THE EFFECT OF NON-SEVERE TRAUMATIC BRAIN INJURY ON THE FUNCTIONAL ORGANISATION OF THE DEFAULT MODE NETWORK

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by

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g	Hedge's corrected measure of effect size
p_{unc}	Uncorrected p-value
p_{FDR}	False discovery error corrected p-value
γ	Gyro-magnetic constant
ρ	Spin density
β	Estimated parameter
ε	Residual error
ϕ	Signal phase
$\dot{z}_t$	Time derivative state variable
z	State variable
Λ	Averaged parameter estimate
Λ_i	Precision matrix
Λ_o	Prior precision matrix
θ	Model parameters
α	Learning rate
∇	Gradient
Σ	Summation

LIST OF ABBREVIATIONS

BD	Block design
BMS	Bayesian model selection
BPA	Bayesian parameter averaging
CN	Cerebellar network
CRT	Choice reaction task
CT	Computerised tomography
CTMT	Comprehensive Trail-Making Test
DAN	Dorsal attention network
DCM	Dynamic causal modelling
DMN	Default mode network
EC	Effective connectivity
EEG	Electroencephalography
FC	Functional connectivity
FFX	Fixed-effects
fMRI	Functional magnetic resonance imaging
FPN	Frontoparietal network
HC	Healthy control group
MR	Matrix reasoning
PEB	Parametric empirical Bayes
PLV	Phase-locked value
RAVLT	Rey Auditory Verbal Learning Test
RCFT	Rey Complex Figure Test
RFX	Random-effects
ROI	Region of interest
RSN	Resting-state network
SD	Standard deviation
SMN	Sensorimotor network
SN	Salience network
SRT	Simple reaction task
TBI	Traumatic brain injury

TBI_1	One-month post-TBI group
TBI_2	Six-month post-TBI group
TBI_3	One-year post-TBI group
VN	Visual network
WASI	Wechsler Abbreviated Scale of Intelligence
WCST	Wisconsin Card Sorting Test

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KESAN KECEDERAAN OTAK TIDAK TERUK AKIBAT TRAUMA KEPADA ORGANISASI KEFUNGSIAN RANGKAIAN MOD LALAI

ABSTRAK

Organisasi Rangkaian Keadaan Rehat (RSN) boleh memberikan gambaran tentang aspek fungsi otak. Rangkaian Mod Lalai (DMN), salah satu daripada RSN, ialah satu set kawasan otak yang aktif apabila individu itu tidak terlibat dalam tugas tertentu, sebaliknya dalam keadaan rehat atau introspeksi. DMN telah terlibat dalam pelbagai fungsi kognitif, seperti ingatan, pemprosesan rujukan kendiri, dan kognisi sosial. Kecederaan otak traumatik (TBI) adalah punca biasa kerosakan saraf yang boleh menjejaskan struktur dan fungsi DMN. Walau bagaimanapun, kebanyakan kajian mengenai kesan TBI terhadap DMN telah memfokuskan kepada kes yang teruk atau sederhana, manakala kesan TBI yang tidak teruk masih tidak jelas. Kajian ini meneroka kesan jangka panjang TBI yang tidak teruk pada organisasi kefungsian DMN menggunakan pengimejan resonans magnetik kefungsian (fMRI) dan elektroensefalografi (EEG), serta penilaian neuropsikologi dan tugasan masa tindak balas. Semua peserta menjalani pengimbasan keadaan rehat (fMRI: Sihat, n = 20, TBI, n = 20; EEG: Sihat, n = 25, TBI, n = 25), manakala subset dari peserta dinilai menggunakan ujian neuropsikologi dan masa tindak balas tugasan. Selain itu, subset dari peserta kembali untuk pengimbasan dan penilaian kali kedua dan ketiga. Semua data kefungsian telah dipraproses dan dimasukkan ke dalam analisis statistik, manakala penilaian luar pengimbasan dianalisis statistik secara berasingan dan kemudian dimasukkan ke dalam analisis korelasi dengan ketersambungan fungsi fMRI. Empat nod DMN telah dianalisis untuk organisasi kefungsian dalaman dan antara rangkaian: precuneus atau korteks singulat posterior (PCC), korteks prefrontal

tengah (MPFC), dan lobulus parietal bawah dwibelah (IPL). Analisis dalam dan antara kumpulan peserta telah dijalankan untuk meneroka perubahan organisasi kefungsian antara kumpulan sihat dan TBI. Perubahan yang ketara merentas masa telah dikesan dalam pengaktifan, ketersambungan fungsi dan ketersambungan efektif, ketersambungan EEG global, prestasi neuropsikologi, dan skor masa tindak balas dalam kumpulan TBI, berbanding dengan golongan yang sihat. Bukti keplastikan juga diperhatikan, terutamanya pada titik masa enam bulan. Oleh itu, kajian ini mempunyai kepentingan dalam menjelaskan penyusunan semula DMN kesan dari TBI yang tidak teruk dan kesan jangka panjangnya pada aspek fungsi otak, dalam perihal ketersambungan dan domain kognitif.

