Social cognition: implications of traumatic brain injury

Niall Bourke

Computational, Cognitive and Clinical Neuroimaging Laboratory | Division of Brain Sciences | Department of Medicine | Imperial College London

June 2020

This thesis is submitted for the degree of Doctor of Philosophy | PhD

“Once there was a mountain called peak XV, nothing was known about it, but in 1852 surveyors found it was the highest in the world and they named it Everest” ~ The conquest of Everest by Sir John Hunt, as cited by Public Service Broadcasting

Reader Summary

Based on Robert Brown's 8 questions (Brown, 1997).

1. **What is the central question?**

What social and emotional deficits are present following traumatic brain injury? What neural correlates are seen with these processes?

2. **What did you do?**

- An analysis of legacy data on a large cohort of TBI patients was conducted to re-assess the concept of "frontal" behaviour using quantitative neuroimaging methods.
- A newly developed diffusion imaging technique that allows for more quantitative and biologically meaningful analysis of in vivo brain structure was conducted on a subset of patients from the previous analysis. These results were correlated with measures of dysexecutive function.
- These patients were followed up to test a social reward discounting paradigm.
- A battery of digital tasks was developed (available on tablets, smartphones, web) to assess wellbeing, and test performance on emotional recognition and metacognitive abilities.

3. **Why did you do it?**

- Some behaviours are described as being "frontal" in nature. This mostly follows from famous case studies such as that of Phineas Gage. Here I quantitatively analysed data from 102 patients with frontal lesions and compared them to patients without frontal lesions and controls, looking at effects of white matter damage independent of focal damage.
- New imaging techniques and analyses allow us to investigate brain microstructure with improved sensitivity, helping us better understand real-world behaviour and function.
- Aspects of social behaviour, such as decision evaluation, may fall under executive functioning. Additionally, apathy has previously been found to be an issue in TBI patients through self-report and caregiver reports. Further objective assessments were aimed at exploring apathy in relation to social decision making in more detail.
- Little has been done in TBI patients to understand social and emotional deficits post-injury, despite being commonly reported issues. Digital assessments make it easier and more reliable to collect data both in the clinic and remotely and to track performance/wellbeing over time.

4. **What happened?**

- Non-lesion patients show similar behavioural deficits to those with focal lesions. This can be partially explained through results from quantitative diffusion imaging, which show damage in the brain independent of focal lesions.
- Advanced imaging techniques appear to be more sensitive when relating to cognitive performance.
- Apathy did not appear to be a factor in explaining patient behaviour. However, it seems patients did not distinguish between self and other, and may be more sensitive to reward than controls.
- Patients performed indicated some difficulty with emotional processing and reported lower levels of wellbeing compared to controls.

- Patients were impaired on metacognition for processing speed but not emotional processing.

5. What do the results mean in theory?

- Developing techniques in quantitative imaging may prove more reliable than traditional visual inspection in identifying damage present following TBI.
- TBI can lead to deficits in social cognitive functioning. Patients may show signs of executive dysfunction, for instance by not incorporating all available information, leading to inappropriate decision making.
- Digital assessments of social cognitive function and wellbeing are feasible ways to investigate patients' behaviour and state.
- Metacognition could be fractionated across cognitive domains, with TBI patients overestimating performance in some domains but not others.

6. What do the results mean in practice?

- Quantitative MRI measures, including multi-modal assessments of volume, diffusion, and neurochemistry, should be performed on patients with head injuries.
- More attention should be given to emotional and social issues following discharge, as this may have an impact on rehabilitation engagement, personal relationships and return to work.
- Special consideration should be given to seemingly well patients if they show signs of executive dysfunction, as this may lead to long-term impairments in social cognition.
- Digital assessments can be flexibly adapted to assess patients' performance, either in the clinic or at home. This would allow longitudinal monitoring of cognitive functioning that individuals may be struggling with.

7. What is the key benefit for the readers?

- Compared to lesion localisation, newer quantitative MRI methods are better-suited to inform our understanding of individual cognitive functioning.
- Application of a new multi-shell diffusion imaging technique shows that it has potential in investigating the neural correlates of social functioning in TBI patients
- Deficits in social cognition and emotional processing after TBI are highlighted and investigated, informing a largely neglected area of brain injury research with important consequences in treatment and rehabilitation.
- Introduction of novel digital and remote assessments, which are reliable and flexible methods of evaluation that should be further explored and implemented in practice.

8. What remains unresolved?

As TBI is a heterogeneous disorder, development of neuroimaging measures and evaluation of the neural correlates are needed in order to identify the many disrupted paths that may lead to similar behavioural output. This could be done using a disconnection framework with analysis from multi-modal imaging. Additionally, social cognition and emotional processing is a complex area. Development of assessments, ecological validation and replication are required.

Acknowledgements

First and foremost, I would like to thank my parents and brothers, who have always been a source of support. Their encouragement and guidance have helped me overcome any difficulties faced. Without this, I would not be where I am today.

Importantly, the many patients and controls that have given their time to support my research must be acknowledged. Through research and the outpatient clinic, they have shaped me and my knowledge immeasurably.

I have met many wonderful people along the way during my post-graduate academic journey with countless inspiring and thought-provoking conversations, of which there are too many to name. I am very appreciative of the support and guidance given to me during and after my MSc by Owen O'Daly. I offer my deepest gratitude for the opportunities he has granted me, providing me with advice and the opportunity to pursue research which I have enjoyed. Sara de Simoni, who is extremely friendly and has at no point hesitated to provide guidance. Peter Jenkins, who I worked closely with when I first joined the TBI group and had many good coffee breaks and chats about rugby. Emma, who is an excellent desk buddy. Rich and Eyal have done their best to impart some level of technical knowledge upon me; at the very least, there have been numerous fascinating conversations. Greg, who probably knows everything and is one of life's genuinely good people. Lucia is a force of nature and an inspiration. She has been immensely supportive and has provided valuable career and life guidance. Célia is a pleasure to talk to and a source of positive encouragement as well as constructive feedback. Special thanks are given to my wonderful friends and housemates Anthony and Nuria, who I have shared many great experiences with over the last few years. I have been immensely lucky to have friends that have supported me both socially, emotionally and academically.

Writing has always been a struggle for me. I have been lucky to have Helen supporting me with kindness and affection. She has even managed to teach me a thing or two about English grammar while proofreading this thesis.

