsequently observed between RD_a and NP_c which were as follows: attention versus ALIC – R (*r* = -0.602*; p* < 0.05), executive versus ALIC – R (*r* = -0.680*; p* < 0.05), attention versus SCR – L (*r* = 0.589*; p* < 0.05), overall versus SCR – L (*r* = 0.587*; p* < 0.05), visuospatial versus SFO – L (*r* = -0.593*; p* < 0.05) and executive versus UNC – L (*r* = -0.566*; p* < 0.05). Increased RD_c values were associated with NP_a as follow: visuospatial versus CST – L (*r* = -0.591*; p* < 0.05), attention versus SCP – L (*r* = 0.603*; p* < 0.05), language versus SCP – L (*r* = 0.603*; p* < 0.05), executive versus SCR – L (*r* = -0.578*; p* < 0.05), memory versus SS – R (*r* = -0.763*; p* < 0.01), memory versus FX/ST – R (*r* = -0.600*; p* < 0.05), language versus FX/ST – L (*r* = 0.600*; p* < 0.05), memory versus SFO – R (*r* = 0.688*; p* < 0.05) and memory versus IFO – R (*r* = -0.633*; p* < 0.05). Lastly, association of RD_c with values of NP_c are as follows: attention versus GCC (*r* = -0.898; *p* < 0.01), executive versus GCC (*r* = -0.760; *p* < 0.01), overall versus GCC (*r* = -0.626*; p* < 0.05), overall versus FX (*r* = -0.652*; p* < 0.05), executive versus SCP – R (*r* = 0.715; *p* < 0.01), executive versus CP – L (*r* = -0.608*; p* < 0.05), memory versus ALIC – R (*r* = -0.624*; p* < 0.05), executive versus ALIC – R (*r* = -0.631*; p* < 0.05), attention versus ALIC – R (*r* = -0.766; *p* < 0.01), attention versus ALIC – L (*r* = -0.686*;*

$p < 0.05$), executive versus ALIC – L ($r = -0.803$; $p < 0.01$), executive versus PLIC – L ($r = -0.637$; $p < 0.05$), executive versus ACR – R ($r = -0.658$; $p < 0.05$), attention versus ACR – L ($r = -0.698$; $p < 0.05$), overall versus ACR – L ($r = -0.595$; $p < 0.05$), executive versus ACR – L ($r = -0.793$; $p < 0.05$), memory versus EC – R ($r = -0.614$; $p < 0.05$), overall versus EC – R ($r = -0.594$; $p < 0.05$), memory versus EC – L ($r = -0.591$; $p < 0.05$), executive versus EC – L ($r = -0.611$; $p < 0.05$), overall versus EC – L ($r = -0.709$; $p < 0.05$), memory versus FX/ST – R ($r = -0.600$; $p < 0.05$), memory versus IFO – R ($r = -0.674$; $p < 0.05$) and overall versus IFO – R ($r = -0.644$; $p < 0.05$). No association was found between domain of visuospatial and FA values in the chronic phase. MD values were also not associated with memory domain during the chronic phase. Lastly, no correlation found between domain of language and RD values in the chronic phase. (Kindly refer to Table 4.9).

Table 4.9: Pearson Correlation of Neuropsychological Performance against Changes in FA, MD, and RD of the Various Brain Tracts Both at Acute and Chronic Phase.

DTI Metrics	*White Matter tracts of Interest*	*Acute*					*Chronic*				
		Attention	*Language*	*Memory*	*Visuospatial*	*Executive*	*Attention*	*Language*	*Memory*	*Visuospatial*	*Executive*
FA	BCC (acute)		-0.447*								
	ML – L (acute)			-0.161*							
	CGC – R (acute)		-0.506*								
	CGC – L (acute)		-0.501*								
	CGH – R (acute)					0.489*					
	SLF – R (acute)		-0.476*								
	SLF – L (chronic)			0.638*							
	ALIC – R (acute)						0.667*				
	ALIC - R (chronic)						0.750†		0.662*		0.695*
	ALIC – L (acute)						0.664*				
	ALIC - L (chronic)						0.720†				0.790†
	GCC (chronic)	0.588*					0.877*				0.856†
	SCC (chronic)		-0.641*								
	CST (chronic)				0.772†						
	SCP – L (chronic)	-0.593*									
	SS – R (chronic)			0.804†							
	TAP – R (chronic)				0.589*						
	FX (chronic)						0.701*				0.634*
	ML – R (chronic)							-0.650*			
	SCP – R (chronic)							-0.674*			-0.668*
	PLIC - L (chronic										0.613*
	ACR - R (chronic)										0.614*
	ACR - L (chronic)						0.623*		0.633*		0.823†
MD	SCP - R (acute)				-0.464*	-0.502*					
	CP - L (acute)			-0.573†							
	SLF - R (acute)		0.471*								
	SFO - L (acute)	-0.685†								-0.769†	

Cont. MD	SFO - R (chronic)				0.648*						
	IFO - R (acute)	-0.548*									
	IFO - R (chronic)			-0.701*							
	IFO - L (chronic)							-0.719†			
	UNC - L (acute)					-0.454*				-0.650*	
	ACR - L (chronic)				0.638*		-0.640*				
	SS – R (chronic)			-0.582*							
	FX/ST - R (chronic)			-0.594*							
	FX (chronic)						-0.617*				
	EC - R (chronic)										-0.588*
RD	BCC (acute)		0.481*								
	GCC (chronic)						-0.898†				-0.760†
	FX (acute)			0.529*							
	ML - L (acute)			0.468*							
	CGC - L (acute)		0.509*								
	SLF - R (acute)		0.541*								
	SFO - L (acute)	-0.574†								-0.593*	
	SFO - R (chronic)			0.688*							
	ALIC - R (acute)						-0.602*				-0.681*
	ALIC - R (chronic)						-0.766†		-0.624*		0.631*
	ALIC - L (chronic)						-0.686*				-0.803†
	SCR - L (acute)						0.589*				
	SCR - L (chronic)					-0.578*					
	UNC - L (acute)										-0.566*
	CST - L (chronic)				-0.591*						
	SCP - R (chronic)										0.715†

Cont. RD	SCP - L (chronic)	0.603*	0.603*								
	SS – R (chronic)			-0.763†							
	FX/ST - R (chronic)			-0.600*					-0.600*		
	FX/ST - L (chronic)		0.600*								
	IFO - R (chronic)			-0.633*					-0.674*		
	CP - L (chronic)										-0.608*
	PLIC - L (chronic										-0.637*
	ACR - R (chronic)										-0.658*
	ACR - L (chronic)						-0.698*				-0.793†
	EC - R (chronic)								-0.614*		
	EC - L (chronic)								-0.591*		-0.611*

*Correlation is significant at $p < 0.05$ (two-tailed).
†Correlation is significant at $p < 0.01$ (two-tailed).
DTI = diffusion tensor imaging; FA = fractional anisotropy; MD = medial diffusivity; RD = radial diffusivity.

