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Neuroimage Analysis Of Traumatic Brain Injury In Human Patients

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**NEUROIMAGE ANALYSIS OF TRAUMATIC BRAIN INJURY IN
HUMAN PATIENTS**

by

HARDIK J. DOSHI

THESIS

Submitted to the Graduate School

of Wayne State University

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Table of Contents

ACKNOWLEDGEMENT.....	II
LIST OF TABLES.....	IX
LIST OF FIGURES, CHARTS AND PLOTS.....	XI
LIST OF ABBREVIATIONS.....	XIV
CHAPTER 1: INTRODUCTION TO TBI.....	1
DEFINITION.....	1
GLOBAL SEVERITY.....	2
EPIDEMIOLOGY.....	4
CAUSES.....	5
TBI MECHANISM.....	7
CATEGORIZATION OF TBI.....	10
<i>Neuro Imaging in TBI.....</i>	<i>16</i>
CHAPTER 2: CEREBRAL VENOUS BLOOD FLOW CHANGES IN MILD TRAUMATIC BRAIN INJURY AT THE ACUTE STAGE	21
<i>Motivation and Rationale Behind The Study.....</i>	<i>21</i>
<i>Susceptibility Weighted Imaging (SWI) Introduction.....</i>	<i>22</i>

<i>Gradient Echo Imaging Basics</i>	24
<i>Magnetic Susceptibility Basics</i>	27
<i>Geometry Effects</i>	28
<i>Creating Susceptibility Weighted filtered phase images</i>	30
<i>Merging Magnitude and Phase Images</i>	30
<i>Susceptibility Weighted Imaging and Mapping(SWIM)</i>	31
MATERIALS AND METHODS	34
IMAGE PROCESSING.....	38
<i>Skull-Stripping</i>	40
<i>Complex Thresholding</i>	42
<i>Zero Filling</i>	45
<i>Inverse Filtering</i>	46
<i>Selection of the Major Vessels</i>	47
<i>Getting the Susceptibility Values</i>	48
RESULTS	48
CHAPTER 3: CEREBRAL ARTERIAL BLOOD FLOW CHANGE IN MILD TRAUMATIC BRAIN INJURY AT THE ACUTE STAGE	56

ASL FUNDAMENTALS	56
PATIENT RECRUITMENT AND METHOD	60
<i>Processing Steps</i>	63
RESULTS	64
DISCUSSION.....	66
CHAPTER 4: VOLUMETRIC ANALYSIS OF CINGULUM IN RETIRED NFL PLAYERS: ITS RELATIONSHIP WITH NFL EXPERIENCE AND SUBJECTS' COGNITIVE AND FUNCTIONAL PERFORMANCE	70
INTRODUCTION TO CHRONIC TRAUMATIC ENCEPHALOPATHY (CTE).....	70
<i>Risk Factors</i>	71
<i>Clinical Symptoms</i>	72
<i>Diagnosis/Treatment</i>	73
<i>Pathology Findings</i>	74
SUBJECT RECRUITMENT AND METHOD.....	75
<i>Patient Group and Imaging Parameters</i>	75
<i>Neuropsych Tests</i>	77
<i>Processing steps</i>	79
<i>Statistical Analysis</i>	82

RESULTS	83
<i>Part 1:- Correlations (Bivariate).....</i>	<i>83</i>
<i>Part 2:- Mediation Models.....</i>	<i>85</i>
DISCUSSION.....	86
CHAPTER 5: HEMORRHAGIC LESIONS AND ITS CLINICAL CORRELATION BASED ON VENOUS AND ARTERIAL DAMAGE IN TRAUMATIC BRAIN INJURY	92
INTRODUCTION.....	92
PATIENT RECRUITMENT AND METHOD	94
<i>Patient Recruitment.....</i>	<i>94</i>
<i>Clinical & Outcome Assessments</i>	<i>96</i>
<i>Neuroimaging Protocol.....</i>	<i>96</i>
<i>Image Analysis.....</i>	<i>97</i>
<i>Statistical Analysis.....</i>	<i>100</i>
RESULTS.....	101
DISCUSSION AND CONCLUSIONS	105
REFERENCES.....	108
ABSTRACT.....	134

AUTOBIOGRAPHICAL STATEMENT 137

List of Tables

Table		Page
1.1	Glasgow Coma Scale (GCS). Maximum possible score = 15, Minimum possible score = 3 (Teasdale & Jennett, 1974).....	11
1.2	TBI severity classification based on GCS. From Jennett and Teasdale (Jannett & Teasdale, 1981).....	12
1.3	Ommaya and Gennarelli classification system (Ommaya & Gennarelli, 1974).....	13
1.4	Multiple indicators of TBI (Stein, 1996).....	14
1.5	Head injury severity scale (Stein, 1996).....	14
2.1	Patients' and Controls' demographic data and cause of injury...	33
2.2	SAC scores of the patient' group.....	35
2.3	Group mean values for each vein and student's T-test comparison between control & patient group (T-Test1) and control and follow-up group (T-Test2). Following are the veins: Vein 1: Left Septum, Vein 2: Right Septum, Vein 3: Central Septum, Vein 4: Left Thalamo-striate, Vein 5: Right Thalamo-striate Vein 6: Internal Cerebral Vein, Vein 7: Left Basal Vein of Rosenthal Vein 8: Right Basal Vein of Rosenthal.....	53
2.4	Comparing patients' SAC scores with controls' normalized	

	SAC score (M. McCrea et al., 1998).....	54
3.1	Patients' and Controls' demographic data and cause of injury...	60
3.2	Comparison of mean rCBF values for different structures between control and patient group. <i>p</i> value shows level of significance for Student's T-Test. ** indicates significant difference.....	64
3.3	Comparison of mean rCBF values for different lobes between control and patient group. <i>p</i> value shows level of significance for Student's T-Test. ** indicates significant difference.....	64
4.1	Mean standard deviation and range of Age, BDI_II Score, MMSE Score, and other playing career data information.....	77
4.2	Output of the mediation analysis model including No. of years in NFL (input), PCC volume (Mediator) and BDI_II score (Output).....	83
5.1	Clinical data of the Patient group with TBI, N.A. = Not Available.....	91
5.2	ANOVA analysis between Groups with more venous damage and freestanding damage.....	100

List of Figures, Charts and Plots

Figure		Page
1.1	Male Vs. Female TBI rate per 100,000 across different age-groups (D.J. Thurman et al., 1999)	5
1.2	Example of a normal CT scan image.....	17
1.3	An example of SWI image.....	18
1.4	MRI images (A) ASL image (B) DTI-FA image (C) FLAIR image.....	19
2.1	sequence arrangement for gradient echo sequence (Zhen, 2009).....	24
2.2	Magnitude Image.....	37
2.3	High Pass Filtered Phase Image.....	37
2.4	SWI Image.....	38
2.5	minimum Intensity Projection (mIP) Image.....	39
2.6	A Screen shot of the MRicro program for Skull striping.....	40
2.7	(a) Original Magnitude Image (b) Skull-striped Magnitude Image (c) Skull-striped Phase Image.....	41
2.8	Complex Thresholding Menu.....	42
2.9	(a): Input Phase Image (b): Complex Threshold Output Phase Image.....	43

2.10	Zero Filling Menu.....	44
2.11	3-D Inverse Transform Filter Menu.....	45
2.12	Major Veins Selected.....	47
2.13	Plots of inter-reader correlation for all 8 major veins. Following are the veins: Vein 1: Left Septum, Vein 2: Right Septum, Vein 3: Central Septum, Vein 4: Left Thalamo-striate, Vein 5: Right Thalamo-striate Vein 6: Internal Cerebral Vein, Vein 7: Left Basal Vein of Rosenthal Vein 8: Right Basal Vein of Rosenthal.....	48
2.14	Mean values and error bars of blood oxygen saturation values in major veins. Here * shows statistically significant difference. Following are the veins: Vein 1: Left Septum, Vein 2: Right Septum, Vein 3: Central Septum, Vein 4: Left Thalamo-striate, Vein 5: Right Thalamo-striate Vein 6: Internal Cerebral Vein, Vein 7: Left Basal Vein of Rosenthal Vein 8: Right Basal Vein of Rosenthal.....	52
3.1	PASL, CASL and VS-ASL principles (Liu & Brown, 2007)....	57
3.2	A Flow Chart for ASL describing image processing steps.....	62
3.3	Comparing Cerebral Blood Flow in Thalamus and Striatum between Control and Patient Groups.....	64
3.4	Comparing Cerebral Blood Flow in lobes between Control and Patient Groups.....	65
4.1	A flow-chart showing processing steps.....	79

4.2	(A) Region of interest for PCC and (B) Region of interest for ACC.....	80
4.3	(A) Plot of PCC volume vs. BDI_II score ($p = 0.001$). (B) Plot of ACC volume vs. BDI_II score ($p = 0.023$).....	82
4.4	Plot of Number of years in NFL vs. number of concussions suffered in NFL ($p = 0.0001$).....	82
5.1	Example of continuous vein in mIP SWI image.....	95
5.2	(A), (B): Bleeds associated with Veins.....	96
5.3	Freestanding Bleeds.....	96
5.4	Pearson's Correlation between GCS score and Number of lesions associated with Veins.....	98
5.5	Pearson's Correlation between GCS score and Volume of lesions associated with Veins.....	99
5.6	Group Difference between subjects with more venous associated and more freestanding bleeds.....	99
5.7	Group difference in number of Lesions in groups with severe ($GCS \leq 9$) and moderate-mild ($GCS > 9$) TBI ($p = 0.039$).....	101

List of Abbreviations

TBI: Traumatic Brain Injury

CDC: Centers disease Control and Prevention

mTBI: Mild Traumatic Brain Injury

CSF: Cerebral Spinal Fluid

DAI: Diffuse Axonal Injury

WSTC: Wayne State Tolerance Curve

FEM: Finite Element Model

GCS: Glasgow Coma Scale

PTA: Posttraumatic Amnesia

ACRM: American Congress of Rehabilitation Medicine

WHO: World Health Organization

CT: Computed Tomography

SWI: Susceptibility Weighted Imaging

MRI: Magnetic Resonance Imaging

fMRI: Functional Magnetic Resonance Imaging

DTI: Diffusion Tensor Imaging

FA: Fractional Anisotropy

FLAIR: Fluid Attenuated Inversion Recovery

WMH: White Matter Hyper intensities

SNR: Signal to Noise Ratio

SWIM: Susceptibility Weighted Imaging and Mapping

SAC: Standard Assessment of Concussion

TR: Repetition Time

TE: Echo Time

FOV: Field of View

GRE: Gradient Recall Echo

mIP: Minimum Intensity Projection

SPIN: Signal Processing for NMRI

BET: Brain Extraction Tool

ICV: Internal Cerebral Vein

ROI: Regions of Interest

CBF: Cerebral Blood Flow

ASL: Arterial Spin Labeling

BOLD: Blood Oxygen Dependent Level

SPECT: Single Photon Emission Computed Tomography

PET: Positron Emission Tomography

CASL: Continuous Arterial Spin Labeling

PASL: Pulsed Arterial Spin Labeling

VS-ASL: Velocity Selective Arterial Spin Labeling

SPM8: Statistical Parametric Mapping 8

WFU pickatlas: Wake Forest University pickatlas

PCS: Post Concussion Syndrome

CMRO2: Cerebral Metabolic Rate of O₂

CTE: Chronic Traumatic Encephalopathy

LOC: Loss of Consciousness

NFL: National Football League

PHQ: Patient Health Questionnaire

MMSE: Mini Mental State Examination

BDI: Beck Depression Inventory

VBM: Voxel Based Morphometry

ACC: Anterior Cingulum Cortex

PCC: Posterior Cingulum Cortex

DMC: Detroit Medical Center

GOS-E: Extended Glasgow Outcome Scale

Chapter 1: Introduction to TBI

Definition

Due to a very vast and varied research as well as a large number of different symptoms, implications, treatments and outcomes it has been a real difficult task to come out with a simple definition for Traumatic Brain Injury (TBI) that could help to explain it in a very comprehensive way (Kraus & McArthur, 1996). For example, the term head injury has been used very widely instead of brain injury or TBI. This is a misleading misnomer since a neurological component is not always present in all head injuries. So in a way, the term TBI can be considered a subset of head injury. Again there is a lack of consistency when it comes to definition of TBI in research. To illustrate one of other difficulties, some researchers considered skull fracture as defining characteristics. This would be erroneous since 9 out of 10 skull fractures are not associated with a brain injury and positive predictive value of skull fracture for intracranial injury is only about 22 % (Masters et al., 1987). So to try and come up with a universally consistent definition of the TBI, Centers for Disease Control and Prevention (CDC) published *Guidelines for Surveillance of Central Nervous System Injury* (D.J. Thurman, Sniezek, & Johnson, 1995). As per CDC definition,

“Craniocerebral trauma, specifically, an occurrence of injury to the head (arising from blunt or penetrating trauma or from acceleration/deceleration forces) that is associated with any of these symptoms attributable to the injury: decreased level of consciousness, amnesia, other neurological or neuropsychological abnormalities, skull fracture, diagnosed intracranial lesions or death.”

Global Severity

Since there is very less awareness about the implications of the TBI in general population, it has been often named as “silent epidemic”. This is due to the complexity of the injury itself as well as the long term deterioration in the cognitive, motor, sensory and language abilities. The symptoms may not be visible at the time of injury or right after injury, which makes diagnosis even more challenging. TBI is a leading cause of millions of disabilities or deaths worldwide each year. As per CDC data, only in United States about 1.7 million TBI cases are reported each year (D.J. Thurman et al., 1999). Out of these, about 81 % were emergency department visits. Around 16 % patients were hospitalized and about 3 % of the patients died (D.J. Thurman et al., 1999).

This shows approximately from 150-300+ TBI per 100,000 people every year suffer from TBI. TBI has been a severe problem in some other developed countries as well. Different researchers across the world have found that there have been a big number of reported cases. There have been few studies conducted by different researchers, across different countries on a long time period. Jennet et al., showed that in 1974, there was a TBI related hospitalization and death incident rate of 313 per 100,000 population in Scotland(Jennett & Bond, 1975). Nestvold et al., showed that the same rate in Arkershus County in Norway was 236 per 100,000 in 1974(Nestvold, Lundar, Blikra, & Lonnum, 1988). Tiret et al., showed that in the Aquitaine in France has an incident rate of 281 per 100,000 population in 1986(Tiret et al., 1990). A study from South Australia by Hillier et al., shows the incident rate as high as 322 per 100,000 population in 1987(Hillier, Hiller, & Metzger, 1997). A study by Vazquez-Barquero et al., in 1988 showed the incident rate of 91

per 100,000 populations in Cantabria, Spain(Vazquez-Barquero et al., 1992). In a study by Engberg, Teasdale et al., in 1998, showed the incident rate of 157 per 100,000 populations in Denmark (Zasler, Katz, & Zafonte, 2007). TBI has been even more severe problem in the developing countries and regions. As per the data from South Africa, Taiwan and India, the TBI rate is even higher. There are several reasons for that but mainly it consists of road accident patients. There are few studies conducted in China, Taiwan, India and South Africa. A study in 1985 by Zhao et al., shows the incident rate of 64 per 100,000 populations in rural area of China(Zhao & Wang, 2001). As showed in 1987 by Brown et al., they reported a incident rate of 316 per 100,000 populations in Johannesburg, South Africa(Brown & Nell, 1991). Same way in 1992 Gururaj et al., reported an incident rate of 122 per 100,000 population in Banglore, India(Gururaj, 1995), Chiu et al., in 1994 reported the incident rate of 220 per 100,000 populations in Taipei, Taiwan(Chiu et al., 1997).

The world has seen huge advancements in healthcare and hospital set-up over past 20 years. Due to this there have been less and less mild TBI patients hospitalized. This is largely due to fully advanced ambulance and other outpatient facilities. This also decreases the actual extent of the patients. Along with this, a worldwide variation in defining TBI, different rules for admissions in different hospitals, availability of advanced medical care, quality of the healthcare system and varied data collection methods obstructs the clarity of the bigger worldwide picture. And obviously these are even bigger issues in the developing countries. Right now there is not adequate data from the developing countries and more comprehensive studies needs to be conducted on a larger level. Apart from this a real big hindrance is non-reported cases. Mainly in case of mild TBI (mTBI) a large portion of the patients go unreported. Back in 1987, Fife suggested that only 16 % of the reported TBI

cases were hospitalized (M. A. McCrea, 2008). Also there are few reports that suggest that about 25 % of the patients do not get the medical care required. This is a huge amount of population going unnoticed. Due to this kind of problems actual picture and impact of TBI on the society remains somewhat unclear. But nonetheless it requires more attention.

Epidemiology

In a recent report, CDC concluded that TBI is a cause of about 15.1 % of all hospitalization in all injury. When it comes to patients who died, the number goes as high as 30.5 %. It also accounts for about 5 % of the total emergency department visits. This numbers shows the degree of severity of TBI.

As far as TBI in different sexes is concerned, CDC found a difference between male and female (Figure 1.1). The results show that for different age group males have about 140 % more annual TBI rate (D.J. Thurman et al., 1999). The following plot suggests the same difference across different age groups between male and female. There has been more injury occurrence in the children (age-group between 0-14 years) and older adults (age \geq 65 years). But the plot has a small peak in the age-group of 15-24 years.

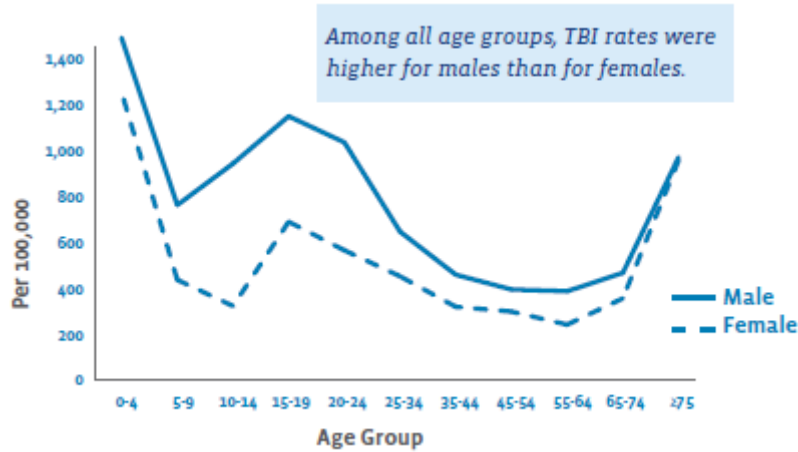


Figure 1.1: Male Vs. Female TBI rate per 100,000 across different age-groups (D.J. Thurman et al., 1999).

Causes

There are several reason and events that can result into TBI. Major causes includes motor-vehicle accident (MVA), assault, fall and sports injury (M. A. McCrea, 2008). Among them, MVA accounts for 35.2 %, falls 17.3 % and assaults 10 % of the total incidents (M. A. McCrea, 2008). Motor vehicle accident is one of the leading causes of TBI. Back in the days, this was the main contributor to the total TBI injuries as well as deaths due to those injuries. Back in 1970s, there was a death rate of 4.6 per 100 million miles traveled in highways. This rate came down significantly and dropped to nearly half in 1980 when the death rate was 2.3 per 100 million miles traveled (M. A. McCrea, 2008). The reasons for this drastic decrease include better safety measures such as airbags and safety/seat belts. The other big reason for the TBI occurrence is falls. In general, senior people tend to suffer TBI after falls in winter. This might be due to higher head-to-body ratio. This is a very big factor and there have been constantly increases in fall induced TBI.

Another major cause of TBI is sports injury. Players suffer from concussions to major head trauma. Some of the major sports are cycling, boxing, hockey, football, soccer etc. Athletes playing these sports are susceptible to head trauma. A lot of these patients have some issues that go unnoticed. Players can be conditioned physically for the sports by training and other drills. But the same is not possible for brain. Therefore there is a need to make sure these patients get required protective gears and accessories. Especially protective gears like helmets could be very helpful. Around 1300 people die every year in bicycle related incidents (Friede, Azzara, Gallagher, & Guyer, 1985). Other major sport is boxing. Atha et al., compared a punch by a professional boxer to a 13 pound mallet swung at the speed of 20 miles per hour (Atha, Yeadon, Sandover, & Parsons, 1985). Over the years due to some preventive measures, better guidelines and availability on onsite doctor, casualty or severity of the injury could be reduced. Soccer is one of the most popular games worldwide. There have been several TBI cases reported every year.

Football is very popular specially in the United States and it is one of the more susceptible sports to TBI. Players are at high risk of being exposed to head or neck injury. Players suffer many concussions during practice as well as games. Looking at the increasing popularity of the game every year, it is important to take preventive measures and make necessary changes in the rules to make it safer. One of the major steps forward in this direction was exclusion of the “head butting” or “face tackling” (Zasler et al., 2007). It played a huge part towards reducing the head injuries. As reported by Blyth et al., only between 4 years of 1971 and 1974, there were 59 deaths due to intracranial injuries in football registered by National Football Head and Neck Injury Registry (Blyth CS & F., 1974). Although TBI is only about 5 % of the total injuries, it consists of total of 70 % of the

deaths. As per Mueller et al., 250,000 concussions each year is a conservative approximation. It also causes about 8 deaths every year (Mueller, 1998). Looking at all this numbers we can get a better idea of how critical the issue is. And apart from the fatalities, the players suffer long term cognitive, motor and other difficulties over the years. This is another issue to be addressed. And this only accounts for reported or registered cases. There are numerable cases going unnoticed at the practice sessions and casual games at the school level. Considering all the issues, it is very important to take necessary steps to reduce the casualties and injuries. That includes measures such as bringing in laws or rules that reduces athletes' exposure towards injury. Developing and using more and more advanced protective gears such as helmets is very important. A very good preseason training and conditioning can prevent players to avoid rash tackle or challenge and keep him safe from injury. Also proper evaluation of an injured player before coming back to the game is very crucial. Often it is the multiple hits that cause severe problems. So it is important that an expert evaluates him before he re-enters the field. Other factors contributing to TBI include drugs and alcohol, pediatric head trauma, child abuse etc.

TBI Mechanism

TBI generally results from mechanical impact or acceleration-deceleration injuries that cause skull fractures, compression of cerebral tissues, and tearing of white and gray matter and subsequent hemorrhage. TBI can lead to a spectrum of histopathological changes that includes hemorrhagic contusion, intra cerebral hemorrhage, subarachnoid hemorrhage, and widespread white matter damage. Therefore, histological damage after TBI can be both focal and diffuse. Another way of injury is contrecoup contusions which is

most common after deceleration of the head in which injury can occur away from the point of impact. Also the severity of secondary injury depends on the severity of primary injury and its location.

Grossly speaking, closed head injury can occur via two ways: direct impact or internal forces. Both involve accelerations and deceleration. Acceleration and Deceleration cause deformation of the tissue that can cause physiological and mechanical injury. There is a debate going on whether it is from rotational or translational forces or both. There are mainly two types of brain injury observed. One is focal and other is diffuse injury. Focal injury includes epidural hematoma, subdural hematoma, intracerebral hematoma etc. On the other hand, brain swelling and diffuse axonal injury (DAI) can be categorized as diffuse injuries. These are mainly primary injuries. There are lots of different secondary injuries observed. Cell death, hypercarbia, cerebral edema, cytotoxic edema, vasogenic edema, intracranial pressure changes, hyper excitation etc. are examples of secondary injury.

The most prevalent type of injury severity is mild TBI, or called concussion. Mild concussions may or may not involve loss of consciousness. It causes confusion, disorientation, post-traumatic and retrograde amnesia. It causes loss of consciousness for less than 24 hours. Even in mild TBI or brain concussion, diffuse axonal injury (DAI) could also be an important pathology. It is basically mechanical disruption or stretching of axons in major white matter tracts. It may extend into the midbrain and brainstem as well. MRI shows micro hemorrhages in corpus callosum, periventricular and other regions. Though 70% of DAI case are severe TBI and it has 42% to 64% of mortality rate, mild TBI patients still could suffer DAI at microscopic level evidenced by advanced imaging

techniques(Zasler et al., 2007). Pathology of DAI can be explained as impairment of axonal transport followed by axonal swelling and retraction balls(Zasler et al., 2007). Primary DAI can be caused by direct axonal disruption. Secondary DAI have some signature anatomy such as progressive changes in axonal cylinder, disconnection between the axons, retraction balls, white matter tracks in corpus callosum, brainstem etc(Zasler et al., 2007).

Coming back to the injury mechanism, first one is translational motion. It is caused by linear acceleration. It usually is seen near the center of gravity of the skull. A curve named Wayne State Tolerance Curve (WSTC) has been established. It is a foundation for the Head Injury Criteria (HIC) published by the National Highway Traffic administration (NHTSA) as a national standard of motor vehicle safety design test (Zasler et al., 2007). It shows the relation between acceleration level and impulse duration necessary to observe the impact. An alternative is named Head Injury Curve. In it, Versace suggested alternative in which effective acceleration was raised to 2.5 powers and multiplied by time duration. Other type of injury is rotational injury. From Wayne State University (WSU) FEM brain model, we can estimate strain experienced by smaller structure even inside the brain. Usual strain locations are fornix, corpus callosum, midbrain, hippocampus etc. Correlations between strain and brain injury locations, symptoms with memory and cognitive problems have been reported. It is easy to prevent brain injury than treat it because usually once a person suffers a brain injury; it takes considerably long amount of time to heal it (Zasler et al., 2007).