The many people in the C3NL past and present I have not mentioned have shaped my academic experience. And finally, many thanks must be given to my PhD supervisors Prof. David Sharp and Dr. Adam Hampshire. Without their guidance, this body of work and more would not have been possible.

Statement of contribution

Chapter 3

The first experimental chapter (Ch. 3) includes legacy data collected from previous research in the TBI group at Imperial College London.

Chapter 4

Dr Maria-Yanez Lopez provided substantial help with analysis and social support with this chapter. This data was collected with Dr Peter Jenkins as part of a clinical trial investigating dopaminergic disruption while I was a research assistant prior to beginning this PhD.

Chapter 5

Chapter 5 was made possible with support from Dr Matt Apps and Dr Patricia Lockwood at Oxford University. Following discussion at a conference, equipment and paradigm scripts were shared in order to run this study. Dr Anthony Gabay provided assistance with analysis. Prof. Masud Husain offered useful comments on results.

Chapters 6 & 7

Programming of the cognitive paradigms was performed by Will Trender (WT) & Adam Hampshire (AH). Concept and design of the emotional processing tasks were done by myself and AH based on prior literature, and programming was done by WT. Concept and design of the social learning task were done by myself and AH, and programming was done by AH. I constructed the Empathy Quotient, Context Task and Big 5 based on existing measures. This platform was constructed and maintained by AH, Pete Hellyer, Maria Balaet and WT.

Collection of the data was supported by Emma-Jane Mallas, Amy Jolly, Karl Zimmerman and Dr Neil Graham. I conducted all statistical analysis of the presented data.

All other work in this thesis is my own, conforming to the guidelines set out by Imperial College London for submission of a PhD thesis. All other work is referenced appropriately.

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Figure 3, reprinted from:

Carlén, M. (2017). What constitutes the prefrontal cortex? Science, 358(6362), 478–482.

https://doi.org/10.1126/science.aan8868

Figure 17, reprinted from:

Lockwood, P., Hamonet, M., Zhang, S. *et al.* Prosocial apathy for helping others when effort is required. *Nat Hum Behav* 1, 0131 (2017). https://doi.org/10.1038/s41562-017-0131

Statement of publication

The results of this thesis have been prepared or submitted for publication. As of final submission Chapter 4 has been accepted for publication in Brain Communications.

Bourke et al., (accepted), Traumatic brain injury: a comparison of diffusion and volumetric magnetic resonance imaging measures, Brain Communications,

DOI:10.1093/braincomms/fcab006

Availability of scripts

Selected curated scripts from image processing and statistical analysis in this PhD have been or will be made available on GitHub at:

https://github.com/Nialljb/TBI-PhD

Abbreviations

ACC	Anterior Cingulate Cortex
AMI	Apathy Motivation Index
AMICO	Accelerated Microstructure Imaging via Convex Optimization
ANOVA	Analysis of Variance
ANTS	Advanced Normalisation Toolbox
ASD	Autism Spectrum Disorder
BBC	British Broadcasting Company
BCBToolkit	Brain Connectivity and Behaviour Toolkit
BDI	Beck Depression Inventory
BFI	Big Five Inventory
BIC	Bayesian Information Criterion
CDC	Centre for Disease Control
CFQ	Cognitive Failures Questionnaire
CG	Care-Giver
CI	Confidence Interval
CJ	Confidence Judgment
CON	Controls
CRT	Choice Reaction Time
CSF	Cerebral Spinal Fluid
CT	Computerised Tomography
D-KEFS	Delis-Kaplan Executive Function System
DAI	Diffuse Axonal Injury
DARTEL	Diffeomorphic nonlinear registration
DaT	Dopamine Transporter
DLPFC	Dorsolateral Prefrontal Cortex
DMN	Default Mode Network
DMPFC	Dorsomedial Prefrontal Cortex
DTI	Diffusion Tensor Imaging
DWI	Diffusion Weighted Imaging
EF	Executive Function
EMC	Emotional Control
EMD	Emotional Discrimination
EPI	Eco Planar Imaging
EQ	Empathy Quotient
FA	Fractional Anisotropy
FDR	False Discovery Rate
FDT	FMRIB Diffusion Toolbox
FLAIR	Fluid Attenuated Inversion Recovery
FMRIB	Oxford Centre for Functional MRI of the Brain
FOV	Field of View
FrSBe	Frontal Systems Behavioural Rating Scale

FSL	FMRIB Software Library
FTD	Fronto-Temporal Dementia
GCS	Glasgow Coma Scale
GLM	General Linear Model
GM	Grey Matter
GOSE	Glasgow Outcome Scale Extended
GRAPPA	Parallel imaging technique
HD	Huntington's Diseases
ICA	Independent Component Analysis
ICV	Intracranial Volume
ID	Identification
IFG	Inferior Frontal Gyrus
IMSEG	Image Segmentation
IQR	Inter-Quartile Range
ISOVF	Isotropic Volume Fraction
LARS	Lille Apathy Rating Scale
LEHR	Low Energy High Resolution
LOC	Loss of Consciousness
MATLAB	Matrix Laboratory
MC	Motor Control
MCC	Mid-Cingulate Cortex
MD	Mean Diffusivity
MITE	Mind in the Eyes
MNI	Montreal Neurological Institute
MPAI	Mayo-Portland Inventory
MPFC	Medial Frontal Cortex
MPRAGE	Magnetization Prepared - Rapid Gradient Echo
MRI	Magnetic Resonance Imaging
MS	Multiple Sclerosis
MTL	Medial Temporal Lobe
MVC	Maximum Voluntary Contraction
NDI	Neurite Density Index
NIH	National Institute for Health
NIPYPE	Neuroimaging in Python
NODDI	Neurite Orientation, Density Dispersion Imaging
NPI	Neuropsychiatric Inventory
OCEAN	Openness, Conscientiousness, Extraversion, Agreeableness, Neuroticism
ODI	Orientation Dispersion Index
OFC	Orbito Frontal Cortex
OLS	Ordinary Least Squares
PAL	Paired Associates Learning
PAT	Patient