CHAPTER 5: DISCUSSION

5.1 Maxillofacial Trauma

The current study investigated the relationship between various white matter microstructures, as measured by DTI metrics and co-relates with the neuropsychological outcome in subjects with pure MF injuries. The baseline neuropsychological assessment was completed on an average of 6.25 hours following full GCS recovery, and the neuroimaging procedure was completed within an average of 24 hours post-trauma in order to identify the structural changes at a very early stage before they were subject to confounds such as changes specific to environmental and recovery parameters. Subsequently, both a repeat imaging and neuropsychological assessment were performed at an average of 6 months post trauma to characterize any pertinent changes over time.

A total of 21 patients in our study had facial fractures distributed among three thirds of the facial region namely upper, middle and lower third, the highest incidence of injury was seen in the middle third (57%), followed by lower third (10%) and the least injury was seen in upper third with 9%. Almost more than 90% of subjects in this study are known to be motorcyclist and every one of them was reported wearing open face helmet with full visor during the time of collision.

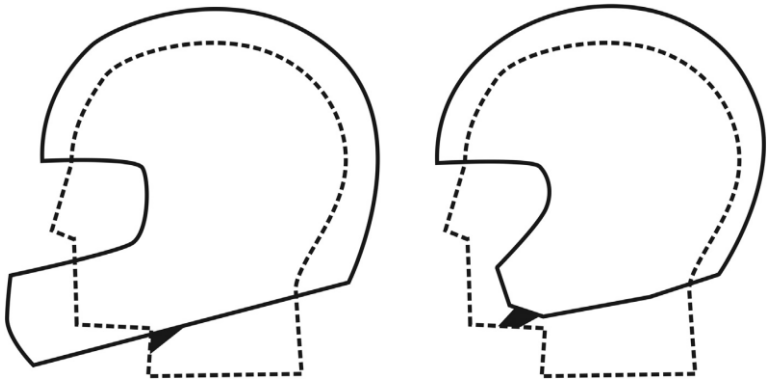

Figure 5.1: Left= Full Face Helmet; Right= Open Face Helmet.

In study done by Albuquerque and colleagues (2014) proved that both above mentioned types of crash helmets did not always offer adequate protection against craniomaxillofacial injury, especially open-face helmets. His study proved that results for TBI were statistically greater for those wearing open-face helmets compared with full-face helmets ($p < 0.05$). Their data showed that the open face helmet type provided protection to the upper third of facial skeleton. However, this protection did not extend to the midface and mandible. This evidence supports the idea that the open-face helmets offer little or no protection against TBI, probably because the structure of the helmet does not absorb enough energy from the impact; thus the energy is dissipated directly onto the face, especially the midface region (Lopes Albuquerque et al., 2014).

Similarly, Pappachan and colleagues (2012) reported that the forces to the facial skeleton can be applied from an anteroposterior, superior, inferior and lateral directions. Whereas most of the authors like Bank and Lee et al. (2009) reported that facial fractures are associated with a decreased risk of brain injury, Davidoff et al. (1986) and Keenan et al. (1999) found facial fracture to be highly associated with TBI. These forces with level and location of point of impact will determine the pattern of injury. Fractures of the cranium rarely extend into the region of facial skeleton. On the other hand, fractures originating in the facial skeleton can extend into the cranium for instance fractures of the frontal bone, cribriform plate of ethmoid and fractures of the temporal bone. The significance of these displacing forces can be used to analyse the mechanism behind injuries sustained during MVA (Pappachan & Alexander, 2012).

In addition, Pappachan's study (2012) has proved that the nasal bones were the most fragile of the facial bones, with tolerance levels for minimal fracture in the 25–75 lbs. range. The maxilla displayed low tolerance level in the range of 140–445 lbs., corresponding to the relatively thin anterior wall of maxilla. The fragile zygomatic arch displayed tolerance levels between 208 and 475 lbs., whereas the body of the zygoma

displayed a higher tolerance level with a grouping in the 200–450 lbs. range (Pappachan & Alexander, 2012). The frontal bone displayed the highest tolerance levels with grouping between 800 and 1600 lbs. The mandible is much more sensitive to lateral than to frontal impacts. The anatomic configuration of the mandible approximates a rigid semi-circular link with pinned joints at its free ends. The tolerance level increases in proportion to the relative size and area of the mandible involved. The lowest tolerance level of 425 lbs. was associated with fracture of a single condyle. Fractures of both condyles occurred at 535 and 550 lbs. Fractures of the symphysis occurred at 850 and 925 lbs.(Pappachan & Alexander, 2012). From these, it proves that midfacial skeletal structures are the most vulnerable region for fracture due to its low impact tolerance factor and the relative fragility of its framework which acts as a cushion for trauma directed towards the cranium from an anterior or anterolateral direction. Facial injury should always be of clinical concern with associated brain damage because it can be a marker for substantial transfer of energy to the brain (Pappachan & Alexander, 2012). The common fractures seen in our study were in the midface region, which explains the majority of cerebral white matter injuries due to MVA are the result of rapid deceleration when the moving head strikes an immovable object, e.g., the road. This produces the features of distortion aggravated by the brain mobility.

