STUDY OF MILD-MODERATE TRAUMATIC BRAIN INJURY USING TRACT-BASED SPATIAL STATISTICS (TBSS) AND ITS RELATIONSHIP WITH COGNITIVE FUNCTION

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by

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LIST OF ABBREVIATIONS

AD	Alzheimer disease
AxD	Axial diffusivity
ADC	Apparent diffusion coefficient
BET	Brain Extraction Tool
CT	Computed tomography
CTMT	Comprehensive Trail Making Test
DTI	Diffusion Tensor Imaging
dMRI	Diffusion Magnetic Resonance Imaging
DWI	Diffusion Weighted Imaging
EDH	Extradural hemorrhage
FA	Fractional anisotropy
FDT	FMRIB Diffusion Toolbox
FMRIB	Functional Magnetic Resonance Imaging of the Brain
FSL	FMRIB Software Library
FWE	FamilyWise Error
GCS	Glasgow Coma Scale
LI	Laterality index
MAVLT	Malay version of the Auditory Verbal Learning Test
MD	Mean diffusivity
MRI	Magnetic Resonance Imaging
RCFT	Rey Complex Figure Test
RD	Radial diffusivity
ROI	Region of interest
SAH	Subarachnoid haemorrhage
SDH	Subdural hemorrage

TBI	Traumatic brain injury
TBSS	Tract-based spatial statistics
TE	Echo time
TFCE	Threshold-Free Cluster Enhancement
VBM	Voxel-based morphometry
WASI	Wechsler Abbreviation Scale of Intelligence
WCST	Wisconsin Card Sorting Test

KAJIAN KECEDERAAN OTAK TRAUMATIK RINGAN-SEDERHANA MENGGUNAKAN STATISTIK RUANG BERDASARKAN TREK (TBSS) DAN HUBUNGANNYA DENGAN FUNGSI KOGNITIF

ABSTRAK

Ketidakupayaan dalam fungsi kognitif adalah kesan sampingan yang tidak dapat dielakkan dalam kecederaan traumatik otak. Walaubagaimanapun, tahap ketidakupayaan fungsi kognitif mempunyai hubungan yang tidak tetap dengan tahap kecederaan traumatik otak dan masa selepas kecederaan. Pada asasnya, patologi di sebalik jenis kecederaan ini adalah disebabkan kehadiran kecederaan aksonal yang meluas (*diffuse axonal injury*) walaupun dalam kecederaan traumatik otak yang ringan. Oleh itu, kajian ini bertujuan untuk mengkaji tentang keadaan ketersambungan jirim putih pada pesakit kecederaan traumatik ringan-sederhana otak dalam fasa subakut, iaitu dalam tempoh 10 minggu kecederaan untuk menentukan hubungannya dengan skor ujian neuropsikologi. Kajian prospektif kawalan kes telah dijalankan melibatkan 11 pesakit lelaki dewasa dengan kecederaan otak traumatik ringan-sederhana dan 11 subjek kawalan lingkungan umur berpadanan. Pengimejan resonan magnet difusi *(diffusion magnetic resonance imaging)* dan ujian neuropsikologi telah dijalankan dalam tempoh 10 minggu selepas kecederaan. Perbezaan dalam nilai anisotropi pecahan (*fractional anisotropy - FA*) antara pesakit dan kumpulan kawalan telah diperiksa menggunakan teknik *statistik ruang berdasarkan trek (TBSS)*. Nilai FA yang signifikan anatara pesakit dan kumpulan kawalan kemudiannya dihubungkaitkan dengan ujian neuropsikologi dalam kumpulan pesakit. Beberapa kelompok dengan voksel puncak pengurangan FA yang signifikan ($p < 0.05$) dalam rangka jirim putih dilihat pada pesakit berbanding kumpulan kawalan, di mana kelompok ini

kemudiannya diambil sebagai *region of interest*. Kelompok ini terletak di fronto-oksipital fasikulus superior, longitudinal fasikulus superior, uncinate fasikulus, dan cingulum, serta jirim putih di kawasan genu korpus kalosum, korona radiata anterior, korona radiata superior, radiasi thalamik anterior dan sebahagian daripada frontal gyrus inferior. Analisis *region of interest* mendedahkan nilai FA mempunyai hubungkait yang signifikan dengan skor *Malay version of Auditory Verbal learning Test (MAVLT) immediate recall* di kawasan genu korpus kalosum (r = 0.62, p = 0.004) dan fasciculus fronto-occipital superior kanan (r = 0.50, p = 0.026). Skor *matrix reasoning* (penaakulan matriks) mempunyai hubungkait positif dengan nilai FA di kawasan fronto-oksipital fasciculus superior di sebelah kanan (r = 0.45, p = 0.045) dan korona radiata anterior di sebelah kiri (r = 0.47, p = 0.036), dan dalam masa yang sama mempunyai hubungkait negatif di kawasan longitudinal fasciculus superior di sebelah kanan (r = -0.49, p = 0.030). Manakala nilai difusi min *(mean diffusivity - MD)* mempunyai hubungkait positif dengan kedua-dua skor *Rey Complex Figure Test (RCFT) immediate* (r = 0.593, p = 0.015) dan *delayed* (r = 0.640, p = 0.002) di fasciculus longitudinal superior di sebelah kanan. Semasa fasa sub-akut kecederaan otak traumatic ringan-sederhana, pesakit menunjukkan penurunan nilai FA dan peningkatan nilai MD secara tidak normal berbanding dengan kumpulan kawalan, yang mencadangkan gangguan saluran jirim putih. Hubungkait antara nilai FA dengan skor neuropsikologi selanjutnya membuktikan kemerosotan kognitif yang mungkin disebabkan oleh gangguan struktur.

