Depression and Anxiety following a Traumatic Brain Injury

Amanda Jane Osborn

October 2016

This dissertation is submitted in fulfilment of the requirements for the degree of Doctor of Philosophy (Ph.D in Medicine) in the Faculty of Health Sciences, School of Psychology, at the University of Adelaide

Table of Contents

ABSTRACT

Traumatic brain injuries (TBI) are one of the leading global causes of death and disability, creating a substantial public health and socio-economic burden. The personal consequences of a TBI can also be extensive, commonly encompassing functional, cognitive and psychological problems. These impairments can, in turn, affect relationships, employment status, leisure activities and independence. The present thesis focuses on two of the most common psychological outcomes following TBI: depression and anxiety. Both undermine an individual's quality of life, although their impact is not yet fully understood.

The prevalence of depression and anxiety varies widely in the existing literature, but our understanding of what might be contributing to this variability is limited. This makes it difficult to identify who is most at risk of developing depression and/or anxiety following a TBI and when they are most susceptible. Crucially, this constrains our capacity to understand the trajectory of psychological problems after a TBI which, in turn, hampers clinicians' ability to identify and implement targeted interventions for those who are most in need. The variability in rates likely reflects differences in how these problems are investigated, with data relating to the incidence, characteristics, risk factors and outcomes of TBIs collected in both epidemiological and clinical contexts. Adding to the problem is the fact that depression and anxiety are frequently measured using a variety of assessment methods and, moreover, there are often differences between the samples that are being examined, with studies evaluating individuals who have a variety of injury, and pre- and post-morbid characteristics. Thus, four studies were designed in order to examine these issues and comprehensively investigate whether, and to what extent, different methodologies and sample characteristics influence depression and anxiety after a TBI.

The first study (Chapter 3) assessed the prevalence of clinical diagnoses of major depressive disorder (MDD)/dysthymia and self-reported 'cases' of clinically significant levels of depression following adult TBI. Data from 99 studies were meta-analysed. Overall, depression

was found to be very common after a TBI, with 27% of people diagnosed with MDD/ dysthymia and 38% reporting clinically significant levels of depression.

Next, Chapter 4 built on these findings by comparing levels of self-reported depression in people with and without a TBI who were living in the general community. The sample was recruited as part of a large, longitudinal study - the Personality and Total Health (PATH) Through Life project - which measured the health and well-being of young (20-24 years), middle-aged (40-44) and older adults (60-64), on three occasions (waves), four years apart. Across the total sample, clinically significant levels of depression were more prevalent in those who had sustained a TBI, regardless of the length of time that had elapsed since their injury.

The next study (Chapter 5) focussed on anxiety, with data from 41 studies meta-analysed in order to examine the prevalence of generalized anxiety disorder (GAD) and self-reported 'cases' of clinically significant anxiety. Anxiety was also found to be common after TBI, with 11% of people formally diagnosed with GAD and 37% reporting clinically significant levels of anxiety on self-report questionnaires.

Lastly, data from the PATH study were analysed (Chapter 6) in order to compare the levels of self-reported anxiety in people with and without a TBI. In cross-sectional analyses, across the total sample, clinically significant levels of anxiety were more prevalent (at each wave) in people who had incurred a TBI, regardless of the time that had elapsed since the injury. Moreover, comorbid anxiety and depression in those with a TBI was common, reinforcing the need for clinicians to identify and treat both problems in order to minimise their cumulative burden. Importantly, this thesis highlights a broad range of variables that influence the prevalence of depression and anxiety and, thus, should be considered by researchers and clinicians alike.

DECLARATION

I, Amanda Osborn, certify that this work contains no material which has been accepted for the award of any other degree or diploma in my name, in any university or other tertiary institution and, to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference has been made in the text. In addition, I certify that no part of this work will, in the future, be used in a submission in my name, for any other degree or diploma in any university or other tertiary institution without the prior approval of the University of Adelaide and where applicable, any partner institution responsible for the joint-award of this degree.

I give consent to this copy of my thesis when deposited in the University Library, being made available for loan and photocopying, subject to the provisions of the Copyright Act 1968. The author acknowledges that copyright of published works contained within this thesis resides with the copyright holder(s) of those works. I also give permission for the digital version of my thesis to be made available on the web, via the University's digital research repository, the Library Search and also through web search engines, unless permission has been granted by the University to restrict access for a period of time.

I acknowledge the support I have received for my research through the provision of an Australian Government Research Training Program Scholarship.