Middle third region (57 %) fractures were the most common facial bone fractures in our patients' collective, indicating that they occur more commonly in MF trauma than any other facial bone fracture. Due to relatively low level of force required for this type of injury as compared to upper and lower third region (Pappachan & Alexander, 2012), the high number of concomitant intracerebral white matter microstructural changes is not surprising. Our observation that the middle third facial fractures in isolation or combination with other facial fractures are more associated with head injuries is similar

to the findings of Haug et al., who stated that the mid-facial fractures had more than twice the chance of sustaining head injuries (Scheyerer et al., 2015).

5.2 Relationship between MF injuries with WM tracts and Its Correlation with Neuropsychological Performances

The observed relationship between MF injuries and WM structural alteration indicates that facial fractures are a good sign that the patient has suffered a level of potentially brain – damaging energy. Due to this observation, and the high incidence of concomitant brain injuries in MF trauma, it is justifiable to assume potential brain injuries for all patients with any kind of facial injury until proven otherwise. The results of the present study demonstrated that the presence of MF trauma can predict and possibly influence the neuropsychological outcome over time in these patients with possible undiagnosed mTBI. These results were clearly marked by signs of altered cerebral WM integrity both acutely and over time, captured through advanced DTI neuroimaging. DTI metrics (FA, MD and RD) has provided quantitative information about the microstructural damage occurring in patients acutely and chronically.

Previous study done by Veeramuthu and colleagues (2016) reported that during acute stage of mTBI, DTI metrics showing;

a) Low FA, high MD and high RD values indicates vasogenic edema of the brain due to release of intracellular protein into brain parenchyma.
b) High FA, low MD and low RD values indicates cytotoxic edema (intracellular edema) and usually has a poorer outcome than the former.
c) Last but not least, a high FA and MD and unchanged RD values usually indicate reactive astrogliosis (migration of astrocytes to injured site) hence increases cells density and reduces diffusivity of the affected area (Veeramuthu et al., 2016).

In this study, comparison of patients with pure MF injury and healthy controls revealed that the majority of the white matter showed some evidence of vasogenic edema and axonal disruption in the MF injury group. Based on the pattern of DTI findings, reduced FA coupled with increased MD and RD values in acute phase were seen rather scattered in the commissural, projection and association fiber bundles such as pontine crossing tract (PCT), splenium of corpus callosum (SCC), anterior limb of internal capsule (ALIC), posterior limb of internal capsule (PLIC), superior corona radiata (SCR), posterior corona radiata (PCR), cingulum (CGC), cingulum hippocampus (CGH), external capsule (EC), superior longitudinal fasciculus (SLF), superior fronto – occipital fasciculus (SFO) and inferior fronto – occipital fasciculus (IFO). Other tracts, including the middle cerebellar peduncle (MCP), base of corpus collasum (BCC), retrolenticular of internal capsule (RLIC), sagittal stratum (SS) and tapatum (TAP) showed similar trends, although they did not reach statistical significance. Results showing reduced FA_a along with increased MD_a and RD_a of the SLF – R tract in patient group and its association with language domain in acute phase are similar finding as previous study done by Veeramuthu and colleagues (2016) and Arfanakis and colleagues (2002). This impairment with obvious deviation of DTI metrics indicates an ongoing edematous process, which is not observed by conventional CT or MRI.

In contrast, changes seen in left medial lemniscus (ML – L_a); was more suggestive of ongoing process of reactive astrogliosis occurring within the tract in relation to domain of memory in the acute phase. Higher FA_a, MD_a and RD_a value of the CGC – L also negatively correlated with language function acutely. Its corresponding positive association with RD at baseline best explains the influence of reactive astrogliosis on cognition in the acute stage. We also found that acute – phase DTI parameters in selected WM tracts were significantly associated with chronic domain – specific cognitive deficits. This include those of the ALIC – R and ALIC – L where the presence

of association between tracts with chronic deficits in attention function likely reflects the long term effect of acute vasogenic edema with concurrent reactive astrogliosis.

In terms of neurocognitive performance in acute stage, the MF injury group generally performed poorly across the attention and executive function domains in comparison to healthy control and remained impaired with minimal improvement in the domain of executive function at 6 – months follow up. These neurocognitive alterations were also associated with the changes observed in the DTI parameter. Interestingly, the changing dynamics and the reversibility of axonal damage and dysfunction of the WM tracts were very strongly associated with the changes of neurocognitive performances at follow – up, predominantly in all the domains but language.

In chronic phase, the continued alteration of DTI metrics found across FA_c, MD_c and RD_c implies significant changes in WM integrity. It means demyelination or axonal disruption may have taken place which predisposes the specific tract to be permanently damaged (Armstrong, Mierzwa, Marion, & Sullivan, 2016). This disruption may be irreversible, especially when a reduced FA_c and elevated MD_c and RD_c are noted. Conversely, results of DTI metrics that show a reduction of FA_c, unchanged MD_c and slightly altered RD_c would refer to minor structural damage without evident of gross tissue loss and such changes have also been implicated as part of the dual effects of reactive gliosis (Kinnunen et al., 2011).

In our study, during follow up however, these patients showed signs of structural recovery with values of partial normalization in DTI parameter indicated by statistically significant increased FA_c values and significantly reducing MD_c and RD_c values in comparison to their baseline measures. DTI metrics measured at chronic phase was significant across 8 tracts namely CP – L, PLIC – L, EC – L, BCC, ALIC – L, SCR – L, SS – L, SFO – L and IFO – L. The mixed association between certain neurocognitive

performances in the chronic phase (e.g., attention, language, memory and executive function) and FA_c, MD_c and RD_c of several tracts (i.e., ALIC –R, ALIC – L, GCC, FX, ML – R, SCP – R, PLIC – L, ACR – R and ACR – L) though not being normal, is not completely unexpected. The plausible explanation for association between the cognitive changes (deterioration) and structural recovery observed during follow – up would be the occurrence of diaschisis phenomenon which was first advocated by Von Monakow in 1914. Currently the term diaschisis used to describe a depression of regional neuronal metabolism and cerebral blood flow caused by dysfunction in an anatomically separate but functionally related neuronal region. Von Monakow's concept of neurophysical changes in distant brain tissue to the focal lesion led to a widespread clinical interest. The areas of the brain are connected by vast organized neuronal pathways that allow one area of the brain to influence other areas more distal to it. Understanding these dense pathways helps to link a lesion causing brain damage in one area of the brain to degeneration in a more distal brain area (Stanley et al., 2004).