STUDY OF MILD-MODERATE TRAUMATIC BRAIN INJURY USING TRACT-BASED SPATIAL STATISTICS (TBSS) AND ITS RELATIONSHIP WITH COGNITIVE FUNCTION

ABSTRACT

Traumatic brain injury (TBI) is known to lead to cognitive function impairment. The degree of impairment, however, varies depending on the severity and time post-TBI. Diffuse axonal damage has been discovered as the underlying pathology even in mild TBI. Thus, this study aims to determine the state of white matter putative connectivity in patients with mild-moderate TBI in the subacute phase, or within 10 weeks of injury, and its correlation to cognitive scores. A case-control prospective study was conducted involving 11 male patients with mild-moderate TBI and an age-matched control group of 11 adult male volunteers. Diffusion MRI scanning and cognitive testing were performed within 10 weeks of injury. The difference in fractional anisotropy (FA) values between TBI patients and control group was studied using tract-based spatial statistics (TBSS). Then, the FA values that were significantly different between patients and controls were correlated with neuropsychological tests in the TBI group. When comparing patients to the control group, several clusters with peak voxels of substantial FA reductions ($p < 0.05$) in the white matter skeleton were seen. These clusters were later treated as region of interest and were found in the superior fronto-occipital fasciculus, superior longitudinal fasciculus, uncinate fasciculus, and cingulum. White matter fibres in the region of the genu of the corpus callosum, anterior corona radiata, superior corona radiata, anterior thalamic radiation, and a portion of the inferior frontal gyrus also contained these clusters. Region of interest analysis revealed FA values significantly correlated with Malay version of Auditory Verbal Learning

Test (MAVLT) immediate recall scores in the region of genu of corpus callosum (r = 0.62, p = 0.004) and right superior fronto-occipital fasciculus (r = 0.50, p = 0.026). Matrix-reasoning scores positively correlated with FA values in the region of right superior fronto-occipital fasciculus (r = 0.45, p = 0.045) and left anterior corona radiate (r = 0.47, p = 0.036), while having negative correlation in the region of right superior fronto-occipital fasciculus (r = -0.49, p = 0.030). Mean diffusivity (MD) values significantly have positive correlation with both Rey Complex Figure Tests (RCFT) immediate (r = 0.593, p = 0.015) and delayed (r = 0.640, p = 0.002) scores in the right superior longitudinal fasciculus. During the sub-acute phase of TBI, the mild-moderate TBI patients showed unusually decreased FA values and increase MD values compared to controls, which suggested disruption of white matter tracts. The correlation between FA values with neuropsychological scores further provide evidence of cognitive impairment probably responsible by the structural disruption.

CHAPTER 1

INTRODUCTION

1.1 Background of the study

Traumatic brain injury (TBI) is recognised as a major cause of disability worldwide (Dewan et al., 2019; GBD, 2016) and it is an emerging research priority, with large comparative research studies for example from North America and Europe (Menon & Maas, 2015; Yue et al., 2013). Local studies related to TBI in Malaysia also show an increment over the last two decades (Arulsamy & Shaikh, 2020), corresponding to the Royal Malaysian Police (PDRM) report that about 1.74% of the population was involved in road traffic accidents (PDRM, 2020), a major contribution to the TBI epidemiology (Dewan et al., 2019).

According to Langlois and Sattin (2005), TBI is referred to as a "silent pandemic" because, despite the alarming statistics, society is mostly heedless of the scope of the issue. Standardized TBI monitoring is also inadequate. To make it worse, due to its heterogeneous pathological injuries obtained from brain damage (van Eijck et al., 2018) there are uncertainties to determine the optimum guidelines in handling the patient either in the aspect of physical, mental or cognitive perspective.

However, regardless of the degree of severity, TBI survivors are prone to experiencing deficits in cognitive and functional performance, which impair daily life functioning, and inevitably degrade the quality of life of those affected significantly in the acute stage.

1.2 Problem statement and study rationale

The heterogeneity in the neuropathological presentation of traumatic brain injury makes it difficult to determine precise prognosis especially in the prospect of neuropsychological function. Many studies reported that the post-effect of TBI, apart from physical adversity, is commonly compromised memory-related function, decision-making, attention and information processing-speed (Beadle et al., 2018; Hashim et al., 2017; Panenka et al., 2015; Palacios et al., 2011).

The association between TBI and impairment in neuropsychological performances is attributed to diffuse axonal injury, and can be observed across a range of injury severities (Hulkower et al., 2013; Smith & Meaney, 2000). Diffuse axonal injury is selective vulnerability of white matter axons to damage, specifically caused by rotational acceleration forces (Davceva et al., 2012; Zhang et al., 2006).

1.3 Justification and benefits

The prognosis of patients with TBI is complicated due to its heterogeneity of pathological injuries leading to broad impairments in cognitive achievements. Therefore, it is crucial to put additional study of investigation of the structural white matter integrity in brain injured patients in order to correlate with their neuropsychological performance test scores. The current study would explore the microstructural white matter changes in both level of whole brain and region-of-interests (ROI) in Malay traumatic brain injury patients by utilising diffusion MRI. There have been many studies on cognitive impairments in traumatic brain injuries using diffusion MRI, but not in the population of Malay ethnic specifically.