Amanda Osborn

Signed: _____ Date: _____

ACKNOWLEDGEMENTS

There are a number of wonderful people who have contributed their time, knowledge and support throughout my PhD journey, and for that I am truly grateful. I wish to extend my heartfelt thanks and gratitude to my mentor, Professor Jane Mathias. I am profoundly grateful for all the years of encouragement, advice and support that you have given me, despite the various changing circumstances that have accompanied so much of my candidature! Thank you for working with me to develop my skills as an academic researcher and for your enduring commitment to this aim. I am also enormously indebted to Dr Kate Fairweather-Schmidt, thank you for your guidance, insightful comments and moral support. I remain immensely appreciative of those unconventional weekend phone calls that allowed me to press on through my statistical dilemmas. Moreover, my research would have been impossible without the aid of the Centre for Research on Ageing, Health and Wellbeing at the Australian National University. For this reason, my sincere thanks are extended not only to Professor Kaarin Anstey for her feedback and support, but also to all the academic and professional staff, and participants, who have contributed to the PATH project.

I also wish to thank Libby, who has shared this tumultuous PhD journey with me. I am forever indebted for our innumerable conversations, the inspirational example you set and the motivation you provided. Finally, George, I am incredibly grateful for your support throughout this journey. Your constant encouragement, in addition to your incredible reserves of patience and understanding, have enabled me to remain true to this dream.

LIST OF TABLES

Chapter 2

Chapter 3

Online Supplementary Data.

Chapter 4

Supplemental Digital Content

Chapter 5

Electronic Supplementary Material

Chapter 6

Electronic Supplementary Material

Chapter 7

LIST OF FIGURES

Chapter 3

Chapter 5

Chapter 6

Chapter 7

ABBREVIATIONS

ACRM:	American Congress of Rehabilitation Medicine
AIS:	Abbreviated Injury Scale
APA:	American Psychiatric Association
APOE	Apolipoprotein E
AUDIT:	Alcohol Use Disorders Test
BAI:	Beck Anxiety Inventory
BDI:	Beck Depression Inventory
CDC:	Centers for Disease Prevention and Control
CES-D:	Center for Epidemiologic Scale – Depression
CI:	Confidence Interval
CIDI:	Composite International Diagnostic Interview
CIS:	Clinical Interview Schedule
CT:	Computed Tomography
DIS:	Diagnostic Interview Schedule
DSM:	Diagnostic and Statistical Manual
GAD:	Generalized Anxiety Disorder
GAS:	Goldberg Anxiety Scale
GCS:	Glasgow Coma Scale
GDS:	Goldberg Depression Scale
GEE:	Generalised Estimating Equations
HADS:	Hospital Anxiety and Depression Scale
HAM-D:	Hamilton Depression Rating Scale
ICD:	International Classification of Diseases
LOC:	Loss of Consciousness
Leeds:	The Leeds Scale for the Self-assessment of Anxiety and Depression
MADRS:	Montgomery Asberg Depression Rating Scale
MDD:	Major Depressive Disorder
MINI:	Mini-International Neuropsychiatric Interview
MOOSE:	Meta-Analysis of Observational Studies in Epidemiology

MRI:	Magnetic Resonance Imaging
N_{fs}:	Failsafe *N* statistic
NFI:	Neurobehavioral Functioning Inventory
OR:	Odds Ratio
PATH:	PATH Through Life Project
PHQ-9:	Patient Health Questionnaire -9
PSE:	Present State Examination
PTA:	Post-Traumatic Amnesia
PTSD:	Post-Traumatic Stress Disorder
SADS-L:	Schedule for Affective Disorders and Schizophrenia
SCAN:	Schedules for Clinical Assessment in Neuropsychiatry
SCID-1:	Structured Clinical Interview for DSM-IV Axis I Disorders
STAI:	State Trait Anxiety Inventory
TBI:	Traumatic Brain Injury
UK:	United Kingdom
US:	United States
W1:	Wave one PATH assessment
W2:	Wave two PATH assessment
W3:	Wave three PATH assessment
WHO:	World Health Organization
ZSDS:	Zung Self-rating Depression Scale

PREFACE

Context

Traumatic brain injuries (TBI) are one of the leading causes of death and disability, creating a substantial public health and socio-economic burden (World Health Organization [WHO], 2006). It is estimated that approximately 5.3 million people in the United States (US), and nearly 7.7 million people in Europe, are living with a permanent TBI-related disability (Rubiano, Carney, Chesnut, & Puyana, 2015). Moreover, the incidence of TBI (new TBIs per annum) is rising (Maas, 2016), with increasing motor vehicle use in low- to middle-income countries, more falls in older adults, and heightened public awareness about the importance of seeking medical attention, all contributing to higher rates (Faul & Coronado, 2015; Peeters et al., 2015; Roozenbeek, Maas, & Menon, 2013). These data suggest that epidemiological research that informs the prevention and treatment of TBIs needs to be intensified (Faul & Coronado, 2015; Maas, 2016; Roozenbeek et al., 2013).