Economic Burden

There are several economic implications of the TBI. The direct and indirect costs include direct medical care costs, loss of income due to premature death, work-loss due to injury and disability. A research study by Max et al. reported that the total lifetime cost for the injured patients that year was estimated \$ 37.8 billion (Max, MacKenzie, & Rice, 1991). This cost includes direct expenses, work-loss and disability related costs and income loss due to death. They are respectively 12 %, 55 % and 34 %. Another study by Thurman et al. in 1995 estimated the total lifetime costs for the patients in the same year to be \$ 56.3 billion (Miller, Hayes, & Newcomb, 2001). As investigated by Lewin et al. in 1992, in the year 1991 the TBI related total economic burden was estimated as high as \$ 48.3 billion (Lewin, 1992). Although new studies are required to get new estimates in this time period, just based on this data we can assume that the current costs would be in the order of \$ 100 billion considering higher healthcare costs, epidemiological data and inflation.

Categorization of TBI

There have been multiple approaches used to define mTBI. But in almost all of them the classification is based on the severity of the injury. One of the most common and recognized classification methods is using Glasgow Coma Scale (GCS)(Zasler et al., 2007). Glasgow Coma scale is basically a neurological grading system which grades the patient's clinical consciousness based on their motor, verbal and visual responses (See Table 1.1) (Teasdale & Jennett, 1974)

Function	Score	Response
Motor	6	Obeys verbal commands
	5	Localizes to noxious stimuli
	4	Normal flexion to noxious stimuli
	3	Abnormal flexion to noxious stimuli
	2	Extension to noxious stimuli
	1	No response to noxious stimuli
Verbal	5	Fully oriented and converses
	4	Disoriented and converses
	3	Voices appropriate words
	2	Makes incomprehensible sounds
	1	No vocalization
Eye opening	4	Opens eyes spontaneously
	3	Opens eyes to verbal commands
	2	Opens eyes to noxious stimuli
	1	No eye opening

Table 1.1: Glasgow Coma Scale (GCS). Maximum possible score = 15, Minimum possible score = 3 (Teasdale & Jennett, 1974).

As we can clearly see that GCS has been designed to assess a patient's condition when the patient arrives at the emergency department or at the trauma care center. There have been a few studies which show that GCS is an indicator of the patient's TBI severity and it is also indicative of the outcome of the TBI. Based on this score, TBI can be classified in 3 categories.

TBI Severity	GCS Score
Mild	13-15
Moderate	8-12
Severe	3-9

Table 1.2: TBI severity classification based on GCS.
From Jennett and Teasdale (Jennett & Teasdale, 1981)

GCS is a very widely used measure. It is very sensitive to the severe neurological dysfunction. But it can be sometimes misleading in case of subtle conditions. For example, 15 have been considered a perfectly normal response. In other words a person with GCS of 15 has no neurological dysfunctional problem. But in a lot of cases patients with GCS score of 15 required treatment. So sometimes using GCS it is very tough to predict an mTBI patient. Also GCS has some limitations. For example, it does not consider some of the common mTBI symptoms such as nausea, headache, dizziness etc. Also it does not take into account changes in mental status such as confusion, amnesia, disorientation and lack of concentration. So it is very useful in an emergency setting to assess patient's condition. But relying only on that sometimes can mislead and ignore mTBI.

Since GCS is not a perfect measure to define mTBI, there have been some other classification criteria suggested. In an effort Ommaya and Gennarelli came up with a differentiation criteria based on cerebral concussion. As per their definition, cerebral concussion can be defined as “ *a graded set of clinical syndromes following head injury wherein increasing severity of disturbance in level and content of consciousness is caused by mechanically induced strains affecting the brain in a centripetal sequence of disruptive effect*”

on brain function and structure”(Ommaya & Gennarelli, 1974). Based on the definition they came up with a grading system that rates patients from grade 1 to 7 with 1 being very mild and 7 being death of the patient.

Grade	Change in mental status	Symptoms	Pathophysiology
1	Confusion	Normal consciousness without amnesia	Cortical-subcortical disconnection (CSD)
2	Confusion and amnesia	Normal consciousness with confusion and PTA	CSD; possible diencephalic disconnection
3	Confusion and amnesia	Normal consciousness with confusion, PTA and retrograde amnesia (RGA)	CSD plus diencephalic disconnection (CSDD)
4	Coma (paralytic)	Confusion with PTA and RGA	CSDD plus mesencephalic disconnection (CSDMD)
5	Coma	Persistent vegetative state	CSDMD
6	Death	Fatal Injury	CSDMD

Table 1.3: Ommaya and Gennarelli classification system (Ommaya & Gennarelli, 1974)

There have been some different more inclusive grading systems to define mTBI. Apart from GCS, it also includes posttraumatic amnesia (PTA) and duration of loss of consciousness. Table 1.4 explains one such effort by Stein et al.

Measure	Mild	Moderate	Severe
GCS	13-15	9-12	3-8
Loss of consciousness	<20 minutes	20 minutes to 36 hour	>36 hours
PTA	<24 hours	1-7 days	>7 days

Table 1.4: Multiple indicators of TBI (Stein, 1996)

There has been a novel all inclusive severity scale proposed by Stein et al. It does not include just GCS and PTA. It also includes the symptoms and characteristics at the acute stage. It has been shown in the table 1.5.

Severity	GCS and acute injury symptoms
Minimal	GCS=15, No loss of consciousness (LOC) or amnesia
Mild	GCS=14 or 15 and amnesia; LOC<5 min or impaired memory
Moderate	GCS=9-13 or LOC>5 min. or focal neurologic deficit
Severe	GCS=5-8
Critical	GCS=3-4

Table 1.5: Head injury severity scale (Stein, 1996)

Apart from all these different severity scales and differentiation methods, some committees and groups have tried to come up with a definition for mTBI. As an effort to do so, American Congress of Rehabilitation Medicine (ACRM) came up with a definition. As per ACRM,

“a patient with mild traumatic brain injury is a person who has a traumatically induced physiological disruption of brain function, as manifested by at least one of the following symptoms:

- *Any period of loss of consciousness*
- *Any loss of memory for events immediately before or after the accident*
- *Any alteration in mental state at the time of accident*
- *Focal neurological deficit that may not be transient*

But where the severity of the injury does not exceed the following:

- *Loss of consciousness of 30 minutes*
- *After 30 minutes, an initial GCS score of 13-15*
- *PTA not greater than 24 hours.”(Kay, Harrington, & Adams, 1993)*

CDC also came up with a definition of mTBI. As per the CDC report,

“A case of mTBI is an occurrence of injury to the head resulting from blunt trauma or acceleration or deceleration forces with one or more of the following conditions attributable to the head injury during the surveillance period:

Any period of observed or self-reported transient confusion, disorientation, or impaired consciousness, any period of observed or self-reported dysfunction of memory (amnesia) around the time of injury

- *Observed signs of other neurological or neuropsychological dysfunctions such as*
- *Seizures acutely following the injury*
- *Among infants and young children irritability, lethargy*

Any period of observed or self-reported loss of consciousness lasting 30 minutes or less.

More severe brain injuries were excluded from the definition of mTBI and include one or more of the following conditions attribute to the injury:

- *Loss of consciousness lasting longer than 30 minutes*
- *PTA longer than 24 hours*
- *Penetrating Craniocerebral injury “.(Control, 2003)*

So there have been several efforts towards developing a proper, all inclusive, comprehensive definition for mTBI. But so far there have not been a single definition that can include all the cases. This makes the diagnosis of mTBI more difficult and ultimately lots of patients don't receive required medical attention and care. To date, the ACRM definition and CDC definition on mild TBI might be the most widely used definition.

“Silent Epidemic”

As reported earlier, more than 1.7 million people suffer from TBI annually (D.J. Thurman et al., 1999). Out of all these, about 85 % of the cases are mild TBI cases (Bazarian et al., 2005). As per a World Health Organization (WHO) report, there were around 100-300/100,000 population mild TBI cases treated in hospitals (Carroll LJ, Cassidy JD, Holm L, Kraus J, & VG, 2004). In a 2005 study by Bazarian et al., reported that 503/100,000 populations were reported as mTBI cases who visited emergency department (Bazarian et al., 2005). And apart from these, a lot of cases go unnoticed every year. These people neither get any medical attention or any medical care. All these numbers give us a very clear idea why it is called a “silent epidemic”. In general, highest patients were seen in the age groups of younger than 24 and older than 75 (Bazarian et al., 2005). Considering the inconsistencies in gathering the data, mTBI certainly has a bigger impact than estimated and more comprehensive studies are required for a better estimation of the overall impact.

Neuro Imaging in TBI

Traumatic brain injury is very common in emergency settings. Timely diagnosis of type and severity of injury could help physicians to prescribe appropriate medication could help the surgeons with the surgery. Imaging provides diagnosis in early stages of TBI.

Magnetic Resonance Imaging (MRI) and Computed Tomography (CT) are two major imaging techniques. Although MRI provides different modalities for injury specific imaging, CT is a preferred technique in the emergency setting (Zee & Go, 1998).

A CT scan is performed on patients with head injury in acute setting. Fast imaging and availability are two major advantages of a CT scan. Based on tissue's x-ray absorption ability, different tissues show different contrast in a CT scan image. Fluids and soft tissues are seen as different shades of gray. Bones are very bright and air is very dark (Zasler et al., 2007). An example of a normal brain CT scan is shown in figure 1.2.



Figure 1.2: Example of a normal CT scan image
(www.migrain-aura.com, 2007)

Although CT scan provides a quick image in an emergency setting, Magnetic Resonance Imaging (MRI) provides more details. It gives much more information of brain stem, cranial nerves, skull base and different soft tissues. An MR image shows contrast based in T1 and T2 relaxation properties of the tissue. Based on different weighting used, an MR image could provide specific diagnosis for a specific pathological lesion. For example, Susceptibility Weighted Imaging (SWI) sequence is very sensitive to iron (E. M.

Haacke et al., 2005). It can detect iron in the form of bleed or hemosiderin as well as deoxyheme in veins. This is very useful in detecting small hemorrhages. Figure 1.3 shows an example of an SWI image.

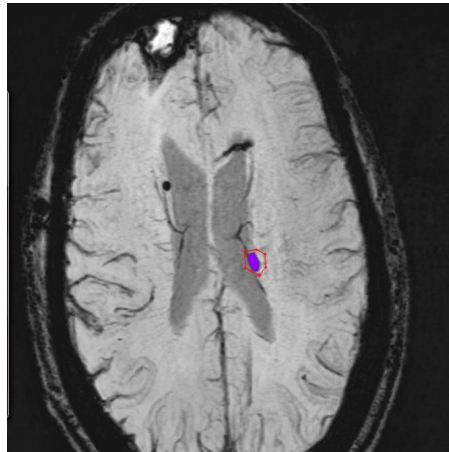


Figure 1.3: An example of SWI Image

Different MR sequences are sensitive in detecting specific pathology. T1 and T2 images provide very good contrast between tissue types. It also provides information regarding any structural damages. T2 weighted FLAIR is very sensitive in detecting White Matter Hyper intensities (WMHs). Correlation between WMHs and functional deficits has been reported in TBI (Hopkins et al., 2003). Diffusion Tensor Imaging (DTI) investigates neuronal integrity. Arterial Spin Labeling (ASL) magnetically tags the blood and measures blood flow to the brain. Figure 1.4 shows an example of ASL, DTI functional anisotropy (FA) and FLAIR image.

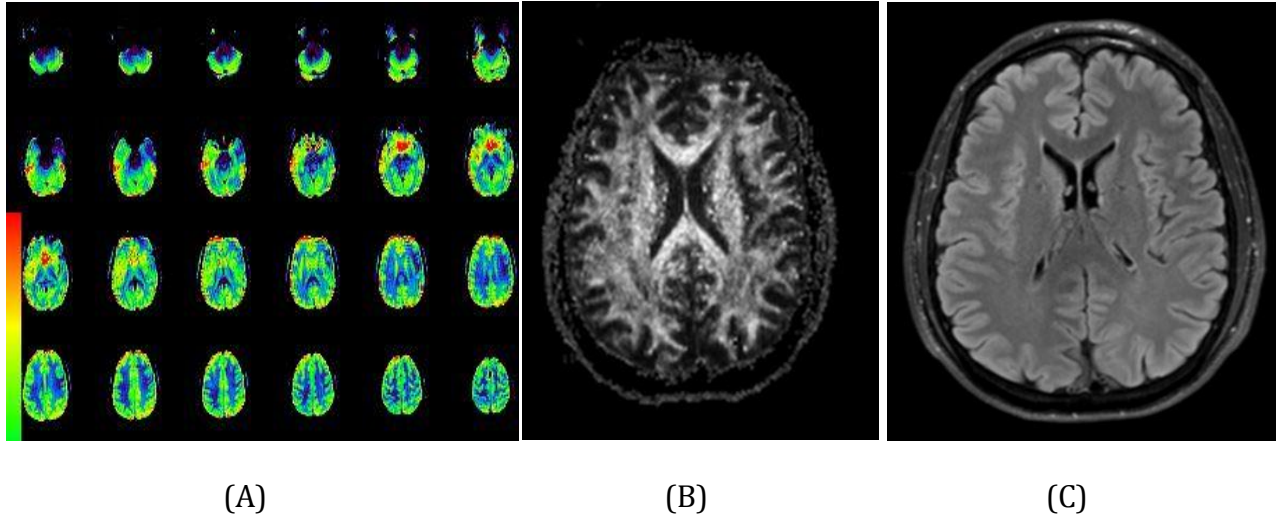


Figure 1.4: MRI images (A) ASL image (B) DTI- FA image (C) FLAIR image

Advanced imaging techniques such as fMRI, SPECT and PET are being used more frequently now. But its application at acute stage is still very limited (Davis et al., 2000). Functional MRI (fMRI) detects the changes in the blood flow. Based on this we can observe changes in brain activity. fMRI along with Single Photon Emission Computed Tomography (SPECT) and Positron Emission Tomography (PET) measures the functional outcome after injury. SPECT and PET use radio isotopes to observe changes in metabolism. PET detects the changes in glucose metabolism. Functional and structural diagnoses sometimes overlap and sometimes they complement each other. It is necessary to use structural imaging like MRI and CT along with functional imaging such as SPECT, PET or fMRI to get the accurate estimation of injury severity and its impact. This might be the correct approach to predict accurate injury outcome.

To sum up, TBI and in particular mTBI is a major cause of concern and it needs more attention. More research needs to be done towards accurate diagnosis of specially mTBI. So

a lot of patients who are ignored could get required medical attention. Imaging provides early diagnosis and assessment of the injury severity. Results from imaging could hold the key in better outcome prediction and designing future medication.

Chapter 2: Cerebral Venous Blood Flow Changes in Mild Traumatic Brain

Injury at the Acute Stage

Motivation and Rationale Behind The Study

TBI is a very serious epidemic in United States as well as in the world. Due to several variables, there is no effective treatment available for TBI at this time. It is necessary to understand the causes of these factors and try to come up with an effective treatment solution. One of the major consequences of TBI is on cerebral blood flow auto regulation. Cerebral blood flow auto regulation is often found disturbed after TBI. There have been studies indicating changes in CBF after TBI. There have been several studies indicating decreased CBF after moderate-severe trauma (Barclay, Zemcov, Reichert, & Blass, 1985; Fieschi, Battistini, Beduschi, Boselli, & Rossanda, 1974; Overgaard & Tweed, 1974; Prat, Markiv, Dujovny, & Misra, 1997). Also there are few studies indicating opposite results at the acute stage after TBI (Bouma & Muizelaar, 1992, 1993, 1995; Kelly et al., 1996; Kelly et al., 1997; Marion, Darby, & Yonas, 1991; Muizelaar et al., 1989). Changes in CBF at very acute stage are very complex and difficult to predict. A better estimation could be very critical in terms of tackling the problem in short as well as long term. It could also help to prescribe future medication and prevent worsening of the injury. There are no reported studies to author's knowledge which investigates changes in CBF at very acute stage (within 24-48 hours) in mild TBI human patients. There are also no reported studies to author's knowledge that observes the changes in both arterial and venous side at very acute stage. The main objective behind this study is to try and understand the changes in CBF at acute stage after TBI. For this purpose, we used a combination of SWI and ASL

sequences acquired in an MRI scan. By using combination of both the sequences, we can get the whole picture of the cerebral blood flow including the arterial side as well the venous side.

Susceptibility Weighted Imaging (SWI) Introduction

Over the years there have been huge leap in the development of imaging techniques. MRI being one of the most useful and widely used techniques, it has very wide applications. But in terms of using MRI as a part of the clinical protocol, it takes a long time for a method to be a part of it. Conventional imaging techniques such as spin density, T1 and T2 weighted imaging have been part of the radiological clinical protocol for a while (Zhen, 2009). For a new technique to be part of the same protocol it takes long time. Generally once the idea of the technique has been proposed it has been used for research purposes for some time. First they are applied on phantoms and dummies. Later they are applied on real patients. Once the larger community once approves the technique based on its practical application, the studies are conducted on larger bases. Later based on its practical application and significance it is accepted worldwide by radiologist and neurologists. Susceptibility weighted imaging (SWI) also went through the same phases before clinicians all over the world started using it widely. Before SWI, generally for all the conventional imaging magnitude image was used for viewing and diagnosis purposes. Phase images were ignored and discarded without consideration. SWI basically increases the contrast based on the local magnetic susceptibility of the tissues. And phase images contain vital information about this susceptibility differences locally between these different tissue types (E. M. Haacke et al., 2005; E. M. Haacke, Xu, Cheng, & Reichenbach, 2004;

Reichenbach, Venkatesan, Schillinger, Kido, & Haacke, 1997). This is very useful piece of information when it comes to quantifying iron content (E. M. Haacke et al., 2005). After oxygen has been delivered, the deoxyhemoglobin contains heme iron. Since to this heme iron has different susceptibility than the surrounding tissues, it can be measured relatively. And since this amount of heme iron is proportional to the oxygen left or oxygen saturation, we can estimate the oxygen saturation. For many years, phase information was not used. Main reason behind that was that due to other magnetic fields in the background, it was not possible to separate out the vital phase information of the difference in tissue susceptibility. But Reichenbach JR et al., in 1997 came up with a method to remove all these junk artifacts (Reichenbach, Venkatesan, Schillinger, et al., 1997). This helped to get the required phase information of the tissue level. This was a very vital development in terms of susceptibility weighted imaging applications. Once the unwanted junk was removed from the phase images, it was very clear that we can see different types of tissue contrast based on the condition. One more very important post processing step was marrying the magnitude and phase information [25]. This SWI image has phase and magnitude information.

There are many different applications of various MRI techniques. It ranges from various type of information acquisition from anatomical to metabolic to functional. For example, functional MRI (fMRI) focuses on the blood oxygenation level dependent (BOLD) signal changes with functional tasks of the brain. On the other hand, diffusion tensor imaging (DTI) focuses on the motion of the water molecule along the neurons/fiber track. Same way, conventional methods like T1 and T2 provides structural information. SWI along with this structural information offers additional piece of data. It contains tissue

information, which has different susceptibility from surroundings. Deoxyhemoglobin, ferritin or hemosiderin are different forms of possible iron content. There are several diseases or conditions like trauma, stroke, aging, multiple sclerosis, tumors, vascular malformation etc which could be monitored for the amount of iron using SWI. Also with the time, there will be more and more practical applications of SWI considering the advantages and information it provides.

Gradient Echo Imaging Basics

Traditionally MRI scans were taken using free induction decay (Bydder & Steiner, 1982; Young et al., 1982). But in this method because of the field inhomogenities there was a significant amount of signal loss. So the idea of spin echo was proposed. After that soon the superconductive systems were manufactured. Because of that spin echo really became common. This lead to many technical advancements (Edelstein, Hutchison, Johnson, & Redpath, 1980; Frahm, Haase, & Matthaei, 1986; Haase, Frahm, & Matthaei, 1986). As suggested by Mugler et al., in 1990, it was possible to get rid of a lot of artifact in a magnitude image using short TE gradient echo sequences (Mugler & Brookeman, 1990). The limitation of huge signal loss, it was not feasible to get a good three dimensional data. The slice thickness was very crude in the order of few mm. Once it became apparent that 3d gradient echo imaging can be really handy, acquisition of data with better resolution, lower signal loss and longer echo time was possible (Zhen, 2009). One very important output of this was that it provided with a better signal to noise ratio (SNR). Due to this it was possible to go on and analyze the phase images (E.M. Haacke, Lai, & Yablonskiy, 1995; Reichenbach, Venkatesan, Yablonskiy, et al., 1997).

In any MRI sequence to get a contrast between tissues it is necessary to create any kind of transverse magnetization. The transmit coil does this part by generating and rf pulse. Assuming the main magnetic field is B_0 and magnetization due to it is M_0 . This M_0 is fully or partly tipped into the transverse plane due to the radio frequency pulse applied by transmit coil. Let's assume that this deflection is created with an angle of θ with reference to the x-plane. But due to this tipping, it creates a y-component which is measured by the receiver coil. This data is encoded and sampled. To make sure there is no transverse component remaining before the next pulse, rf spoiling is applied. This was achieved by changing the axis of radio frequency. Figure 2.1 explains this sequence.

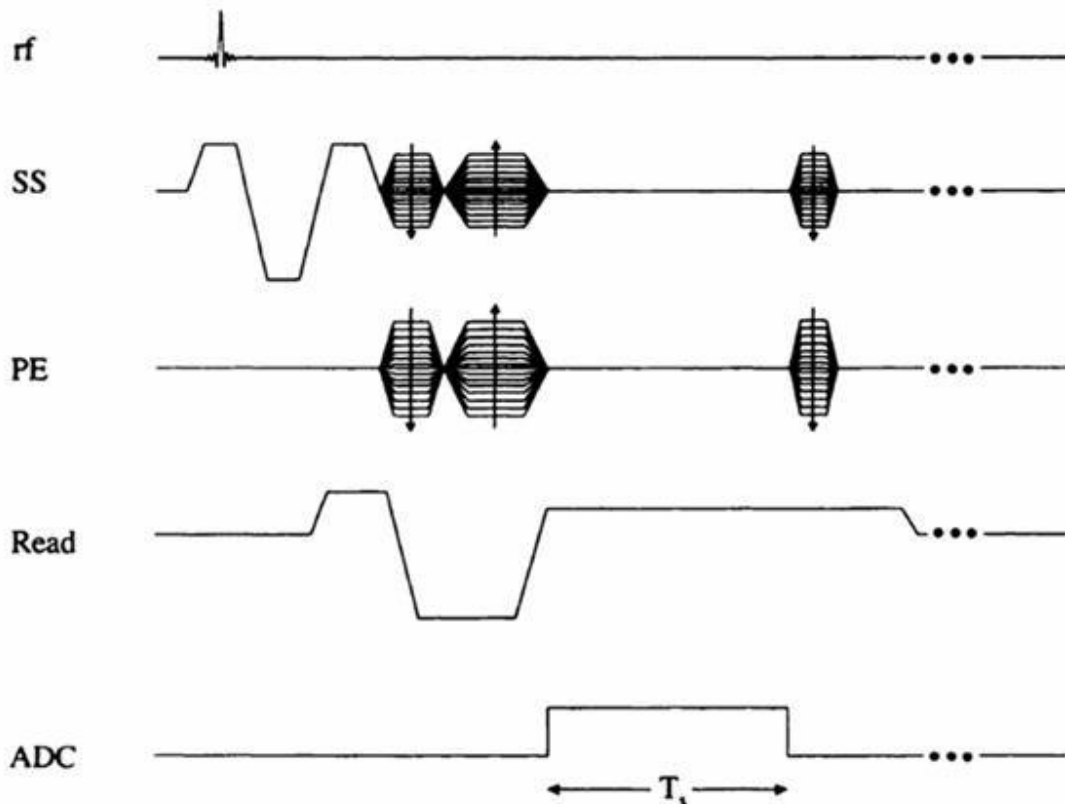


Figure 2.1 : Pulse sequence arrangement for gradient echo sequence (Zhen, 2009).

This is essentially a short TR gradient echo sequence. The magnitude response can be estimated as

$$\rho_m(\theta) = \rho_0 \sin \theta \exp(-TE/T2^*) (1 - \exp(-TR/T1)) / (1 - \cos \theta \exp(-TR/T1)) \quad (1)$$

Here θ is the angle, as explained earlier, with which the M_0 is tipped. It is also called flip-angle. T_1 is of course the longitudinal relaxation time for any given tissue type. TR is the repeat time and is ρ_0 the spin density for any given tissue. Of course above equation explains only the magnitude part of the response. The whole response can be explained by (Zhen, 2009)

$$\rho(\theta) = \rho_m(\theta) \exp(-i\gamma\Delta BTE) \quad (2)$$

Here γ is the gyromagnetic ratio and ΔB is the variation in the local magnetic field. Let's start with basic Larmor equation.

$$\omega = \gamma B_0 \quad (3)$$

And equation for the phase is (Zhen, 2009)

$$\Phi = \omega t \quad (4)$$

So phase difference between two different tissue types can be explained as (Zhen, 2009)

$$\Delta\Phi = \Delta\omega TE \quad (5)$$

But, $\Delta\omega = \gamma\Delta B$ (6)

$$\Delta B = \Delta\chi B_0 \quad (7)$$

Using equations (6) and (7), we can rewrite equation (5) as (Zhen, 2009)

$$\Delta\Phi = -\gamma\Delta\chi B_0 T E \quad (8)$$

This suggests that changes in phase are directly proportional to the changes in the susceptibility at the local tissue level.