1.4 Research questions

1. How is the integrity of structural white matter disrupted in mild and moderate TBI patients?
2. How does the cognitive performance between TBI patients and healthy controls differ?
3. What is the correlation between cognitive performance scores and fractional anisotropy (FA) values in regions of interest within the brain of TBI patients?
4. What is the correlation between cognitive performance scores and mean diffusivity (MD) values in regions of interest within the brain of TBI patients?

1.5 Study objectives and hypotheses

General objective: To identify alterations of structural connectivity indicating diffuse axonal injury after mild or moderate TBI and to associate the alterations with cognitive deficits by applying neuropsychological performance tests.

Specific objectives

1. To compare white matter damage in the brains of mild and moderate TBI patients
2. To determine cognitive performance of TBI patients and healthy controls
3. To correlate cognitive performance scores with FA values in region of interests within the brains of TBI patients.
4. To correlate cognitive performance scores with MD values in region of interests within the brain of TBI patients

Hypotheses

Null hypothesis 1: There is no disruption in the integrity of structural white matter in mild and moderate TBI patients

Alternative hypothesis 1: There is disruption in the integrity of structural white matter in mild and moderate TBI patients

Null hypothesis 2: TBI patients will not have reduced performance in neuropsychological assessment tests compared to healthy control

Alternative hypothesis 2: TBI patients will have reduced performance in neuropsychological assessment tests compared to healthy control

Null hypothesis 3: There is no correlation between cognitive performance scores with FA values in regions of interest within the brain of TBI patients

Alternative hypothesis 3: There is significant correlation between cognitive performance scores with FA values in regions of interest within the brain of TBI patients

Null hypothesis 4: There is no correlation between cognitive performance scores with MD values in regions of interest within the brain of TBI patients

Alternative hypothesis 4: There is significant correlation between cognitive performance scores with MD values in regions of interest within the brain of TBI patient.

CHAPTER 2

LITERATURE REVIEW

2.1 Traumatic brain injury

Traumatic brain injury (TBI) remains a critical public health concern globally since injuries to the brain is liable to result in death and disability (Hyder et al., 2007). The definition and diagnosis of TBI has changed over the decade but consensually used definition is by Menon et al., (2010), which stated that TBI is an external force-induced change in brain function or other signs of brain dysfunction. As the definition suggests, it is nondegenerative- and noncongenital-acquired insult to the brain.

Despite the low likelihood of death, TBI survivors will invariably experience long-term physical, cognitive, and psychological impairments that will impair their everyday functioning, regardless of the degree of their injury (Rosenfeld et al., 2012). In fact, it is associated with a significant socioeconomic burden in terms of high healthcare costs and loss of employment capability (Ma et al., 2014).

Fundamental characteristic of TBI is loss or alteration of the conscious state. The Glasgow Coma Scale (GCS; Teasdale and Jennett 1974) is the simple, durable, and in fact most extensively used physiological measure for the classification of TBI severity at the initial assessment stage. A scoring system is utilised to track responsiveness trends for visual, verbal, and motor features. The GCS score for a typical, healthy person is 15 when the eye opening, verbal, and motor exam scores are added together. Consequently, this scale directs the following classification: mild head damage (scale 13 to 15); moderate head injury (scale 9 to 12); and serious head injury (3-8). However, the results based on this scale lead initial choice give no indication of the underlying structural or functional damage as well as limits in long-term prognostication (Smith et al., 2019). On that account, TBI patients with the same GCS value have the possibility to obtain distinct pathological injuries altering different functions (Palacios et al., 2011).

The duration of loss of consciousness and post-traumatic amnesia (PTA), a momentary condition of bewilderment that follows a TBI, can also be used to classify the severity of TBI. A mild TBI is defined as having a loss of consciousness for less than an hour or amnesia lasting less than 24 hours; a moderate TBI is defined as having a loss of consciousness for more than 24 hours or post-traumatic amnesia lasting longer than a week (Hart et al. 2016).

Despite the different levels of brain injury based on several clinical outcomes assessed during the admission of patients, the architectural scaffolding that happen to the brain due to the injury can be quite similar regardless of the level of TBI. The feedback mechanism of the brain towards external force/foreign body inclusively affected by its own underlying architectural structure, i.e. skull, subdivision of the brain regions, and the physiological properties of the cranial tissues (Marion, 1999). Depending on the magnitude of the external force/foreign body, a considerable highlight is that every brain feedback is under distinctive mechanical loading condition. Based on the apprehend facts, TBI can be divided into closed head injury, penetrating (open) head injury, and explosive blast injury (Ng & Lee, 2019).

Concurrent brain damage caused by head injury leads to heterogeneous display of the pathology causing it is recognise as a highly complex in term of diagnosis. From the clinical standpoint, the process of head injury can be divided into; primary injury (focal and diffuse brain injury), secondary or progressive injury.

Focal brain injury as the name suggests, applies to injury confined in a single region of the brain due to direct concussion or compression forces. It is commonly come with the evidences of skull fracture and localized contusion at the core of the injury, which is known as coup injury (Schmidt et al., 2004). Necrosis of neuronal and glial cells at the coup caused blood supply being compromised and contributed to primary vascular injuries, an occurrence of localized bleeding either in the brain (intracerebral hematomas), on the surface of the brain (acute subdural hematomas, subarachnoid hemorrhage, extradural hematoma), or in the cortical gray matter (cerebral contusion) (Ng & Lee, 2019). The primary vascular injuries routinely emerged in the population of moderate or severe head injury (Meaney et al., 2014). All of this injures are readily visible using standard imaging technique (CT, MR) even though true focal injuries are rare.