THE EFFECT OF NON-SEVERE TRAUMATIC BRAIN INJURY ON THE FUNCTIONAL ORGANISATION OF THE DEFAULT MODE NETWORK

ABSTRACT

The organisation of the resting-state networks (RSNs) can provide insight into the functional aspects of the brain. The default mode network (DMN), one of the RSNs, is a set of brain regions that are active when the individual is not engaged in a specific task, but rather in a state of rest or introspection. The DMN has been implicated in various cognitive functions, such as memory, self-referential processing, and social cognition. Traumatic brain injury (TBI) is a common cause of neurological impairment that can affect the structure and function of the DMN. However, most studies on the impact of TBI on the DMN have focused on severe or moderate cases, while the effect of non-severe TBI remains unclear. This study explored the longitudinal effects of non-severe TBI on the functional integrity and network organisation of the DMN using functional magnetic resonance imaging (fMRI) and electroencephalography (EEG), as well as neuropsychological assessments and reaction time tasks. All participants underwent resting-state scanning (fMRI: Healthy, n = 20, TBI, n = 20; EEG: Healthy, n = 25, TBI, n = 25), while a subset of the participants was assessed using a neuropsychological battery of tests and reaction time tasks. Additionally, a subset of the participants returned for the second and third time scanning and assessments. All functional data were preprocessed and entered into statistical analysis, while the off-scanning assessments were statistically analysed separately and then entered into correlation analysis with the fMRI functional connectivity. Four nodes of the DMN were analysed for their intra and internetwork functional organisation: the precuneus or posterior cingulate cortex (PCC), medial prefrontal cortex (MPFC), and bilateral inferior parietal lobules (IPL). Within and between-group analyses were conducted to explore the alteration of functional organisation between the healthy and TBI groups. Significant alterations were detected in activation, functional and effective connectivity, global EEG connectivity, neuropsychological performance, and reaction time scores within the TBI groups across time, compared to the healthy control. Evidence of plasticity was also observed, particularly in the six-month time point. Therefore, this study holds significance in elucidating the reorganisation of the DMN following non-severe TBI and its long-term effects on the functional aspect of the brain, both in connectivity and cognitive domains.

CHAPTER 1

INTRODUCTION

1.1 Research Background

Traumatic brain injury (TBI) is a debilitating disease that has long-lasting effects on its survivors, including cognitive, motor control, and behavioural changes (Imms et al. 2019; Maas et al. 2022; Delmonico et al. 2024). The public health burden of TBI is estimated to cost billions annually, ranging from hospitalisation and treatment costs to the loss of productivity (Humphreys et al. 2013; Wu et al. 2016; Badhiwala et al. 2019; van Dijck et al. 2019; Freire et al. 2023). Moreover, TBI survivors often need rehabilitation to return to optimal quality of life (Sacco et al. 2016; Oberholzer and Müri 2019), and a wide range of support from and for their caregivers is also essential (Humphreys et al. 2013; Caeyenberghs et al. 2016; Azman et al. 2020).

The brain is a complex organ responsible for cognitive functions, the retention of experience and memory, the regulation of metabolic processes, and the control of movement (Zhang 2019; Moini and Piran 2020a). It is a dynamic self-organising system that evolves from mutual interactions between neuronal activity and environmental stimulus (Karawani et al. 2018; Chen, Novakovic-Agopian, et al. 2020). There are approximately 50 to 100 billion neurons (Lent et al. 2012; Fornito et al. 2016; Banich and Compton 2018; Gage and Baars 2018a), interconnected via axons and forming specialised brain networks and functions. These connections are vulnerable to insults, especially by external forces.

In cases of TBI, the functional integrity of the resting-state networks (RSNs) can reveal a lot about the state of the brain following TBI. Shearing of the axons due to the mechanical insult of the brain can lead to traumatic axonal injuries (TAI) and diffuse axonal injuries (DAI) (Barlow 2013; Huang et al. 2017; Nelson et al. 2019; Wooten et al. 2019; Abdullah et al. 2022) while structural disconnections can lead to functional impairments that may resolve without intervention (Dall'Acqua et al. 2017; Gordon et al. 2018), and often these injuries resulted in alteration of the organisation of the RSNs. These impairments to the RSNs can predict the outcome of other brain functions, such as cognitive, memory, and attention, which are often worse than healthy. Hence, the neuroimaging study of the RSNs, regardless of structural or functional, is indispensable to assessing and diagnosing any damage or impairments that may affect the normal performance of the brain.

The development of neuroimaging modalities has paved a new way to image the brain structurally and functionally. Physiologically, the neurons communicate with each other by sending electrical signals, and in the process of doing so, consume oxygen for metabolism (Thompson 2018; Newman 2019). Based on this knowledge, the neuronal ensembles can be captured using two commonly used neuroimaging methods: nuclear magnetic resonance of the oxygen-carrying blood and electrophysiological recording of the electrical synapses (Alsuradi et al. 2022). Nuclear magnetic resonance is the basis for functional magnetic resonance imaging (fMRI) and electrophysiological recording can be obtained via electroencephalography (EEG). The fMRI relies on the blood-oxygen-level-dependent (BOLD) signal that reflects the level of oxygen consumption as the brain processes information (Kim and Ogawa 2012; Fornito et al. 2016; Chen, Zhao, et al. 2020). EEG, on the other hand, detects subtle electrical signals of the neurons and amplifies them to enable functional interpretation (Gage and Baars 2018b; Gaudet et al. 2020).

In this study, the functional organisation of the default mode network, one of the RSNs, was investigated in a cohort of mild to moderate TBI patients (henceforth known as the non-severe TBI), using two different neuroimaging modalities: the fMRI and EEG. Subsequently, the study aims to present the complementary findings between these fundamentally different modalities. By this, simultaneous or separately acquired fMRI and EEG data can complement each other to overcome the disadvantages inherent to each modality (Mele et al. 2019; Drenthen et al. 2021) and subsequently shed light on how non-severe TBI affects the functional re-organisation of the DMN.