Magnetic Susceptibility Basics

When an object is kept in an external magnetic field it responds in a certain way. This response is known as magnetic susceptibility (Zhen, 2009). Considering availability of a uniform magnetic field, induced magnetization can be given as

$$M = \chi H \quad (9)$$

Here M represents the magnetization induced and χ is the magnetic susceptibility relating M and H. But,

$$H = B_0 / \mu_0 - M \quad (10)$$

And $B = \mu H \quad (11)$

Here, H is the magnetic field, μ is permeability defined by $\mu = \mu_0 \mu_r$ where μ_0 is permeability in the vacuum and μ_r is relative permeability. Taking this relative permeability as

$$\mu_r = 1 + \chi \quad (12)$$

We can derive

$$M = \chi B_0 / \mu_0 / (1 + \chi) \quad (13)$$

Since the value of X is extremely small for the linear materials

$$M = XB_0 / \mu_0 \quad (14)$$

This suggests that induced magnetization is directly proportional to the main field and magnetic susceptibility (Zhen, 2009). Depending on the magnetic properties of different substances the value of X varies. For example, value of X is negative for diamagnetic substances. And for the paramagnetic substances, value of X is positive. To take an example, X is 0.45 ppm (parts per million) for deoxygenated blood (Zhen, 2009). Out of all biological tissues, the susceptibility is very less typically lesser than 0.0001 (Schenck, 1996). And at the same time, it is not necessary that iron in any form will be detected. For example if it is shielded by an oxygen molecule, the susceptibility value X becomes zero and it will not be detected (Saini, Frankel, & Stark, 1998; Schenck, 1996).

Geometry Effects

As discussed earlier, since the susceptibility value $X \ll 1$, we usually neglect the effects due to this background tissue. But in the discussion of local magnetic field variation due to the object's geometry it is important to consider that since these local field variation are the reason we get local phase variation in MR. To take an example, for a cylindrical object field variation inside the object can be explained as

$$\Delta B_{in} = \Delta X B_0 (3 \cos^2 \theta - 1) / 6 + X_e B_0 / 3 \quad (15)$$

This expression includes Lorentzian sphere term. Angel with the main magnetic field is θ , $\Delta X = X_i - X_e$, where X_i and X_e are susceptibility changes inside and outside the

cylinder respectively. Considering no effects of the $X_e B_0/3$ term, by removing it we can write

$$\Delta B_{in} = g_{in} \Delta X B_0 \quad (16)$$

$$\text{So, } g_{in} = (3\cos^2\theta - 1) / 6 \quad (17)$$

Let say, for a cylindrical object such as a blood vessel,

$$\Delta B_{in} = \Delta X_{do} B_0 (3\cos^2\theta - 1) / 6 \quad (18)$$

$$\text{Here, } \Delta X_d = 4\pi A (0.18\text{ppm}) \text{Hct} (1-Y) \quad (19)$$

Here, In the equation, A is absolute susceptibility of blood in vivo dependent constant. Y represents oxygen saturation and Hct is Hematocrit. This was about the variation of the field inside the object. But when we are talking about the variation in the field outside, it gets more complex. It can be explained as

$$\Delta B_{out} = \Delta X_{do} B_0 \sin^2\theta \cos(2\varphi) a^2 / r^2 / 6 \quad (20)$$

Here r is the distance to the cylindrical axis, φ is the angel vector r makes to the projection of the main field direction onto a plane perpendicular to the axis of the vessel. Here one very important assumption is that the blood vessel is a cylinder with radius a and with an angel of θ with the main field.

This is still about simpler shapes such as cylinder. More complex the geometry, more complex the calculations get. But crux here is that the geometry changes the local field variation, which in turn leads to susceptibility differences. This results into the variations in the phase of the final MR image.

Creating Susceptibility Weighted filtered phase images

First priority is to remove the low frequency components from the phase image due to background field changes. It has been filtered and divided in to the original phase image. Generally a 64 by 64 high pass filter is used to achieve this. Output image is generated by complex division of the original image $\rho(r)$ and complex image $\rho_n(r)$, which is truncated to an $n \times n$ complex image (Wang et al., 2000).

$$\rho'(r) = \rho(r) / \rho_n(r) \quad (21)$$

Once the artifacts due to this background field changes in removed, we have a very good image with good differentiation between different types of tissues depending upon their relative susceptibilities.

Merging Magnitude and Phase Images

It is very important to get a cleat contrast between two adjacent structures or tissues. One major problem with phase images is that due to phase inside and outside of the tissue, it is tough to differentiate between tissues of different susceptibilities. To overcome this problem it is necessary to suppress certain phase values. To achieve this, a phase mask is created which helps in increasing contrast in the magnitude image. Final SWI image is a multiplication of this phase mask and original magnitude image (E. M. Haacke et al., 2004).

Generally this mask has values between 0 and 1. Depending upon the application and requirement the mask is given values. For example, when there is no need of any enhancement or changes, mask gets the value of 1 in those pixels. Other pixels are assigned

different values depending on the phase of interest. As an example, if phase of interest is negative, mask can be designed as,

$$f(x) = (\pi + \Phi(x))/\pi \quad \text{for } -\pi < \Phi(x) < 0. \quad (22)$$

$$= 1 \quad \text{otherwise.}$$

Here phase at any location x is given by $\Phi(x)$. To create a better and optimized image the mask is multiplied multiple times to the original magnitude image get the best result.

$$P''(x) = f^m(x) \rho(x) \quad (23)$$

Each image created with different number of times phase multiplication has a different contrast. One other advantage of this kind of processing is that we get the information of the signal changes from phase as well as $T2^*$. Since both are complement to each other, it provides vital inclusive information. So marrying phase and magnitude information ensures correct tissue differentiation.

Susceptibility Weighted Imaging and Mapping(SWIM)

Having a capability to measure iron in nonheme or heme form is very important. To achieve this using the local magnetic susceptibility information has been proposed with using fast Fourier transform. As proposed by Deville et al, it can be determined using a k -space expression to analyze distant dipolar fields (Deville, Bernier, & Delrieux, 1979). One of the options is to implement inverse of Green's function (Kressler et al., 2010). The main goal here is to get the reconstruct the local susceptibility distribution. To achieve this, a phase image has been high-pass filtered and a Fourier transform has been applied onto it

first. After that, a regularized inverse filter $g^{-1}(k)$ has been applied (E. M. Haacke, Tang, Neelavalli, & Cheng, 2010). This filter can be defined as

$$g(k) = 1/3 - k_z^2 / |k|^2 \quad (24)$$

Here k_x , k_y and k_z are coordinates in the k -space. $|k|^2 = k_x^2 + k_y^2 + k_z^2$. As we can clearly see, the filter has limitations. The value of the filter becomes zero when $k_z^2 / |k|^2$ become zero. Which means, when $2 k_z^2 = k_x^2 + k_y^2$, the filter has a zero value. And since we are applying the inverse filter, the $g^{-1}(k)$ becomes undefined. To avoid running into this problem, we need to regularize the filter in way that (24) the filter $g(k)$ has a minimum value a , so that the inverse value stays properly defined and (25) the inverse filter $g^{-1}(k)$ is blandly brought down to zero as k tends towards k_{z0} . Here note two things that by k -space we are talking about the Fourier domain. Not the regular k -space data in MRI. Secondly, for which value of k the equation (24) is satisfied, is considered as k_{z0} . As mentioned earlier, a constant a is defined so that $|g(k)| < a$. This preventing the inverse filter from too large values, which in turn increases the noise points near the singularities. Now to blandly bring inverse filter to zero, smoothing has been achieved by multiplying $g^{-1}(k)$ by $\alpha^2(k_z)$, where $\alpha(k_z)$ can be defined as,

$$\alpha(k_z) = (k_z - k_{z0}) / (b\Delta k_z) \quad \text{when } |(k_z - k_{z0})| \leq b\Delta k_z \quad (25)$$

$$\alpha(k_z) = 1 \quad \text{when } |(k_z - k_{z0})| > b\Delta k_z$$

Where Δk_z is the k -space sampling interval in z direction. The idea is that the filter which is at its maximum peak at distance b pixels from the singularity starts reducing and brings to

zero at the singularity. Calling the high-pass filtered or unwrapped phase image as $\Phi(k)$, the regularized inverse filter can be calculated as

$$X(r) = FT^{-1} (g_{reg}^{-1}(k) \Phi_{zf-proc}(k)) / (\Phi B_0 TE) \quad (26)$$

Here, $\Phi_{zf-proc}(k)$ is the Fourier transform of the high-pass filtered phase image. Subscript *zf-proc* denotes to high-pass filtered, zero filled phase image. Here one very important point is that we are imposing a $g_{reg}^{-1}(k) = 0$ condition here. That means that we are measuring relative susceptibility, not absolute susceptibility.

Now as per the discussion above, the filter is limited by two constants *a* and *b*. The chosen values are very crucial in improving quality of the filter. Value of *a* tells us to how large amount the streaking effect will occur. The main reasons behind this are ill-posedness of the inverse approach and discretization errors (E. M. Haacke et al., 2010). The factor *a* has both advantages and disadvantages. As discussed earlier, it stops the filter from being ill-defined, due to discretization; it adds step-wise discontinuity in the filter when it comes to singularity. In other words, the transition is not smooth. To avoid these abrupt transition, $\alpha(k_z)$ has been defined. So as per equation (25), the inverse filter value is blandly reduced when it is coming from a distance of *b* pixel from the singularity towards the singularity, where the value becomes zero. So *b* can be defined as

$$b = |k_{za} - k_{zo}| / \Delta k_z \quad (27)$$

This way, we can reduce the amount of dipole effect seen in the phase images. We can also eliminate the phase differences due to some of the bigger vessels. It is possible to get the consistent susceptibility through the whole vessel.

Materials and Methods

The study was conducted in collaboration with Detroit Medical Center and Wayne State School of Medicine. Patients were recruited from the Detroit Medical Center with consent. All patients met with the criteria defined by American Congress of Rehabilitation Medicine (ACRM). All the patients were scanned at acute stage within 24 to 48 hours after injury. Total 14 patients were scanned and SWI sequence was acquired. All of these patients had Glasgow Coma Scale (GCS) in the range of 13 to 15. For mTBI patients, neurocognitive status was measured using standard assessment of concussion (SAC). This test also includes attention, orientation and memory status. This gives a general idea of patients overall status and sometimes helps clinicians to diagnose a patient. 18 age and gender matched controls were also scanned for comparison.

<u>Case ID</u>	<u>Age</u> (Years)	<u>Gender</u>	<u>Race</u>	<u>Scan Timing</u>	<u>ER</u> GCS	<u>Injury</u> Mechanism
<u>Patients</u>						
2	29	M	Caucasian	10 Days	15	MVA
4	20	M	Caucasian	27 Hours	15	Fall
6	21	M	Black	4 Days		MVA
7	25	M	Black	17 Hours	15	Assault
9	56	M	Indian	26 Hours	15	MVA
11	35	M	Black	36 Hours		Fall
14	30	M	Caucasian	7 Days	15	Fall
15	36	F	Black	9 Hours	15	MVA

16	19	M	Black	3 Hours	15	MVA
17	23	M	Black	9 Hours	15	MVA
18	21	F	Caucasian	2 Days	15	MVA
19	30	F	Asian	8 Hours	15	Hit by a car
001	27	F	Caucasian	41 Hours		MVA
002	24	M	Caucasian	46 Hours		Fall
Mean	28.29			55.28 Hours		
Std. Dev.	9.6			68.82 Hours		
<u>Controls</u>						
001	24	F	Chinese			
003	45	M	Caucasian			
005	22	M	Caucasian			
006	27	M	Chinese			
007	23	F	Chinese			
008	22	F	Chinese			
009	65	F	Chinese			
036	52	F	Caucasian			
037	44	M	Caucasian			
038	41	M	Caucasian			
039	28	F	Caucasian			
040	27	F	Afghanistani			
041	29	M	Caucasian			

042	33	M	Caucasian
043	66	F	Caucasian
044	38	M	Hispanic
045	28	M	Caucasian
046	21	M	Black
Mean	35		
Std. Dev.	14.42		

Table 2.1: Patients' and Controls' demographic data and cause of injury

Table 2.2 shows SAC scores of the patient group.

Patient ID	Orientation	Memory	Concentration	Delayed Recall	Total Score
011	5	15	4	5	29
014	5	15	5	0	25
015	5	13	4	1	23
016	5	14	2	4	25
017	5	12	2	0	19
018	5	14	3	2	24
019	5	15	3	2	25
Mean	5	14	3.29	2	24.28
Std. Dev.	0	1.15	1.11	1.91	2.98

Table 2.2: SAC scores of the patients'

The patients were scanned on a Siemens 3T VERIO magnet. They were scanned with a 32 channel head coil. The Repetition time (TR) was 39 milliseconds and Echo time (TE) was 20 milliseconds. The flip angle was 20 degrees. Field of view for the acquisition was 256x256. The in-plane resolution was 0.5x1x2. It was later interpolated to 1x1x2 in-plane resolution.

SWIM processing was performed on the whole dataset. As mentioned in the previous section, SWI is a T2* Gradient recall echo (GRE) based sequence with a longer echo time (TE). But instead of throwing the phase images away, it integrates both magnitude and phase image and utilizes information from both images. Basically magnetic susceptibility between different tissue types is different and SWI uses this property. Especially iron has very high susceptibility than surrounding tissue. Hemoglobin in the blood has a lot of iron. But when it is bound with the oxygen, it is shielded. So the huge susceptibility difference due to iron is not evident. But when blood delivers the oxygen, we have deoxyhemoglobin. In this molecule, due to no oxygen, iron is not shielded and we can see the susceptibility difference. This is the basic mechanism that makes SWI very sensitive to the venous blood. As discussed earlier, SWIM method has been proposed to map this venous blood regardless of size and orientation of the vein. For this a regularized inverse filter has been applied to the Fourier transform of the high pass filtered phase image. As described earlier, we can obtain relative change in susceptibility map from

$$\Delta\chi(r) = FT^{-1} [G^{-1} * [FT[\Delta B_{\text{local tissue}}(r)]]]$$

Here, G^{-1} is the regularized inverse filter. $\Delta\chi(r)$ is the susceptibility change or difference.

Image Processing

The SWIM processing is a very unique and complex method. To process the data out in-house SPIN software was used. The processing includes several preprocessing steps. First the magnitude and phase images are acquired from the scanner. The scanner gives the high pass filtered phase image. The high pass filter used for filtering is usually 96x96 hanning filter. Figure 2.2 and 2.3 are examples of the two images.

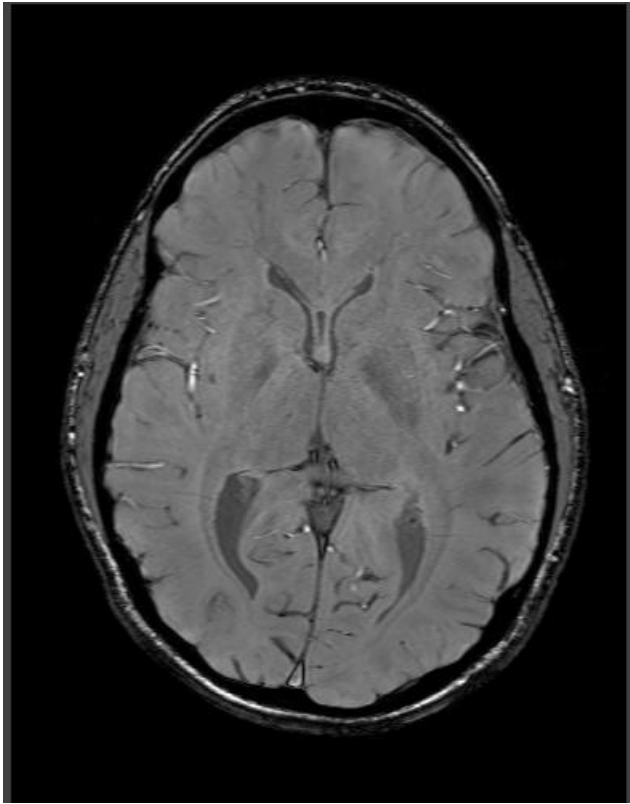


Figure 2.2: Magnitude Image

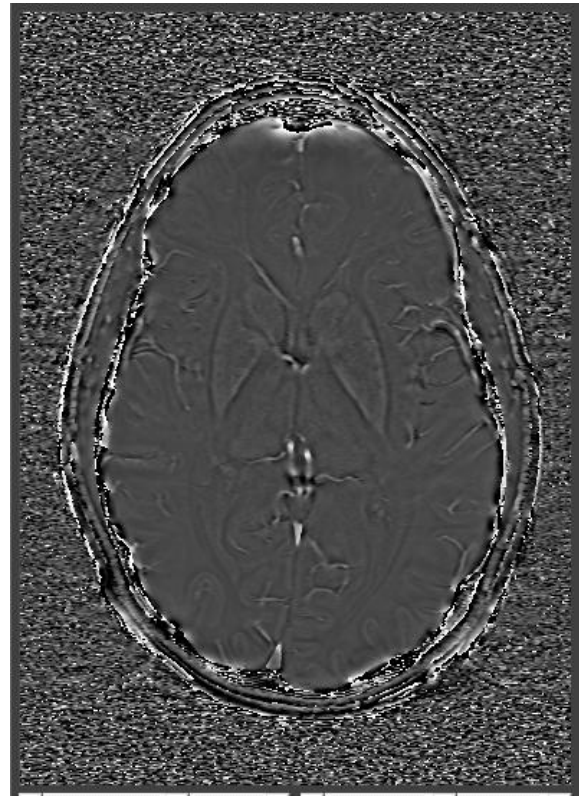


Figure 2.3: High Pass Filtered Phase Image

The SWI sequence is very sensitive since it marries both phase and magnitude information. For this the magnitude image has been multiplied four times with the phase

image. This gives more stress to the phase information and creates a new image known as SWI image. This is a unique image which is very useful in detecting micro-bleeds and hemorrhages.

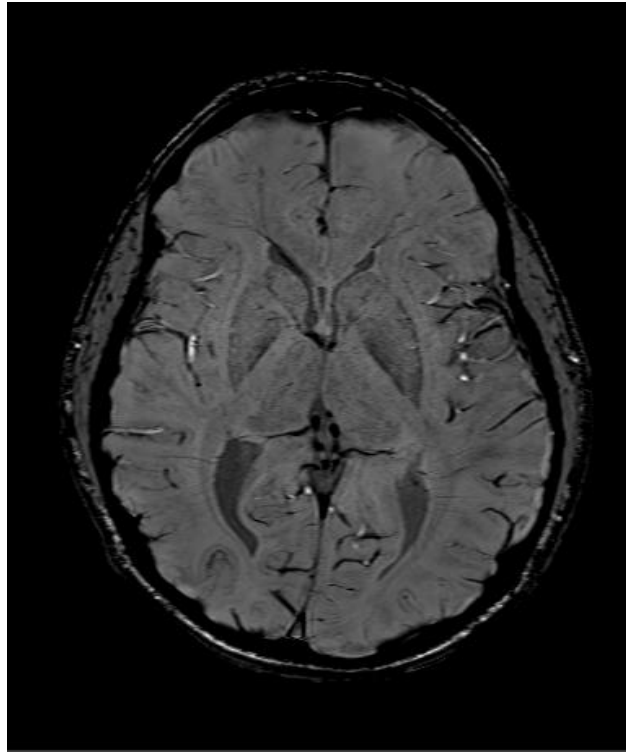


Figure 2.4: SWI Image

As seen in figure 2.4, the final SWI image has lot more information than just magnitude image. Since we are putting more weight to the phase information, it helps to visualize the venous information much better. A better image for visual purpose can be created by combining and stacking few images. This is called Minimum intensity projection (mIP). Basically in this we can stack the 4 images into a single image and the lowest

intensity information would be included out of all four slices. This gives a great new means to visualize the continuity of the vein. Figure 2.5 is an example of such image.

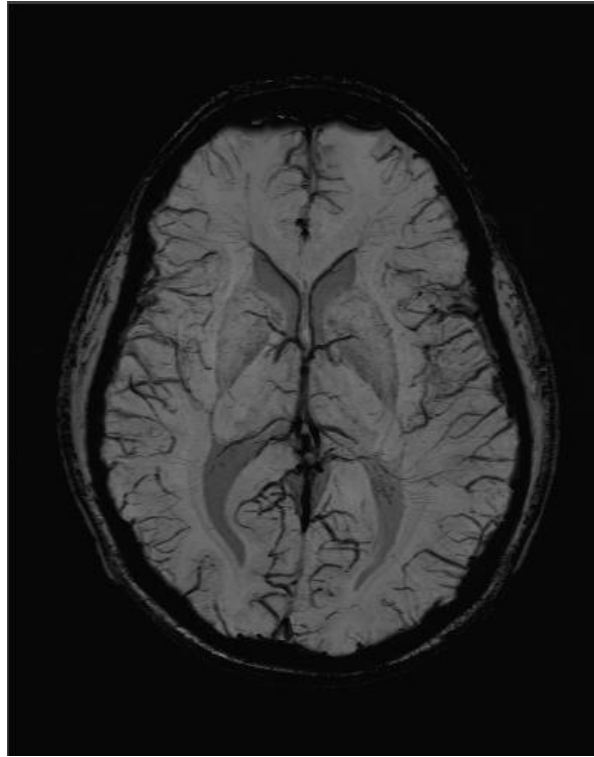


Figure 2.5: minimum Intensity Projection (mIP) Image

The mIP image has a good contrast (Figure 2.5). But more importantly it gives a unique and all new means of visualizing the venous structures. Due to this, we can also see the attached micro bleeds and hemorrhages.

Skull-Stripping

The first step includes the removal of the skull. There are some air-tissue interface artifacts in the image. It is necessary to remove them. So the phase image needs to be skull stripped. The magnitude image has been skull-stripped first. For this the software package

MRicro (MRicro, Version 1.40) has been used. A screen shot of the software has been shown in the figure 2.6.

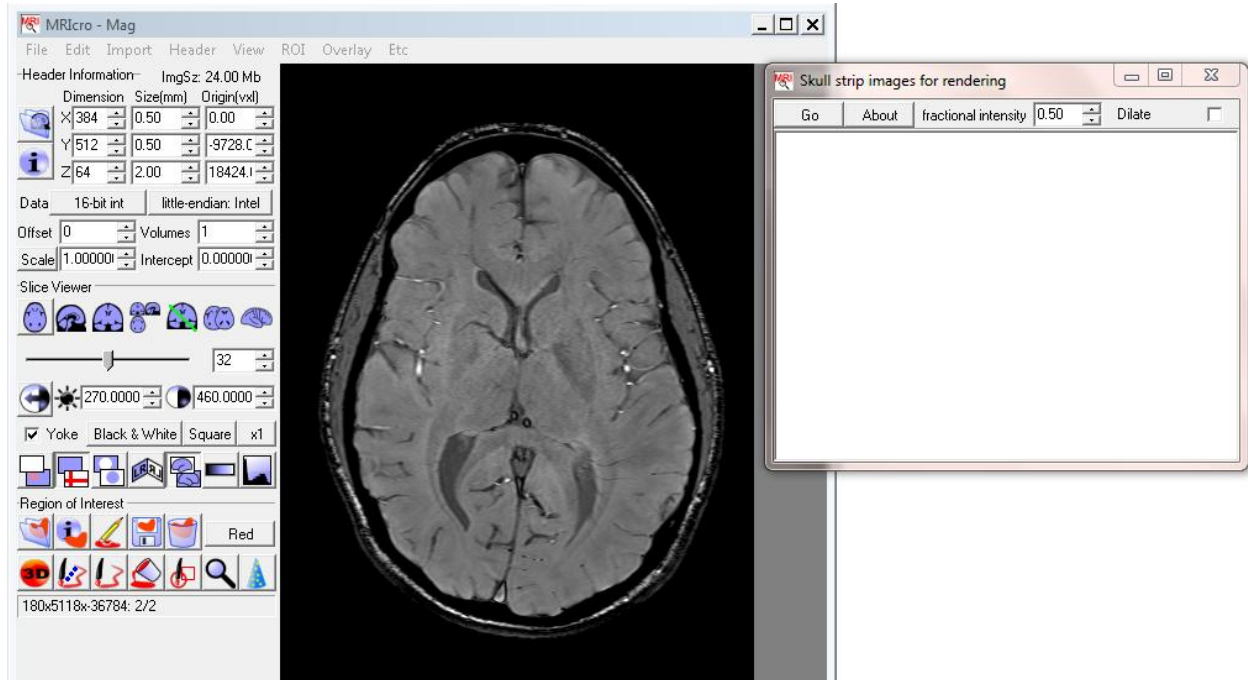


Figure 2.6: A Screen shot of the MRicro program for Skull stripping

The program MRicro uses Brain Extraction Tool (BET) developed by Steve Smith (S. M. Smith, 2002). It is a very convenient, easy-to-use and efficient tool. The program assumes intensity as mass and finds a “center of gravity” based on that. So there might be a problem when the “center of gravity” is not near the center of the image. The changes in the processing can be made by changing the default threshold values of 0.5. The lesser the threshold value, the output is more volume left and a smoother brain. It can be changed according to the requirements. Usually the output images are well skull striped. To skull strip the phase image, a mask from the skull striped magnitude image has been applied onto the phase image. Figure 2.7 shows the resulting skull striped magnitude and phase images.