The consequences of sustaining a TBI can be substantial. At an individual level, these commonly encompass functional, psychological and cognitive impairments (Andelic et al., 2009; Mathias & Alvaro, 2012; Rabinowitz & Levin, 2014; Whelan-Goodinson, Ponsford, Johnston, & Grant, 2009a). These impairments can, in turn, affect relationships, employment status, participation in sporting and leisure activities, and the ability to undertake 'normal' daily activities (e.g., travelling independently on public transport, driving) (Colantonio et al., 2004; Grauwmeijer, Heijenbrok-Kal, Haitsma, & Ribbers, 2012; Schwab, Gudmudsson, & Lew, 2015; Wise et al., 2010; Wood, Liossi, & Wood, 2005). Importantly, the aforementioned functional constraints further impact at a societal level, with substantial economic costs and loss of productivity resulting from full or partial disability (for a review see Humphreys, Wood, Phillips, & Macey, 2013). Although all TBI sequelae warrant attention, the current thesis will focus on two common outcomes: depression and anxiety. Both psychological problems are

known to considerably undermine an individual's quality of life, however, their impacts following TBI are not yet fully understood.

Motivation / problem statement

The prevalence of depression and anxiety (proportion of individuals experiencing these problems at any given time) varies widely in the extant literature, hampering clinicians' and researchers' understanding of the extent of these disorders within given populations. It is also difficult to identify who is most at risk of developing depression and/or anxiety following a TBI and when they are most susceptible. Crucially, this constrains our capacity to understand the trajectory of psychological problems following a TBI which, in turn, hampers clinicians' ability to identify and implement interventions for those who are most in need.

Currently, it is uncertain whether variability in the reported rates of depression and anxiety reflects different methodologies. For example, data relating to the incidence, prevalence, characteristics, risk factors and outcomes of TBIs are collected in a variety of epidemiological and clinical contexts; each of which has unique limitations. Whereas large-scale population studies are likely to encounter challenges in the accurate/consistent identification of TBI incidence data, clinical studies are hampered by recruitment and retention issues (Corrigan, Selassie, & Orman, 2010; Van Reekum, Cohen, & Wong, 2000). Adding to this is the fact that researchers have often examined samples that are heterogeneous in terms of their injury and pre- and post-morbid characteristics and, moreover, that depression and anxiety are frequently measured using a variety of assessment methods. These differences reduce the utility of findings by limiting the capacity to make direct comparisons and, thus, impact on the conclusions that can be drawn. Further, an estimated 30-40% of people who suffer a TBI do not seek medical attention, resulting in a large proportion of those who have sustained a TBI being overlooked (Setnik & Bazarian, 2007). Currently, clinicians and

researchers have little understanding of whether, and to what extent, these individuals suffer from depression and/or anxiety.

Aim and scope

The aim of this thesis was, therefore, to investigate depression and anxiety following TBI in order to advance our understanding of the frequency and severity of these outcomes, and to improve the clinical utility of this research. Although a wide range of neuropsychiatric conditions can occur after a TBI (e.g., social phobias, schizophrenia, obsessive-compulsive disorder), this thesis sought to improve our understanding of the two *most common* psychological problems, depression and anxiety, following TBI. Moreover, depression and anxiety are often comorbid, suggesting that both separate and joint consideration of these problems will contribute unique and crucial information.

Importantly, the present thesis focuses on civilian TBIs (i.e., excludes both veterans and those currently serving in the military) because combat environments expose military personnel to high levels of physical and emotional trauma, which increases their risk of psychological problems compared to civilians (Chapman & Diaz-Arrastia, 2014). Thus, military and civilian samples should be investigated independently. Individuals with penetrating TBIs (e.g., gunshot wounds) and acquired brain injuries that had a non-traumatic aetiology (e.g., stroke, tumour, meningitis) were also excluded because the causes, mechanisms, neuropathological damage and outcomes of these injuries differ from non-penetrating TBIs (e.g., blunt head trauma) (Coetzer, Daisley & Newby, 2013; Ylioja, Hanks, Baird, & Millis, 2010). Finally, adults, rather than children, were examined because differences in anatomical, physiological and behavioural development have the potential to influence TBI outcomes (McCrory, Collie, Anderson, & Davis, 2004).