1.2 Problem Statement

This study sought to better understand the effects of non-severe TBI on the functional organisation of the brain, by comparison to the healthy population. While most injury cases and the literature focused on the mild spectrum of TBI (Hou et al. 2019; Lefevre-Dognin et al. 2021; Pugh et al. 2021), moderate TBI can also give important insight into how the brain organises itself after experiencing an injury. Together, non-severe TBI constitutes the majority of TBI cases in the emergency department (Arulsamy and Shaikh 2020; Lefevre-Dognin et al. 2021), yet the full extent of non-rehabilitated non-severe TBI on the functional reorganisation of the DMN remains elusive. Thus, the inclusion of both mild and moderate TBI under non-severe TBI will cover a wider range of participants and their functional responses to the injury.

The severity of TBI measured through the Glasgow Coma Scale (GCS) often serves as a basic benchmark for assessing the outcome of patients and the impact on their quality of life (Teasdale 2015; Kaltiainen et al. 2018; Gardner et al. 2020).

However, the relationship between the severity of TBI and its debilitating effects can be described as non-linear at best. TBI is a heterogeneous disease and often results in a wide range of outcomes, influenced by many factors (van der Horn et al. 2020; von Steinbuechel et al. 2023). The presence of physical injuries such as fractures and bleeding, persistent symptoms, and the pattern of brain injury can greatly influence the outcome of TBI survivors, which sets them apart from uncomplicated TBI of the same severity (von Steinbuechel et al. 2023). Moreover, inherent differences in terms of gender, educational background, and even-handedness often had an impact on the organisation of brain networks and outcome post-injury (Lu et al. 2019; Mazlan et al. 2021). Therefore, a homogeneous sample of participants in terms of controllable variables such as gender, handedness and uncomplicated injuries can help us understand a part of the wide range of TBI research areas, helping us map the activation and connectivity of the TBI survivors belonging to these specific characteristics.

Furthermore, the recovery process following TBI and examining the differences in recovery patterns at different time points, particularly in the subacute and chronic phases of TBI has not been fully understood. Recovery is a complex and dynamic process that varies greatly among individuals. By examining the recovery patterns at different time points, it is hoped that insight into the underlying mechanisms of TBI recovery and the factors that may influence recovery outcomes can be gained. Furthermore, the study will focus on non-rehabilitated TBI survivors, as this population has received less attention in the literature. By studying the recovery patterns in this population, a better understanding of the natural recovery process without the influence of rehabilitation and interventions can be understood. This information may be useful in developing more effective rehabilitation strategies for TBI survivors.

To date, to the best of our knowledge, this is one of the first studies in Malaysia to analyse and map brain activation and functional connectivity (FC) among TBI patients longitudinally by using the resting-state paradigm, while most functional studies before focused on task-based paradigms that measure specific cognitive functions. Research concerning the longitudinal progression of recovery for TBI patients in Malaysia has also been scarce, with most publications focused on the acute and subacute phases of injury (Arulsamy and Shaikh 2020). Interestingly, while the worldwide trend of TBI cases showed that most admissions to hospitals involved mild TBI, a majority of TBI studies in Malaysia investigated the severe spectrum of TBI (Arulsamy and Shaikh 2020) followed by mild and moderate TBI. Therefore, the emphasis was placed on investigating the non-severe cohort of the TBI population.

The longitudinal nature of this study enabled the discovery and assessments of the estimated time when recovery takes place, marked by when the TBI survivors performed on par with the healthy population. In general, the earlier that appropriate treatment is initiated after a TBI, the better the chances of a good recovery. Additionally, the biomarkers of TBI discovered through the resting-state study can be of importance in detecting the debilitating effects that may be present in TBI survivors. Therefore, the knowledge is hoped to assist the clinical management of TBI survivors, improve the detection of TBI patients, and predict impairment to the integrity of other brain functions which can subsequently be used to improve the prognosis and the quality of life post-TBI.

1.3 Research Questions

Several research questions needed to be investigated based on the list of objectives. The study was looking through the effect of non-severe TBI on the integrity of the DMN in terms of its functional and effective connectivity, electrophysiological profiles, as well performance in cognitive-demanding tasks. In general, the study attempted to answer the following questions: What were the debilitating effects of non-severe traumatic brain injury on the functional reorganisation of the DMN, and when did recovery take place following TBI?

Specifically, this study seeks to answer the following:

1. What are the effects of TBI on the activation, functional connectivity, and effective connectivity of the resting-state networks, particularly the DMN?

2. What are the effects of TBI on the brainwaves, specifically the lower bands associated with resting-state networks?

3. What are the effects of non-severe TBI on the cognitive aspects of its survivors?

4. What are the correlations between cognitive performance and functionally impaired resting-state networks?

5. Is there any evidence of brain plasticity as time progresses?

1.4 Research Objectives

The following objectives (general and specific) are devised to answer the research questions.

1.4.1 General Objectives

To study the effect of non-severe TBI on the functional integrity and network reorganisation of the default mode network through longitudinal resting-state study and compare them with the healthy population.

1.4.2 Specific Objectives

1. To compare the effect of non-severe TBI on the functional integrity of the DMN through the analysis of BOLD activation at one-month, six-month, and one-year post-TBI with the healthy control (HC), using the resting-state fMRI study.

2. To compare the functional connectivity within and between the DMN and other RSNs in HC and non-severe TBI at one-month, six-month, and one-year, via seed-to-voxel and region of interest (ROI) analysis, as well as the graph metrics using resting-state fMRI study.

3. To compare the effective connectivity of the DMN between HC and non-severe TBI at one-month, six-month, and one-year via analysis of dynamic causal modelling (DCM) using resting-state fMRI study.

4. To compare the effect of non-severe TBI at one-month, six-month, and one-year post-TBI with the HC on the resting-state brainwave profiles through spectral scalp-time and time-frequency analysis using resting-state EEG study.