The primary mechanism of diaschisis is functional deafferentition, which is loss of the input of information from the part of the brain that is now damaged. During follow – up, the vasogenic or cytotoxic oedematous of previously altered white matter tracts would have resolved but the loss of the damaged structure disrupts the function of the remaining intact systems and causes a physiological imbalance. Hence, some function may be restored with gradual readjustment of the intact neurons but suppresses distal neuronal areas through intervention and the brain's natural neuroplasticity (Stanley et al., 2004). The decrease in information and neural firing to the distal brain area causes those synaptic connections to weaken and initiates a change in the structural and functional connectivity around the white matter tracts which possibly explains this interesting phenomenon where continued cognitive impairment or further deterioration is seen especially in language and executive function domains, with paradoxical

structural recovery was noted during follow - up.(Veeramuthu et al., 2015). Taken together, our study further strengthens evidence for physiogenic influences on the prolonged functional and neuropsychological sequelae in patients with MF injuries.

5.3 The Response of Cerebral White Matter Neuronal Structures towards TAI Arising from Pure MF injuries.

The main concern with WM injury from TBI is traumatic axonal injury (TAI). TAI occurs in multiple neuroanatomical regions and is defined clinically as diffuse axonal injury (DAI) (Main et al., 2017). Axonal injury can be caused by immediate (primary) axotomy which occurs at the time of injury or delayed (secondary) axotomy which evolves over a few minutes or hours after impact (Jang, 2011). The focal damage to the axonal cytoskeleton is followed by formation of axonal swellings and varicosities proximal to the site of injury. These swellings contain accumulated protein material which cannot be transported due to disruption of axoplasmic flow (Talbott et al., 2005). TAI occurs in a pattern of damaged axons distributed among adjacent intact axons within the white matter shown in Figure 5.2.

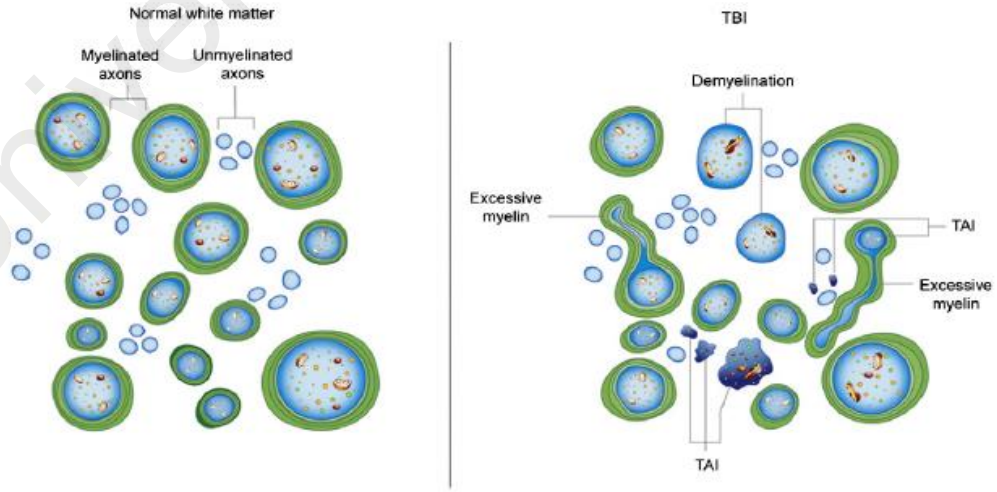

Figure 5.2: Milder forms of TBI may cause complex pathology of axons and myelin.

TAI is characterized by a pattern of degenerating axons dispersed among intact fibers. Unmyelinated axons are particularly vulnerable to degeneration after TAI. The myelin sheath collapses as the axon degenerates. In addition, the dispersed white matter axons damaged by TAI may be a subset of only one or two axons among a cohort of 20 or more axons unsheathed by surviving oligodendrocytes. This mismatch of axon integrity among the cohort may dysregulate myelin maintenance signals to the oligodendrocytes, resulting in aberrant myelin synthesis. A combination of effects may explain the long excessive myelin figures observed in models of mild TBI (Figure 5.2). Separate from the axons undergoing TAI, viable axons may also lose function due to demyelination. Important early elements initiating axon damage include altered calcium fluxes, mitochondrial dysfunction, and the generation of reactive oxygen species (Armstrong et al., 2016).

Table 5.1: Diverse cell types in CNS responses to damage and disease

CNS Intrinsic Cells	Blood – borne Non – neural Cells
CNS Intrinsic Neural Cells - Neurons - Oligodendrocytes - Astrocytes - NG2 – OPC - Neural stem / progenitor cells - Ependyma	**Leukocytes** - Monocyte/macrophage - Neutrophils - Eosinophils - NK cells - T cells - B cells
CNS Intrinsic Non – Neural Cells - Microglia - Perivascular fibroblasts - Pericytes - Endothelia and progenitors	**Other Bone Marrow – Derived Cells** - Platelets - Fibrocytes - Mesenchymal (bone marrow stromal)

Various non – neural intrinsic lineage cells play critical roles in CNS damage and disease (Table 5.1). Microglias are well documented as highly sensitive early responders that stimulate and recruit other cells, as well phagocytose debris. Fibroblast-related cells, including perivascular fibroblasts, meningeal fibroblasts, and pericytes, contribute to tissue replacement by forming fibrotic scar tissue after severe damage.

Endothelia and endothelial progenitors are prominent during tissue replacement after CNS injury. Blood-borne immune and inflammatory cells of different kinds play prominent roles in CNS responses to damage and disease and have been studied and reviewed. In addition to well-known roles in phagocytosis and removal of debris, there is also now increasing evidence that subtypes of leukocytes play active roles in tissue repair (Perry & Teeling, 2013).