PCA	Principal Component Analysis
PD	Parkinson's Disease
PET	Positron Emission Tomography
PFC	Prefrontal Cortex
PMHQ	Physical and Mental Health Questionnaire
POMP	Percentage of Maximum Possible
PTA	Post Traumatic Amnesia
QOL	Quality of Life
QOLIBRI	Quality of Life after Brain Injury
RIFG	Right Inferior Frontal Gyrus
RMSEA	Root Mean Error of Approximation
RMSR	Root Mean Square Error
ROI	Region of Interest
RT	Reaction Time
RTA	Road Traffic Accident
SBR	Signal Binding Ratio
SCT	Stop-Change task
SD	Standard Deviation
SDC	Spherical Deconvolution
SF	Short-Form
SM	Samsung
SMH	Saint Mary's Hospital
SN	Salience Network
SNI	Social Network Index
SPECT	Single Photon Emission Tomography
SPM	Statistical Parametric Mapping
SPRS	Sydney Psychosocial Reintegration Scale
SRT	Simple Reaction Time
STS	Superior Temporal Sulcus
SV	Subjective Value
SWI	Susceptibility Weighted Imaging
TBI	Traumatic Brain Injury
TBSS	Tract Based Spatial Statistics
TD	Target Detection
TDCS	Transcranial Direct Current Stimulation
TE	Echo Time
TFCE	Threshold-Free Cluster Enhancement
TLI	Tucker-Lewis Index
TOM	Theory of Mind
TOMMS	Test of Memory and Malingering
TPJ	Temporal Parietal Junction
TR	Relaxation Time
TV	Television

UK	United Kingdom
VLPFC	Ventrolateral Prefrontal Cortex
VLSM	Voxel-Based Lesion Symptom mapping
VMPFC	Ventromedial Prefrontal Cortex
WM	White Matter

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Chapter 1 | Introduction

This chapter covers the background literature and sets out the aims and main hypotheses of this thesis.

1.1 Statement of thesis aims

This thesis aims to explore how social and emotional processing may be affected following traumatic brain injury (TBI). I will utilise multimodal neuroimaging, including structural, and diffusion magnetic resonance imaging (MRI) and single-photon emission tomography (SPECT), to evaluate the neural correlates of executive functioning and established measures of social and emotional processing. Novel app-based behavioural assessments of social and emotional processing, including aspects of decision making, wellbeing and metacognition, will also be investigated to evaluate deficits in TBI patients compared to healthy controls. The objectives of this thesis are:

- To assess the relative contributions of focal damage and diffuse axonal injury (DAI) to commonly reported impairments of executive functioning
- To compare multiple diffusion metrics, including novel multi-shell models with volumetric measures, and evaluate how these neuroimaging metrics relate to cognitive function
- To test how TBI patients incorporate social information during an effort-based social decision-making paradigm
- To develop and evaluate new emotional processing paradigms and wellbeing assessments that can be conducted remotely
- To investigate metacognitive performance in TBI patients using confidence judgments of task performance

1.2 Hypotheses

The main hypotheses of this thesis are:

- TBI patients experience DAI that can explain the presence of cognitive deficits beyond what is seen with focal damage
- Structural and diffusion MRI will show varying sensitivity to differences between healthy controls and patients, along with varying specificity to cognitive performance.
- TBI patients will exhibit higher reward discounting when effort is involved, relative to healthy controls. This increased reward discounting will be associated with a higher degree of behavioural apathy.
- TBI patients will have reduced performance on objective measures of emotional processing, which will be related to reported measures of wellbeing.
- Metacognition, measured by confidence judgements of task performance will vary across cognitive tasks. TBI patients will show an overall higher bias in metacognitive insight compared to controls, indicating an underestimation of deficits present.

1.3 Chapter Summary

In the first chapter, I will review the background of social cognition following traumatic brain injury. I will identify gaps in the literature and hopefully address some outstanding questions throughout the thesis. Areas I will focus on include executive functioning, emotional processing, and metacognition.

Chapter 2 is a general methods chapter detailing the techniques used across different studies described in this thesis.

In chapter 3, I will perform a legacy analysis on a large cohort of TBI patients to identify the relative contributions of focal lesions to executive functioning compared to DAI.

Chapter 4 contains a subset of TBI patients from the previous chapter. Here, I will compare novel multi-shell diffusion imaging with conventional diffusion tensor imaging and volumetric analysis. This neuroimaging analysis will be conducted in relation to cognitive performance.

Chapter 5 describes a follow-up visit for patients in chapter 4 to assess social decision making and effort in relation to apathy.

Chapters 6 investigates social and emotional processes as well as wellbeing in a newly developed digital platform, which can be delivered in person, on the web, or via a mobile app.

In Chapter 7, I will look at metacognition concerning cognitive performance, using the remote, app-based assessments described in the previous chapter.

In the final chapter, I will summarise the main findings of the thesis. I will discuss how this work contributes to our understanding of TBI, and the future directions that may be taken for further work in this area.

1.4 Traumatic brain injury (TBI)

TBI is currently defined by the Centre for Disease Control (CDC) as "a disruption in the normal function of the brain that can be caused by a bump, blow, jolt to the head, or penetrating head injury." While such a definition is easily understandable and encompasses common causes of TBI, the incorporation of a pathological perspective is essential in a research context to enable comparison across studies. A more precise definition for research is "an alteration in brain function, or other evidence of brain pathology, caused by an external force" (D. K. Menon et al., 2010).

TBI represents a complex, heterogeneous collection of potential symptoms and pathophysiological changes. In milder cases where structural or physiological alterations may not be detected, profound functional disruption may still be found. These cases are often labelled as concussion, or perhaps more appropriately as symptomatic possible TBI (Sharp & Jenkins, 2015). Despite the absence of physiological alterations in mild TBI cases, up to 22% of patients report dissatisfaction with life or functional impairment one-year post-injury (McMahon et al., 2014). More severe cases may present with a range of neuroimaging findings, from microbleeds to DAI and focal lesions resulting from mechanisms such as direct impact, penetrating injuries, and acceleration-deacceleration forces. Around 65% of moderate-severe TBI patients have ongoing cognitive complaints. Due to the common feature of frontal lobe injuries in TBI, there is a strong emphasis on executive dysfunction (Rabinowitz & Levin, 2014). Social cognitive impairment has been reported across all severities, with a prevalence ranging from 25-88% (Milders, 2019).

1.4.1 Operational definition of severity

As TBI is a heterogeneous disorder with varying mechanisms, clinical presentations and outcomes, a clear operational definition is required to classify the severity of the injury. Here I will be following the Mayo classification of severity (Malec et al., 2007)(
Table 1). Classification of severity is essential for symptom management, outcome prediction, and of course, for use in research studies. Methods that rely on single measures such as the lowest Glasgow Coma Scale (GCS) (Teasdale et al., 2014) are susceptible to error, for example in cases requiring intubation (Blennow et al., 2016). The Mayo classification extends on such approaches by incorporating information from medical records, such as loss of consciousness (LOC), lowest Glasgow Coma Scale (GCS), post-traumatic amnesia (PTA), and neuroimaging findings. In the absence of a complete medical history, this system allows for a more accurate retrospective classification of injury, without relying on single-measure definitions.