In contrast to focal brain injury, diffuse brain injury has more distributed injuries throughout the brain and primarily emphasized by diffuse axonal injury, characterized by multiple focal hemorrhages throughout the brain. The initial mechanism involved rapid acceleration and deceleration of brain leading to the intense shear and strain forces induced axonal white matter injury in selected widespread brain regions (Marion, 1999; Ng & Lee, 2019). It accounts for approximately 70% of TBI cases (Ng & Lee, 2019). Pathologically, the brainstem, corpus callosum, and cerebral hemispheres were the most often affected areas, however the thalamus, fornices, and basal ganglia were also susceptible to diffuse injury (Palacios, 2013). Because of specific crucial regions disrupted, diffuse axonal injury inclined to compromise neuropsychological performances of the affected individual.

Based on a systematic review on the diffuse axonal injury by van Ejick et al., (2018), patients with the injury have 62% probability of unfavourable outcome, with the risk of unfavourable outcome three times higher than TBI without the diffuse axonal injury. The study further mentioned location of the lesion mostly affected the outcome especially in the area of corpus callosum.

In most cases, subsequent sequelae from the initial damage last for hours, days, or even years in the worst case scenario. The consequences of diffuse bilateral injury to numerous brain regions involved in memory circuitry, attention, and executive function are made worse by a secondary chain of events that typically includes increased intracranial pressure, cerebral haemorrhage, hypotension, and hypoperfusion, which particularly affects the thalamus and hippocampus (Krishnamurthy & Laskowitz, 2016; Walker & Tesco, 2013). Figure 2.1 shown different types of TBI.

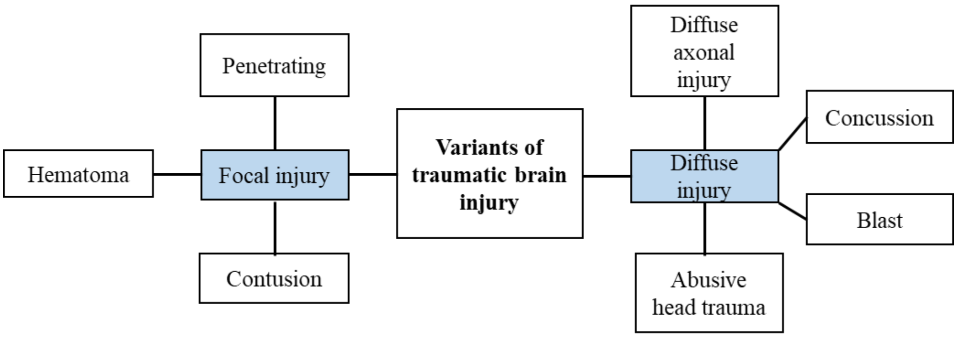

Figure 2.1 Variants of TBI classified depending on clinical presentation and prognosis.

2.2 Cognitive function

TBI individuals substantially have cognitive abilities compromise following the injury. One of the most frequently impacted functions after TBI is memory, particularly working memory, which can result in the disorder's most severe long-term repercussions (Sharp & Jenkins, 2015; Toglia et al., 2017). The encoding, consolidating, storing, and retrieval of information are based on functionally distinct components according to current theories of memory; yet, these components rely on a largely autonomous brain system with vulnerable areas (Mollayeva et al., 2019; Preston & Eichenbaum, 2013). Preston and Eichenbaum (2013) stated the involvement of prefrontal cortex, specifically medial prefrontal cortex and hippocampal in information pathway; to which preliminary engagement of stimuli within medial temporal lobe depending on type of stimuli received, (perirhinal cortex and lateral entorhinal cortex processed episodic contextual memory, whereas parahippocampal cortex and medial entorhinal cortex processed spatial contextual memory). Moreover, working memory activities in healthy individuals stimulate the bilateral frontal and parietal lobes as well as portions of the superior temporal lobe. The working memory network also involves brain areas associated with language for verbal working memory tasks (Broca’s area and inferior supramarginal gyrus (Paulesu et al., 1993) as well as areas associated with vision with spatial/visual working memory tasks (superior occipital gyrus, right calcarine, bilateral fusiform gyrus) (Salmon et al., 1996).

Thus, injury affecting areas associated with memory might also lead to compromise other executive function of the brain since the executive system depends prominently on the prefrontal cortex and its major circuits, and injury to them arise a wide range of behavioural problems in challenging, non-routine situations (Wood & Worthington, 2017).

2.3 Neuropsychological Assessment and TBI

Apart from clinical evaluation to examine the sequelae of TBI, the integration of information from neuropsychological aspect is broadly considered to further elucidate the cognitive, behavioral, and emotional manifestation from injury's impact. It is to provide evident-based brain-behavior relationship alteration. Nevertheless, to assess such relationship, the administration of assessments were holistically selected so that it is appropriate to prevent the practice of underpathologizing or overpathologizing patients, and it is firstly begin with test selection. Several factors were considered while choosing test selection, which includes reliability over time, measurement error susceptibility, and theoretical validity of the test (Soble et al., 2017; Sherman et al., 2011). Lesion analysis research demonstrating the connections between the test and neural structures and systems is also important (Soble et al., 2017). Other than those, there are imperative demographic factor that has the possibility to regulate the baseline assumption such as age, education level, type and accomplishment in occupation, their ethnicity and native tongue as well as physical adversity. All of these considerations should be identified to prevent potential ceiling or floor effects in the selected tests.