When there is TAI, acute damage can be divided broadly into three overlapping but distinct phases: (1) cell death and inflammation, (2) cell proliferation for tissue replacement, and (3) tissue remodelling. The first phase of response in the injury includes both very rapid events that occur over timescales of seconds to hours and more gradually progressing events that develop over days. Blood-borne molecules namely platelets rapidly form aggregates for haemostasis and also signal to local cells. Leukocytes then infiltrate heavily to monitor for pathogens, remove debris, and provide molecular signals involved in wound repair over a variable number of days or longer depending on severity of tissue damage. Certain CNS intrinsic cells such as microglia and NG2-OPC immediately migrate to sites of tissue damage. Astrocytes, in contrast, remain in situ and do not migrate either to or away from injury sites but can swell osmotically depending on the severity of injury or ischemia (Talbott et al., 2005).

The second phase of response to acute CNS tissue damage occurs from about 2 to 10 days after the insult and is characterized by the proliferation and local migration of cells that implement tissue repair and replacement. Reactive astrogliosis occurs in this phase where a compact astrocyte scar is formed primarily from newly proliferated elongated astrocytes generated by local astroglial progenitors that gather around the edges of damaged tissue containing inflammatory and fibroblast-lineage cells. In mature lesions, these astrocyte scar borders will precisely demarcate and separate persisting areas of non-functional, non-neural lesion core tissue from immediately surrounding and

potentially functional neural tissue. Changes in astrocyte function or morphology which occur during astrogliosis may range from minor hypertrophy to major hypertrophy, domain overlap, and ultimately, glial scar formation (Perry & Teeling, 2013).

The third phase of response to acute tissue damage generally begins toward the end of the first week after the insult and is distinguished by tissue remodelling that includes events that are completed within weeks, such as scar organization, as well as chronic events that can continue over many months. During remodelling phase, this astrocyte scar border serves as a protective barrier that restricts the migration of inflammatory cells from the non-neural lesion core into surrounding viable neural tissue. Disruption of astrocyte scar formation in different kinds of transgenic loss-of-function models leads to increased lesion size, increased death of local neurons, increased demyelination, and decreased recovery of function after traumatic or ischemic focal insults (Perry & Teeling, 2013).

In mTBI, widespread changes in FA are frequently observed, especially in frontal, mid – line and temporal regions (Maller et al., 2014). Our findings of reduced FA, coupled with increased MD and RD in the acute phase are indicative of vasogenic edema along with myelin breakdown as previously reported by Veeramuthu and colleagues (2015). On the other hand, an increased FA coupled with reduced MD and RD in the acute phase were observed in SCP – R and UNC – L. A definitive mechanistic explanation for current results is challenging at best given the many constraints of an in vivo human clinical imaging study. With this caveat in mind, perhaps the most plausible explanation for the current observations of increased fractional anisotropy (FA) following mTBI are cytotoxic edema or changes in water content within the myelin sheath. Cytotoxic edema is considered irreversible and therefore confers a poor prognosis. The mechanical forces of MF injuries typically result in the stretching of axons and related supporting structures such as

oligodendrocytes, altering the function of gated ion channels and resulting in an increase in intracellular water and a decrease in extracellular water. Besides these, the increased FA, MD, and rather an unchanged RD in the acute phase of this study were seen in RLIC –L, is most likely indicative of reactive astrogliosis, which is a process where fibrous astrocytes migrate to the site of injury, locally increasing the density of the cells and diffusivity of the affected tissue (Veeramuthu et al., 2016).

Neuroimaging detection of hemorrhages within white matter tracts has become interpreted as indicative of concurrent TAI. However, only 10% of closed head trauma patients demonstrate admission CT scans with petechial hemorrhages in the grey–white matter junctions associated with TAI while approximately 80% of TAIs are non-hemorrhagic and better detected with MRI (Adamson et al., 2013). However, axon damage often occurs in the absence of vascular damage in mild TBI. These findings have indicated that axons are more vulnerable than blood vessels to damage from TBI. Definite interpretation of these findings as evidence for TBI in patients requires DTI – histology correlations. While histological confirmation of DTI in animal models of TBI can be performed, these are not feasible in humans except at autopsy. Although the neuropathological mechanisms underlying these observed changes in WM are not completely understood, changes of this type generally are thought to be related to the following processes: disruption to the organizational structure of the tissue, axonal degeneration, and demyelination (Wozniak et al., 2007).

In the non-injured developing brain, diffusion anisotropy in white matter, as measured by DTI, is a function of a number of factors including axon structure, axon packing, tissue water content, and myelin, among others (Mori & Zhang, 2006). It is becoming increasingly clear that axonal damage from TBI cannot be conceptualized simply as a static event (Arenth, Russell, Scanlon, Kessler, & Ricker, 2014). The initial tearing, shearing, and misalignment of the axons initiates a series of events that leads to

further WM damage, including Wallerian degeneration (dying of the neurons following axonal damage) and loss of myelin. There is evidence that this subsequent damage continues over the next several days as disruption of axonal transport contributes to further axonal loss via axonal swelling and disconnection (Povlishock, 2000). Further structural changes continue for the next several months as illustrated by studies showing progressive loss of tissue volume over time (Travers et al., 2012). Additionally, myelin degeneration is thought to continue for one to two years post-injury (Meythaler, Peduzzi, Eleftheriou, & Novack, 2001). Our findings of decreased FA and increased MD and RD in patients with MF injuries compared to controls is in accordance with previous studies in acute or sub-acute phase of MF injuries (Nelson et al., 2016).

During follow – up, an interesting phenomenon where continued cognitive impairment or further deterioration was seen despite having paradoxical structural white matter tracts recovery. Von Monakow's theory believes that injuries from TBI cause focal and non – focal disturbances in areas of brain. The first is focal diaschisis, which refers to the remote neurophysiological changes that are caused by a focal lesion based on von Monakow's definition. The second type of diaschisis is non – focal diaschisis and it focuses on the changes in the strength and direction of neural pathways and connectivity between brain areas. Concept of diaschisis occurs when a lesion causes damage that also disturbs the structural and functional connectivity to the brain areas distal to the lesion (Stanley et al., 2004). Although the WM tract's oedematous phenomenon would have resolve during the follow – up, decrease in information and neural firing to the distal brain area causes those synaptic connections to weaken and initiates a change in the structural and functional connectivity around that area. The severity of these factors is manifested in altered neuronal excitability, hypo – metabolism and hypo – perfusion. This type of diaschisis has only been a topic in recent study as a result of the advancement of brain imaging tools and technology and it could

be a plausible explanation for the deterioration or impairment seen in cognitive domains (language and executive function) despite having a paradoxical structural recovery.