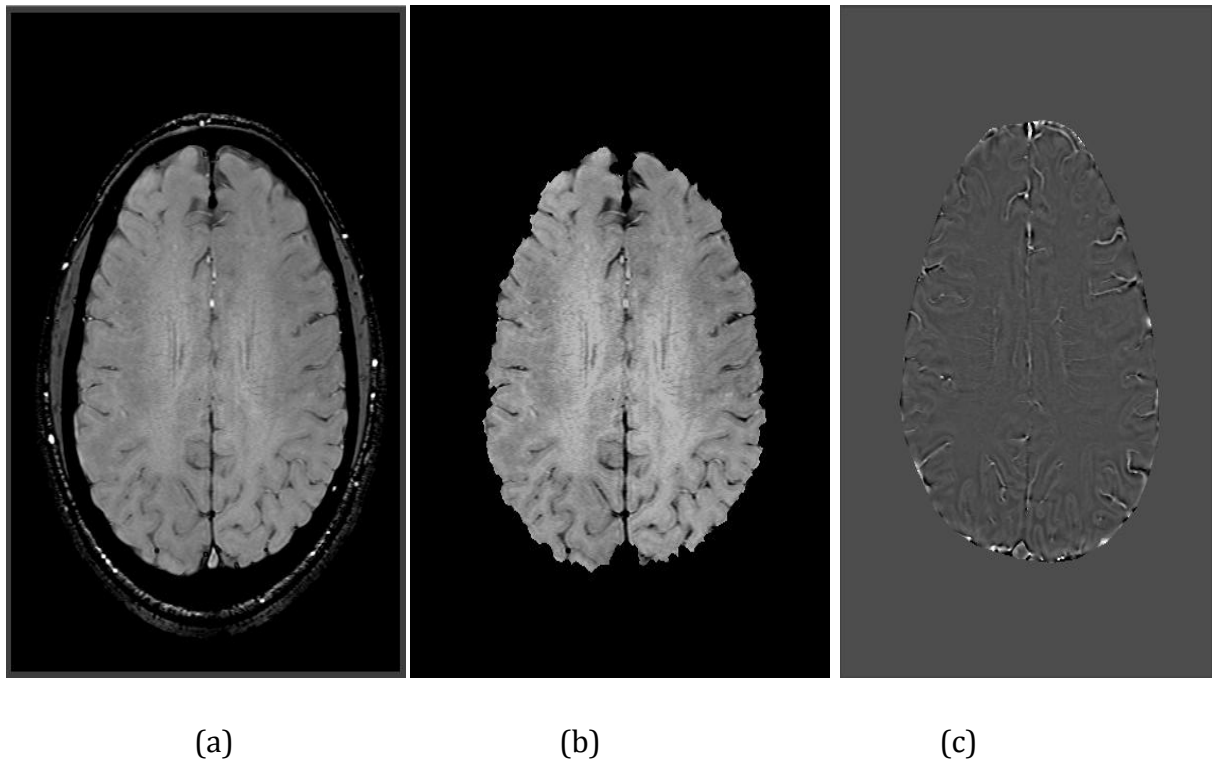


Figure 2.7: (a) Original Magnitude Image
 (b) Skull-stripped Magnitude Image
 (c) Skull-stripped Phase Image

So as part of preprocessing, the magnitude image has been skull striped and phase image has been high-pass filtered and skull striped.

Complex Thresholding

The next step is Complex Thresholding. Before sending images into the pipeline, it is necessary to remove unwanted noisy pixels. This is accomplished by complex thresholding. It basically uses an algorithm based on the proposed method by Pandian et al., in 2008 (Pandian, Ciulla, Haacke, Jiang, & Ayaz, 2008). The basic idea behind the algorithm is to find

out the voxels that lie outside the σ standard deviation. Moreover it has a threshold based on the minimum connectivity. That means it is necessary to connect certain number of voxels in the same cluster if they are to be included. Figure 2.8 is an example of the screen window.

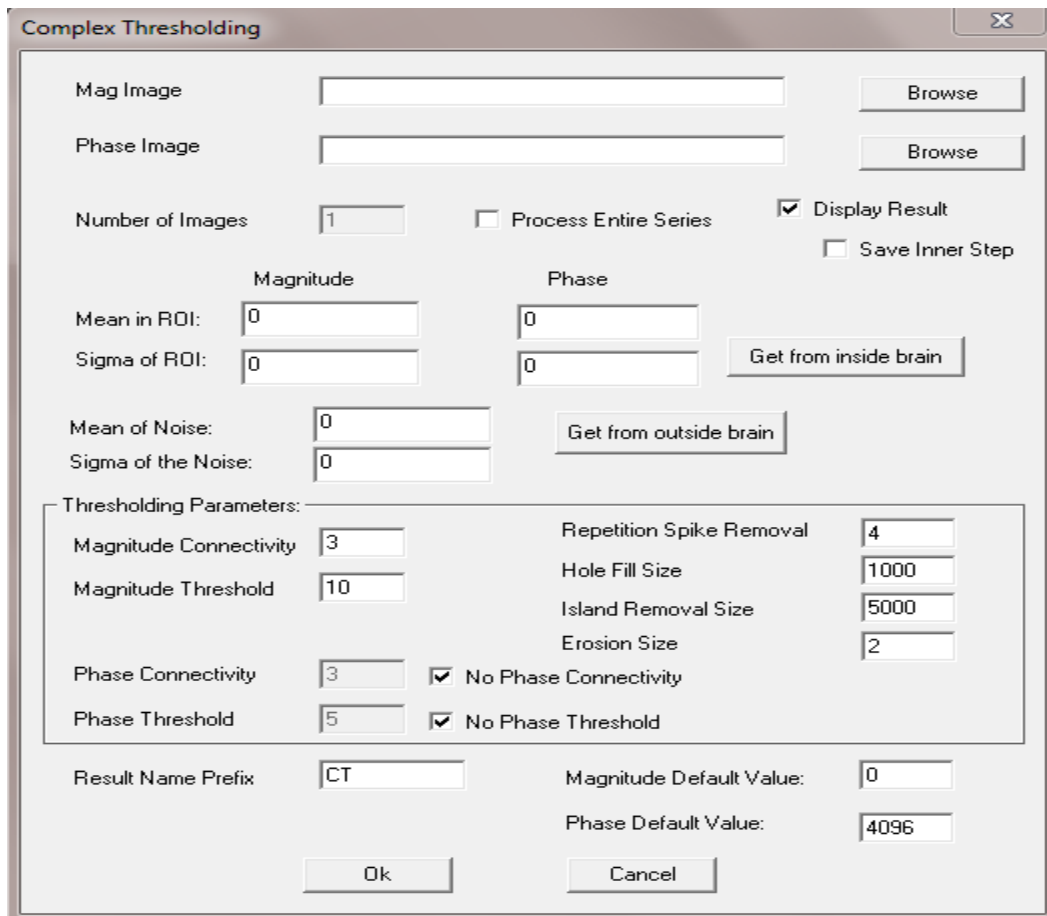


Figure 2.8: Complex Thresholding Menu

The figure 2.8 shows a typical complex thresholding window. Mag and Phase images are the tabs where we input the magnitude and phase images. After that, a mean and standard deviation values are included from magnitude as well as phase images from inside the brain. An area outside the brain is also selected in the magnitude image. In the

threshold parameters, magnitude and phase connectivity defines the minimum number of connected voxels to be included. Magnitude threshold is the number of standard deviation from the mean the threshold is set for. If there is some part of the tissue separate from the brain and smaller than a defined specific number, then that will be removed. This number is defined by Island Removal Size. Hole fill size functions as a checking operator. If the removed numbers of pixels are less than a certain number, it will be filled back. This number is defined in Hole Fill Size. Magnitude and Phase default values indicate the intensity values of the new pixels that are removed or filtered. If not skull striped before, phase images can be skull striped in this step as well. Figure 2.9 shows the input and output of the complex thresholding process.

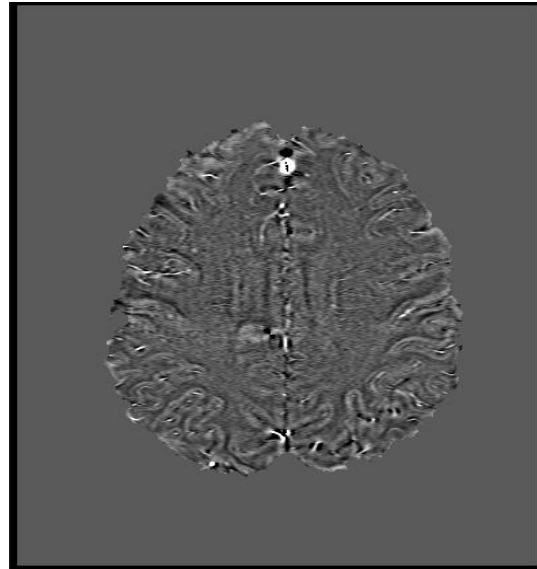
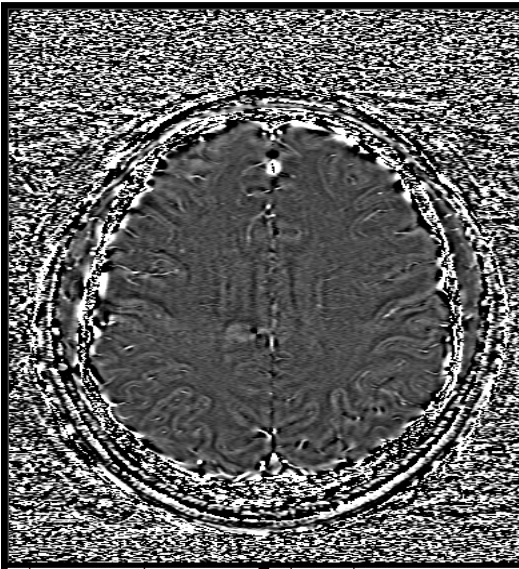


Figure 2.9 (a): Input Phase Image

(b): Complex Threshold Output Phase Image

In the above figure, (a) is the input of the complex thresholding process and (b) is the output of it. As we can see, it performs the skull stripping very efficiently as well. Suggested values for phase and magnitude connectivity are usually 3. Suggested Hole fill size, Island Removal Size and Erosion Size are respectively 1000, 9000 and 2.

Zero Filling

It is recommended to keep the total field of view in the ratio of 1:1:4. To obtain this ration, generally the image matrix is filled with extra slices as well as outside of the image as per required. Generally the image matrix has been converted to the 512x512x128 matrix size. Shown below is the input menu for the zero filling function.

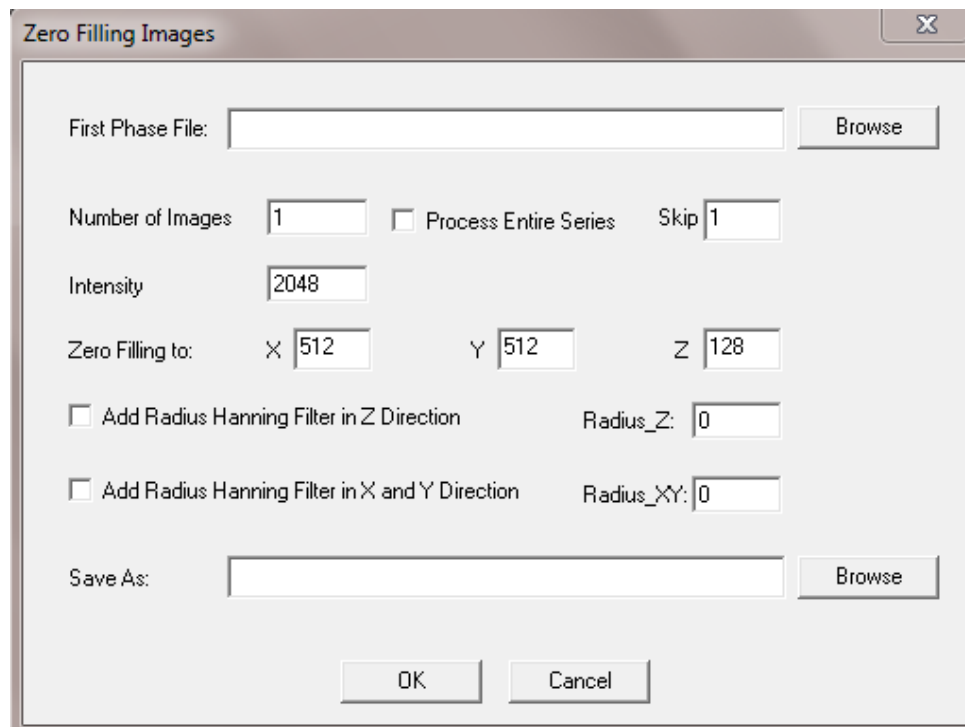


Figure 2.10: Zero Filling Menu

It is a very simple and minimal input menu. Intensity has been selected 2048. We can select or browse the first phase image and put it as an input. Matrix size has been selected as 512x512x128. If a hanning filter is added, the radius of the filter has been selected using Radius_z or Radius_XY for filter in z direction or in XY plane direction respectively. Basically this would add required slices before and after the image slices in the matrix to change it to the specified matrix size.

Inverse Filtering

This is the final step of the SWIM processing. As explained earlier, in this a regularized inverse filter has been applied onto the Fourier transform of the phase image. The menu has been described below.

The screenshot shows a dialog box titled "Three Dimensional Ideal Inverse Filter Parameters". It contains the following fields and controls:

- First Phase File:** A text input field with a "Browse" button to its right.
- Voxel Size:** A group box containing three input fields: X (0.5), Y (0.5), and Z (1). To the right of these fields is a "skip" label and an input field with the value 1.
- Rotation:** A group box with three radio buttons: "Axial" (selected), "Saggital", and "Coronal".
- Number of Images:** An input field with the value 1.
- Process Entire Series:** A checked checkbox.
- Field Strength:** An input field with the value 3.
- EchoTime:** An input field with the value 20.
- Threshold Value:** An input field with the value 0.1.
- Add Radius Hanning Filter:** An unchecked checkbox.
- Radius:** An input field with the value 0.
- Save As:** A text input field with a "Browse" button to its right.
- Buttons:** "OK" and "Cancel" buttons at the bottom center.

Figure 2.11: 3-D Inverse Transform Filter Menu

As shown in figure 2.11, we just have to add the technical parameters such as TE, TR, and Field strength and voxel size. We can browse the image and save the output image is the desired folder.

Selection of the Major Vessels

The next part of the analysis is selection of the major veins. We selected 10 major, prominent and consistent vessels for the analysis. This included the following vessels. First three are Left, right and central Septum veins. The Septum veins are deep frontal veins. They receive blood supply from the anterior part of the frontal lobe mainly. It runs along the anterior walls of the frontal horns of the ventricles. It runs behind the frontal part of the Corpus Callosum called Genu. The next big vessels selected were left and right Thalamo-striate veins. As the name suggests, it basically receives blood from thalamus and striatum area. The next selected major vein was Internal Cerebral Vein (ICV). They are major veins and choroidal veins, thalamo-striate veins and septum pellucidum veins are drained into the internal cerebral vein. They are drained into the Cerebral Vein of Galen. The next big veins are Basal Vein of Rosenthal. Developing in the temporal lobe's medial surface, it runs medio-posteriorly. It also drains in the Vein of Galen. Next small veins selected were trans-medulla veins. These are very small veins and runs across the medulla. The major vessels are shown in the figure below.

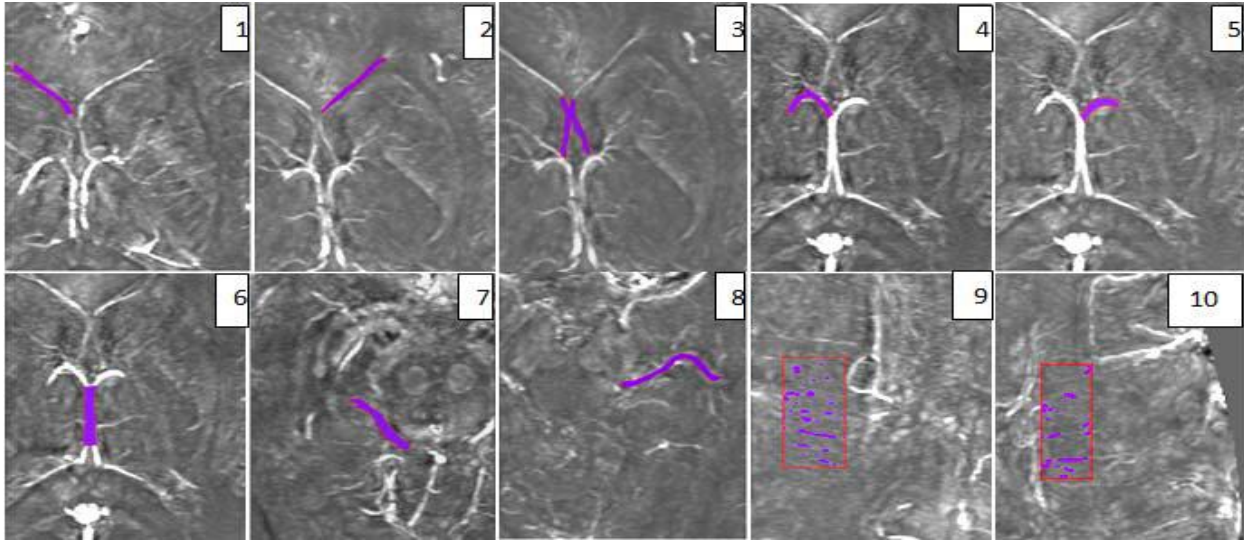


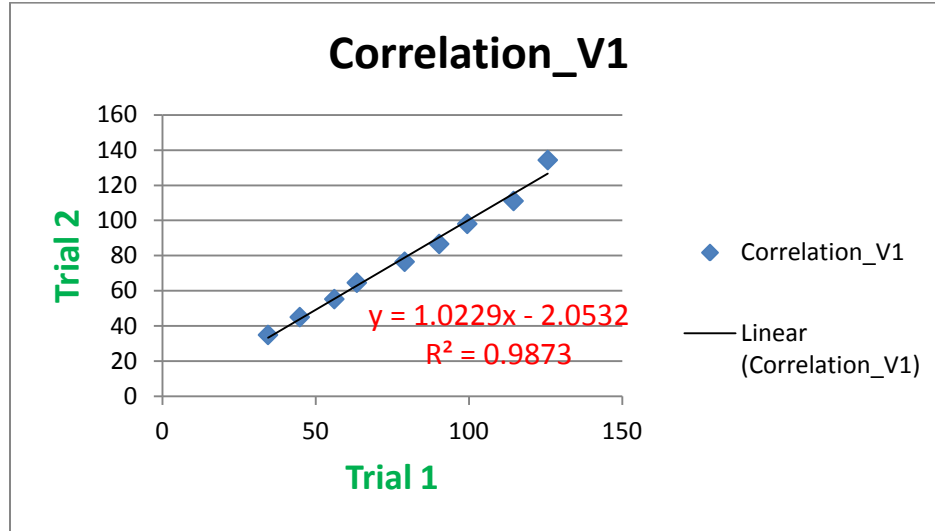
Figure 2.12: Major Veins Selected

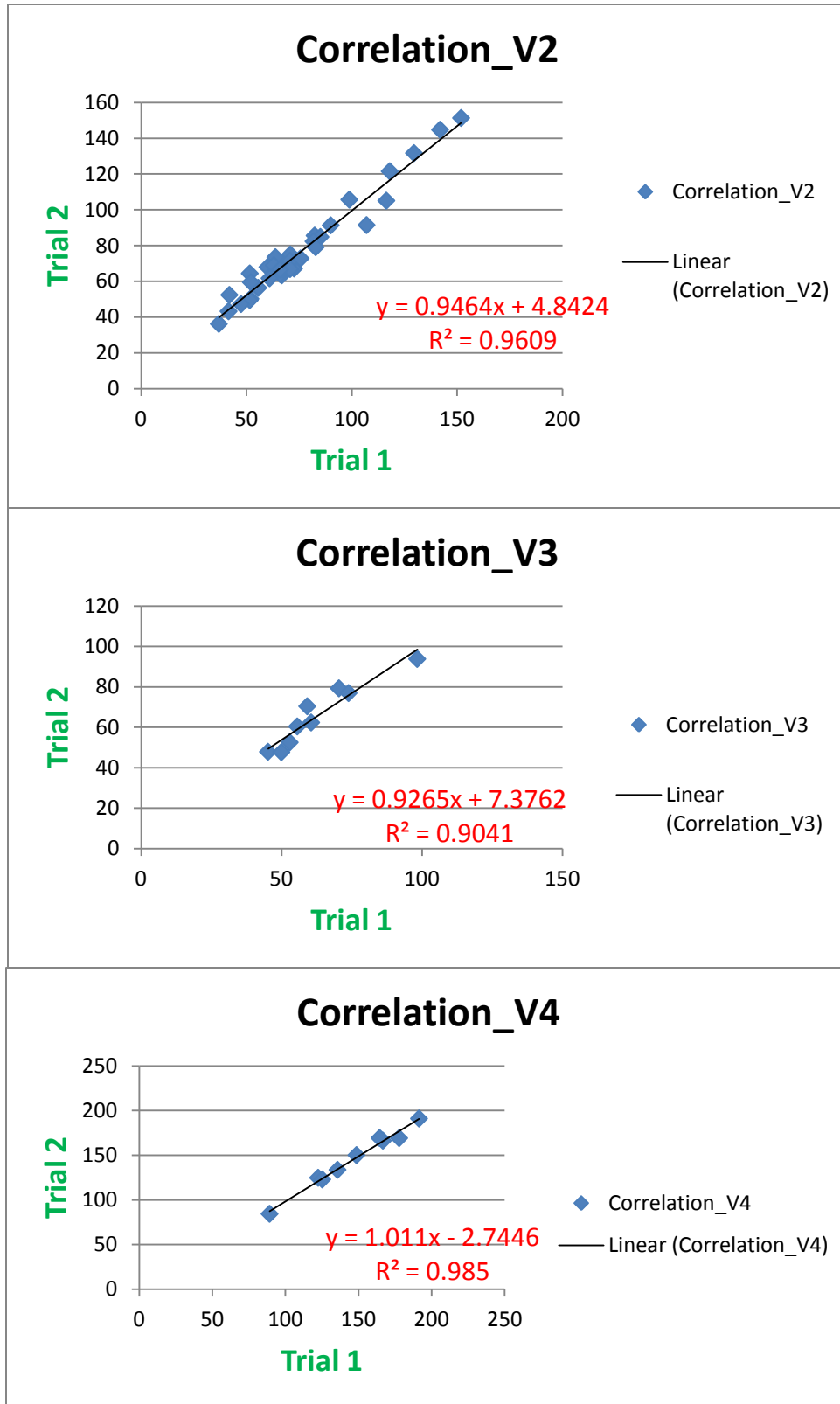
A semi-automated approach was adapted to get the relative susceptibility values. Baseline for each case was selected by taking average of the means of the brain tissue intensities. After that the Regions of Interest (ROIs) were selected for each vessel. For each ROI, minimum, maximum, mean, standard deviation and total number of pixels were recorded.

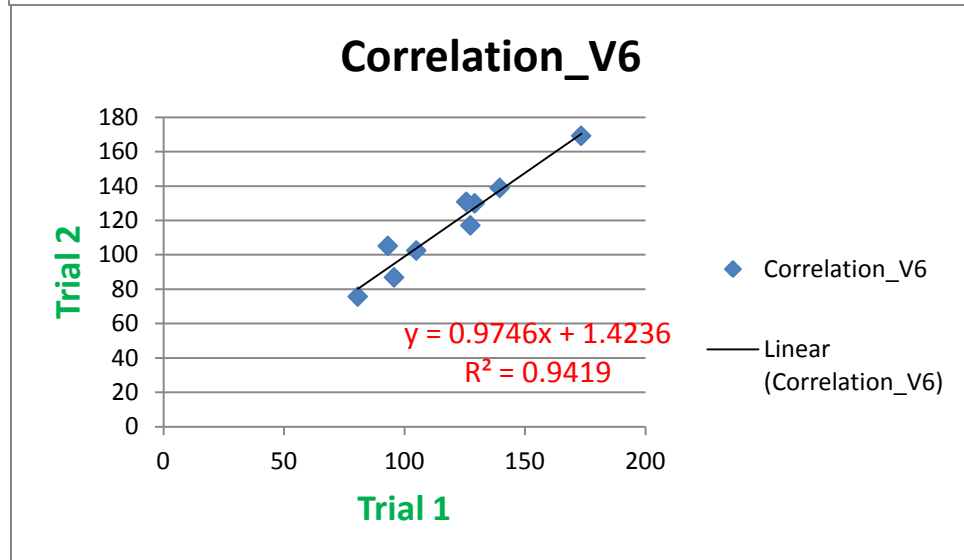
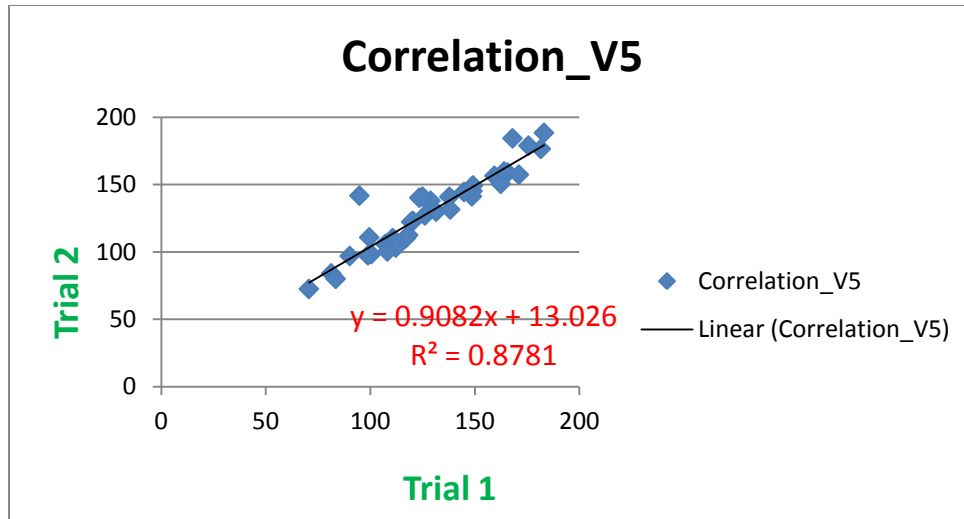
Results

The intensity values were recorded semi-automatically. It is necessary to make sure that the method is consistent across different users as well as same user. To achieve this intra reader and inter reader tests were performed. Inter reader tests shows that this study can repeated with same consistency regardless of different users. The analysis was done by a graduate student. The student was trained to follow the same procedure. Student was not

aware of the previous analysis. The correlation was as high as R^2 value as high as 0.98. The plots are as follows.