Table 1: *The Mayo TBI classification system (Malec et al., 2007)*

A. Classify as *Moderate-Severe (Definite) TBI* if one or more of the following criteria apply:

Death due to this TBI
Loss of consciousness of 30 min or more
Post-traumatic anterograde amnesia of 24 h or more
Worst Glasgow Coma Scale full score in first 24 h <13 (unless invalidated upon review e.g., attributable to intoxication, sedation, systemic shock)
One or more of the following present:

- Intracerebral haematoma
- Subdural haematoma
- Epidural haematoma
- Cerebral contusion
- Haemorrhagic contusion
- Penetrating TBI (dura penetrated)
- Subarachnoid haemorrhage
- Brainstem injury

B. If none of Criteria A apply, classify as *Mild (Probable) TBI* if one or more of the following criteria apply:

Loss of consciousness momentarily to less than 30 min
Post-traumatic anterograde amnesia momentarily to less than 24 h
Depressed, basilar or linear skull fracture (dura intact)

C. If none of Criteria A or B apply, classify as *Symptomatic (Possible) TBI* if one or more of the following symptoms are present:

Blurred vision
Confusion (mental state changes)
Daze
Dizziness
Focal neurological symptoms
Headache
Nausea

1.4.2 Socioeconomic implications of TBI

The global burden of disease studies place incidents of TBI at 369 (95% CI: 331-412) per 100,000 population, based on data between 1990-2016 (James et al., 2019). With an estimate of 1.4 million attending hospital per year with a recent head injury in the UK. TBI is a costly burden to the UK in many ways, constituting the leading cause of death and disability in people under the age of 40 (National Clinical Guideline Centre (UK), 2014). Within TBI, road traffic accidents are one of its major causes, with an increasing burden of accidental falls in older adults over the age of 65 (Majdan et al., 2016).

The public health and socioeconomic consequences of TBI are essential issues for several reasons (Ghajar, 2000; Rubiano et al., 2015). There are evident cost implications not only on the individual but also on society as a whole as a burden upon healthcare systems; the latter pertains both acutely as well as to long-term support for survivors with a lifelong disability. Secondary costs, such as loss of productivity and associated caregiver burden, may also arise. A 2010 study estimated the average direct costs of each TBI per year in Europe as around €3,590, with indirect costs of around €5,219 (Olesen et al., 2012). Beyond these financial implications, social and emotional problems are common, and include depression, impulsivity, or impaired decision-making, affecting interpersonal relationships years after the initial insult (Roozenbeek et al., 2013).

1.4.3 Pathophysiology

The pathophysiology of TBI is a complex disease process resulting in structural and functional impairment (Werner & Engelhard, 2007). TBI may result in diffuse or focal brain damage. Clinical convention emphasises focal injuries such as contusions, lacerations or haemorrhages—all easily identifiable and targeted during acute management. These injuries arise from primary mechanical damage during trauma, either due to direct contact with an external object or from the brain hitting the inside of the skull. Consequent secondary processes such as tissue hypoxia, metabolic dysfunction, or expanding oedema may lead to the development of further focal injuries, or the expansion of existing lesions (Ng & Lee, 2019). A cascade of secondary mechanisms following the initial insult results in neuroinflammation and apoptosis, resulting in expanding tissue damage (Kunz et al., 2010).

In contrast to the above localised injury mechanisms, diffuse axonal injury (DAI) can result from high shear forces across axons during rapid acceleration and deceleration and cause widespread damage throughout the brain. This damage can impair the structural connectivity

of the brain, resulting in suboptimal communication between cortical regions. DAI is seen in 70% of TBI cases (Kunz et al., 2010), and is reported across all levels of severity (Johnson et al., 2013). The presence of DAI in medial structures following acceleration and deacceleration forces is partially explained by computational modelling of brain injury. These finite element models indicate that midline structures such as the corpus callosum and the brainstem suffer the highest strain rates following TBI (Ghajari et al., 2017). Advances in vivo measurements, most commonly diffusion tensor imaging (DTI), have highlighted the role of DAI as an essential factor in behavioural consequences and functional outcome of TBI. While generally accepted that focal and diffuse injuries co-occur, little evidence exists to examine the relative contributions of each to functional outcomes after TBI. This will be discussed in more detail in chapter 3.

1.4.4 Neuroimaging assessment of brain injury

Lesion studies

Modern neuropsychology developed from early case studies on focal lesions, a notable example being that of Phineas Gage in 1848 (Harlow, 1993). Gage was a 25-year-old railroad worker who suffered, but miraculously recovered from, a penetrating injury of his frontal lobe following an explosion. Once a death sentence, brain disorders such as TBI became more survivable with advances in medical care, allowing for the inference of behavioural origins in the malfunctioning brain. In the aftermath of Gage's injury, he was described as having undergone a severe personality change, becoming very irritable. Since this quintessential case study, research on the link between brain and behaviour has seen a dramatic increase. Several prominent patient cases of specific focal damage and their accompanying behavioural deficits have been documented. In 1861, Pierre Paul Broca described two patients with lesions to the posterior inferior frontal gyrus, both of whom

demonstrated a consequent loss of fluent speech. The phenomenon is now known as a common sequela following stroke affecting this region (Plowman et al., 2012), and the area has since been named after Broca himself. With great fortune, Broca decided to preserve these brains at the time, and over 140 years later, new insights have been gained from the application of neuroimaging measures on these landmark cases (Dronkers et al., 2007). For example, new investigations have clearly indicated that the damage in each of these cases was more extensive than previously described. As we are standing on the shoulders of giants, advancements in empirical research have allowed us to make unprecedented progress towards our understanding of the complexity of language and the broader network of regions involved.

Another important case study of functional disability following localised trauma was patient H.M., who experienced profound memory impairments after a bilateral medial temporal lobe resection, a surgical intervention intended to control his seizures (Scoville & Milner, 1957). The onset of H.M.'s seizures have been speculated to be traumatic in nature, coinciding with reports of him falling off a bicycle aged 7, although the veracity of this theory is still unclear (Squire, 2009).