The high number of accompanying intracerebral WM microstructural changes observed through this study emphasizes the need to screen all trauma patients (with MF fracture) for brain injuries, irrespective of obvious signs and symptoms to ensure that no concomitant injury is overlooked. We hypothesized that poor cognitive performance would be directly related to white mater tract damage and therefore used Tract-Based Spatial Statistics (TBSS) to examine DTI metric changes between acute and chronic time points and to explore how these relate to acquire cognitive deficits after MF trauma.

CHAPTER 6: CONCLUSION

6.1 Conclusion

In conclusion, our study shows no evidence that facial fractures are protective of traumatic brain injury by the presence of intracranial white matter tracts abnormalities seen from the advanced neuroimaging MRI – DTI. The lack of evidence for intracerebral injury in patients with MF trauma on conventional imaging has led to the examination of DTI as possible approaches to revealing microstructural white matter changes that have the potential to help grade tissue damage severity, track its development, and provide prognostic markers for clinical outcome.

Moving forward, DTI should be used in concert with CT and conventional MRI, which have proven benefit for the assessment of mTBI at acute and chronic time points, respectively. Improved analysis techniques such as tract-based spatial statistics and quantitative tractography may provide greater sensitivity and reliability for assessing mTBI pathology in MF trauma than the older methods used in the majority of the existing DTI literature. This study showed that DTI can be used to predict cerebral white matter microstructural recovery in pure MF trauma patients. DTI has great potential to help identify the subclinical axonal injury neuropathology that is thought to be common in mTBI. It may become especially valuable in patients with normal MRI and CT scans that continue to exhibit persistent symptoms. Specific structure-function relationships may enable the use of DTI to predict persistent cognitive deficits, which may be especially useful when accurate neuropsychological assessments cannot be performed.

Longitudinal DTI studies in conjunction with neuropsychological assessment should elucidate the natural history of how symptoms and microstructural pathology evolve over time. Future large-scale multicentre studies, despite potential difficulties, will determine whether DTI can serve as a predictive imaging biomarker for long-term

cognitive deficits that would be of value for triaging patients to clinical trials of experimental neuroprotection therapies and cognitive rehabilitation methods, as well as for monitoring their response to these interventions.

6.2 Limitations

We acknowledge several limitations of the present study. First, the study was undertaken at a single designated trauma centre. This might cause selection bias and, thus limiting the external validity of the findings. Second, the low number of fractures hinders interpretation of the data.

6.3 Recommendations

There are few recommendations that might be executed to improve the outcome of this study.

- To investigate WM changes in MF trauma patients of different aetiologies other than MVA, thus enables the surgeon to predict the outcome.
- To collect data from multiple trauma centres in order to have better study population.

6.4 Conflicts of Interest

There were no conflicts of interest.

REFERENCES

Abdul Latip, L. S., Ahmad Alias, N. A., Ariff, A. R., Shuaib, I. L., Abdullah, J., & Naing, N. N. (2004). CT scan in minor head injury: a guide for rural doctors. *J Clin Neurosci, 11*(8), 835-839. doi: 10.1016/j.jocn.2003.12.017

Abdul Manan, M. M., & Várhelyi, A. (2012). Motorcycle fatalities in Malaysia. *IATSS Research, 36*(1), 30-39. doi: 10.1016/j.iatssr.2012.02.005

Adamson, C., Yuan, W., Babcock, L., Leach, J. L., Seal, M. L., Holland, S. K., & Wade, S. L. (2013). Diffusion tensor imaging detects white matter abnormalities and associated cognitive deficits in chronic adolescent TBI. *Brain Inj, 27*(4), 454-463. doi: 10.3109/02699052.2012.750756

Ahmed, A., Sadullah, A. F. M., & Shukri Yahya, A. (2016). Field study on the behavior of right-turning vehicles in Malaysia and their contribution on the safety of unsignalized intersections. *Transportation Research Part F: Traffic Psychology and Behaviour, 42*, 433-446. doi: 10.1016/j.trf.2015.03.006

Arenth, P. M., Russell, K. C., Scanlon, J. M., Kessler, L. J., & Ricker, J. H. (2014). Corpus callosum integrity and neuropsychological performance after traumatic brain injury: a diffusion tensor imaging study. *J Head Trauma Rehabil, 29*(2), E1-E10. doi: 10.1097/HTR.0b013e318289ede5

Armstrong, R. C., Mierzwa, A. J., Marion, C. M., & Sullivan, G. M. (2016). White matter involvement after TBI: Clues to axon and myelin repair capacity. *Exp Neurol, 275 Pt 3*, 328-333. doi: 10.1016/j.expneurol.2015.02.011

Assaf, Y., & Pasternak, O. (2008). Diffusion tensor imaging (DTI)-based white matter mapping in brain research: a review. *J Mol Neurosci, 34*(1), 51-61. doi: 10.1007/s12031-007-0029-0

Beaulieu, C. (2002). The basis of anisotropic water diffusion in the nervous system - a technical review. *NMR Biomed, 15*(7-8), 435-455. doi: 10.1002/nbm.782

Chang, V. H., Lombard, L. A., & Greher, M. R. (2011). Mild traumatic brain injury in the occupational setting. *PM R, 3*(10 Suppl 2), S387-395. doi: 10.1016/j.pmrj.2011.08.007

Dube, A., Rao, G., & Tanwar, A. (2014). Pattern of Maxillofacial Injury Associated with Head Injury at a Neuro Surgical Centre: An Analysis of 250 Cases.