5. To compare the effect of non-severe TBI at one-month, six-month, and one-year post-TBI with the HC on cognitive performance and

psychological profiles by analysing the reaction time tasks and psychological test performance.

6. To compare the correlational relationship between cognitive, neuropsychological performance, and the functional aspect of the brain within the non-severe TBI group at one-month, six-month, and one-year.

1.5 Research Hypotheses

In predicting the general objective, it is hypothesised that,

1. There will be significant differences between the healthy and non-severe TBI groups at one-month, six-month, and one-year post-TBI in terms of 1) functional integrity, 2) effective connectivity, and 3) electrical brain profile during resting-state neuroimaging, as well as in 4) electrical brain profile and 5) accuracy and time in attention modulation of the DMN during reaction time tasks.

2. Null hypothesis: there is no significant difference between the control and non-severe TBI groups at one-month, six-month, and one-year post-TBI in terms of 1) functional activations, 2) effective connectivity, and 3) electrical brain profile during resting-state neuroimaging, as well as in 4) electrical brain profile and 5) accuracy and time in attention modulation of the DMN during reaction time tasks.

Specifically, the following hypotheses predict the outcome of the specific objectives stated previously:

- There is a significant difference in functional integrity within the regions of the DMN between healthy and non-severe TBI groups at one-month, six-month, and one-year post-TBI.

- There is a significant difference in the functional organisation of the DMN in the healthy and non-severe TBI groups at one-month, six-month, and one-year post-TBI.

- There is a significant difference in the causal connectivity of the DMN in the healthy and non-severe TBI groups at one-month, six-month, and one-year post-TBI.

- There are differences in the amplitude of the low-frequency brainwaves associated with the resting state in regions attributed to the DMN between the HC and TBI groups at one-month, six-month, and one-year post-TBI, indicating altered brain activations.

- There are differences in the global phase-locked frequencies between the HC and TBI groups at one-month, six-month, and one-year post-TBI, indicating altered global brain connectivity.

- There is a significant difference in the scores of attention and neuropsychological assessments between the healthy and non-severe TBI groups at one-month, six-month, and one-year post-TBI.

- There is a significant difference in correlation between the functional connectivity, reaction time scores, and neuropsychological scores in the HC and TBI groups at one-month, six-month, and one-year post-TBI.

1.6 Significance of the study

According to current literature, there was a gap in knowledge of TBI in the non-severe TBI group, particularly in the moderate spectrum of the injury. To date, most resting-state TBI studies focused on mild TBI (Hou et al. 2019; Lefevre-Dognin et al. 2021; Pugh et al. 2021), which may be motivated by a better chance of recovery and prognosis. On the other hand, moderate TBI is occasionally grouped with severe TBI, which can be inappropriate in terms of patient management (Godoy et al. 2016). Severe TBI often involves serious head injuries that result in prolonged unconsciousness and a vegetative state with a low chance of full recovery, while moderate TBI can still make for a better prognosis compared to the severe spectrum (Ghneim et al. 2022), with outcomes sometimes on par with mild TBI.

Therefore, this study embarked on the mission to understand how mild and moderate TBI affect the functional organisation of the brain networks, specifically the DMN. While there are several studies conducted using neuroimaging modalities at the global level regarding TBI populations, currently, to the best of our knowledge, this is the first study in Malaysia to investigate the biomarkers of the DMN concerning TBI, with the integration of two resting-state neuroimaging modalities among the Malaysian population. Furthermore, the inclusion of neuropsychological assessments and attentional tasks can provide better insight into the current efforts to understand neural plasticity and its correlation with cognitive performance following TBI.

1.7 Theoretical and conceptual frameworks

Understanding the neural mechanisms underlying TBI is critical for developing effective treatments and interventions for individuals who have experienced TBI.

Therefore, by integrating the findings and theoretical concepts from the literature, the investigation of the functional organisation and neural correlates of DMN in individuals with TBI can be carried out. To better visualise the objectives of the research, a conceptual framework is shown in

Figure 1.1, in which the progression of injury was represented at the cellular level and functional plasticity (Banich and Compton 2018; Freire et al. 2023).

To further guide this research, a theoretical framework that integrates key concepts of the conceptual framework and the relationship between all possible variables was developed. These frameworks are based on the idea that TBI can result in a wide range of cognitive and neural impairments, such as memory loss, attention deficits, and changes in cognitive processing, which are associated with damage to the brain regions. The hypothesis is that changes in DMN can predict these impairments, and this study proposes that the injury can disrupt communication between different brain regions within and between the DMN. Additionally, the theoretical framework also takes into account the idea that the cognitive and neural impairments associated with TBI can be influenced by various factors, including the demographic profile of the victims, the severity of the injury, and the individual's pre-injury cognitive and emotional functioning. Therefore, the theoretical framework accounts for these factors, but they are controlled to eliminate any confounding effects on the neural mechanisms of DMN and performance impairments in TBI.

Overall, the theoretical and conceptual frameworks provide a foundation that guides this research on the neural mechanisms of DMN alterations and impairment in individuals with TBI and how it can be ameliorated. The theoretical framework of this study aims to examine the relationship between independent variables and dependent variables, with the potential influence of moderating variables. Specifically, the recovery time is considered a moderator in the changes of the dependent variables. Furthermore, the control variables are held constant in this analysis, as their effect on the dependent variables will not be examined within the scope of this study. The theoretical framework is visualised in Figure 1.2, while the list of variables is included in Figure 1.3.