Medical cases such as these drove theories of localisation of function during the 20th century. With advancing imaging techniques and analysis, however, there has been a recent shift towards network theories to explain behavioural impairment. One question that has been asked is, "could a neuroscientist understand a microprocessor?" (Jonas & Kording, 2017). This tongue-in-cheek question raises a significant limitation of functional localisation. The brain is a complex system with a vast circuitry of connections. While there are undoubtedly hub regions that exhibit preferential importance for specific cognitive functions, such a

simple explanation is unlikely to be a fitting or comprehensive one for the majority of human behaviour. There may be phenotypical behavioural impairments, in that the cause of specific deficits may arise through interactions between different potential disruptions in the system. These may present as focal damage to a node within a network, damage to connections between critical regions, or neurochemical disruptions which may affect functional connectivity.

Case studies of observed behavioural phenomena are essential in sparking questions to better our understanding of human behaviour and brain function. Scientific research progresses from individual patient descriptions and their reported symptoms, forming a basis which we may extend towards the assessment of samples of patients with similar injuries (T. Shallice & Burgess, 1991; Stuss & Alexander, 2007). This group sampling provides us with more accurate inferences about potential outcomes and links to reported behaviour. Among other methods, acute CT following TBI has been used to predict mortality at one year (Wardlaw et al., 2002). However, these are poor predictors of functional outcomes (Sherer et al., 2006).

On the other hand, advances in lesion studies have been remarkable in stroke literature, where increasing sample sizes and novel statistical methods have been used to investigate relationships between lesions on a voxel-based level and outcomes on cognitive tests (Meyer et al., 2016; Rorden et al., 2007; Seifert et al., 2016). In chapter 3, I will describe this type of voxel-based lesion symptom mapping within a large cohort of TBI patients, concerning symptoms classically described as "frontal". Other measures in neuroimaging, including assessments of volume and white matter structure, may explain behaviour in the absence of apparent focal damage and will be discussed in this thesis.

Volume

MRI techniques allow us to estimate the volume of brain tissue in vivo. White and grey matter volume are known to change as a function of age. MRI analysis has been of great interest in translational research in neurological conditions. Healthy ageing sees a decline in global brain volume (Peters, 2006; Scahill et al., 2003), and changes in tissue volume are used as markers of brain health and predictors of mortality (J H Cole et al., 2018). Increased rates of atrophy are seen in neurological disorders such as Alzheimer's disease, and have therefore been identified as a potential biomarker in its prodromal phase (Coupé et al., 2019). Higher levels of atrophy are likewise seen following TBI (Cole et al., 2015). In this cohort, they can be used to compare relative differences from age-matched controls and investigate potential relationships with cognitive function.

White matter structure

As mentioned, DAI is one of the critical mechanisms of TBI. This form of white matter damage may arise due to several pathological processes stemming from shearing forces occurring at the time of injury. Over the last few decades, imaging techniques such as diffusion tensor imaging (DTI) have been developed to evaluate microstructural changes in vivo. In particular, DTI provides an estimate of restricted diffusion within the white matter, allowing for surrogate markers of structure and relative directionality in vivo. Fractional anisotropy (FA) is a measure of the principal eigenvector of diffusion, providing information on directionality and constituting one of the key metrics in DTI. FA provides information on white matter structures within the TBI literature, and allows the measurement of their relationship to cognitive performance (Bonnelle et al., 2012; Kinnunen et al., 2011; L. M. Li, Violante, Zimmerman, et al., 2019).

Further advances in DTI have allowed for the acquisition of multiple diffusion readings, enabling the development of more sophisticated models such as neurite orientation and dispersion imaging (NODDI) (Zhang et al., 2012b). These provide metrics that further fractionate FA into indices such as neurite density and orientation dispersion. These developing methods may provide more sensitive estimations of white matter structure. My work on multi-shell diffusion imaging in TBI patients will be discussed in more detail in chapter 4.

Molecular imaging

In contrast to the previous methods, another neuroimaging approach lies in molecular imaging. Previous work has indicated that disruption to the dopaminergic system occurs in around 20% of TBI patients (Jenkins et al., 2018). Through single-photon emission tomography (SPECT) and positron emission tomography (PET), molecular imaging provides quantitative measures of catecholaminergic systems and their potential disruption following injury. Impairment of these systems may be directly related to some of the symptoms seen following TBI and can be directly targeted with drug interventions (Jenkins et al., 2019). Progress in other neurological conditions such as Parkinson's disease, similarly characterised by a profile of disrupted dopaminergic functioning, have shown that this can have a profound effect on motivation and apathy (Le Heron et al., 2018). In chapter 5, I will present work on apathy and dopaminergic disruption in TBI patients and how it may relate to reward discounting.

Disconnection and network analysis

The importance of considering network dysfunction following TBI has been highlighted previously (Sharp et al., 2014). This has often been in the context of DTI and resting state

analysis investigating the DMN (Sharp & Ham, 2011). Novel methods including multi-shell diffusion imaging and the NODDI model may provide additional insights. Additionally, network methods and a combination of the lesion and white matter analysis described above could provide a significant contribution to the understanding of cognitive functioning.

To explore disconnection, one approach is to generate "importance maps" (Kuceyeski et al., 2011). This paper investigated a small sample of TBI patients (n = 15), highlighting white matter regions most likely affected by damage. A more recent approach to this is the 'disconnectome' (de Schotten et al., 2020). In a large sample of stroke patients (n = 1,333) the link between structural and functional networks were explored. This was done by projecting each patient's lesion mask onto a group of healthy controls as a seed region for probabilistic tractography to determine tracts with a high probability of disconnection due to the presence of a focal lesion. An alternative approach to explore network function is a variation on voxel-based lesion-symptom mapping. A connectome-based lesion-symptom mapping explores the potential connections within a graph that may be affected due to the presence of focal lesions (Gleichgerrcht et al., 2017). Lesion network localisation is an approach to identify regions functionally connected to a site of a lesion by using a lesion mask as a seed in an independent set of healthy controls (A. L. Cohen & Fox, 2020; Darby et al., 2018). In the context of TBI an important consideration is that of damaged white matter independent of focal lesions. On the other hand, damage to white matter in the absence of focal lesions following TBI is the ideal scenario for examining graph theory and network disruption from the perspective of connections rather than nodes and its potential relationship to cognitive performance and clinical outcome (M. G. Hart et al., 2016).