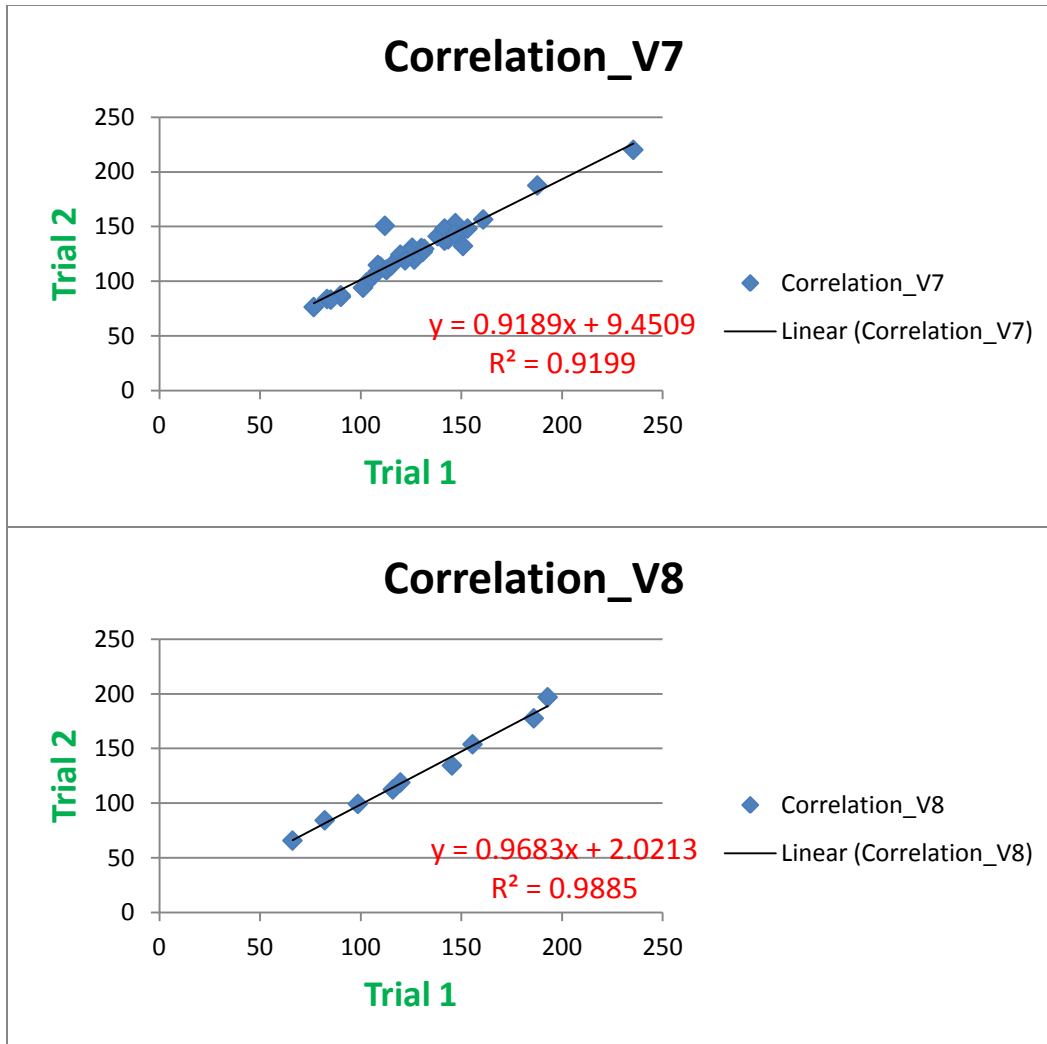


Figure 2.13: Plots of inter-reader correlation for all 8 major veins. Following are the veins: Vein 1: Left Septum, Vein 2: Right Septum, Vein 3: Central Septum, Vein 4: Left Thalamo-striate, Vein 5: Right Thalamo-striate Vein 6: Internal Cerebral Vein, Vein 7: Left Basal Vein of Rosenthal Vein 8: Right Basal Vein of Rosenthal

The intra-reader consistency was checked by the same user after a week from the first analysis. This also shows that the method is consistent and can be trusted. The intra reader tests showed correlation as high as 0.99. This was necessary to show reliability of the method.

Group comparison between patient and control group was conducted. Two tailed Student's t-test was performed for the comparison. In the comparison, mean values for the patients group showed lower values than control group. In particular, right thalamo-striate vein (p-value 0.029) and left basal vein of Rosenthal (p-value 0.05) showed significantly low susceptibility values compared to control group. Mean relative susceptibility values for the follow-up group comes back close to the control levels. Figure 2.14 shows the comparison of mean values with error bars for patient, control and follow-up groups.

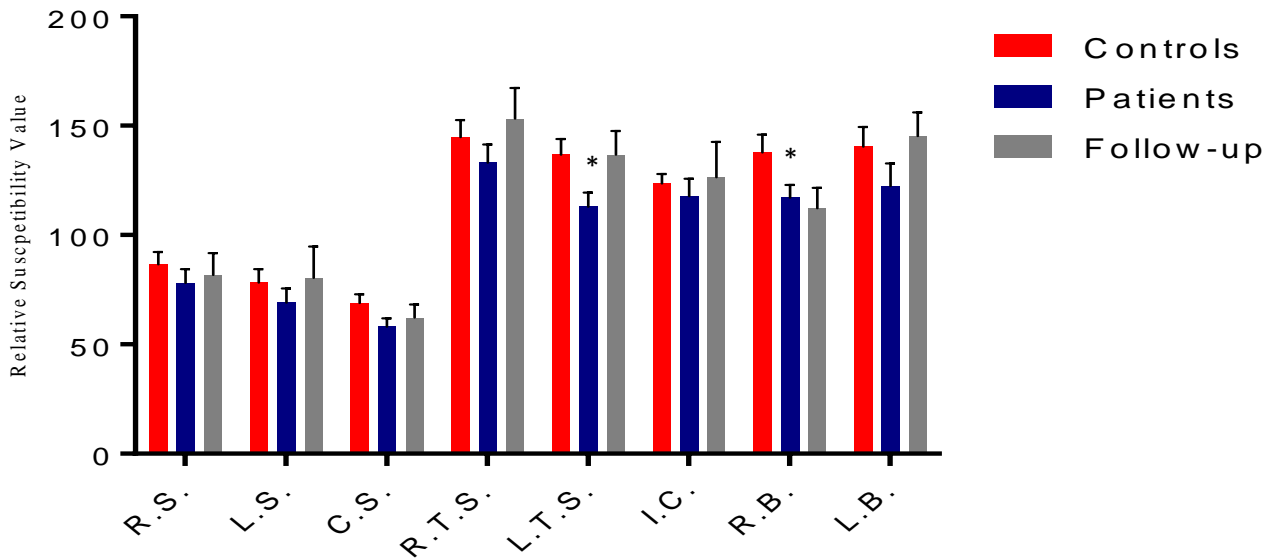


Figure 2.14: Mean values and error bars of blood oxygen saturation values in major veins. Here * shows statistically significant difference. Following are the veins: R.S.: Right Septum, L.S.: Left Septum, C.S.: Central Septum, R.T.S.: Right Thalamo-striate, L.T.S.: Left Thalamo-striate I.C.: Internal Cerebral Vein, R.B.: Right Basal Vein of Rosenthal L.B.: Left Basal Vein of Rosenthal

Table 2.2 shows the group mean values for each vein and student's t-test comparison between control and patient group.

	Vein 1	Vein 2	Vein 3	Vein 4	Vein 5	Vein 6	Vein 7	Vein 8
Controls (mean)	86.6	78.3	68.9	145	137	124	138	140
Std. Dev.	23.87	25.88	17.34	33.10	30.58	18.68	34.46	38.5
Patients (mean)	78.0	69.1	58.0	133	113	118	117	122
Std. Dev.	22.31	22.71	13.26	28.8	22.82	27.77	20.58	35.85
Follow-up (mean)	81.8	80.4	62.2	153	137	126	112	145
Std. Dev.	28.21	40.66	17.14	39.77	30.54	45.71	26.63	30.29
T-Test 1	0.345	0.337	0.090	0.325	0.029	0.514	0.084	0.214
T-Test 2	0.665	0.920	0.476	0.433	0.705	0.537	0.153	0.791

Table 2.2: Group mean values for each vein and student's T-test comparison between control & patient group (T-Test1) and control and follow-up group (T-Test2). Following are the veins: Vein 1: Left Septum, Vein 2: Right Septum, Vein 3: Central Septum, Vein 4: Left Thalamo-striate, Vein 5: Right Thalamo-striate Vein 6: Internal Cerebral Vein, Vein 7: Left Basal Vein of Rosenthal Vein 8: Right Basal Vein of Rosenthal

Apart from that, other neuropsychological tests were conducted. Standard Assessment of Concussion (SAC) showed that the patient group has significant lower SAC scores when compared with control group. Delayed recall score was even more significantly lower with the p value of 0.04.

	Orientation mean (SD)	Memory mean (SD)	Concentration mean (SD)	Delayed Recall mean (SD)	Total Score mean (SD)
Controls (N=568)	4.82 (0.43)	14.51 (0.98)	3.40 (1.27)	3.84 (1.11)	26.58 (2.23)
Patients (N=7)	5 (0)	14 (1.15)	3.29 (1.11)	2 (1.91)	24.28 (2.98)
2-tailed T-Test (<i>p</i> value)	0.00	0.28	0.8	0.04	0.08

Table 2.3: Comparing patients' SAC scores with controls' normalized SAC scores (M. McCrea et al., 1998)

SAC scores for controls were not recorded. For comparison, a normalized dataset reported by McCrea et al., of 568 healthy controls has been used (M. McCrea et al., 1998).

In conclusion, patients' group showed lower susceptibility values compared to control group. It comes back to control level in the follow-up scan. This means that there is lower amount of deoxyhemoglobin in the venous side for patient group at acute stage. This implies that there is higher amount of oxygen left in the veins in patient group. This could be because of tissue malfunction. Tissue is not working optimally and due to that there is less oxygen consumption. Another explanation could be that there is higher amount of blood flow on the arterial side. Due to higher supply, there is more oxygen left in veins. To investigate the possible cause we analyzed the cerebral blood flow on the arterial side. For this purpose, we used Arterial Spin Labeling (ASL) sequence.

Chapter 3: Cerebral Arterial Blood Flow Change in Mild Traumatic Brain

Injury at the Acute Stage

ASL Fundamentals

Cerebral Blood Flow (CBF) has been considered as a very useful marker to observe the changes in neuronal activity. Since Roy and Sherrington (Roy & Sherrington, 1890) did their remarkable work, CBF has been considered not only to monitor the neurological activities, but also to understand cognitive and behavioral neuroscience in more details. In simple words, it can be considered as supply of fresh new blood at a particular point in a particular unit time (Guyton, 1977). It is important to understand that cerebral blood flow is different than cerebral perfusion. As mentioned earlier, CBF can be defined as supply of blood through a particular point, whereas the perfusion can be defined as blood supply to the capillary bed (Warner, Kassell, & Boarini, 1987). The CBF is measured in ml blood / (100 gm tissue)/minute. As per the study, a general typical value of CBF has been determined as 60 ml blood / (100gm)/minute (R.B. Buxton, 2002). This figure is consistent for different subjects for gray matter.

In the past, before the Arterial Spin Labeling (ASL), there were different methods used. One of the most popular methods used was blood oxygen dependent level (BOLD). This method has several drawbacks like low sensitivity, low accuracy estimation of location, low frequency fluctuation etc. Because of these limitations, it was difficult to use the method efficiently for CBF estimations. Apart from this MRI method, other methods like radioactive tagging were used. But there are different issues associated with it. Of course to

start it with, first and obvious one is dangers due to radioactive tagging substances. To reduce this effect as well to reduce affect from previous measurement, it is necessary to keep a certain time gap between measurements (Wintermark et al., 2005). Apart from several other issues need to be addressed as well. One of them is that we need a specific instrument just for this application. Patient stability and mobility are important issues as well. Other modern techniques include single photon emission computed tomography (SPECT) and positron emission tomography (PET). Most commonly used model to calculate the blood flow is the one proposed by Meier and Zierler. Let's assume that blood flow shown as F , coming from arterial and tissue concentration is a time dependent function for the tracer. Here, arterial concentration can be shown using $C_A(t)$ and tissue concentration can be shown using $C_T(t)$ for the tracer (Meier & Zierler, 1954). It is important to include the input as well as output of the tracer. So that means, $C_T(t)$ is dependent to the input as well as clearance of the tracer. Now it is delivered via arteries. So the input is dependent on the arterial concentration. So It can be explained using $F * C_A(t)$. A residue function $r(t)$ can be used to describe the amount of tracer that still remains in the tissue at time t after entering in at $t=0$ (Calamante, Thomas, Pell, Wiersma, & Turner, 1999). If a function A_{eff} dependent on the residue function and arterial concentration can be described, then the concentration in the tissue can be defined as $C_T(t) = F * A_{eff}$ (R.B. Buxton, 2002). Assuming that the inflow from the arteries and its removal are constant, and then CBF maps can be derived as scaled by A_{eff} (R. B. Buxton et al., 1998).

In case of Arterial Spin Labeling (ASL) the tracer is magnetically labeled water molecules. With blood a huge amount of water molecules enter the brain in the arteries. The idea is to invert the z-component or longitudinal component. In this way we can tag the

water molecules. Due to this inversion, the T1-weighted signal is reduced. Idea here is to first take a control image. Later take an image after tagging the water molecules. The difference between the images is the reduced T1-weighted signal, which is due to the tagging. This is the method used by most of the ASL techniques to estimate CBF.

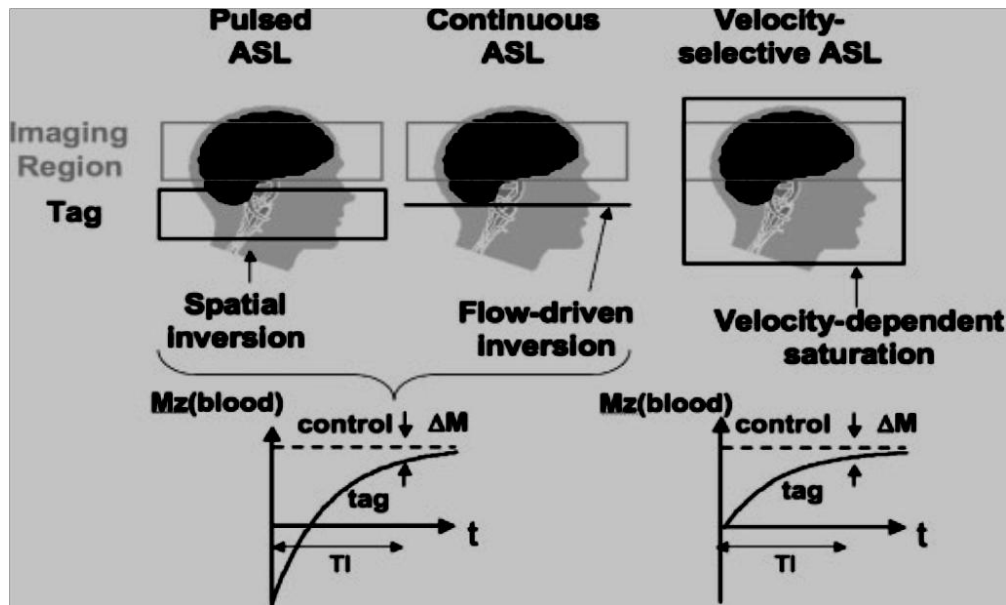


Figure 3.1: PASL, CASL and VS-ASL principles (Liu & Brown, 2007)

Basic mechanism of the general ASL techniques can be explained as shown in figure 3.1. The idea is to first get a control image without any tagging. After that, via inversion of the longitudinal component, the blood is tagged magnetically. Due to this inversion we have a delayed T1 time. So the signal is lesser. After that a specific amount of time T1 is allowed to pass. In this time, the tagged blood enters the scanning plane or volume. As we can see in the plot, due to inversion, when blood reached the imaging slice, it still has lesser signal in T1-weighted image. Based on this, a difference between control and tagged image is acquired, which is directly proportional to CBF.

Based on different labeling techniques, speed of the blood and location, there are mainly 3 different types of ASL techniques. They can be explained as follows.

Pulsed Arterial Spin Labeling (PASL): In this method a saturation or inversion RF pulse is used to tag some part of the brain. Usually in this sequence RF pulse as short as 5 ms- 20 ms are used (Edelman, Wielopolski, & Schmitt, 1994). It is a widely used technique because of the advantages such as very less power consumption in RF pulse as well as higher amount of efficiency while tagging. But it has few downsides as well. The efficiency of this method is heavily dependent on the coverage and uniformity of the applied pulse. Depending on the RF pulse the imaging slab can be decided. As mentioned earlier, it is a very widely used method. Some of the most common sequences are EPISTAR(Edelman et al., 1994), FAIR(Kim & Tsekos, 1997; Kwong, Wanke, Donahue, Davis, & Rosen, 1995) and PICOPE (Wong, Buxton, & Frank, 1997).

Continuous Arterial Spin Labeling (CASL): As far as tagging method is concerned, CASL is a bit different than PASL. In this a smaller slab is tagged. A relatively longer RF pulse as long as 1 s – 3s is used. But along with the RF pulse, a gradient is also applied. By combination of the gradient and RF pulse, a slice or slab closer to the imaging plane has been excited or tagged. The reason behind is to make sure that the coming blood flow is perpendicular to the imaging slice. The tagging can be explained by a concept known as flow driven adiabatic inversion (Garcia, de Bazelaire, & Alsop, 2005). Adequate tuning of RF pulse and gradient is necessary to get the optimal efficiency. Now since the tagging is performed far more closely to the imaging plane, we have more tagged molecules in the imaging slice compared to PASL, which means it has a better efficiency. But on the

downside, since it is a continuous method, total RF power required is more than PASL. Also the amount of radiation energy exposed to the patient has been limited by Food and Drug Administration (FDA) guidelines. A sequence dubbed pseudo CASL has been proposed to avoid this issue. It uses repeated RF pulses (Garcia et al., 2005).

Velocity Selective Arterial Spin Labeling (VS-ASL): As the name suggests, this is a tagging method based on velocity. In this method, a cut-off velocity has been decided. Whichever protons are faster than this particular velocity are dephased from the MR signal. RF pulse with gradient has been applied for this. Thus it is independent from the location selectivity (Wong et al., 2006). Generally a cut-off speed limit is set to 1 cm/sec. Based on this cut-off; the technique would dephase blood in arteries with more than 50 microns diameter.

Patient Recruitment and Method

This is the same dataset as mentioned earlier for SWI processing. In collaboration with Detroit medical center and Wayne State School of Medicine total 9 patients were scanned and ASL sequence was acquired. All of these patients had Glasgow Coma Scale (GCS) in the range of 13 to 15. For mTBI patients, neurocognitive status was measured using standard assessment of concussion (SAC). This test also includes attention, orientation and memory status.

<u>Case ID</u>	<u>Age</u> (<u>Years</u>)	<u>Gender</u>	<u>Race</u>	<u>Scan Timing</u>	<u>ER</u> <u>GCS</u>	<u>Injury</u> <u>Mechanism</u>
<u>Patients</u>						
7	25	M	Black	17 Hours	15	Assault
14	30	M	Caucasian	7 Days	15	Fall
15	36	F	Black	9 Hours	15	MVA
16	19	M	Black	3 Hours	15	MVA
17	23	M	Black	9 Hours	15	MVA
19	30	F	Asian	8 Hours	15	Hit by a car
001	27	F	Caucasian	41 Hours		MVA
Mean	27.14			55.28 Hours		
Std. Dev.	5.52			68.82 Hours		
<u>Controls</u>						
001	24	F	Chinese			
002	23	M	Indian			
006	27	M	Chinese			
007	23	F	Chinese			
008	22	F	Chinese			
036	52	F	Caucasian			
037	44	M	Caucasian			
038	41	M	Caucasian			
040	27	F	Afghanistani			

041	29	M	Caucasian
042	33	M	Caucasian
046	21	M	Black
Mean	30.08		
Std. Dev.	10.24		

Table 3.1: Patients' and Controls' demographic data and cause of injury

The patients were scanned on a Siemens 3T VERIO magnet. They were scanned with a 32 channel head coil. The Repetition time (TR) was 2830 milliseconds and Echo time (TE) was 11 milliseconds. The flip angle was 90 degrees. Field of view for the acquisition was 384x384. The in-plane resolution was 4x4x4. It was later interpolated to 1x1x2 in-plane resolution.

Traditionally CBF values are recorded via manually selecting the ROIs. Since ASL images have poor resolution, this approach might add error while selecting the ROIs. So a novel method was developed to avoid manual selection of the ROIs. A fully automated process was design to avoid any human errors. Schematic diagram shows the steps of the processing pipeline.

Processing Steps

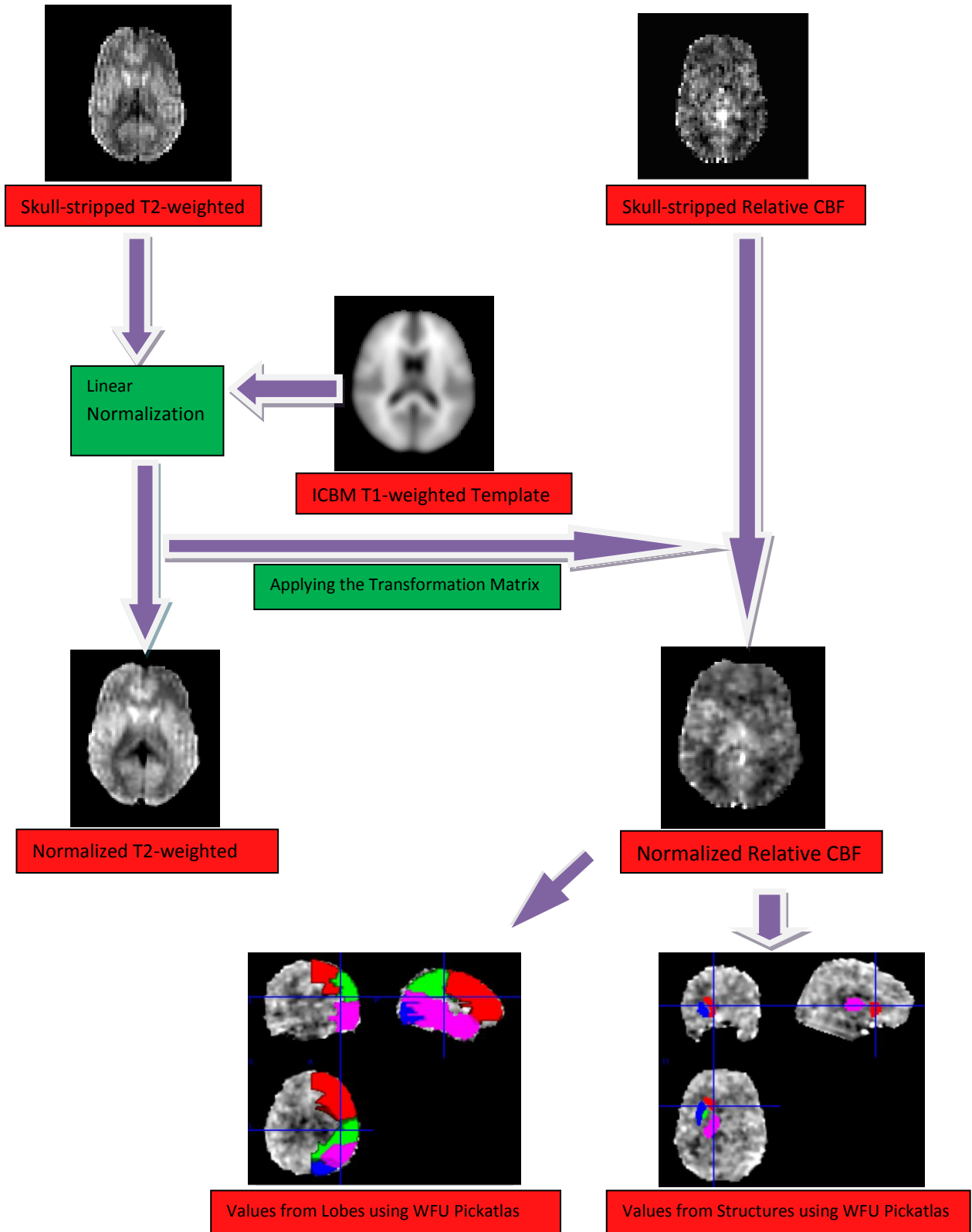


Figure 3.2: A Flow Chart for ASL describing image processing steps

To avoid error due to random selection of the ROIs, an automated procedure was developed. T2 weighted images were first skull-stripped. Skull-stripped T2 weighted images and relative CBF images are in the same space. So T2 weighted images are normalized to T1 weighted ICBM template and transformation matrix is applied onto the relative CBF images. For normalization MATLAB based Statistical Parametric Mapping 8 (SPM8) (Ashburner & Friston, 1997; Buchel & Friston, 1997; Holmes, Poline, & Friston, 1997).

After bringing all the images into the ICBM standard space, ROIs were selected using Wake Forest University pickatlas (WFU pickatlas) (Maldjian, Laurienti, Kraft, & Burdette, 2003). Using these predefined ROIs in the ICBM space, relative CBF values from Striatum, Caudate Nucleus, Thalamus, Globus Pallidus, Putamen, and Frontal, Occipital, Parietal and Temporal lobes were recorded.

Results

We observed significantly higher rCBF values in left striatum. In particular in Caudate, Putamen and Pallidum rCBF was significantly high. We also observed elevated rCBF values in left frontal and occipital lobe (Table 3.2). We did not find any significant changes in Thalamus, Globus Pallidus, Temporal and Parietal lobes. Table 3.1 shows mean values of control and patient group and significance (p value).