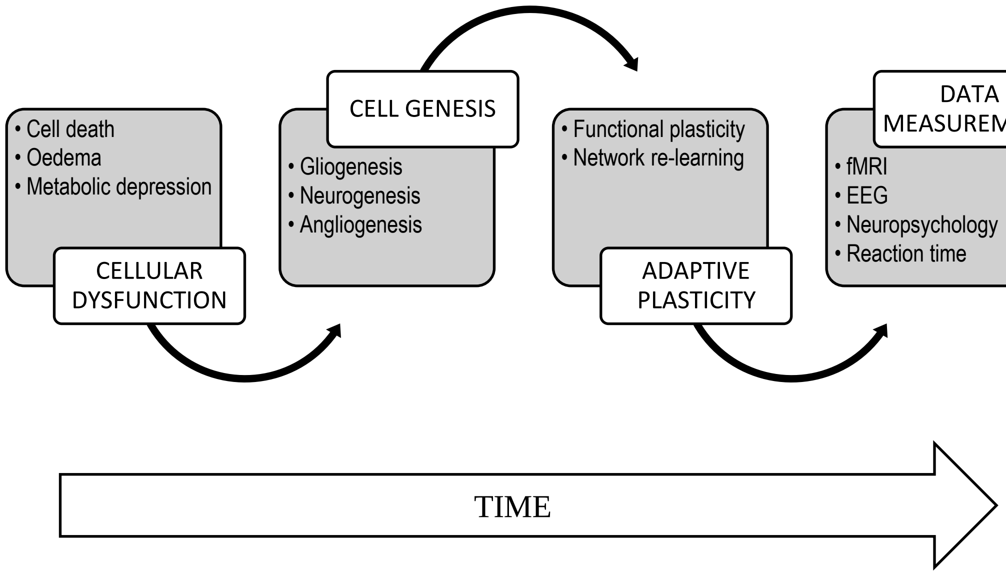

Figure 1.1 Conceptual framework of the progression of TBI from which the theoretical framework is derived (figure adapted and modified from Banich and Compton, 2018)

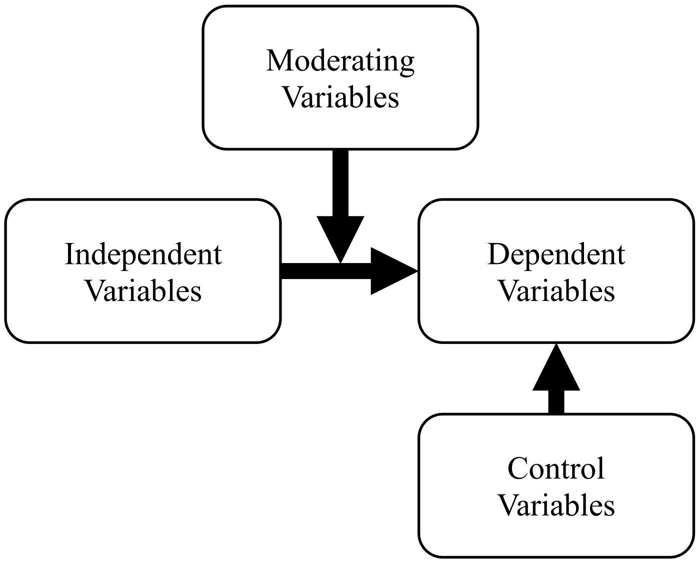

Figure 1.2 Theoretical framework of the research. The independent variables directly influence the outcome of the dependent variables, while being modulated by the moderating variable. The control variables also influenced the dependent variables and were controlled to minimise the confounding effects.

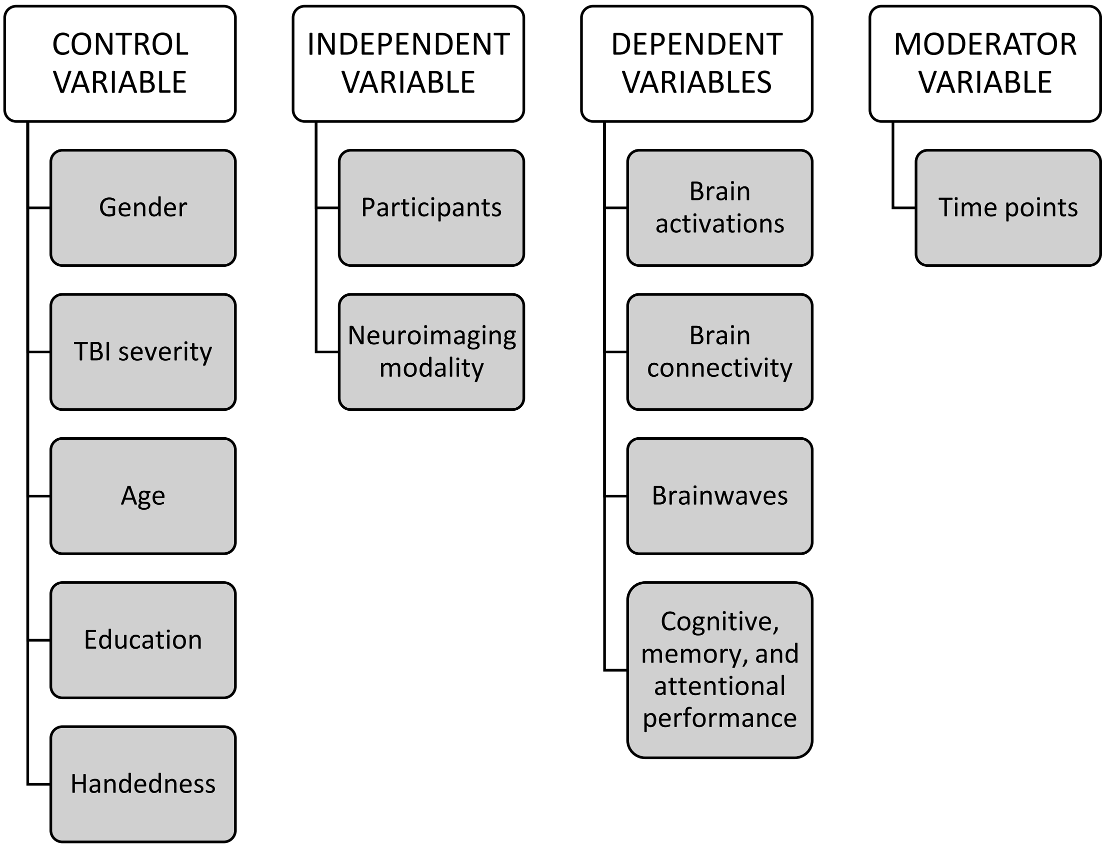

Figure 1.3 The list of variables that were included in the research.