International Journal of Dental and Medical Specialty, 1(2), 2. doi: 10.5958/2394-4196.2014.00002.8

Duckworth, J. L., & Stevens, R. D. (2010). Imaging brain trauma. *Curr Opin Crit Care, 16*(2), 92-97. doi: 10.1097/MCC.0b013e3283374900

Garg, R. K., Afifi, A. M., Gassner, J., Hartman, M. J., Leverson, G., King, T. W., . . . Gentry, L. R. (2015). A novel classification of frontal bone fractures: The prognostic significance of vertical fracture trajectory and skull base extension. *J Plast Reconstr Aesthet Surg, 68*(5), 645-653. doi: 10.1016/j.bjps.2015.02.021

Gomez-Anson, B., Roman, E., Fernandez de Bobadilla, R., Pires-Encuentra, P., Diaz-Manera, J., Nunez, F., . . . Soriano, G. (2015). Alterations in cerebral white matter and neuropsychology in patients with cirrhosis and falls. *PLoS One, 10*(3), e0118930. doi: 10.1371/journal.pone.0118930

Grossman, E. J., Inglese, M., & Bammer, R. (2010). Mild traumatic brain injury: is diffusion imaging ready for primetime in forensic medicine? *Top Magn Reson Imaging, 21*(6), 379-386. doi: 10.1097/RMR.0b013e31823e65b8

Hohlrieder, M., Hinterhoelzl, J., Ulmer, H., Hackl, W., Schmutzhard, E., & Gassner, R. (2004). Maxillofacial fractures masking traumatic intracranial hemorrhages. *Int J Oral Maxillofac Surg, 33*(4), 389-395. doi: 10.1016/j.ijom.2003.10.011

Ilvesmaki, T., Luoto, T. M., Hakulinen, U., Brander, A., Ryymin, P., Eskola, H., . . . Ohman, J. (2014). Acute mild traumatic brain injury is not associated with white matter change on diffusion tensor imaging. *Brain, 137*(Pt 7), 1876-1882. doi: 10.1093/brain/awu095

Isik, D., Gonullu, H., Karadas, S., Kocak, O. F., Keskin, S., Garca, M. F., & Eseoglu, M. (2012). Presence of accompanying head injury in patients with maxillofacial trauma. *Ulus Travma Acil Cerrahi Derg, 18*(3), 200-206. doi: 10.5505/tjtes.2012.01047

Jang, S. H. (2011). Diffusion tensor imaging studies on corticospinal tract injury following traumatic brain injury: a review. *NeuroRehabilitation, 29*(4), 339-345. doi: 10.3233/NRE-2011-0710

Ji, B., Wang, C., Song, F., Chen, M., & Wang, H. (2012). A new biomechanical model for evaluation of fixation systems of maxillofacial fractures. *J Craniomaxillofac Surg, 40*(5), 405-408. doi: 10.1016/j.jcms.2011.07.011

Kinnunen, K. M., Greenwood, R., Powell, J. H., Leech, R., Hawkins, P. C., Bonnelle, V., . . . Sharp, D. J. (2011). White matter damage and cognitive impairment after traumatic brain injury. *Brain, 134*(Pt 2), 449-463. doi: 10.1093/brain/awq347

Lopes Albuquerque, C. E., Nogueira Arcanjo, F. P., Cristino-Filho, G., Mont'alverne Lopes-Filho, A., Cesar de Almeida, P., Prado, R., & Pereira-Stabile, C. L. (2014). How safe is your motorcycle helmet? *J Oral Maxillofac Surg, 72*(3), 542-549. doi: 10.1016/j.joms.2013.10.017

Macciocchi, S. N., Seel, R. T., & Thompson, N. (2013). The impact of mild traumatic brain injury on cognitive functioning following co-occurring spinal cord injury. *Arch Clin Neuropsychol, 28*(7), 684-691. doi: 10.1093/arclin/act049

Main, K. L., Soman, S., Pestilli, F., Furst, A., Noda, A., Hernandez, B., . . . Adamson, M. M. (2017). DTI measures identify mild and moderate TBI cases among patients with complex health problems: A receiver operating characteristic analysis of U.S. veterans. *Neuroimage Clin, 16*, 1-16. doi: 10.1016/j.nicl.2017.06.031

Maller, J. J., Thomson, R. H., Pannek, K., Rose, S. E., Bailey, N., Lewis, P. M., & Fitzgerald, P. B. (2014). The (Eigen)value of diffusion tensor imaging to investigate depression after traumatic brain injury. *Hum Brain Mapp, 35*(1), 227-237. doi: 10.1002/hbm.22171

Manson, P. N., Stanwix, M. G., Yaremchuk, M. J., Nam, A. J., Hui-Chou, H., & Rodriguez, E. D. (2009). Frontobasal fractures: anatomical classification and clinical significance. *Plast Reconstr Surg, 124*(6), 2096-2106. doi: 10.1097/PRS.0b013e3181bf8394

Meythaler, J. M., Peduzzi, J. D., Eleftheriou, E., & Novack, T. A. (2001). Current concepts: Diffuse axonal injury–associated traumatic brain injury. *Archives of Physical Medicine and Rehabilitation, 82*(10), 1461-1471. doi: 10.1053/apmr.2001.25137

Mori, S., & Zhang, J. (2006). Principles of diffusion tensor imaging and its applications to basic neuroscience research. *Neuron, 51*(5), 527-539. doi: 10.1016/j.neuron.2006.08.012

Mueller, B. A., Lim, K. O., Hemmy, L., & Camchong, J. (2015). Diffusion MRI and its Role in Neuropsychology. *Neuropsychol Rev, 25*(3), 250-271. doi: 10.1007/s11065-015-9291-z

Nelson, C. G., Elta, T., Bannister, J., Dzandu, J., Mangram, A., & Zach, V. (2016). Severe Traumatic Brain Injury: A Case Report. *American Journal of Case Reports, 17*, 186-191. doi: 10.12659/ajcr.897116

Nordin, R., Rahman, N. A., Rashdi, M. F., Yusoff, A., Rahman, R. A., Sulong, S., . . . Ramli, R. (2015). Oral and maxillofacial trauma caused by road traffic accident in two university hospitals in Malaysia: A cross-sectional study. *Journal of Oral and Maxillofacial Surgery, Medicine, and Pathology*, *27*(2), 166-171. doi: 10.1016/j.ajoms.2014.01.001