Structure	Controls mean value (n=12)	Std. Deviation	Patients mean value (n=9)	Std. Deviation	P value
Left Thalamus	2184.25	98.36	2236.86	80.66	0.22
Right Thalamus	2217.42	97.18	2272.43	105.46	0.28
Left Striatum	2127.25	63.20	2190.50	44.74	0.01**
Right Striatum	2145.00	67.93	2201.00	76.80	0.14

Table 3.1: Comparison of mean rCBF values for different structures between control and patient group. *p* value shows level of significance for Student's T-Test. ** indicates significant difference.

Lobe	Controls mean value (n=12)	Std. Deviation	Patients mean value (n=9)	Std. Deviation	P value
Frontal	2005.52	30.82	2065.67	62.38	0.03**
Temporal	2065.38	49.13	2115.33	81.68	0.11
Occipital	2053.54	22.81	2137.58	89.19	0.028**
Parietal	2102.92	44.56	2141.67	69.67	0.1

Table 3.2: Comparison of mean rCBF values for different lobes between control and patient group. *p* value shows level of significance for Student's T-Test. ** indicates significant difference.

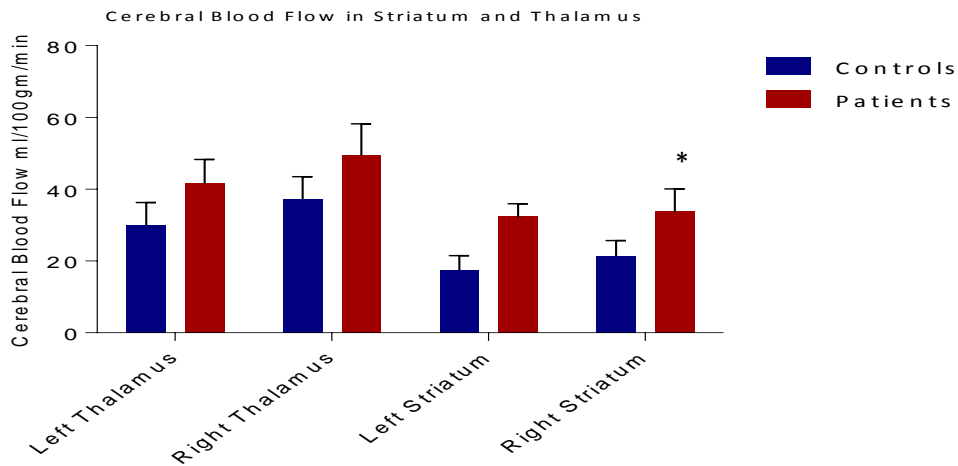


Figure 3.3: Comparing Cerebral Blood Flow in Thalamus and Striatum between Control and Patient Groups

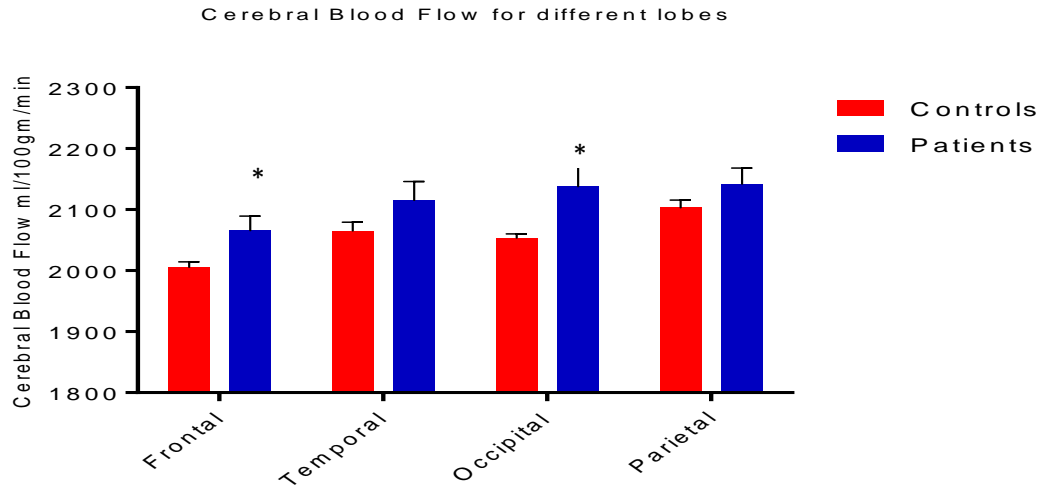


Figure 3.4: Comparing Cerebral Blood Flow in lobes between Control and Patient Groups

Neuropsych tests scores including delayed recall, Standard Assessment of Concussion (SAC) and Post Concussion Syndrome (PCS) were compared with the rCBF values. We did not find any correlation between these scores and the rCBF values in the structure.

Discussion

SWI analysis indicated that relative susceptibility values in the veins for patient group are lower than control group. Specially in left thalamo-striate vein and right basal vein of Rosenthal there was significantly lower relative susceptibility. This implies that there is higher amount of oxygen left in the veins for the patient group compared to control group. This is in contrast with earlier studies (Shen et al., 2007). But our study group included mild TBI human patients. The study by Shen et al analyses susceptibility after

head impact induced using marmarou model in rats (Marmarou et al., 1994). So the severity and mechanism of the injury varies between both the study groups. But considering this, there could be few explanations for decreased relative susceptibility. One could be a deficit in oxygen consumption at tissue level after injury. In a lot of studies it has been shown that due to injury Cerebral Metabolic Rate of O₂ (CMRO₂) and CBF coupling has been disrupted (S. F. Chen et al., 2004; Harris, Mironova, Chen, Richards, & Pickard, 2012; Hovda, Yoshino, Kawamata, Katayama, & Becker, 1991; Vink, Faden, & McIntosh, 1988). Lower CMRO₂ has been observed in these studies. This suggests that tissue is unable to absorb optimal amount of O₂. Another proposition that might explain the lower relative susceptibility value is that there might be increased CBF. Due to increased CBF there could be higher amount of oxygen left in the veins. This suggests that functionally there might be very little wrong at the tissue level. But in very early stage brain might be trying to over compensate the damage.

Results of ASL data analysis indicated that in patient group left side of the striatum has significantly higher CBF than control group. There have been several studies indicating decreased CBF after moderate-severe trauma (Barclay et al., 1985; Fieschi et al., 1974; Overgaard & Tweed, 1974; Prat et al., 1997). But our study was different than other studies in two aspects. All the patients were mild and they were scanned at very acute stage (24-48 hours after injury). There has been no previous study to our knowledge with such specific population.

Although the increase CBF contradicts some of the earlier publication, there are few studies indicating higher levels of CBF after trauma (Bouma & Muizelaar, 1992, 1993, 1995;

Kelly et al., 1996; Kelly et al., 1997; Marion et al., 1991; Muizelaar et al., 1989). Muizelaar et al suggested that with higher GCS score CMRO₂ rate is significantly higher for TBI patients (Muizelaar et al., 1989). Marion et al observed that after injury CBF peaked to a significant high at 24 hour time point (Marion et al., 1991). Obrist et al studied CMRO₂ and CBF in 75 patients. They observed that with higher GCS score, CMRO₂ increases. Also CBF reaches its highest peak at 24 hours after injury (Obrist, Langfitt, Jaggi, Cruz, & Gennarelli, 1984). This supports other studies. Bouma et al also observed that rCBF reaches its peak between 24 to 48 hours after injury (Bouma & Muizelaar, 1993). Bouma et al also showed that after injury at acute stage, in first 24 hours, CBF value reaches its peak (Bouma & Muizelaar, 1992). This was supported by their another study (Bouma & Muizelaar, 1995). This was also supported by Mendelow et al (Mendelow et al., 1985). In an animal study, Prat et al observed that the animals impacted with lesser weight showed an increase in CBF between one and three hour time points after injury. Which followed by a decrease in CBF (Prat et al., 1997).

Our analysis indicated higher CBF rate after trauma at acute stage. This shows higher amount of oxygen supplied. At the same time, it showed lower amount of relative susceptibility values. This indicated higher amount of oxygen left in the veins. Several studies have shown that brain tries to meet the energy demand in extreme conditions such as starvation and trauma (Prins, Lee, Fujima, & Hovda, 2004). This is accomplished by using other substrates such as b-hydroxybutyrate (bHB) (McKenna, Tildon, Stevenson, & Hopkins, 1994), lactate (Brandt, Waters, Rispler, & Kline, 1984) etc. A possible mechanism behind this could be efforts of the brain to maintain the CMRO₂ rate. There have been few studies showing decreased CMRO₂ (Vespa et al., 2005). But absence of any structural

damage in CT or MRI suggests that it is due to reversible injury to the brain. It discounts the possibilities of defects due to cell loss. It could be temporary inability of brain to use oxygen efficiently via glucose uptake. It is possible that to overcome this mitochondrial dysfunction and lower CMRO₂, brain is trying to restore the CMRO₂ levels by increasing CBF.

It is possible that after mild trauma brain suffers few reversible damages. Brain tries to establish the equilibrium and in the process it tries to over compensate the damage. This explains the increased levels of CBF and consequently increased levels of oxygen in the veins.

Chapter 4: Volumetric analysis of cingulum in retired NFL players: Its relationship with NFL experience and subjects' cognitive and functional performance

Introduction to Chronic Traumatic Encephalopathy (CTE)

Chronic Traumatic Encephalopathy (CTE) is a neurodegenerative disease caused by single or multiple closed head mild TBIs (mTBI)(D. J. Thurman, Branche, & Sniezek, 1998). CTE was first reported by Dr. Harrison Martland in 1928 in boxers. Later the same was noticed in other players playing sports like American football, soccer, hockey etc. Athletes, who suffered CTE, have complained about depression, anger, memory loss, substance abuse etc(B. I. Omalu, Bailes, Hammers, & Fitzsimmons, 2010). Here, it is important to make a distinction between CTE and post-concussive syndrome (PCS). In PCS, the symptoms are evident right after the injury. While in case of CTE, the symptoms are reported after few years of the initial injury (Daneshvar et al., 2011). CTE has been believed to be one of the causes for Alzheimer's disease and Parkinson's disease (Guskiewicz et al., 2005a). As per McKee et al., there are about 1.6-3.8 million sports concussions recorded in United States only each year (McKee et al., 2009). This number obviously is not accurate in terms of actual instances. There are several injuries which go unnoticed or undiagnosed. Apart from this, players are under constant pressure to perform and survive. So sometimes they don't report or neglect the injury (Daneshvar et al., 2011). In a very remarkable study, McKee et al. reported that about 90 % (46 out of 51) of the total CTEs were reported in athletes(McKee et al., 2009). In fact, athletes with no reported or recorded concussion

history have also been diagnosed with CTE (Baugh et al., 2012). Especially athletes of American football, Hockey, wrestling, soccer and boxing are more prone to CTE. Apart from the athletes, soldiers are at heavy risk of developing CTE. They suffer constant and repeated concussions in the battlefield. This could develop later into CTE. Post-mortem is the only means to detect CTE as of now. The main motivation behind this study is to come up with an objective indicator that would help in detection and understanding of the CTE and factors leading to its outcomes.

Risk Factors

There are several reported risk factors that would lead towards CTE. Most significant factor is mTBI. Number of head injuries and its severity are major factors. In particular, athletes who participate in the contact sports are more susceptible to CTE. In sports like American football, hockey, wrestling and boxing there are more chances of CTE occurrence (Saulle & Greenwald, 2012). Omalu et al. reported that about 17% of the retired boxing players were diagnosed with CTE (B. I. Omalu et al., 2010). In another study, Crisco et al. reported that an average college football player suffers an average of 420 impacts each season. The maximum number reported in as high as 2,492 (Crisco et al., 2011). This is a very high number. Impact severity is a major component. One of the major factors is the position of the player (McKee et al., 2009). For example, in football linebacker and quarterback suffer different number of impacts. Severity of the impact also depends on the position.

It is still not clear that CTE is manifested by multiple impacts or a single impact. Also the amount of trauma necessary to trigger the CTE is not clear. Traditionally it has been

believed that multiple impacts cause CTE. In a study Johnson et al. reported that few subjects who suffered single impact showed classic CTE pathological signs in the post mortem (Johnson, Stewart, & Smith, 2012). But they did not present any clinical symptoms. Had they suffered more impacts, they might have shown more clinical symptoms. Total number of years participated is also a risk factor. With prolonged career, there are more chances of injuries. Also sometimes athletes carry a previous injury, which is aggravated due to more injuries.

Soldiers fighting in the battlefield are very susceptible to the CTE. With the amount and frequency of trauma they suffer, there are high chances they suffer from CTE. Age is a major risk factor. Since at young age the brain is developing, a severe impact might show a magnified outcome. At the same time, since the young brain has more plasticity, it might tackle minor injuries much better (Blaylock & Maroon, 2011).

Clinical Symptoms

The obvious symptoms of the CTE may not show up during the participation period of the athlete. As published by McKee et al. classic symptoms were reported in the age range of 25 to 76 years. Most of the athletes reported the symptoms towards the end of the career or after few years of the career was over (McKee et al., 2009). In the early stages subjects reported symptoms like headaches, irritation, confusion, violent behavior, dizziness, disorientation and abnormalities in the speech. Patients suffer from several social and financial difficulties. Poor money management, insomnia, substance abuse, emotional and physical abuse, divorce, bad relationship management, paranoia, bankruptcy and different phobias have been reported in such athletes (B. Omalu et al.,

2011). With the time symptoms tend to worsen. In the later stages, patients suffer from higher loss of motor function, poor speech, vertigo, deafness, bradykinesia, gait, ocular abnormalities and tremors. Few athletes also showed symptoms of Parkinsonism and dementia (Saulle & Greenwald, 2012).

Diagnosis/Treatment

Unfortunately there is only way to diagnose CTE is via post mortem analysis (Gavett, Stern, & McKee, 2011). There is no consensus on any of the pre mortem technique that could give a definitive diagnosis. Also the similar symptoms and similar history of trauma can confuse the diagnosis with Alzheimer's disease and Dementia. Age could be a factor to differentiate the Alzheimer's. Several techniques such as DTI and MR spectroscopy are being tried as a potential tool for detection of CTE. Also levels of tau and phosphor-tau in the cerebrospinal fluid are considered as potential indicators of CTE (Gavett et al., 2011; Kumar et al., 2009).

There are no treatment options available for CTE. So it's more vital to take preventive steps. Effective protective gear is necessary in contact sports. Especially efficient helmets and mouth guard are very vital. Helmets with larger size and thicker protective padding are proven more effective (Viano & Halstead, 2012). While protecting head, equal care should be taken to protect neck. Another aspect of the preventative measure is to make sure that rules are as strict as possible. There should be harsh penalties for the player who makes rash challenges. Coaches and support staff should be aware of the consequences. Medical staff should be ready in case of medical emergency.

Pathology Findings

Most common findings in the post mortem are as weight and volume related. Significant amount of atrophy has been reported after the CTE. General findings include loss of neurons, reduction in weight of the brain, enlarged ventricles, atrophy in grey matter and shrinking of corpus callosum. In the descending order, frontal lobe, temporal lobe and parietal lobe showed more atrophy (36%, 31% and 22% respectively)(McKee et al., 2009). Occipital lobe did not show a lot of changes. Cingulate cortex has been studied in many of the previous projects and has been associated with CTE and depression (Corbo, Clément, Armony, Pruessner, & Brunet, 2005; Levine et al., 2008; Rauch et al., 2003; Yount et al., 2002).

It has been reported that cingulate cortex plays part in memory and emotional processing and attention related tasks (Hayden & Platt, 2010; Mason et al., 2007). It has very close association with dorsolateral prefrontal cortex, orbital frontal cortex and precuneus (Carmichael & Price, 1995; Hayden & Platt, 2010; Maddock, Garrett, & Buonocore, 2003; Pandya, Van Hoesen, & Mesulam, 1981). Cingulate cortex is considered a cortical hub (Hagmann et al., 2008; Raichle et al., 2001). It has been also reported that cingulate cortex might be involved in regulation of cognitive tasks (Hampson, Driesen, Skudlarski, Gore, & Constable, 2006). Considering all these factors, change in the volume of cingulate cortex might be a cause of depression in CTE. It is necessary to conduct few more comprehensive studies to understand the role of cingulate cortex in CTE and its outcome.

Subject Recruitment and Method

Patient Group and Imaging Parameters

43 retired football players were scanned. The average age of the players was 45.6 ± 9.30 years (range 30-60 years). Apart from that, data from each player's playing career was recorded. This includes duration of professional, college and high school football career and number of concussions and dings each player had suffered at each level of their career. Average playing span in NFL was 6.7 ± 3.2 years with a range of 2-14 years.

Subjects were excluded if they had a history of certain previous medical conditions that might confound the interpretation of neurological, neuropsychological or neuroradiological testing. The exclusion criteria were:

- (1) History of brain surgery
- (2) History of brain tumor, stroke, multiple sclerosis, or seizures which began prior to entering the National Football League (NFL) (except febrile seizures)
- (3) History of HIV or AIDS
- (4) History of significant head injury from auto accidents or other non athletic trauma to the head
- (5) History of concussion/ MTBI resulting in minutes of Loss of Consciousness (LOC) or hospitalization after having finished playing in the National Football League

(6) History of open heart surgery, organ transplant surgery, or carotid artery surgery

(7) History of treatment with chemotherapy or radiation therapy for cancer affecting the brain or spinal cord

(8) History of renal failure requiring dialysis or liver failure resulting in cirrhosis or request for liver transplant

(9) History of significant alcohol abuse and/or drug abuse in the past or present manifested by having been suspended by a league at some time during their career for one of these problems, having been arrested for a DUI related to alcohol or drugs at some point, having been treated in a rehabilitation facility for drug or alcohol abuse at some point and/or a history during the past five years of daily use of an illegal drug, daily intake of more than four beers or more than two “hard liquor” drinks per day.

Other exclusion criteria were age beyond 60 years old.

Along with neurological examination, sensory and motor testing, deep tendon and abnormal reflex examinations, examination of cranial nerves, examination of Tinel signs and funduscopic examination was performed.

The MRI data was acquired on Siemens 1.5 T magnet. The parameters of the T1 sequence were as following: $T_R = 2000\text{ms}$, $T_E = 4.84\text{ ms}$, Flip angle = 8 degrees, Bandwidth =160, Field of view was 512x512, Slice thickness of 2 mm and resolution was 0.5x0.5x2.

Neuropsych Tests

A detailed Neuropsych test was conducted for each subject. Each subject was questioned for any of the following complains: headaches, dizziness, blurry vision, diplopia, visual loss, hearing loss, tinnitus, speech difficulty, difficulty reading or writing, difficulty swallowing, weakness of the extremities, numbness anywhere on the body, seizures or other episodes of LOC, gait difficulty, tremors or other involuntary movements, changes in handwriting or incontinence. Also to check the memory and/or cognitive losses few questions were asked. These included questions regarding memory loss, forgetfulness, difficulty concentrating, mental errors at work, errors in banking or checking or bill paying activities, difficulty thinking of words or names, confusion, getting lost in familiar places and whether family or friends had told the subject about any observed cognitive or memory difficulties.

Depression was scored as follows: 0 = not depressed, 1 = Beck Depression Inventory (BDI) score of 14-19 and not depressed by Patient Health Questionnaire (PHQ) criteria, 2 = BDI score 20 or above or (not and) depressed by PHQ criteria and 3 = BDI score 14 or above and depressed by PHQ criteria. The range of Mini Mental State Examination (MMSE) scores was between 25 and 30. BDI_II scores were 9.6 ± 9.25 and MMSE scores were 28.35 ± 1.27 for the whole subject group. Table 4.1 shows mean, standard deviation and range of age, BDI_II score, MMSE score, total number of years in football and NFL, total concussions and dings suffered during football career as well as playing in NFL.

A registered nurse questioned the players regarding their life after football. This included their income, housing, public assistance, violent issues, social situation during

their childhood and potential exposure to abuse or violence. Also a detailed family history including psychiatric and neurological disorders was recorded.

Examining neurologist collected the information regarding player's playing career by questioning them with specific questions. Each player was asked about their active playing duration at each level (Including NFL, college, high-school and pre high- school). They were also asked about their position in the team. Their involvement in any other contact sports, duration in that sport and possible head injury when playing that sport were also questioned. First each participant was asked about possible concussions he might have suffered at each level of football. After that the definition of concussion used by NFL MTBI committee (Pellman et al., 2004) was read to them. After that they were asked about the concussions they might have suffered that fit into the definition of concussion. Number of "dings" they might have suffered was also asked. "Ding" was defined as momentary abnormal sensation in the head occurring immediately upon head impact, with complete resolution within a few seconds and with no residual effects. Same way, any other injury outside the field was also recorded based on participant's recollection. Each player was asked to recollect each instance of injury. Players were asked to remember when did it occur, weather it was during a game or not and specific details about the injury. Each participant was asked about presence of LOC and/or amnesia and its duration. Each player was asked if any medical diagnostic test such as CT or MRI was performed and also about the result of the test. They were also asked about symptoms such as dizziness, poor memory, and nausea, loss of concentration, headaches, vomiting, depression and poor vision. If they suffered any of these, for how long they suffered was also asked. In particular they were asked about any permanent symptoms after the injury.

<u>Variable</u>	<u>Mean</u>	<u>Standard Deviation</u>	<u>Range</u>
Age	45.6 years	9.30 years	30-60 years
BDI_II Score	9.6	9.26	0-35
MMSE Score	28.35	1.27	25-30
No. of Years played in NFL	6.73 years	3.24 years	2-14 years
Total number of years played football	16.96 years	4.34 years	8-25 years
No. of Concussions suffered in NFL	6.86	6.50	0-25
Total concussions suffered	9.05	7.08	0-25
No. of Dings suffered in NFL	13.03	7.95	0-25
Total dings suffered	15.02	7.95	0-30

Table 4.1: Mean standard deviation and range of Age, BDI_II Score, MMSE Score, and other playing career data information.

Processing steps

Main objective of this study is to observe the effect of different factors such as volumes of the brain structures and data from player's playing career such as number of years they played or number of concussions they suffered. Also observe individually and combined how these factors affect players' depression and other Neuropsych test score outcomes. Traditionally analysis is performed either manually by hand or by an automatic algorithm. Drawing the ROIs by hand is a time consuming process. There are also chances

of manual error while drawing the ROIs. To overcome these factors, an automatic robust method was used.

The processing steps are shown in the Figure 4.1. This is a similar approach to Voxel Based Morphometry (VBM). First all the subjects were non-linearly registered to the standard space using SPM8(Ashburner & Friston, 1997; Buchel & Friston, 1997; Friston, 1997; Holmes et al., 1997). A set of predefined ROIs for JHU Talairach T1 template from ROIEditor (Version 1.6, mrstuiio.org) was used. Once all the subjects are in the standard template space, an inverse transform matrix was applied to all the subjects. Along with that, same matrix was applied to the predefined ROIs. After applying this inverse transform routine, we have all the subjects as well as the ROIs back into the native space. All the ROIs in native space were compared with respective segmented tissue type to avoid any type of bad registration (for example, Corpus Callosum was compared with the white matter segmented image to avoid any other tissue type in the ROI). Figure 4.2 shows examples of Anterior Cingulum Cortex (ACC) and Posterior Cingulum Cortex (PCC) ROIs in native space.