1.8 Operational definitions

- Resting state networks refer to the functional organisation of brain networks that can be identified at rest (Fricchione and Beach 2019; Hristopulos et al. 2019), where there are no specific tasks or stimuli presented during the scanning sessions (Lv et al. 2018).

- The default mode network is defined as four regions of the brain that are activated at rest, consisting of the medial prefrontal cortex, the posterior cingulate cortex/precuneus, and the bilateral inferior parietal cortices (Han et al. 2018; Fricchione and Beach 2019; Esménio et al. 2020; Gaudet et al. 2020; Huang, Huang, et al. 2020; Meier et al. 2020).

1.8.1 Control variables

- Gender refers to the classification of humans into male or female according to their physical and biological appearances.

- Mild refers to the TBI severity classification that falls within 13-15 GCS scores (Dailey et al. 2018; Lefevre-Dognin et al. 2021).

- Moderate refers to the TBI severity classification that falls within 9-12 GCS scores (Gilbert et al. 2018; Le et al. 2020).

- Non-severe refers to the classification of mild and moderate TBI under one group.

- Education refers to the number of years of formal education received by the participants.

- Handedness refers to the dominant hand of the participants (de Kovel and Francks 2019).

1.8.2 Independent variables

- Participants refer to the healthy and TBI populations recruited for the study. The participants are grouped into HC, TBI at one-month (TBI_1), six-month (TBI_2), and one-year (TBI_3) groups, according to their time of scanning except for HC which served as the control group.

- Functional MRI (fMRI) is one of the imaging techniques that can measure and map brain activity by detecting changes associated with blood flow associated with the given task/stimuli/events or demand (Kim and Ogawa 2012; Fornito et al. 2016; Chen, Zhao, et al. 2020).

- Electroencephalography (EEG) refers to the neuroimaging technique that measures the electrical synaptic signals at the scalp, exerted by neuronal activities (Gage and Baars 2018b).

1.8.3 Dependent variables

- Brain activations refer to blood-oxygen-level-dependent (BOLD) signals produced by the changing of magnetic properties of the oxygenation of the blood, modelled against the canonical haemodynamic response function (Ashburner et al. 2020)

- Brain connectivity refers to the measurement of statistical associations or temporal correlations between different anatomical regions or remote neurophysiological events in the brain (Whitfield-Gabrieli and Nieto-Castanon 2012; Nieto-Castanon 2020a).

- Brainwaves refer to the bioelectrical activity generated by the neurons that are categorised into theta, delta, alpha, beta, and gamma bands (Schomer and Lopes da Silva 2017)

- Performance refers to the scores of the battery of neuropsychological tests and the accuracy and reaction time of the attention tasks.

1.8.4 Moderator variables

- Time points refer to the interval of the scannings, set at one-month, six-month, and one-year post-injury.