One of the example pertaining demographic affluence on test selection is Rey Auditory Verbal Learning Test (RAVLT), an English-language neuropsychological test. Despite its' common utilization to assess verbal learning and memory, it may not be suitable for the targeted local population in Malaysia specifically among Malay population due to potential language hurdle and cultural variation. Thus, there is Malay version of Auditory Verbal Learning Test (MAVLT), a validated version of RAVLT (Jamaluddin et al., 2009). Initially tested on schizophrenic patients, it was proved to be sensitive in discriminating between healthy individuals and those with the disease (Jamaluddin et al., 2009; Munjir et al., 2015). With good discriminatory validity, this test commonly repeated among TBI population as one of their common sequelae is impairment in memory (Palacios et al., 2011).

After the selection of test is validated and conducted in aimed subjects, second step following is assessment validity, which taken into account the possibility of the secondary influence on the psychometric data collected. Example of secondary influence could be chronic level of discomfort, intentional malingering, somatization or adoption of the sick role (Soble et al., 2017; Woods et al., 2015; Johnson-Greene, 2013). This is to ensure subject's personal performance and symptom report accurately reflect cognitive ability (Soble et al., 2017; Sherman et al., 2020). Assessment validity is in relation to the psychometric properties of personal neuropsychological test and it is irrespective of the test performance result, thus in contrast with the test validity. Generally, the influence could be examined using two approaches, either symptom validity or performance validity (Soble et al., 2017).

If prior evaluation (test and assessment validity) is presuming valid, then psychometric scores obtained can be clinically interpreted to specify the existence of cognitive impairment, provided the scores used is overall performance across a test battery (Soble et al., 2017).

Taking consideration of the steps mentioned above, we stated a few tests that regularly utilised in TBI population in order to elucidate and quantify cognitive alteration. Primary to any test, it is central to establish the level of intelligence and the demand can be fulfilled by WASI, where it is well known for its' quick and reliable measure with 6th in popularity for intelligence evaluation globally according to Rabin et al., (2016). It consists of four subtests: Vocabulary, Similarities, Block Design, and Matrix Reasoning and their raw subtest scores when converted to T scores, producing composite scores. In terms of validity, there was a study reported matrix reasoning subtest of WASI had little predictive validity for TBI while in contrast the subtest was sensitive to the cognitive aftereffects of stroke and dementia, assuming matrix reasoning might demonstrated selective sensitivity (Ryan et al., 2004). However, another study found there is correlation between WASI's overall intelligence quotient (IQ) score and smaller cross-sectional area of corpus callosum post-TBI in adolescent, indicating there was reduction in levels of intellectual functioning following TBI (Ferrazzano et al., 2021).

Rey Complex Figure Test (RCFT) (Rey, 1941) is another neuropsychological test widely used. Individuals with TBI inclined to have broad cognitive deficits, and performance from the RCFT can be employed to determine the extent of impairment of executive functioning (operation definition is perceptual organization, planning, and mental flexibility) as RCFT mainly used to assess the visuo-constructional ability and visual memory. One study by L'Ecuyer-Giguere et al., (2019) discovered that individuals with mild TBI have impaired short- and long-term visual memory, but their visual recognition function relatively retained. This might be due to the RCFT is advantageous to distinguish various visual memory processes (immediate recall, delayed recall, and recognition) (Zhang et al., 2021).

2.4 Magnetic resonance imaging

Magnetic resonance imaging (MRI) is a medical imaging technique used in radiology specifically to form pictures of the anatomy and the physiological processes of the body. At the earlier of the discovery, MRI basically utilized nuclear magnetic resonance (NMR) technology discovered by the Nobel Prize laureate, Edward Purcell and Felix Bloch back in 1946, hence the name was originally Nuclear Magnetic Resonance Imaging (NMRI). However the term “nuclear” invited controversial made patient hardly accepted NMR until study by Damadian proved the theory of cancerous cells could be detected using NMR in 1971 and continuously contributed another significant milestone when he constructed and performed the first whole-body MRI on a patient.

The remarkable advances in clinical and research applications of MRI is concomitantly committed by its’ technology invention. It can be roughly highlighted by the hardware, i.e. main magnet, gradient coils, radiofrequency (RF) and computer system (Edelman, 2014; Serai, 2021), as well as the imaging technique, e.g. pulse sequences, parallel imaging and others (Edelman, 2014).

MRI detects proton signals from water molecules (which made up of hydrogen and oxygen) abundantly consisted in each tissue of the body (Oishi et al., 2011; Watanabe et al., 2019). It works due to intrinsic magnetic feature of proton called ‘spin’ - which under normal circumstances, the proton in the tissues spin (precession) with their axes randomly aligned produces their own small magnetic field with ‘north and south’ poles. When exposed to main magnetic field (B0), the protons’ axes tend to all align in uniform creates a magnetic vector oriented (parallel or antiparallel proton) along the axis of the MRI scanner (Berger, 2002). This generates the net magnetization vector along z-axis (the length of the body). Before going further to the process, there are additional magnetic fields (B1) to envelope the main magnetic field (B0), which produce by gradient coils. They simply lied in orthogonal directions (x-, y-, and z-axes) and used to alter the gradient of magnetic field. xy axes represents transverse component whereas z-axis represents longitudinal component. Noted that parallel or antiparallel proton orientation differs in energy state – parallel orientation are in lower energy state than antiparallel to ascertain the generation of MRI signal. However, it is a lot easier for protons to align in the low energy state (the direction of B0/longitudinal) – explaining net magnetization vector on z-axis.