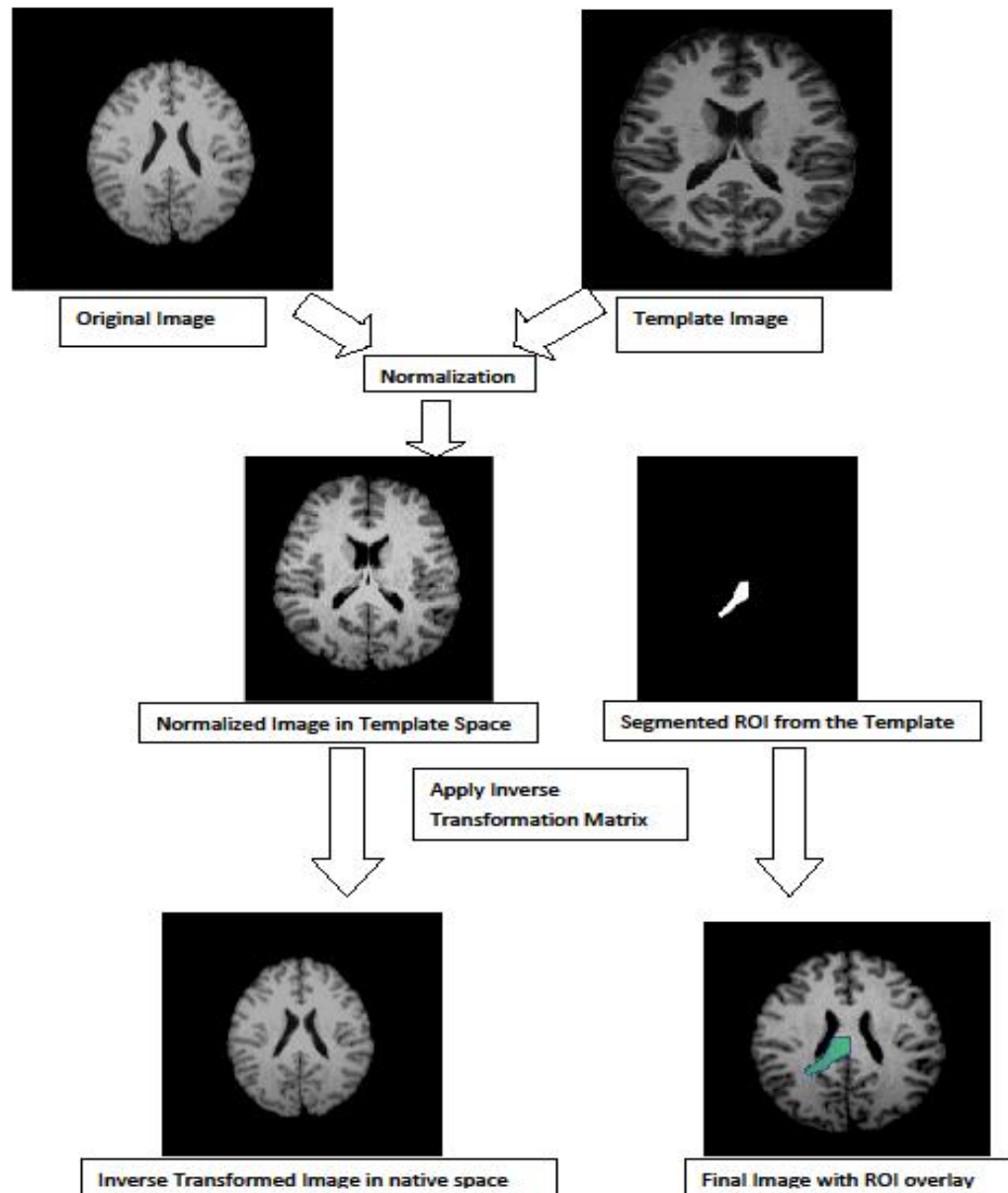


Figure 4.1: A flow-chart showing processing steps

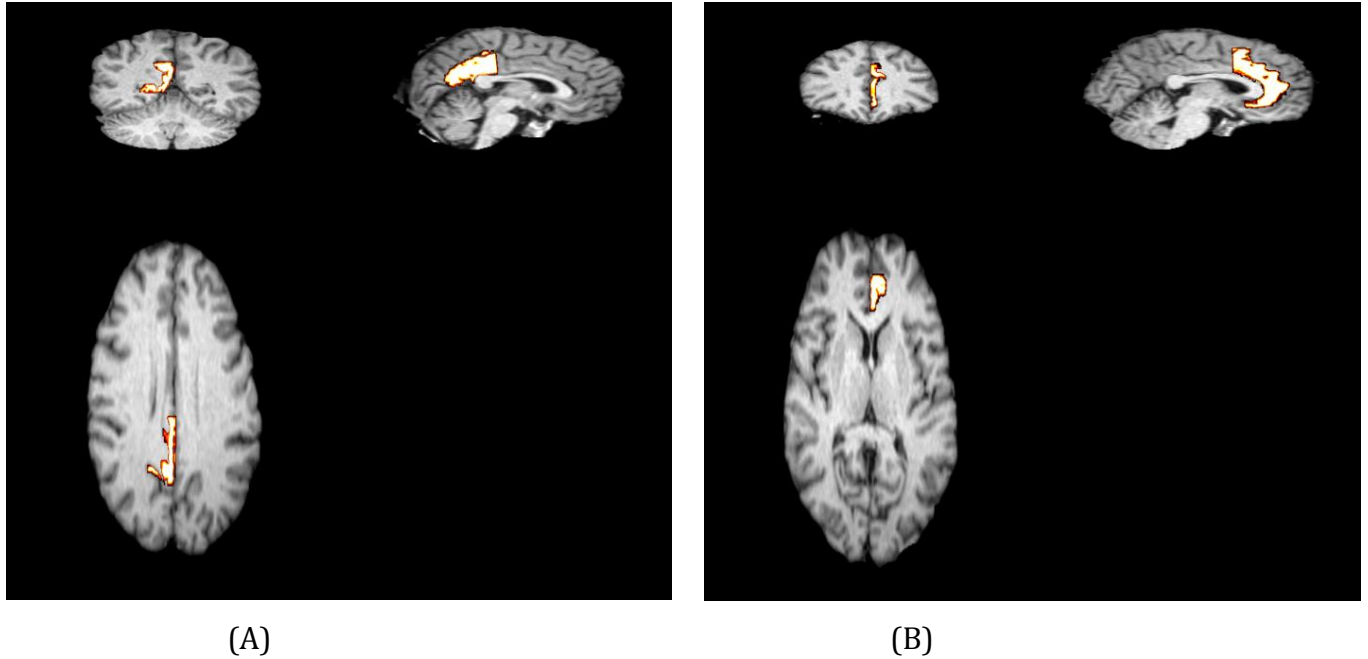


Figure 4.2: (A) Region of interest for PCC and (B) Region of interest for ACC

Statistical Analysis

IBM analytical tool SPSS 21.0 (SPSS, Inc., Chicago IL) was used for the statistical analysis. Two approaches were used for statistical analysis. In the first part, bivariate correlations were checked. Players' career data (such as duration of the career, number of concussion and dings they have suffered) were checked for any correlation with the Neuropsych scores BDI and MMSE. Also volumes of anterior and posterior cingulum cortex (ACC & PCC) were checked for any correlation with Neuropsych test scores or with players' career data.

In the second part, mediation analysis using PROCESS model 4 by Dr. Andrew Hayes was performed (<http://www.afhayes.com/introduction-to-mediation-moderation-and-conditional->

process-analysis.html. "Introduction to Mediation, Moderation, and Conditional Process Analysis: A Regression-Based Approach" By Dr. Andrew .Hayes). In simple terms mediation analysis explains how the relationship between two variables is affected by third variable. The mediation model involves all 3 different factors such as players' career data, volume of brain structures and Neuropsych tests.

Results

Part 1:- Correlations (Bivariate)

In part one of the analyses, player's career data and concussion history were checked for any correlation with BDI_II or MMSE scores. Pearson's Correlation (2-tailed) were performed for each correlation. None of the history data showed any correlation with BDI_II or MMSE scores. Volumes of ACC and PCC were checked for any correlation with BDI_II or MMSE test scores. Volume of PCC showed significant negative correlation with BDI_II score with $p=0.001$. Figure 4.3 (A) shows relation between Volume of PCC and BDI_II score. Considering the multiple comparison effect, volume of ACC was not significantly correlated with BDI_II score. But it was approaching significant negative correlation with $p = 0.023$. Volumes of neither PCC nor ACC showed any significant correlation with MMSE score.

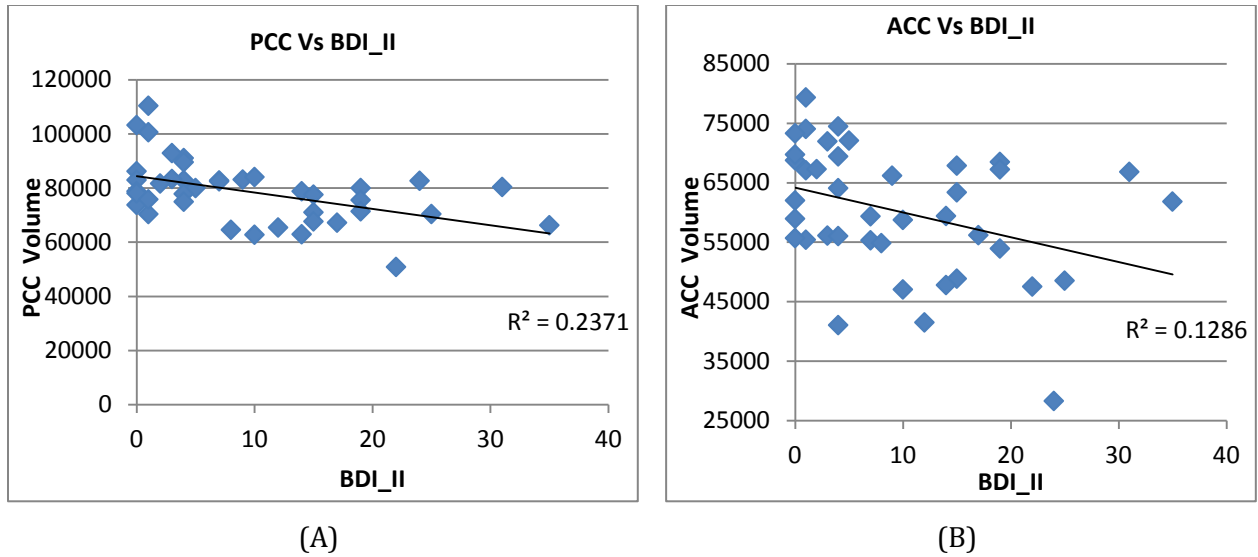


Figure 4.3: (A) Plot of PCC volume vs. BDI_II score ($p = 0.001$). (B) Plot of ACC volume vs. BDI_II score ($p = 0.023$).

Bivariate correlation between number of years played in NFL and number of concussion suffered in NFL were checked. Pearson's correlation indicated that number of years in NFL is strongly correlated with number of concussions suffered in NFL with $p = 0.0001$. Figure 4.4 shows strong correlation between two variables.

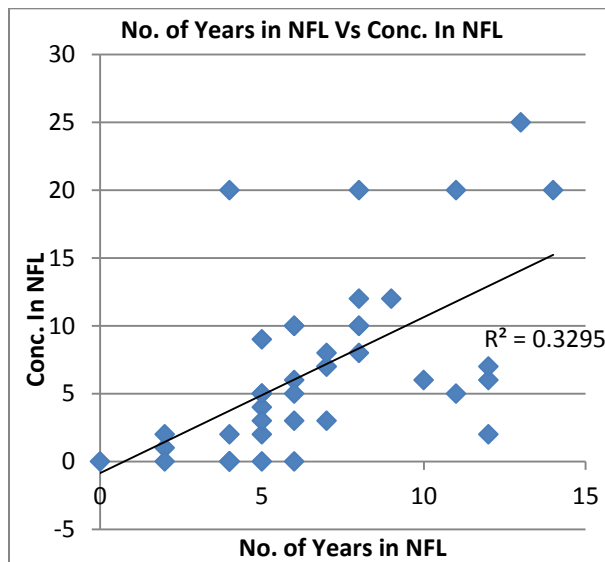


Figure 4.4: Plot of Number of years in NFL vs. number of concussions suffered in NFL ($p = 0.0001$).

Part 2:- Mediation Models

Mediation models were performed using model 4 of PROCESS by Dr. Hayes for the analysis (<http://www.afhayes.com/introduction-to-mediation-moderation-and-conditional-process-analysis.html>. "Introduction to Mediation, Moderation, and Conditional Process Analysis: A Regression-Based Approach" By Dr. Andrew .Hayes). Player's career data and history variables (such as duration of the career, number of concussion and dings they have suffered) were selected as input variables. Volume of ACC and PCC were selected as mediators and BDI_II and MMSE scores were selected as output variables.

One particular model including Number of years in NFL (X), PCC volume (M) and BDI_II (Y) showed evidence of partial mediation.

	Effect Size	Standard Error	p Value
Total Effect	1.27	0.41	0.003
Direct Effect	0.93	0.4	0.026
Indirect Effect	0.34	0.18	

Table 4.2: Output of the mediation analysis model including No. of years in NFL (input), PCC volume (Mediator) and BDI_II score (Output)

Model: → Number of Years in NFL (X-Input Variable), PCC Volume (M-Mediator), BDI_II (Y-Output Variable)

Result:

Total effect of X on Y

Effect	SE	t	p	LLCI	ULCI
1.2747	.4144	3.0760	.0039	.4358	2.1136

Direct effect of X on Y

Effect	SE	t	p	LLCI	ULCI
.9317	.4034	2.3094	.0266	.1142	1.7491

Indirect effect of X on Y

Effect	Boot SE	BootLLCI	BootULCI
PCC .3431	.1844	.0910	.8155

Table 2 shows the output of the mediation model. Both direct and indirect pathways show significant effects. But with the addition of indirect pathway, total output pathway is significantly more correlated with $p = 0.003$. The total model shows significance, which indicates partial mediation. This means PCC volume (indirect pathway) is responsible for almost 27% of the correlation between number of years in NFL and BDI_II score (total effect pathway). None of the other mediation models showed partial or full mediation.

Discussion

CTE has been associated with neurological symptoms such as depression, headaches, confusion, disorientation and violent behavior (J. K. Chen, Johnston, Petrides, & Ptito, 2008; Hart et al., 2013; Jorge et al., 2004; Mayer, Mannell, Ling, Gasparovic, & Yeo,

2011; McKee et al., 2013; B. Omalu et al., 2011; B. I. Omalu et al., 2010; Saullé & Greenwald, 2012). Players with just a single hit are susceptible to worst outcomes. Johnson et al reported that players with a single hits reported classic CTE pathological signs in the post mortem (V. E. Johnson et al., 2012). Depression has been reported most frequently. Usually depression is common for all TBIs. But this group is unique in a sense that these players have suffered mild TBI multiple times over the years. It has been reported that athletes who suffer CTE are at high risk of suffering from depression (J. K. Chen et al., 2008; Guskiewicz et al., 2005b; Hart et al., 2013; B. I. Omalu et al., 2006; B. I. Omalu et al., 2005).

A detailed understanding of relation between CTE and depression is still not fully understood. Few studies have been reported to explain possible causes (E.D. Bigler et al., 1997; J. K. Chen et al., 2008; Corbo et al., 2005; Guskiewicz et al., 2007; Hart et al., 2013; B. Johnson et al., 2012; Mac Donald et al., 2011). This includes several different approaches. Niogi et al reported that white matter micro structural injuries are correlated with neurocognitive impairments (Niogi et al., 2008). Similar approach has been used in some other studies as well (Bendlin et al., 2008; Levine et al., 2008; Mac Donald et al., 2011; Wu et al., 2010). Examining the brain activity by observation of brain connectivity using fMRI has been proposed in few studies (B. Johnson et al., 2012; Mayer et al., 2011). Many researchers have proposed a volumetric analysis approach (Blatter et al., 1997; Gale, Johnson, Bigler, & Blatter, 1995; MacKenzie et al., 2002; Wilde et al., 2005). Also different structures have been proposed to play important part. Anderson et al examined the changes in thalamus following the head injury (Anderson, Wood, Bigler, & Blatter, 1996). They reported decrease in thalamic volume with injury severity. Global volume changes in white matter, grey matter and cerebral-spinal fluid (CSF) has also been analyzed (E. D.

Bigler, 2007; Blatter et al., 1997; Levine et al., 2008). Many researchers have focused on hippocampus volume changes after trauma (E.D. Bigler et al., 1997; Bonne et al., 2001; M. E. Smith, 2005). Decreased hippocampus volume after injury has been reported. Amygdala has also been associated with emotional processing and depression (Bzdok, Laird, Zilles, Fox, & Eickhoff, 2013). Cingulate cortex has been studied in many of the previous projects and has been associated with CTE and depression (Corbo et al., 2005; Levine et al., 2008; Rauch et al., 2003; Yount et al., 2002).

Cingulate cortex has been associated with emotional processing, memory and attention related tasks and wondering minds (Hayden & Platt, 2010; Mason et al., 2007). Cingulum is situated in the central part of the brain and it is closely related to precuneus, orbital frontal cortex and dorsolateral prefrontal cortex (Carmichael & Price, 1995; Hayden & Platt, 2010; Maddock et al., 2003; Pandya et al., 1981). Studies have shown that due to multiple connections and its participation in many brain networks, cingulate cortex is considered a cortical hub (Hagmann et al., 2008). It is metabolically very active (Raichle et al., 2001). Apart from emotional processing and memory related tasks, it has been reported that cingulate cortex might be involved in regulation of cognitive activities (Hampson et al., 2006). So change in cingulate cortex volume is very important to study the relation between CTE and depression.

In our analysis, we checked for any correlation between ACC and PCC volumes and depression scores. Volume of PCC indicated very strong correlation with depression score BDI_II ($p = 0.001$). This is in line with many other published studies showing lesser PCC volumes after head trauma and its correlation with few cognitive and neuropsych tests

(Gale, Baxter, Roundy, & Johnson, 2005; Levine et al., 2008; Yount et al., 2002). Similarly, studies have also reported decrease in ACC volume and its strong correlation with depression, neuropsych and cognitive tests (Bendlin et al., 2008; J. K. Chen et al., 2008; Gale et al., 2005; Rauch et al., 2003). In our study, considering multiple comparison effects, correlation between volume of ACC and BDI_II score was approaching significance ($p = 0.023$). One possible mechanism for volume changes and how it leads to depression has been proposed by Guskiewicz et al (Guskiewicz et al., 2007). There might be loss of neurons after first or initial few concussion. But over their careers, these athletes suffer multiple concussions. This could aggravate initial injury and lead to major structural damage. This might be root cause for major depression.

We also found that number of years played in NFL is strongly correlated with the number of concussions players suffered with $p = 0.0001$. This clearly suggests that player with longer active career is more susceptible to suffer more hits and concussions. Although certain factors such as how actively the player is participating and player's playing position should be considered as well.

In such a complicated scenario where multiple factors are in play, it is necessary to assess how each factor contributes towards the outcome. Mediation analysis was performed to include such various factors. Analysis show that volume of PCC partially mediates the relationship of duration of NFL career and depression score BDI_II. A possible explanation would be explained as follows. Number of years in NFL is significantly correlated with number of concussions ($p = 0.0001$). This leads to decrease in PCC volume. Which is represented by bad depression score BDI_II.

Age has been reported as a contributing factor towards the decreasing volumes (Raz, Ghisletta, Rodrigue, Kennedy, & Lindenberger, 2010; Raz & Rodrigue, 2006). With older age, volumes and atrophy in the brain structures shows significant changes. Atrophy increases along with decreased structural and global volumes with age. Larger ventricles and deeper sulci have also been reported (Raz et al., 2010; Raz & Rodrigue, 2006). It is critical to consider age factor in the analysis. Ignoring the aging effect could lead to false positive results. In our analysis, the age-range of the players was 30-60 years with mean age of 45.6 ± 9.30 years. Effect of aging starts showing up in the range of 45-55 years (Raz & Rodrigue, 2006). In bivariate correlation for this dataset, age did not show any correlation with cingulum volume or with depression scores. Age did not show any significant contribution in any of the mediation models as well. Possible reason for this could be that for this dataset with mean age of 45.6 ± 9.30 years, it is too early to show any significant changes yet. So we can safely discount the effect of aging for the analysis.

Important question is does this dataset represent the total retired NFL players' population? A study published earlier by Guskiewicz et al., 2005, 2007 could be used for comparison purposes (Guskiewicz et al., 2005a; Guskiewicz et al., 2005b; Guskiewicz et al., 2007). Earlier study was conducted via telephone and mail survey. Although there are few serious limitations of the earlier study, it is the only study conducted so far to compare with. In their study, about 24% players reported 3 or more sustained concussions during their NFL career. In our study 34 % players responded the same. The average organized football playing duration in earlier study was 15.9 years compared to 17 years in our study. In our study group, not all the positions have equal representation. No quarterback or kicker was in the group. Also there was just one tight end, two wide receivers and two

running backs were part of the group. On the other hand, there are more linebackers, offensive and defensive linemen and defensive backs are represented heavily. Players playing in these positions have shown tau pathology in postmortem findings (Gavett et al., 2011; B. I. Omalu et al., 2010; B. I. Omalu et al., 2006; B. I. Omalu et al., 2005). So the players group in our study gave greater probability of high level of sustained mTBI.

11.1% players were diagnosed as suffering from depression in the earlier study. In our study, we found that 26.7% of the players reported 4 or more symptoms of depression/anxiety. Also 57.8% population of the group reported 2 or more symptoms. To summarize, the study group well represents the players' age group of 30-60 years. Compared to earlier study, our study represents higher exposure to football with higher number of sustained concussions and possibly higher risk or CTE. In terms of playing positions, our study is dominated with players playing in the position which increases chances of concussion. Also, our group indicated higher amount of depression/anxiety related symptoms compared to earlier study.

It is important to mention that outcomes of this study were limited by certain factors. Dataset consisted modest size of 45 retired NFL players. More comprehensive studies with higher number of participants and wider age range need to be conducted. For this study, there was no control pool. Only correlation analysis between volumes and other data with depression scores was possible. Group analysis with healthy controls was not possible. Another major limitation was that the accuracy of some of the data depends on how correctly player can remember few factors. Variables such as how many concussions player has suffered over the years are always dependent on how well player's memory

serves him. Few more studies are required to consider and overcome all these limiting factors and get a much better explanation of role of Cingulate cortex in CTE.

**Chapter 5: Hemorrhagic lesions and its clinical correlation based on
venous and arterial damage in Traumatic Brain Injury**

Introduction

Traumatic Brain Injury (TBI) causes over 1.7 m injuries every year only in United States. It is one of the major reasons of disabilities and deaths all over the world. It causes significant socio-economic impact. Advance Magnetic Resonance Imaging (MRI) techniques such as Diffusion Tensor Imaging (DTI) and Susceptibility Weighted Imaging (SWI) are very sensitive and useful in detection of vascular and diffuse axonal injuries. SWI is most sensitive non-invasive method to detect any bleed(E. M. Haacke et al., 2005) . It is about 3-6 times more sensitive than T2* GRE sequence, which is current clinical benchmark(Tong et al., 2003). It has been reported that SWI is very effective in detection of abnormal venous structures and bleeds in various diseases (Baik et al., 2012; Hu et al., 2008; Huang et al., 2012; Lu et al., 2012).

During traumatic injury veins and arteries undergo severe pressure and stress. It can easily cause a vessel wall to break down. Given its structure, Veins are more susceptible to break down. Veins have relatively thinner vessel walls, less smooth muscle and poor biomechanical stability(Monson, Goldsmith, Barbaro, & Manley, 2003, 2005). It has been shown that cortical arteries can carry twice the amount of stress than that of veins at half stretch, before breaking down. So it would be critical to analyze the effect of these breakages on the outcome of the patient.

Recovery after vessel breakage is significantly different depending on the type of vessel, location of the rupture and severity of the damage. It is very crucial to design appropriate future medication based on the injury severity. So it would be really advantageous to have a good predictor at the early stage. The main objective of this study is

to observe and understand the effects of trauma on veins and arteries, its implications and to try to establish a reliable injury outcome predictor.

Patient Recruitment And Method

Patient Recruitment

Approval of Human Investigation Committee of Wayne State University and Institutional Review Board of Detroit Medical Center was acquired. Written informed consent was obtained from each subject before enrollment. A total of 28 patients who sustained TBI were recruited from the Detroit Medical Center (DMC) and its affiliates with written consent. Patients with Glasgow Coma Scale (GCS) 12 or lower (moderate to severe TBI) were recruited. Also patients with 13-15 GCS score and also intracranial bleed (mild complicated) were included in the study. If GCS is unavailable, posttraumatic amnesia of greater than 24 hours and/or unconsciousness of more than 20 minutes after injury were the inclusion criteria. Patients' group mean age was 40.51 ± 15.72 years (range 21.24-68.65 years). Patient group included 4 female and 24 male patients. Patients were scanned 360.19 ± 490.21 days post injury (range 12-1853 days).

Case ID	Age (Years)	Sex	Injury Cause	Imaging after injury (Days)	GCS	GOS_E
1	27.23	M	Struck by motor vehicle	31	7	6
2	45.91	M	Sports	692	6	N.A.
3	27.35	M	Assault	75	N.A.	7
4	67.74	F	Fall	12	14	8

5	45.4	M	Fall	149	15	N.A.
6	21.82	F	Struck by motor vehicle	146	N.A.	6
7	26.85	M	Motor vehicle accident	310	6	6
8	57.1	M	Sports	35	12	7
9	40.9	M	Struck by motor vehicle	59	4	3
10	41.25	M	Motor vehicle accident	199	7	8
11	58.63	M	Motor vehicle accident	164	7	N.A.
12	21.69	M	Struck by motor vehicle	58	5	8
13	66.03	F	Struck by stone	57	15	7
14	52.6	M	Fall	41	14	5
15	44.35	M	Motor vehicle accident	366	3	4
16	36.7	M	Struck by motor vehicle	321	7	7
17	39.23	M	Struck by motor vehicle	384	7	6
18	25.77	M	Struck by motor vehicle	24	3	6
19	46.86	M	Struck by motor vehicle	390	5	5
20	48.55	F	Fall	375	15	3
21	58.05	M	Assault	381	12	7
22	41.14.	M	Struck by motor vehicle	61	8	4
23	25.35	M	Struck by motor vehicle	356	3	8
24	59.26	M		1688	15	3
25	25.24	M		1853	13	7
26	62.75	M		28	14	7
27	21.24	M		101	3	6
28	25.63	M		1698	7	6
Mean	40.51			360.19	8.46	6.21
Standard Deviation	15.72			490.21	4.37	1.54
Range	21.24-68.65 years			12-1853	3-15	3-8

Table 5.1: Clinical data of the Patient group with TBI, N.A. = Not Available

Clinical & Outcome Assessments

All patients underwent Glasgow Coma Scale (GCS) examination at the acute stage. Mean GCS score was 8.46 ± 4.37 . Extended Glasgow Outcome Scale (GOS-E) score was recorded for 26 patients. GOS-E scale examines the functional recovery of the patient. Mean GOS-E score was 6.21 ± 1.54 . GOS-E was recorded on an average of 360.19 ± 490.21 days after the injury.

Neuroimaging Protocol

All MRI data were collected on a 3-Tesla Siemens Verio scanner with a 32-channel radio frequency head coil (Siemens Medical Solutions, Erlangen, Germany). SWI is a 3-dimensional, T2* based GRE sequence with long TE and 3-D flow compensation. The phase images were high-pass filtered (96x96 filter size) by using an in-line manufacture-applied filter and then integrated with magnitude images to generate the processed SWI image. SWI parameters are as follows: TR/TE of 30/20ms, Flip angle of 15 degree, bandwidth of 100 Hz/Px, field of view (FOV) of 256x256 mm², 25% oversampling, slice thickness of 2 mm, total 64 slices, 20% distance factor, GRAPPA iPat factor of 2 and resultant voxel size of 0.5x1x2 mm³. SWI sequence acquires phase, magnitude, minimum intensity projection (mIP) and processed SWI images.