1.9 Thesis organisation

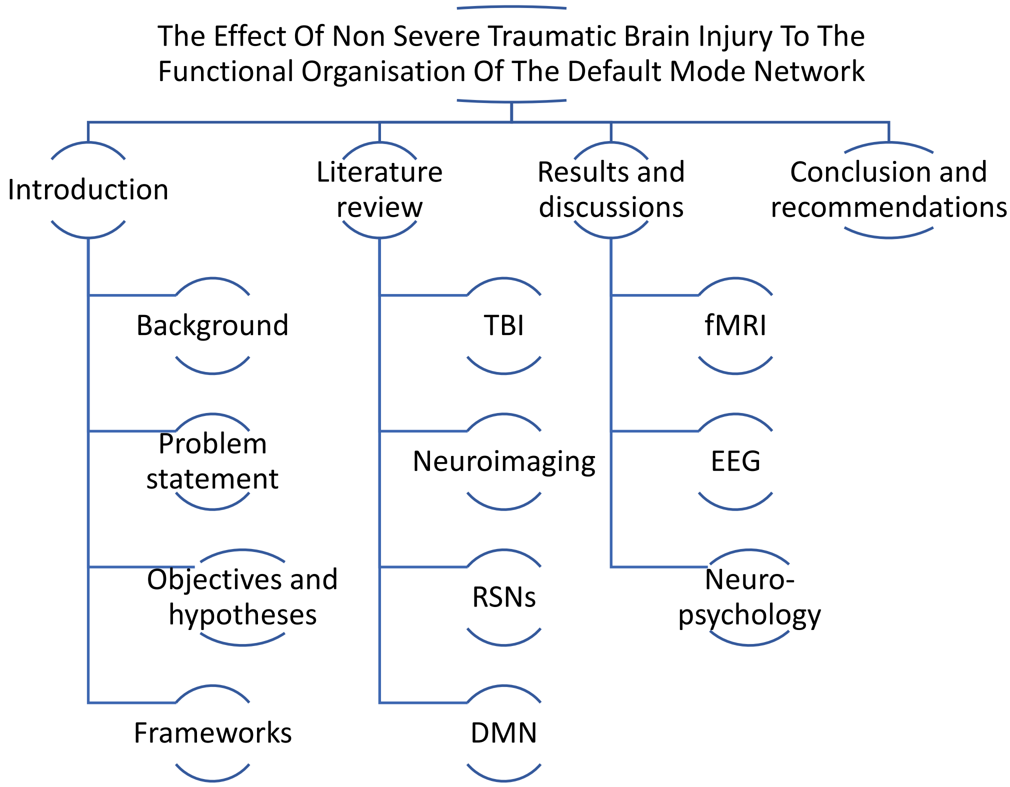

Figure 1.4 The thesis organisation flowchart

To provide readers with a clear understanding of the research conducted and the results obtained, this thesis is organised to progress from the broad topic of traumatic brain injury (TBI) to the specific area of study: the Default Mode Network (DMN) within resting-state networks. As outlined in Figure 1.4, the thesis begins with an introduction that presents an overview of the research topic, including the background, problem statement, research objectives, and scope of the study. This introductory chapter sets the stage for the subsequent chapters by outlining the significance of the research. Following the introduction, a comprehensive literature review is provided. This chapter covers the broader topic of TBI in general, then narrows down to focus on the neuroimaging modalities that have enabled researchers to identify resting-state networks (RSNs). It further delves into the organisation of the

DMN within the human functional network and examines how the DMN is affected by TBI.

In the results and discussion chapters, the functional organisation of the DMN is analysed by comparing a healthy control group with TBI-affected groups over time. This comparison highlights the differences in the DMN's function and structure due to TBI. Finally, the thesis concludes with a summary of the research findings, discussing the limitations of the study and offering recommendations for future research. This chapter provides a comprehensive recap of the entire study, reinforcing the significance of the findings and suggesting directions for further investigation.

1.10 Summary

TBI can have long-term effects on brain function and can be costly in terms of treatment and productivity. The brain's structural and functional connections of the RSNs can be disrupted by TBI, leading to impairments in cognitive, memory, and attention functions. This study aimed to understand the effects of non-severe TBI on the functional organisation of the brain, particularly the default mode network, using two neuroimaging modalities: fMRI and EEG by comparing individuals with TBI to a healthy population. Integrating the findings from these two modalities can assist in better understanding how non-severe TBI affects the functional reorganisation of the default mode network and update clinical management of TBI survivors. This is one of the first studies in Malaysia to analyse brain activation and FC in TBI patients using a resting-state paradigm, in terms of its FC, effective connectivity, and electrophysiological profiles, accompanied by off-scanning performance on cognitive, memory, and attentional tasks. The study also aimed to identify potential biomarkers of TBI that can be used to detect and predict the effects of TBI on brain function and improve the prognosis and quality of life post-TBI. In addition, this study also aimed to discover the estimated time when recovery takes place, in which TBI survivors perform at the same level as the healthy population.

CHAPTER 2

LITERATURE REVIEW

2.1 Introduction

In this chapter, the discussions were outlined regarding traumatic brain injury, its prevalence, pathophysiology, classification, severity in literature, and management; the neuroimaging techniques in TBI research; the functional organisation of the brain as assessed by neuroimaging in terms of the resting state networks and its importance in TBI research; the default mode network as the most important RSN; and the fundamental principles governing the analysis tools that are going to be used in the study.

2.2 Traumatic Brain Injury

TBI occurs when the head suffers a direct force, the brain is distorted from a rapid acceleration-deceleration incident, or an object penetrates the head (Benson 2014; Galicia-Alvarado et al. 2019). It is described as physical injuries inflicted on the brain tissues that can cause temporary or permanent damage to brain functions (Parikh et al. 2007; Han et al. 2018), thus differentiating it from non-traumatic brain injuries such as brain tumours or infections (Teasell et al. 2007). In case of injury, structural and functional connectivity could be affected, either together or separately. For example, TBI can cause physical disruption to the white matter tracts that connect the regions of the brain. In turn, it affects the functional networks of the brain, the fundamental connections for the normal cognitive, motor, and physiological functioning of a human (Galicia-Alvarado et al. 2019; French et al. 2020; Raizman et al. 2020).

On a broader aspect, TBI incurred a significant emotional and socio-economic burden and a substantial cost in public health care (Langlois et al. 2006; Maas et al. 2008; Sours et al. 2015), associated with medical treatment, rehabilitation, and loss of productivity. The total cost of TBI globally is estimated to be more than $400 billion annually (Maas et al. 2022), while the United States costs are estimated to be between $17 billion and $77 billion (Kuceyeski et al. 2019; Rockswold et al. 2019; Alouani and Elfouly 2022). In the context of Malaysian healthcare, the median cost of hospitalisation per patient is estimated to be around $10,356 in 2015 (van Dijck et al. 2019).

The burden of TBI includes both direct and indirect costs. The direct costs, such as hospitalisation and medical treatment, can be significant and can put a strain on the healthcare system (Toshkezi et al. 2018; Chen, Novakovic-Agopian, et al. 2020). The indirect costs of TBI, such as lost productivity and missed work days, are also significant. TBI can affect the normal functioning of the brain, making it challenging to navigate through daily affairs; therefore, seriously impairing the quality of life of its survivors (Stocchetti and Zanier 2016) and can lead to long-term disability and reduced ability to work, which can result in lost income for individuals and their families. This can harm the overall economy, as individuals may have less disposable income to spend on goods and services.