The precessing and uniformly aligned protons absorb energy from externally RF pulses concurrently transmitted by MR machine in order to make the protons spin in a different direction and precessed together in phase eliminating longitudinal magnetization to transverse magnetization resulting them to escalate into a higher energy state. The protons then relax back to their usual alignment once the RF pulse is shut off (low energy state). RF pulse must be applied in multiple manners in order to provide signals and this is known as pulse sequence. The final visual presentation is regulated by the pulse sequence (Jo et al., 2019; Pipe, 2009). Protons emitting excess stored energy in the form of light (photons) upon returning to its resting state and MR machine subsequently captured and converted into an image (Han and Liu, 2020; Berger, 2002). In clinical MRI standard, magnetic field along the different axes produces different gradient, which x-axis produces frequency encoding within the slice, y-axis produces phase encoding within the slice, and z-axis is the slice selection gradient (Serai, 2021) (Figure 2.2).

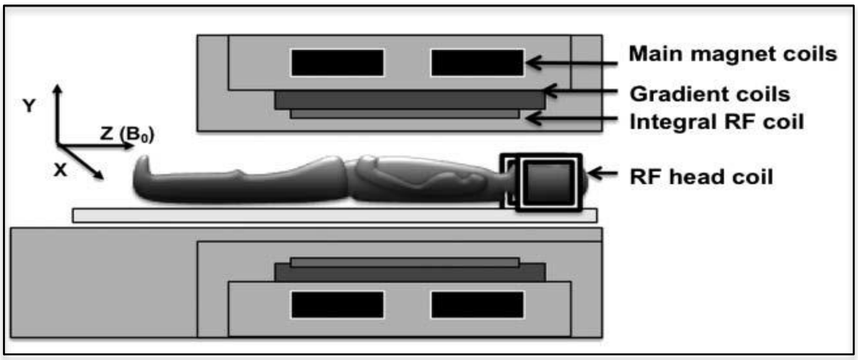

Figure 2.2 Schematic diagram demonstrating relative position of the patient with the main components of MRI scanner: main magnet coils, gradient coils and RF coils (adapted from Currie et al., 2013)

There are different contrast images collected by MR scanner and the liability to choose depend on study question. Repetition time (TR) and echo time (TE) are fundamental factors that influence the generation of contrast image by adjusting accordingly. The typical contrast used for structural anatomical images is T1-weighted (Miyapuram, 2008), which enhances the signal of the fatty tissue and suppresses the signal of water, and on the other hand T2-weighted image enhance the signal of water (Kawahara and Nagata, 2021) because MRI primarily reflect concentration of water and fat (Pipe, 2009). Hence MRI modality is more accurate than CT scans (88% vs 80%) at differentiating disruptions to the white and gray matter (Irimia et al., 2019). Taking into account all the information MRI modality able to facilitate, it is safe to conclude that this modality is conducively suitable for TBI study.

2.5 Diffusion magnetic resonance imaging

Diffusion magnetic resonance imaging (dMRI) is an advanced non-invasive MRI technique that quantifies regional microstructural characteristics of water diffusion within tissue (Mueller et al., 2015; Palacios et al., 2011). The term "diffusion" refers to a random thermal motion based on the theory of "Brownian motion", in which water molecules in uncontrolled movement as they constantly collide with other molecules (Mitchell and Kogure, 2006; Oishi, 2011). It was named after a botanist Robert Brown, who discovered the concept in 1828 as a result of his observations of the pollen floating in water and its connection to thermal agitation (Bigg, 2009). dMRI is an improvement by conventional MRI as it added introduced additional gradient magnetic fields in a pulse sequence making the image contrast sensitive to the thermal or diffusion motion of water (Pipe, 2009). Diffusion-weighted gradient, often known as diffusion sensitising gradient, is the added magnetic field and it is intrinsically create contrast while permitting water molecular displacement over distances of 1-20μm to be recognised (Charles-Edwards & De Souza, 2006). In addition, pulse sequence commonly apply on dMRI is called spin-echo echo-planar sequence (Pipe, 2009).

In diffusion, the intrinsic contrast is present and MRI makes it possible to observe the white matter tracts in real time. Generally, studies of dMRI were based on the underlying concept that water diffusion is highly anisotropic in the tissue of the nervous system. As proposed by Brownian, the thermal random motion of water molecules can be categorized into two: namely isotropic and anisotropic (Beaulieu, 2002). Isotropic diffusion is a condition where water molecules tend to freely move in any direction due to less hindrance, whereas anisotropy happen when water molecules can only diffuse in a single direction, in which is represented by a single axis. The diffusion within white matter substantially tends to be anisotropy due to highly linear organization of axonal tracts encapsulated with hydrophobic myelin sheath that make water molecules diffuse free along than perpendicularly to the long axis of the fibre tracts (Palacios et al., 2011). As regards to the concept, dMRI purposely quantified the anisotropic of water diffusion in tissues to estimate axonal orientation thus constructing the striking three-dimensional maps of connectivity (Le Bihan & Iima, 2015) and is widely used in the brain area as it is made up of white matter and grey matter tissue where the directionality of water diffusion conveniently differentiated. Clinically, the primary uses of dMRI are for acute stroke and other neurological disorders and oncological assessment (Charles-Edwards & De Souza, 2006; Le Bihan & Iima, 2015).