Significance

This thesis was designed to augment our understanding of the long-term impact of a TBI on the depression and anxiety outcomes of adults who have sustained a TBI in a civilian/non-military setting (e.g., motor vehicle & sporting accidents, falls, assaults). Moreover, it will investigate depression and anxiety in both clinical and community-based (non-medical) settings. This enabled a comprehensive examination of these problems among those sustaining TBIs, regardless of whether they had contact with a healthcare system at the time of their injury; thus incorporating people who might otherwise be overlooked in the literature. In particular, this research is intended to assist clinicians by identifying those people who are most at risk of suffering from depression and anxiety after injury, thereby facilitating timely and effective treatment.

Overview of thesis structure

The findings from two meta-analyses and two longitudinal community-based studies are presented in four papers, reported here as separate chapters. Of these papers, three have been published, with the remaining paper in press:

(1) Osborn, A. J., Mathias J. L., & Fairweather-Schmidt A. K. (2014). Depression following adult, non-penetrating traumatic brain injury: A meta-analysis examining methodological variables and sample characteristics. *Neuroscience and Biobehavioral Reviews, 47*, 1-15. doi: 10.1016/j.neubiorev.2014.07.007

(2) Osborn, A. J., Mathias J. L., & Fairweather-Schmidt A. K. (2016) Prevalence of anxiety following adult traumatic brain injury: A meta-analysis comparing measures, samples and postinjury intervals. *Neuropsychology*, *30*(2), 247-261. doi: 10.1037/neu0000221

(3) Osborn, A. J., Mathias J. L., Fairweather-Schmidt A. K. & Anstey, K. J. (2016). Anxiety and comorbid depression following traumatic brain injury in a community-based sample of

young, middle-aged and older adults. *Journal of Affective Disorders*. Advance online publication. doi: 10.1016/j.jad.2016.09.045

(4) Osborn, A. J., Mathias J. L., Fairweather-Schmidt A. K. & Anstey, K. J. (in press). Traumatic brain injury in a community-based sample: a cohort study across the adult lifespan. *Journal of Head Trauma Rehabilitation*.

The thesis structure comprises seven chapters. Chapter 1 reviews the literature on TBI, with a particular emphasis on its epidemiology, risk factors, causes and potential functional, cognitive and psychological outcomes. Chapter 2 reviews methodological and sample characteristics that may impact on depression and anxiety outcomes after a TBI, after which the aims of the thesis are outlined.

The next four chapters contain four journal articles, constituting the empirical research components of this thesis; with each possessing a preamble detailing the study rationale and further contextualising it within the broader research goals. Specifically, Chapter 3 provides a meta-analysis examining depression following TBI, with the findings separately detailed according to various methodological (diagnostic criteria, interview schedule/self-report scale, method of administering self-report scales, type of control group) and sample (time post-injury, injury severity) characteristics. Chapter 4 augments these findings by comparing the depression outcomes of people, with and without a TBI, who were randomly selected from the general population within Australia. Thus, because this study was community-based, there was a greater likelihood of sampling people with mild TBIs who do not seek medical attention and whose outcomes are often overlooked in the existing literature.

Although depression is thought to be the most common psychological problem after a TBI, anxiety is also prevalent and often comorbid with depression, potentially magnifying the negative impact on quality of life. For this reason, Chapter 5 meta-analyses research examining anxiety after a TBI; again highlighting differences in the prevalence rates due to the

approach taken by researchers (i.e., clinical interview and diagnostic criteria employed, self-report questionnaires and their method of administration, time post-injury, injury severity). Following on from this, Chapter 6 examined participants from the general community; but investigated anxiety, and its comorbidity with depression, thereby adding to our understanding of how TBI impacts jointly on anxiety and depression.

Each of the articles was originally prepared to meet the requirements of the respective journals to which they were submitted: Neuroscience and Biobehavioral Reviews; Neuropsychology; the Journal of Head Trauma Rehabilitation and; the Journal of Affective Disorders. However, to ensure consistency, the bibliographic style of the American Psychological Association, Publication Manual (Sixth edition) (American Psychiatric Association, 2009) has been used, and American English spelling applied consistently across the thesis. Accordingly, the chapters may vary slightly from the published and/or submitted versions. A combined reference list for the entire thesis is provided at the end of the thesis, rather than references at the end of each chapter. Tables and figures are numbered consecutively and inserted at the appropriate place within each chapter, and online supplementary material referred to within a chapter is located at the end of that chapter in order to assist the reader.

Finally, Chapter 7 synthesises the findings of each of the studies and discusses the broader issue/conclusions. Limitations of the research are identified, as are the clinical implications of the findings. Suggestions for future research are also discussed.