1.5 Social cognition

1.5.1 Overview

Cognition refers to many internal processes such as perception, attention, memory, and planning, all of which help us make sense of the world around us and thereby determine our behaviours within it (C. D. Frith, 2008). These processes are essential for social interaction and allow us to benefit from the formation of social groups. The recognition and understanding of uniquely social signals such as facial expressions allow us to learn from environmental feedback. Recognition of fear may be necessary for safety, and the identification of anger or sadness may help us adapt our behaviours in order to maximise social cohesion. On the whole, the role of psychological processes in a social context can be referred to as social cognition.

There exists considerable debate over the exact remit of what constitutes social cognition in the scientific literature. For instance, it has been argued that it must relate directly to interaction, rather than to individual processes as mentioned above (De Jaegher et al., 2010). While examining direct social interaction is important, a more pragmatic operational definition of social cognition pertains to the perception of others, the self, and interpersonal knowledge (Beer & Ochsner, 2006). Information to encode and decode the social world must include information regarding one's perception and understanding of others, the self within an environment, and social norms and procedures that have developed over time. This development indicates learning and optimisation from the existence of a social group. As such, the role of metacognition is vital for instructional-based learning, where the self and others share an understanding of common information.

Social cognition can be investigated at different levels. The brain is described as consisting of distinct functional systems, each made up of various processes such as perception, attention and memory (Bullmore & Sporns, 2009). These processes collectively give rise to everyday experiences and contribute to successful social interactions (C. D. Frith & Frith, 2008). Higher-order functions such as self-reflection, theory of mind, and emotional processing are key components of social cognition, which can be measured independently of other cognitive processes (Adolphs, 2003). While a distinction can be made from other elements of cognitive functions such as memory and processing speed (McDonald, 2013; Spikman et al., 2012), it is conceivable that elements of social cognitive functions should interact with other domains, such as attentional processes. There is converging evidence to suggest a role of executive functions (EFs) in self-regulatory processes. As EFs can be trained to a certain degree, this is potentially a useful intervention to address behavioural disturbances (Hofmann et al., 2012; Schweizer et al., 2013).

Arguments over domain-general or domain-specific processes in social cognition are likely redundant and unhelpful. Social behaviour is inherently complex and likely to involve general processes as well those that may be more specific for social functioning. As such, no one measure of social cognition is sufficient to explain behaviour. A broader approach is required, especially in the context of neurological or psychiatric disorders such as TBI, where some elements may be more likely to be affected than others. One such approach may be the development of assessment batteries that span the evaluation of multiple core processes. A conceptual diagram is presented to highlight potential processes involved in social cognition (Figure 1). At any given point a person's state may influence perception of their environment. During the interaction with others, one constantly receives feedback, this is essential for appraisal of appropriate responses.

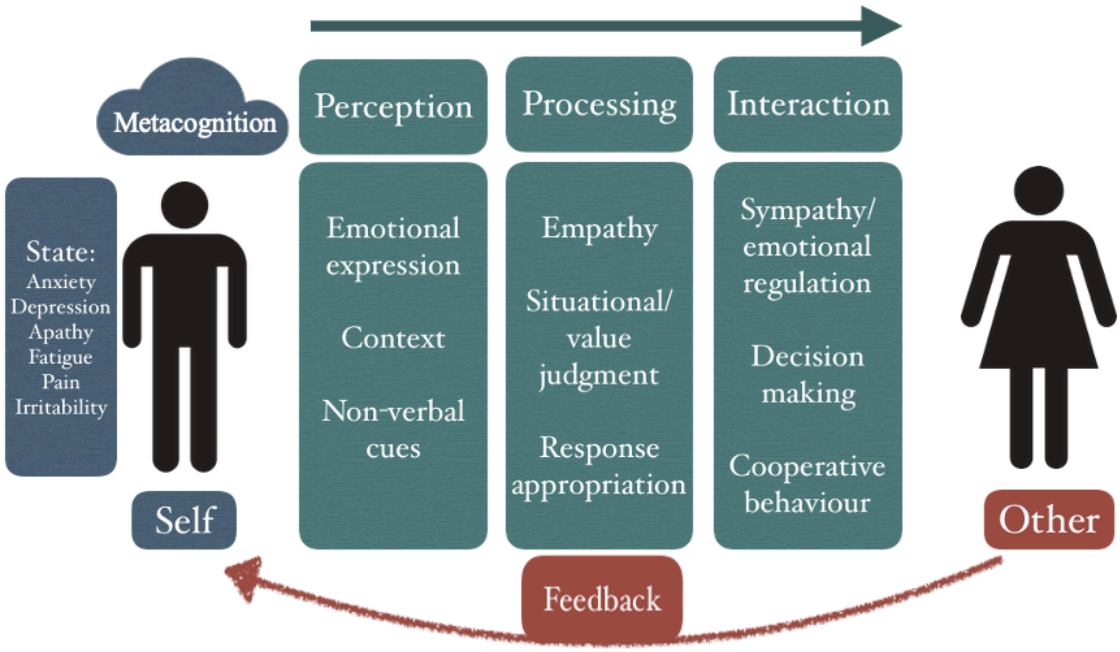


Figure 1: Conceptual diagram of some processes involved in social cognition, from internal states to perception, decision-making and metacognition

Limitations in taxonomy

While functional outcome measures from developmental literature are generally perceived as the gold standard for assessments, these contribute little to our understanding of the underlying causes or cognitive processes that lead to behavioural manifestations (Mehler, 2001). At present, there exists no standard, widely accepted cognitive model of social cognition, nor agreement upon the processes involved. Developmental social cognition (Happé & Frith, 2014) has approached the problem by describing a network of different concepts relating to social cognition. To this aim, the field employs tasks which address critical subprocesses of social cognition such as emotional processing or theory of mind. Critically, tests directed to information processing components of social cognition are also mostly lacking (Happé et al., 2017). This being said, the above approach may be useful in addressing the diagnostic difficulties of social cognitive impairment in TBI, often stemming from heterogeneous symptomology and underlying complex intractable behavioural changes.

Additionally, the field of social cognition research has struggled due to inconsistent taxonomy. Confusion of different words for similar concepts (Affective resonance, emotion sharing, empathy, affective theory of mind as a few examples) or conversely, similar terms for different concepts (Empathy, emotional recognition, TOM) can make it challenging to compare literature and discern reliable inferences across studies.