Diffusion-tensor imaging (DTI) - a modification from diffusion weighted imaging (DWI), is a technique that quantifies water diffusion in multiple spatial directions at voxel level to estimate axonal organization of the brain (Kubicki et al., 2002; Smith et al., 2019). DTI is more advanced than DWI as it measures at least six different spatial directions (Kubicki et al., 2002). The diffusion information of each voxel is represent as 3 x 3 matrix, denoting a diffusion tensor, which express the anisotropic diffusion's natural direction in relation to the three reference frame axes (Stejskal & Tanner, 1965). The diffusion tensor matrix is using a Gaussian model and has three orthogonal (mutually perpendicular) eigenvectors and three positive eigenvalues (O'Donnell & Westin, 2011). The eigenvectors (v1, v2, and v3) (Figure 2.4) indicating directions of the axes, providing the prime eigenvector points in the principal diffusion direction and defines the local tract orientation (Basser et al., 1994). On the other hand, three positive eigenvalues (λ_1, λ_2, and λ_3), indicating the lengths of axes, represents the diffusivity in the direction of each eigenvector. Together, the eigenvectors and eigenvalues form an ellipsoid that symbolizes diffusion probability (O'Donnell & Westin, 2011). The more stretched the ellipsoid is, the higher the anisotropy in the voxel. The orientation input can be changed into a map with colour-coded vectors to overcome the limitation of seeing the vectors in three dimensions (Figure 2.5).

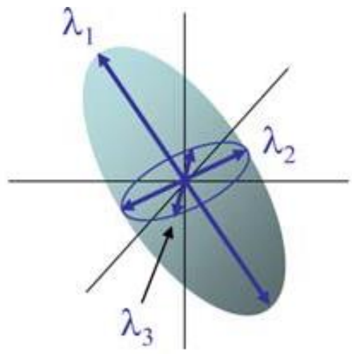

Figure 2.3 Diffusion ellipsoid with three eigenvalues (Adapted from Mori and Zhang, 2006)

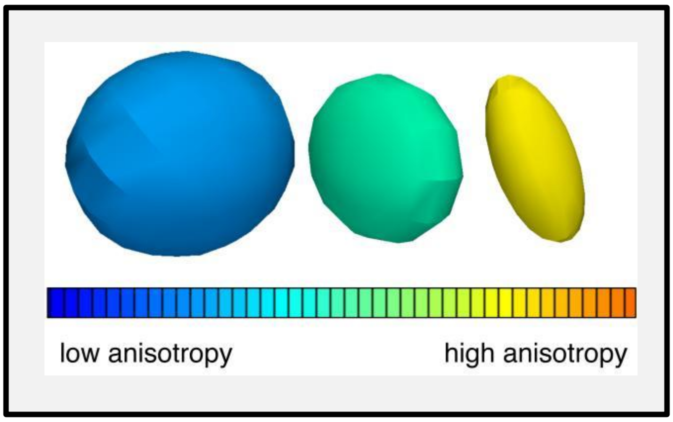

Figure 2.4 Three example of diffusion tensors from a DTI scan of the human brain to illustrate differences in tensor anisotropy and orientation (adapted from O'Donnel and Westin, 2011).

DTI heavily depends on restricted diffusion, and due to the fact that it relatively depends on the integrity of white matter tracts, several quantitative evaluations can be generate from it. Some of the evaluation are in scalar measures, as in fractional anisotropy (FA), mean diffusivity (MD) or Apparent Diffusion Coefficient (ADC), axial diffusivity (AxD), and radial diffusivity (RD) (Curran et al., 2016). FA quantifies the degree of directional dependence of diffusion in a summative manner ranging from 0 to 1 with a greater number suggesting a more pronounced directionality of the tracts (LeBihan, 2003). It is highly sensitive in microstructural changes thus most widely used anisotropy measure. MD denotes total diffusivity in the tissue – quantifies cellular and membrane density, with range value reverse of FA - lower MD described stronger white matter integrity. AxD represents diffusion rate parallel to the main axis (highest diffusion) contrary to RD, which represents diffusion rate perpendicular to the fiber (da Costa Leite and Castillo, 2016), or in transverse directions (Andica et al., 2020). da Costa Leite and Castillo (2016) as well mentioned that there are experimental studies recommend that AxD can be used to evaluate axon integrity and RD is more liable to myelin integrity (Mori and van Zijl, 2002; Tabesh et al., 2011), provided this interpretation should be taken with precautions as it is not occasionally straightforward (da Costa Leite and Castillo, 2016). Scalar indexes of diffusivity can be used in analysis such as Tract-Based Spatial Statistics (TBSS) to interpret white matter connectivity strength. TBSS integrate the robustness of voxelwise and tractography-based analyses (Smith et al., 2006) with critically rely on the accuracy of the diffusion scalar estimations (Maximov et al., 2015).

Other than giving quantitative scalar measurements, DTI also can be visualise in qualitative manner, like probabilistic tractography which estimates trajectories of relative structural connection probability within area of interest, denoting by connection probability index value. Interpretation of tractography map could be intrinsically tricky considering one might take irrational assumption of a unidirectional population fibre tracts inside the voxels without taking into account there might be more than one oriented fibre bundles (Soares et al., 2013).

Regardless of analysis method perform, DTI has been tremendously applied on variety of neuroscientific studies, with abundant of literature including TBI (Palacios et al., 2020; Maller et al., 2010), schizophrenia (Kubicki et al., 2007), autism (Aoki et al., 2013; Lange et al., 2010), dementia (LoBue et al., 2019) as well as aging (Westlye et al., 2010).