Pappachan, B., & Alexander, M. (2012). Biomechanics of cranio-maxillofacial trauma. *J Maxillofac Oral Surg, 11*(2), 224-230. doi: 10.1007/s12663-011-0289-7

Perry, V. H., & Teeling, J. (2013). Microglia and macrophages of the central nervous system: the contribution of microglia priming and systemic inflammation to chronic neurodegeneration. *Semin Immunopathol, 35*(5), 601-612. doi: 10.1007/s00281-013-0382-8

Puljula, J., Cygnel, H., Makinen, E., Tuomivaara, V., Karttunen, V., Karttunen, A., & Hillbom, M. (2012). Mild traumatic brain injury diagnosis frequently remains unrecorded in subjects with craniofacial fractures. *Injury, 43*(12), 2100-2104. doi: 10.1016/j.injury.2012.04.010

Rajandram, R. K., Syed Omar, S. N., Rashdi, M. F., & Abdul Jabar, M. N. (2014). Maxillofacial injuries and traumatic brain injury--a pilot study. *Dent Traumatol, 30*(2), 128-132. doi: 10.1111/edt.12052

Rao, V., & Lyketsos, C. (2000). Neuropsychiatric sequelae of traumatic brain injury. *Psychosomatics, 41*(2), 95-103. doi: 10.1176/appi.psy.41.2.95

Rijken, B. F., Leemans, A., Lucas, Y., van Montfort, K., Mathijssen, I. M., & Lequin, M. H. (2015). Diffusion Tensor Imaging and Fiber Tractography in Children with Craniosynostosis Syndromes. *AJNR Am J Neuroradiol, 36*(8), 1558-1564. doi: 10.3174/ajnr.A4301

Roberts, R. M., Mathias, J. L., & Rose, S. E. (2016). Relationship Between Diffusion Tensor Imaging (DTI) Findings and Cognition Following Pediatric TBI: A Meta-Analytic Review. *Dev Neuropsychol, 41*(3), 176-200. doi: 10.1080/87565641.2016.1186167

Scheyerer, M. J., Doring, R., Fuchs, N., Metzler, P., Sprengel, K., Werner, C. M. L., . . . Wanner, G. A. (2015). Maxillofacial injuries in severely injured patients. *J Trauma Manag Outcomes, 9*, 4. doi: 10.1186/s13032-015-0025-2

Shenton, M. E., Hamoda, H. M., Schneiderman, J. S., Bouix, S., Pasternak, O., Rathi, Y., . . . Zafonte, R. (2012). A review of magnetic resonance imaging and diffusion tensor imaging findings in mild traumatic brain injury. *Brain Imaging Behav, 6*(2), 137-192. doi: 10.1007/s11682-012-9156-5

Stanley F., Peter J. K., Caroline J. (2004). The monakow concept of diaschisis. Origins and perspective. *Arch Neurol*.61:283-288

Talbott, J. F., Loy, D. N., Liu, Y., Qiu, M. S., Bunge, M. B., Rao, M. S., & Whittemore, S. R. (2005). Endogenous Nkx2.2+/Olig2+ oligodendrocyte precursor cells fail to remyelinate the demyelinated adult rat spinal cord in the absence of astrocytes. *Exp Neurol, 192*(1), 11-24. doi: 10.1016/j.expneurol.2004.05.038

Tang, C. Y., Eaves, E., Dams-O'Connor, K., Ho, L., Leung, E., Wong, E., . . . Pasinetti, G. (2012). Diffuse Disconnectivity in tBi: a resting state fMri anD Dti stuDy. *Transl Neurosci, 3*(1), 9-14. doi: 10.2478/s13380-012-0003-3

Travers, B. G., Adluru, N., Ennis, C., Tromp do, P. M., Destiche, D., Doran, S., . . . Alexander, A. L. (2012). Diffusion tensor imaging in autism spectrum disorder: a review. *Autism Res, 5*(5), 289-313. doi: 10.1002/aur.1243

Veeramuthu, V., Hariri, F., Narayanan, V., Tan, L. K., Ramli, N., & Ganesan, D. (2016). Microstructural Change and Cognitive Alteration in Maxillofacial Trauma and Mild Traumatic Brain Injury: A Diffusion Tensor Imaging Study. *J Oral Maxillofac Surg, 74*(6), 1197 e1191-1197 e1110. doi: 10.1016/j.joms.2016.01.042

Veeramuthu, V., Narayanan, V., Kuo, T. L., Delano-Wood, L., Chinna, K., Bondi, M. W., . . . Ramli, N. (2015). Diffusion Tensor Imaging Parameters in Mild Traumatic Brain Injury and Its Correlation with Early Neuropsychological Impairment: A Longitudinal Study. *J Neurotrauma, 32*(19), 1497-1509. doi: 10.1089/neu.2014.3750

Walker, K. R., & Tesco, G. (2013). Molecular mechanisms of cognitive dysfunction following traumatic brain injury. *Front Aging Neurosci, 5*, 29. doi: 10.3389/fnagi.2013.00029

Wozniak, J. R., Krach, L., Ward, E., Mueller, B. A., Muetzel, R., Schnoebelen, S., . . . Lim, K. O. (2007). Neurocognitive and neuroimaging correlates of pediatric traumatic brain injury: a diffusion tensor imaging (DTI) study. *Arch Clin Neuropsychol, 22*(5), 555-568. doi: 10.1016/j.acn.2007.03.004

Yuh, E. L., Cooper, S. R., Mukherjee, P., Yue, J. K., Lingsma, H. F., Gordon, W. A., . . . Track-Tbi, I. (2014). Diffusion tensor imaging for outcome prediction in mild

traumatic brain injury: a TRACK-TBI study. *J Neurotrauma*, *31*(17), 1457-1477. doi: 10.1089/neu.2013.3171

Zelken, J. A., Khalifian, S., Mundinger, G. S., Ha, J. S., Manson, P. N., Rodriguez, E. D., & Dorafshar, A. H. (2014). Defining predictable patterns of craniomaxillofacial injury in the elderly: analysis of 1,047 patients. *J Oral Maxillofac Surg*, *72*(2), 352-361. doi: 10.1016/j.joms.2013.08.015