1.5.2 Social cognition following TBI

Impairments in social cognition have been highlighted as a major component in the sequelae of many neurological disorders and should be incorporated into clinical evaluations (Henry et al., 2016). Health-related quality of life associated with social and emotional functioning is significantly reduced following TBI (Gorgoraptis et al., 2019). Commonly reported impairments include a reduced ability to monitor one's thoughts and behaviour, as well as difficulties in identifying emotions in others and taking their perspective. As such, understanding these social cognitive abilities and their neural mechanisms has a vital role in research and clinical practice. Strong interpersonal relations are a vital feature of normal societal functioning. Abilities relating to these social behaviours are established in early childhood and continue to develop well into adulthood. These behaviours guide everyday decisions and relationships, and their disruption is associated with a variety of poor outcomes such as mental health problems, interpersonal relationships and reduced quality of life (Milders, 2019). Regardless of functional limitations, positive outcomes after injury are consistently linked to better community and social integration as long as 20 years after injury (Andelic et al., 2018).

Increasing efforts have been made towards mapping the neural architecture of social cognition and its component subprocesses in the healthy brain (Figure 2). However, to date,

little evidence supports anatomical localisation for different aspects of social cognition in TBI. As mentioned previously, this ultimately suggests that complex constructs are more likely related to networks rather than location. By including work done on healthy controls and in patients of other neurological conditions, we have begun to develop an understanding of the relationship between social cognition and brain structure/function. The distributed nature of networks associated with social cognitive processes overlap with regions at high risk for focal lesions following TBI, including the amygdala, superior temporal sulcus (STS) and ventromedial prefrontal cortex (VMPFC) (Bickart et al., 2014), make the processing of social signals particularly susceptible to injury (Kennedy & Adolphs, 2012). The neural correlates of specific aspects of social cognition covered in this thesis are discussed in more detail below, with emphasis on the impact of TBI.

Accurate measurement of cognitive impairment following TBI requires the inclusion of social elements, assessments of behavioural control, mood, empathy, QOL, emotional recognition and insight/monitoring of behaviour and cognitive deficits. This can be done through a combination of patient and caregiver reports and objective behavioural tasks, encompassing measures of emotional processing, wellbeing and metacognition through discrepancy scores, as well as confidence judgments on accuracy.

In this thesis, I will primarily focus on three aspects of social and emotional processing that are relevant to improving our understanding of functional outcomes in TBI patients. The first is executive functioning and social behaviour, the second is emotional processing, and the last is metacognition. Each of these themes will be discussed in further detail below and investigated in subsequent chapters via novel behavioural measures and neuroimaging techniques.

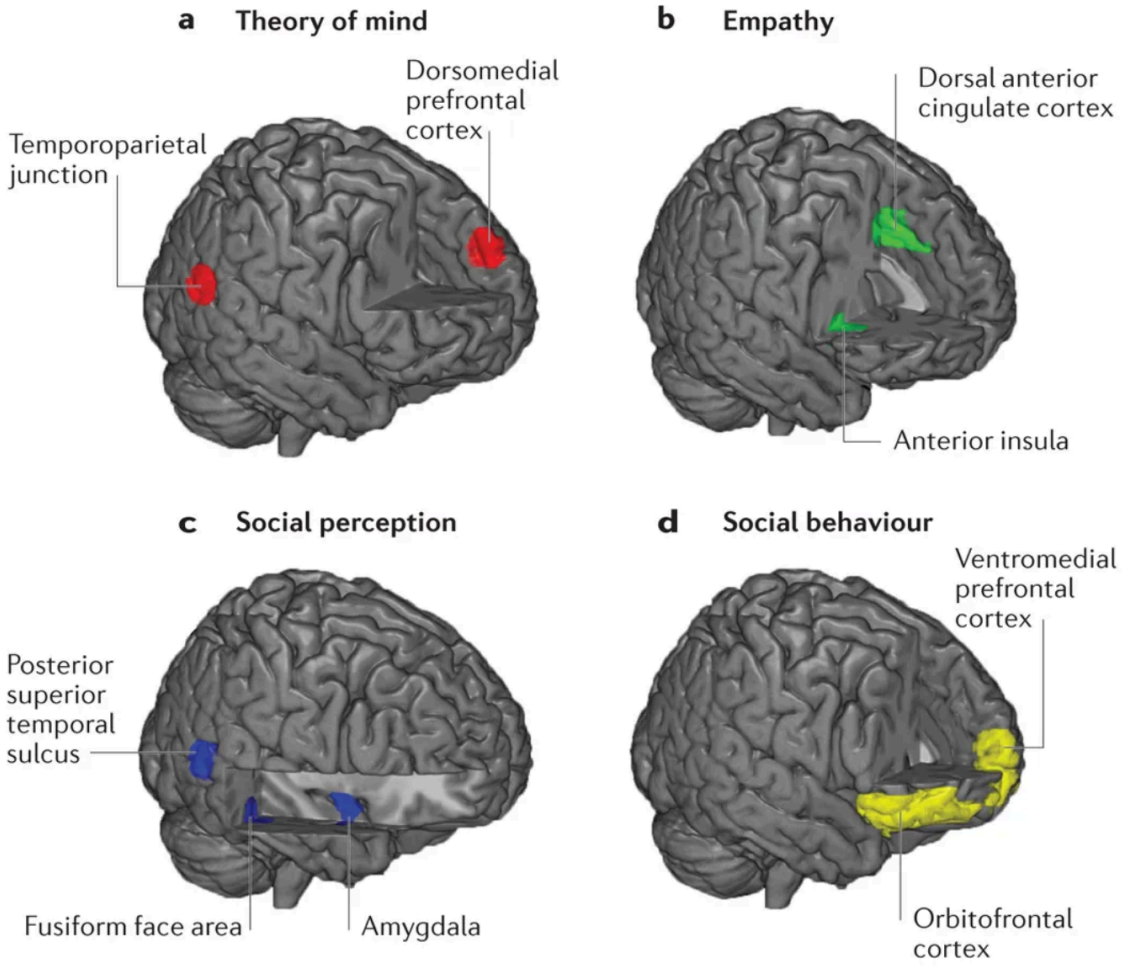


Figure 2: **Brain regions consistently reported for facets of social cognition.** ***Reprinted from (Henry et al., 2016).***

A | The dorsomedial prefrontal cortex integrates social information and is required for reflection. The temporoparietal junction is involved in intention/goal directed behaviour. B | The anterior insula is commonly reported in affective empathy, while the dorsal anterior cingulate cortex is associated with cognitive empathy. C | The amygdala is commonly reported to attribute positive or negative valance to stimuli. The fusiform area is involved with facial processing, while the posterior superior temporal sulcus reportedly contributes social information from biological motion. D | The orbitofrontal and ventromedial cortex are important for attributing meaning, including affective and social information. Medial regions of the frontal lobe may be associated with reinforcement of behaviour whereas lateral regions are more often associated with response inhibition. Damage to these regions are commonly associated with inappropriate behaviour.