2.6 Tract-based spatial statistics (TBSS)

Tract-based spatial statistics (TBSS) is a fully-automated technique that is use to carry out localized statistical testing of diffusion-related data (Smith, 2006) across subjects on the alignment-invariant tract representation (Hakulinen et al., 2012; Smith 2006). This approach is presented as a way to alleviate the alignment problem arises during registration process. The evaluation of tract integrity generally presented by fractional anisotropy (FA), a parameter to quantify the diffusion anisotropy that describe the variability of diffusion according to different directions (Pierpaoli and Basser, 1996).

Before TBSS approach was introduced by Smith, the comparison of tract integrity across subjects were most commonly measured by FA value by simply summarized diffusion characteristics globally (Smith, 2006) which make the interpretation result lack spatial localization. This is because FA parameter is computable voxelwise and the parameter interpretation is quite straightforward. As the area of neuroimaging developed and the interest of research works turn to spatially localizing changes affected by diffusion, approach like voxel–based morphometry (VBM) were utilized even though the technique initially build to find local changes in grey matter density in anatomical brain images (Ashburner and Friston, 2000; Good et al., 2001). However VBM approach required arbitrary spatial smoothing and registration of every individual brain onto standard space could create local misalignment that consequently might change the way of result presentation. TBSS approach might come into benefit as it requires no spatial smoothing and the individual tract were projected onto common space across the subjects hence alleviate the alignment problem arise during registration step. The fundamental rule of TBSS includes (a) approximate nonlinear registration, followed by (b) projection onto the mean FA skeleton, an alignment-invariant tract representation (Smith, 2006).

CHAPTER 3

METHODOLOGY

In this chapter, the study design, study procedure and related methods used in the study are included.

3.1 Study design

This is a cross-sectional case-control study involving TBI patients and healthy controls conducted in Hospital Universiti Sains Malaysia (HUSM), Kubang Kerian Kelantan – Malaysia. The research was conducted from March 2017 until September 2020 at HUSM Kubang Kerian, Kelantan.

3.2 Sample size estimation

The sample size estimation was determined by utilizing G*power version 3.1.9.4 to compute statistical power analysis.

Based on the objectives (3) and (4) which is to correlate cognitive performance scores with diffusion metrics (FA/MD) values in region of interests within the brains of TBI patients:

Exact: Correlation: Bivariate normal model

Analysis: A priori: Compute required sample size – given alpha (α), power, and effect size

Input:

Tails = Two

Correlation rho HI = 0.8

α err prob = 0.05

Power (1 – β err prob) = 0.8

Correlation ρ H0 = 0

Output:

Lower critical r = -0.6663836

Upper critical r = 0.6663836 Total sample size = 9

Actual power = 0.8201599

Sample size after 20% drop out rate = 10.8

In order to reach 80% chance of getting significant, the study used 11 participants per group (22 participants in total) assuming the true correlation between the two variables in the population is 0.8.

3.3 Experimental procedure

The flowchart of study procedure is shown in Figure 3.1.

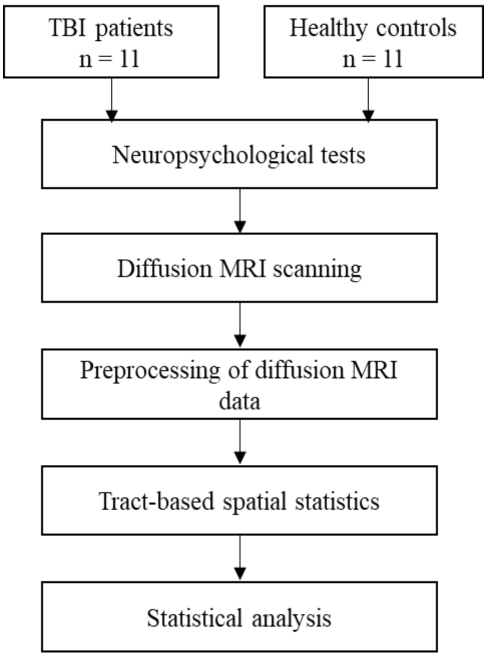

Figure 3.1 Flowchart of study procedure

3.3.1 Sampling method and participants recruitment

This study used non-probability sampling for TBI patients using convenience sampling. This study involves 11 mild-moderate TBI patients and 11 healthy volunteers. The participants are all males with range of age between 18 to 53 years old (patient, mean ± SD = 27.5 ± 13.2; control, mean ± SD = 28.4 ± 10.2). Healthy participants were enrolled after posting adverts around the institution and word of mouth method, while a medical doctor recruited TBI patients based on mild-moderate TBI criteria. During the first stage of recruitment period, there were 15 patients agreed and give consent to participate in the study. However 3 patients were excluded because they were unable to attend the neuropsychological assessment session, 2 more patients were discarded due to low quality of image obtained from MRI scanning machine.

The informed consent form was signed by each participant, who complied with the MRI guidelines. This study was reviewed and approved by the Human Research Ethics Committee of Universiti Sains Malaysia (USMJEPeM/15110486), Health Campus, Universiti Sains Malaysia.

3.3.2 Inclusion and exclusion criteria

The criteria set in this study were list and presented in Table 3.1. The handedness of the participants were examined using the Edinburgh Handedness Inventory (EHI). Participants were asked to state the hand they most frequently used for ten daily tasks, for instance writing, drawing, or using a toothbrush and the score were given that can be translated to laterality index (LI). LI obtained range from 70 to 100 with most participants scored index of 100, representing daily tasks universally carried out using right hand.