Image Analysis

All SWI images were analyzed using our in-house software SPIN (signal processing for NMRI) (MRI Research Institute, Detroit, Michigan). A robust semi-automatic approach was adopted for the analysis. For each case, a baseline signal intensity levels for the brain tissue were recorded. Mean of multiple signal intensity readings of the brain tissue was considered as baseline signal intensity for each subject. 25% of the baseline signal intensity was decided as a threshold via trial and error method to quantify volume. This worked as “low pass” intensity filter to separate bleed from the surrounding tissue with higher intensity. A bigger ROI was drawn around the bleed. Any pixel with intensity value lesser or equal to 25% of the baseline signal intensity level would be considered part of bleed. Total numbers of pixels were recorded for each lesion. This way lesion load was recorded.

The bleeds were divided into two groups. One group associated with veins and other one as freestanding bleeds. SWI being very sensitive to the venous blood, lesions with visible vein association were included in the first group. Other lesions were considered as freestanding bleeds. Along with processed SWI images, minimum Intensity Projection (mIP) images, SWI phase and SWI magnitude images were used to examine the possible venous connection of the bleed. mIP SWI images were processed with window size of 4 SWI slices. That means 4 SWI image slices were collapsed together in one. Pixels with minimum intensity in all four slices would show up in the final single image slice. Veins have lower intensity compared to surrounding brain tissue in SWI images. So we can visualize a continuation of vein over several slices. Figure 5.1 shows an example of how a vein over the several slices could be seen in a single slice in mIP SWI image. In Figure 5.1

whole right septal vein can be seen in a single slice. This helps to detect any association between bleed and vein that might not be clearly conclusive in an individual slice. A simultaneous observation of mIP SWI, phase, magnitude and SWI images would give a very conclusive result regarding possible association between lesion and vein.

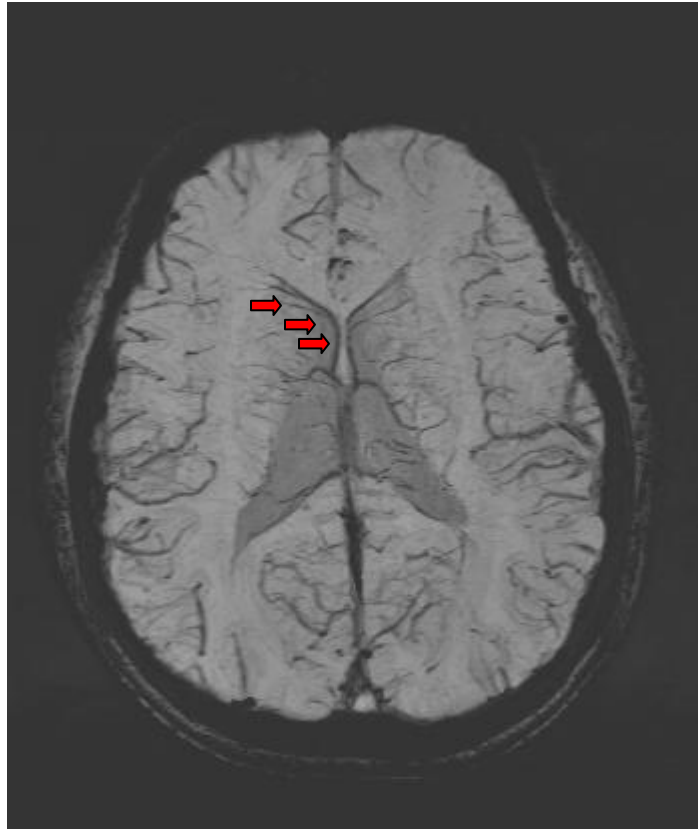


Figure 5.1: Example of continuous vein in mIP SWI image.

Figure 2 shows examples of bleed with clear association with vein. Figure 5.2 (A) shows lesions at and beyond the branching point of left septal vein. Figure 5.2 (B) shows couple of lesions associated with different branches of thalamo-striate vein in both hemispheres of the brain. Figure 5.3 is an example of localized freestanding bleed. Total

number of bleeds associated with veins and freestanding bleeds were recorded. Total number of pixels (Lesion volume) associated with these bleeds were also recorded.

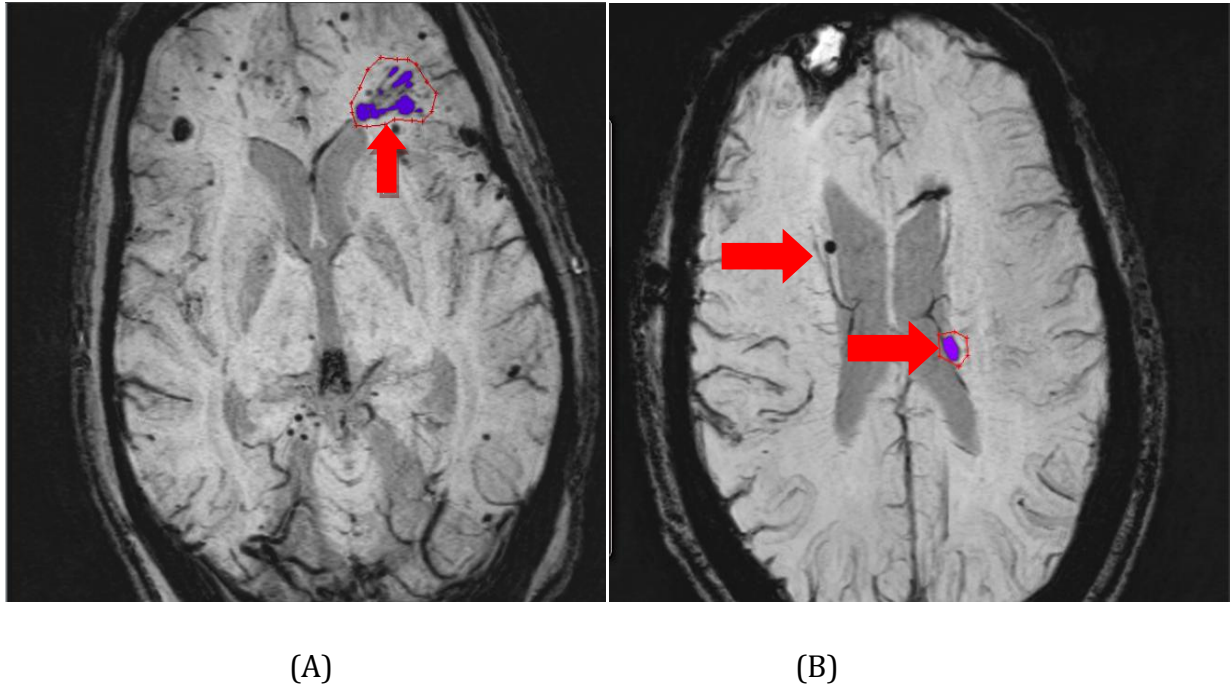


Figure 5.2 (A), (B): Bleeds associated with Veins

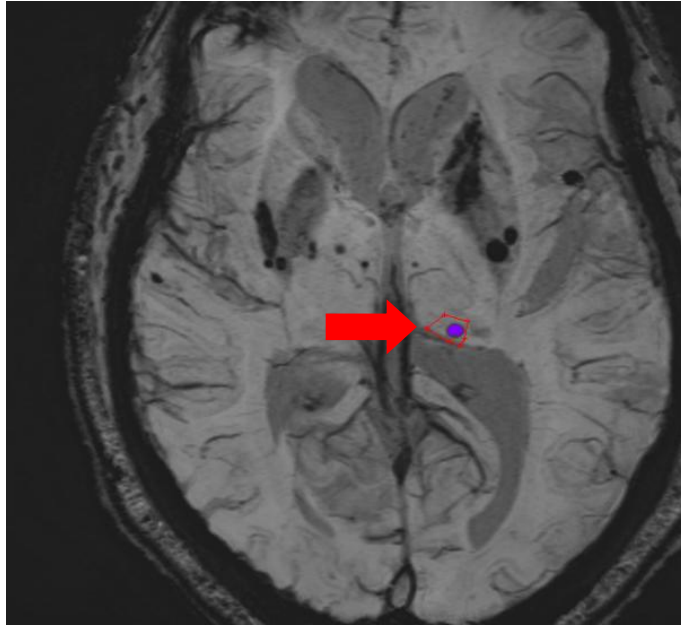


Figure 5.3: Freestanding

Statistical Analysis

Out of 28, 7 cases (patient number 4, 5, 7, 9, 10, 17 and 19) were discarded due to bad image quality and/or motion. Also, 3 patients (patient number 24, 25 and 28) were removed from the analysis. These patients were considered outliers since they were scanned significantly later (1600-1900 days post injury) than other patients. IBM analytical tool SPSS 21.0 (SPSS, Inc., Chicago IL) was used for the statistical analysis. First, Number of Bleeds and lesion volumes were compared against GCS and GOS-E. Pearson's, spearman and Kendall's correlations were performed.

In the second part, the patients were divided into two groups. Group 1 included patients with dominant venous associated bleeds. And group 2 included patients with dominant freestanding bleeds. Patient would be included in group 1 if number of bleeds

associated with veins is more than 50% of total bleeds in that patient. Patient would be included in group 2 if freestanding bleeds were more than 50% of bleeds in that particular patient. Group comparison between the groups was performed using ANOVA.

In the third part of the analysis, patients were grouped based on the severity of their GCS scores. Patients with GCS scores of 9 or below (Severe) were grouped in group 1. Patients with GCS higher than 9 (Moderate-Mild) were grouped as group 2. Group comparisons were performed using ANOVA.

Results

In first part of the analysis, lesion numbers and volumes were compared against GCS and GOS-E scores. Total number of lesions including freestanding bleeds was inversely correlated with GCS ($p = 0.020$). Number of lesions associated with veins and volumes of these lesions were inversely correlated with GCS ($p = 0.015$, $p = 0.019$ respectively). Number of freestanding bleeds did not show significant correlation with either GCS ($p = 0.33$) or GOS-E score ($p = 0.61$). Total volume of the freestanding bleed also did not show any significant correlation with either GCS ($p = 0.60$) or GOS-E score ($p = 0.95$). Figure 5.4 shows inverse correlation of GCS score and number of lesions associated with veins. And Figure 5.5 shows correlation between GCS score and lesion volumes associated with veins.

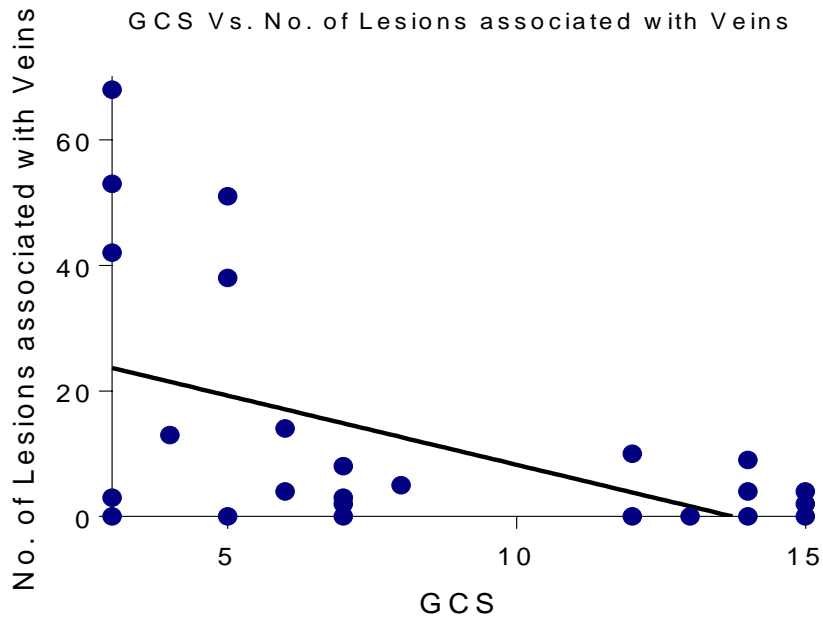


Figure 5.4: Pearson's Correlation between GCS score and Number of lesions associated with Veins

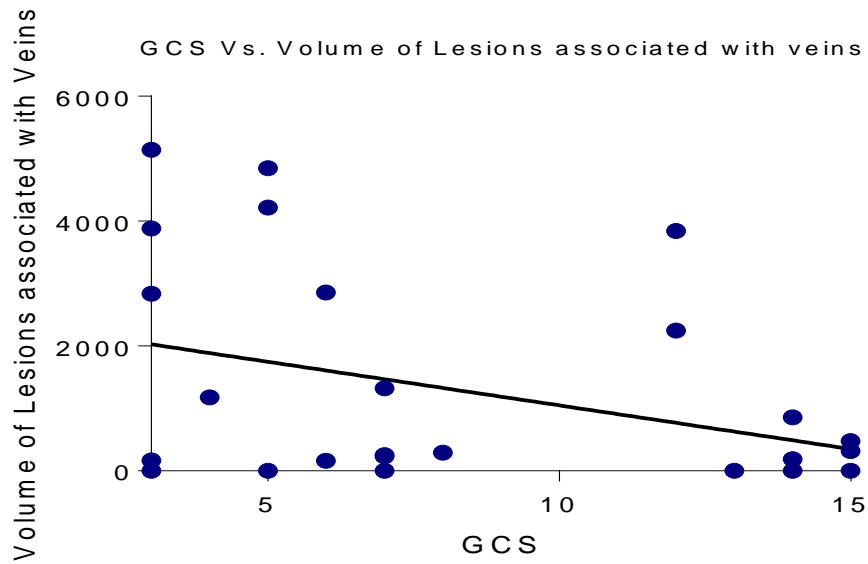


Figure 5.5: Pearson's Correlation between GCS score and Volume of lesions associated with Veins

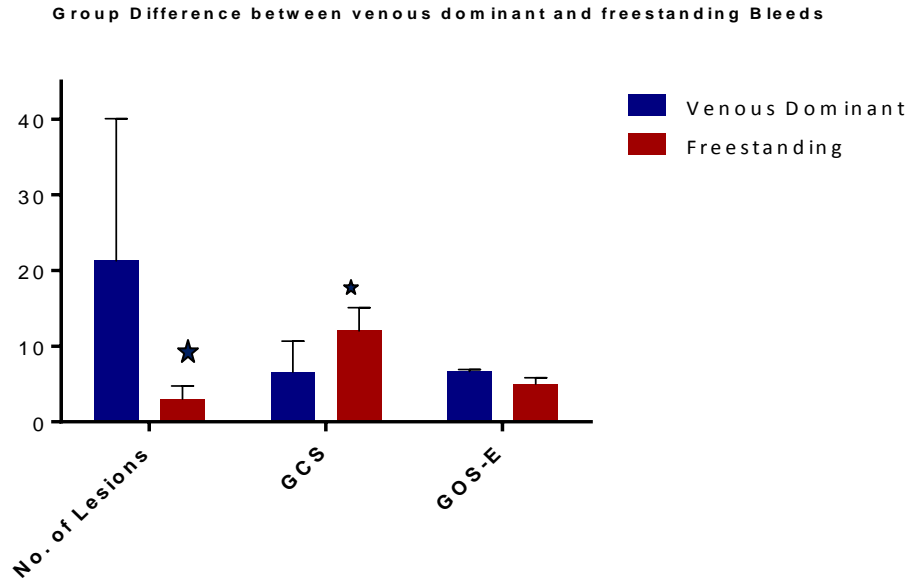


Figure 5.6: Group Difference between subjects with more venous associated and more freestanding bleeds

In the second part of the analysis, group comparisons were performed. Groups were divided based on dominant venous association or freestanding bleeds. Group 1 included patients with more dominant venous component (N=15). Group 2 included patients with more dominant freestanding bleeds (N=5). ANOVA analysis was performed between the groups. Results as shown in Plot 3 indicate that there was significant difference in the number of lesions between the groups with $p = 0.04$. Group 1 had significantly higher amount of lesion numbers compared to group 2 (Group 1 mean = 21.87 ± 18.8 , group 2 mean = 3 ± 1.73). There was significant difference between the GCS scores of the groups with $p = 0.019$. Group 1 has significantly lower GCS compared to Group 2 (Group 1 mean = 6.58 ± 4.1 , Group 2 mean = 12 ± 3.08). Independent samples test was also performed which supported the results from ANOVA.

Group Difference in:	<i>p Value</i>
Number of Lesions	0.041
GCS Score	0.019
GOS_E Score	0.135

Table 5.2: ANOVA analysis between Groups with more venous damage and freestanding damage

In the third part of the analysis, groups were divided based on the severity of the injury. Group 1 included severe patients with $GCS \leq 9$ ($N=11$). Group 2 included mild to moderate patients with $GCS > 9$ ($N=6$). ANOVA analysis was performed between the groups. Results show that there was significant difference in number of lesions between the groups ($p = 0.046$). Group 1 had significantly higher number of lesions compared to Group 2 (Group 1 mean = 18.64 ± 16.97 , Group 2 mean = 3.33 ± 1.75). There was no significant volume difference between the groups ($p = 0.14$). Independent samples test was also performed which supported the results from ANOVA.

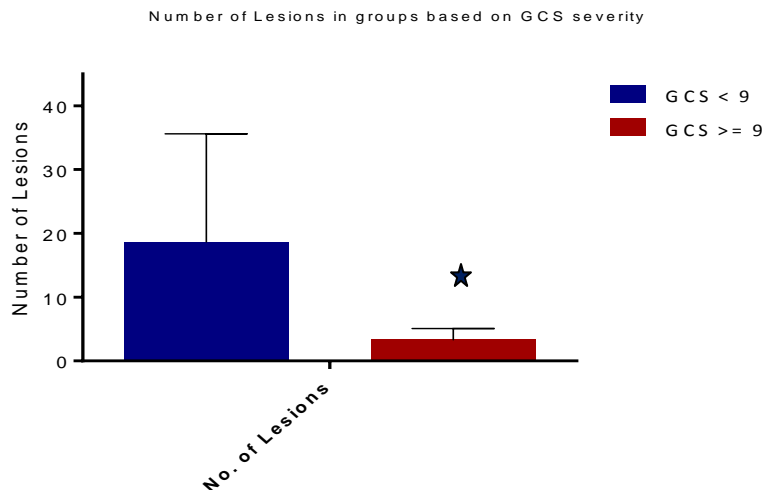


Figure 5.7: Group difference in number of Lesions in groups with severe ($GCS \leq 9$) and moderate-mild ($GCS > 9$) TBI ($p = 0.046$)

In Figure 5.7, we can see the group difference between the groups based on GCS outcome. Severe patients (GCS ≤ 9) have significantly more number of lesion compared to moderate to mild (GCS > 9) patients.

Discussion and Conclusions

SWI is much more sensitive than GRE sequence to detect blood (Tong et al., 2003). Due to thinner walls and poor biomechanical properties veins are more prone to damage compared to arteries (Monson et al., 2003, 2005). In the analysis, results show that total number of lesions is inversely correlated with patient's GCS score. This is in line with several other studies conducted earlier (Ashwal, Babikian, et al., 2006; Ashwal, Holshouser, & Tong, 2006; Babikian et al., 2005; Tong et al., 2004). Number and volume of the lesions associated with the veins show inverse correlation with the GCS score. This suggests that lesions associated with veins have direct impact on the GCS scores. Higher the amount of lesions leads to more severe condition, which is indicated by lower GCS score.

When patients were divided based on dominant venous association or freestanding bleed, it shows that lesions associated with veins are significantly higher than freestanding bleed. This further suggests that veins are more fragile and weak. It has higher chances of rupture than arteries.

Amount of the elastic tissue is directly correlated to the pressure that particular vessel can withstand (Burton, 1951; Silver, Snowhill, & Foran, 2003). Typically blood pressure in arteries is in the range of 80-120 mmHg, while in veins it is less than 10 mmHg. Arteries face about 10 times more tension than veins (Burton, 1951; HADDY, MOLNAR J.I. ,

BORDEN C.W. , & TEXTER E. C. , 1962). To withstand this extra pressure arteries have thicker middle layer. This layer includes much higher amount of elastic fibers, connective tissue and smooth muscle compared to veins(Cold, 1990; Edvinsson, MacKenzie, & McCulloch, 1993; Wolinsky & Glagov, 1964). It has been reported that arteries can withstand more pressure and tension compared to veins before break down or buckling (Han, 2007; Martinez, Fierro, Shireman, & Han, 2010). This is because of thinner venous walls (Martinez et al., 2010). This clearly indicates that veins are more susceptible to rupture than arteries. This might explain the higher number of bleeds associated with veins.

Also GCS is much lesser for the dominant venous component group. This suggests that due to the fragility of the veins, there is more bleeding from the veins, which drives the GCS lower. This might suggest that once ruptured, arteries cause more severe damage and recovery after damage is slower than the venous damage because arteries subject to much higher level of pressure and tensions than the veins. So the patient has less favorable outcome.

Venous drainage system has been generally well explained and documented (Abd el-Bary, Dujovny, & Ausman, 1995; Arnautovic, al-Mefty, Pait, Krisht, & Husain, 1997; Batson, 1957) . But there have been several studies indicating different than known and documented drainage pathways(Doepp et al., 2001; 1970; Gius & Grier, 1950; Schreiber et al., 2003; Valdueza, von Munster, Hoffman, Schreiber, & Einhaupl, 2000). The venous drainage system has also been reported as body posture as well as temperature dependent(Valdueza et al., 2000). Intracranial vessel anomalies have also been

reported(Houser, Baker, Rhoton, & Okazaki, 1972). There have been studies indicating changes in vessel shape and size after trauma(Caruso, Smith, Chang, Wasenko, & Rosenbaum, 1998). It is believed to be caused by vascular lesion or obstruction of the jugular vein. This indicates that venous system contains a certain degree of redundancy that would allow the blood drainage via alternate pathways. This could be a possible explanation for better outcome for the patients with more venous associated lesions. Absence of any alternative pathway for arteries might explain the slower recovery after trauma.

When compared based on the severity of the injury, group difference was observed in number of lesions. This shows similar results as some of the earlier studies (Tong et al., 2004). This clearly suggests that, due to more lesions, patient has worse condition, which in turn is reflected on the GCS score.

In conclusion, clearly veins are more susceptible to damage after the injury compared to arteries. But on the other hand, when arteries rupture, they cause long term damage and slower recovery. Some more comprehensive studies are required to observe the role of different vessels in the event of trauma and how different insults leads to different levels of injury severity and different outcomes. It could be very useful information while assessing the injury severity at early stage and also in deciding future medication.

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Abstract**Volumetric analysis of cingulum in retired NFL players: Its relationship with NFL experience and subjects' cognitive and functional performance**

by

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There are 1.6-3.8 million sports concussions recorded in United States each year. Especially athletes of American football, Hockey, wrestling and boxing are more prone to concussion. After concussion or mild traumatic brain injury (mTBI), subjects may present a constellation of post concussion symptoms (PCS). Further, chronic traumatic encephalopathy (CTE) has been also reported related with sports concussion. It has been reported that cingulum cortex has been reported as susceptible to injury after trauma. The main motivation behind this study is to investigate the effects of multiple traumas on the volumes of anterior and posterior cingulum cortex (ACC & PCC) and determine its effects on Neuropsych and functional test scores. 45 retired National Football League (NFL) players were scanned. The average age of the players was 45.6 ± 9.30 years. Data from each player's playing career including duration of professional, college and high school football

career and number of concussions and dings each player had suffered were recorded. The MRI data was acquired on Siemens 1.5 T magnet. The parameters of the T1 sequence were as following: $T_R/T_E = 2000/4.84$ ms, Flip angle = 8 degrees, Bandwidth =160 Hz/Px, Field of view was 512x512, Slice thickness of 2 mm and resolution was 0.5x0.5x2 mm³. Beck Depression Inventory (BDI_II) and Mini Mental State Examination (MMSE) scores were recorded. BDI_II scores were 9.6 ± 9.25 and MMSE scores were 28.35 ± 1.27 for the group.

All the subjects' images were non-linearly registered to JHU Talairach T1 template using SPM8. A set of predefined ROIs for JHU Talairach T1 template from ROIEditor (Version 1.6, mrstuiio.org) was used. Once all the subjects are in the standard template space, an inverse transform matrix was applied to all the subjects. Same matrix was applied to the predefined ROIs in template space. As a result all the subjects as well as ROIs are back into the native space. IBM analytical tool SPSS 21.0 (SPSS, Inc., Chicago IL) was used for the statistical analysis. Bivariate correlations between volumes of ACC & PCC were checked for any correlation with Neuropsych test scores. In the second part, mediation analysis using "PROCESS" by Dr. Hayes (model 4) was performed to see any mediation effect of volumes of ACC and PCC on the relationship between players' career data and neuropsych scores.

Volume of PCC partially mediates the relationship between number of years played in NFL and BDI_II score (Total effect significance $p=0.003$). Volume of ACC did not mediate any correlation significantly. In bivariate correlation analysis, Volume of PCC is negatively correlated with the BDI_II score ($p=0.001$). Volume of ACC shows tendency in inverse correlation with BDI_II score ($p=0.023$). Number of years played in NFL is directly

correlated with number of concussions suffered in NFL ($p=0.00001$). Players are susceptible to more concussion when they play for longer duration. Mediation model explains that number of years in NFL has some effects on PCC volume, which in turn affects on depression score. Possible mechanism could be loss of neurons due initial concussion. This would be aggravated by more concussions, ultimately leading to change in volume. Cingulum cortex is emotional hub. So changes in PCC volume may reflect on depression score. Also ACC and PCC volumes have inverse correlation with BDI_II score. This also strengthens the hypothesis. This is in line with few earlier studies suggesting that more detailed research is required to look into the role of cingulum cortex in CTE.

Autobiographical Statement

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EDUCATION

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