2.2.1 Prevalence of TBI

Every year, TBI affects a staggering number of people worldwide, with estimates reaching up to 60 million individuals (Gardner et al. 2020; Maas et al. 2022). TBI stands as one of the most prevalent neurodegenerative disorders across many regions of the world (Humphreys et al. 2013; Moreno-López et al. 2016). Different types of trauma can lead to TBI, such as motor vehicle accidents, sports-related concussions, and falls (Barlow 2013; Maas et al. 2022). The causes leading to TBI may be influenced by the socio-economic status and the age of the population. In developed nations, improved traffic safety awareness and the ageing demographic have led to a reduction in TBI cases caused by motor vehicle accidents, while incidents resulting from falls have increased (Centers for Disease Control and Prevention 2021; Maas et al. 2022). This dynamic shifted in developing and low-income nations, where motor vehicle accidents remain the primary cause of TBI cases (Maas et al. 2008, 2022).

In Malaysia, road traffic injuries are a leading cause of TBI and contribute to about 76% of hospital admissions due to major trauma, with 85.4% of those cases involving injuries to the head and neck (Jamaluddin et al. 2009). Moreover, 64% of the major trauma cases were related to TBI (Arulsamy and Shaikh 2020). Young people, particularly of the male gender are at particularly high risk of TBI due to road traffic accidents (Graham et al. 2020; Mazlan et al. 2021). This observation may be driven by a lack of driving skills (Simons-Morton et al. 2019) and an observable pattern of higher risk-taking and willingness to participate in dangerous behaviours (Tamás et al. 2019). In addition, almost 15% of intensive care unit admissions were diagnosed with TBI (Tong et al. 2016). Beyond road traffic accidents, occupational injuries and sports-related incidents are also noteworthy risk factors contributing to the incidence of TBI in Malaysia.

2.2.2 Pathophysiology and Classifications of TBI

Structurally, the human brain is made up of four units: the cortex, subcortex, cerebellum, and brainstem (Ward 2019; Kustubayeva 2020; Moini and Piran 2020b). The biggest of those is the cortex, a layer of grey matter that surrounds the cerebrum (Papo et al. 2014; Gage and Baars 2018a) which is made of about 86 to 100 billion neurons (Fornito et al. 2016; Newman 2019). These neurons are structurally interconnected via the axon, the long projection of the nerve cell that functions as a conductor of electrical impulses (Debanne et al. 2011; Newman 2019). The axonal bundles are called the white matter tracts because the presence of myelin sheath gives up the white appearance (Newman 2019; Moini and Piran 2020c). Figure 2.1 visualises the structural appearance of a neuron.

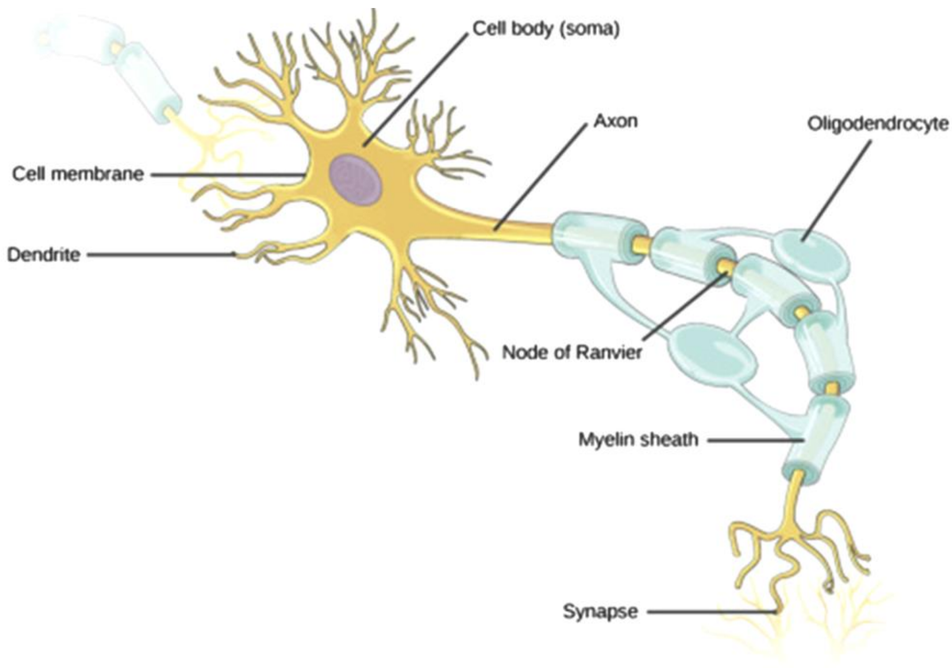

Figure 2.1 A depiction of a neuron (figure adapted from Gage and Baars 2018a, image under public domain).

The cortex is divided into four lobes, as visualised in Figure 2.2; frontal, temporal, parietal, and occipital, all of which play a specialised role in higher brain activities (Newman 2019; Moini and Piran 2020a). The frontal lobe processes consciousness, emotion, and cognitive control; the temporal lobe is associated with language, auditory processing, and memory consolidation; the parietal lobe is involved in visuospatial perception through the optic radiations that end in the occipital lobe, which is the main visual centre of the brain (Moini and Piran 2020c). The subcortex, or the inner brain, comprises the hypothalamus, thalamus, basal ganglia, and limbic system and is important in the processing of emotion and movement control (Gage and Baars 2018a; Moini and Piran 2020d). The cerebellum, located at the posterior part of the brain, is made of a vermis and two lateral hemispheres and plays a role in learning, cognition, and movement, such as modulating motor commands and maintenance of balance (Gage and Baars 2018a; Moini and Piran 2020e). The brainstem, which comprises the midbrain, pons, and medulla, connects the major nerves associated with movement control, sensation, and breathing control to the brain (Gage and Baars 2018a; Moini and Piran 2020f).