1.6 Executive functioning & social behaviour

1.6.1 Executive functioning

Overview

In general, executive functioning (EF) relates to cognitive processes involved in adaptive or goal-directed behaviours. EF is described to have core components comprised of inhibition or self-regulation, working memory, and cognitive flexibility, upon which higher-order EFs such as planning or problem-solving rest (Diamond, 2013). Informally, these processes may collectively be described as being cognitively effortful. An interaction is seen with higher attentional loads in cognitive paradigms and fatigue in TBI patients compared to controls (Ziino & Ponsford, 2006). Even at similar performance levels, higher fatigue is reported in TBI patients than controls, thought to be associated with altered caudate activity (Wylie et al., 2017). Evidence from previous work in our group suggests that fatigue following TBI can be successfully targeted in some cases with dopaminergic treatment (Jenkins et al., 2019).

Inhibitory control, a core feature of EF, affords us the possibility of choice or change rather than automatic, conditioned responses or impulses. Inhibitory responses can be seen in cases such as those where the inhibition of attention or action are warranted (Diamond, 2013). The former is commonly measured with flanker-type attentional tasks (Eriksen & Eriksen, 1974), while the latter is measured with paradigms such as the Stop-signal task (Verbruggen & Logan, 2008) or the Go/No-Go task (V. Menon et al., 2001). In social contexts, inhibition may be a particularly crucial innate feature of behaviour for social cognition, aiding in the regulation of emotions or in restraining inappropriate behaviour.

Working memory, on the other hand, is the ability to hold currently relevant information or maintain information that is no longer perceptually present (Diamond, 2013). There is

considerable evidence to support a common executive working memory construct that is independent of other processes such as processing speed while being predictive of higher-level cognitive function (McCabe et al., 2010). Working memory is vital for several processes such as reasoning or planning, both critically dependent on the ability to hold and mentally process information.

Lastly, cognitive flexibility is the ability to take on another perspective. Cognitive flexibility may involve several processes, such as the inhibition of current views while simultaneously maintaining a new perspective in working memory. Cognitive flexibility is important for the adjustment of mental processes and the generation of appropriate behaviours (Dajani & Uddin, 2015). In clinical neuroscience, this is examined with attentional shifting paradigms such as the Trail making test (Reitan, 1958).

Neural correlates of executive functioning

Go/No-Go, and the Stop-signal task are two commonly adapted paradigms used in the measurement of inhibition. A brief review of the literature suggests that these tasks show separate, but overlapping networks of activation—indicating subtle neural differences between response inhibition and “not going” (C. R. Li et al., 2006; Swick et al., 2011). Within the topic of response inhibition, the anterior insula and pre-supplementary motor area are both key regions.

Impact of TBI on executive functioning

A dysexecutive syndrome can have significant impacts on an individual's social cognitive functioning. Following a TBI, patients and caregivers commonly report disruption to executive processes such as inhibition, alongside deficits in other higher-order processes

necessary for self-regulation; examples of these include apathy and metacognition (Beer et al., 2006; Malloy et al., 1993; Stuss & Alexander, 2007). These impairments can have major implications for interpersonal relationships and patients' return to work, negatively impacting their well-being and quality of life (Formisano et al., 2017).

Focal lesions are associated with dysexecutive behaviour following TBI, as in the quintessential case of Phineas Gage, but this is insufficient to explain the full spectrum of behavioural changes in the majority of patients (Anderson et al., 1995). As a consequence, there has been a gradual shift away from the localisation of function and towards network theories. Evidence that focal regions form nodes relating to executive functioning are seen from MRI studies, showing strong relationships with structural and functional networks (De Simoni et al., 2018). Salience network (SN) function predicts default mode network (DMN) functioning following TBI. This network functioning has been measured in TBI patients with a Stop-signal paradigm (Bonnelle et al., 2012). This paradigm tests the ability to inhibit an action that has already been initiated, a prevalent issue among TBI patients. Recent research has shown that communication within the SN is influenced by structural connections between the right inferior frontal gyrus and anterior insula. The SN is a potentially useful target for transcranial direct current stimulation (TDCS). Although its exact mechanism of action remains unclear, this technique is an experimental method that has shown some potential in modulating cognitive performance. In order to estimate efficacy, dose-response relationships have been conducted in relation to cognitive performance (L. M. Li, Violante, Leech, et al., 2019). TBI patients showed improved response inhibition under a cathodal condition compared to sham; however, TBI patients with structural damage to the right inferior frontal gyrus were non-responders (L. M. Li, Violante, Leech, et al., 2019), suggesting that structural impairments may influence functional connectivity and subsequent behavioural performance.

The current gold standard neuropsychological measure of behavioural dysfunction is the Frontal Systems Behaviour Rating Scale (FrSBe)(Janet Grace & Malloy, 2001). This has been a useful tool in disorders such as behavioural variant frontotemporal dementia (bvFTD) and TBI due to the location of damage involved. Indeed, there is plenty of evidence to support the importance of frontal anatomical regions in executive functioning. Focal damage to the prefrontal cortex, in particular, is frequently hypothesised to explain much of sequelae following TBI (Figure 3). However, little has been done to validate the utility of the FrSBe in relation to the presence of focal lesions vs widespread general damage associated with TBI. In the first experimental chapter, I investigate the relationship of the FrSBe and cognitive measures of executive functioning in moderate-severe TBI patients with frontal lobe lesions using voxel-based lesion symptom mapping. I expand on this and compare this cohort to a group of patients without focal lesions. As previously described, advanced neuroimaging techniques such as DTI may prove particularly beneficial in assessing cases where focal lesions may not be present. DTI has demonstrated considerable utility in examining brain structure in relation to performance on neuropsychological measures and behaviour (Kinnunen et al., 2011). DTI metrics such as FA provide insight into DAI, which may be considered a proxy for microstructural damage throughout the brain (Ghajari et al., 2017). Whole-brain DTI analysis has the added benefit of being an operator-independent assessment, meaning it is not based on a priori assumptions of regional differences. Without an assumption of knowledge regarding the location of the injury, DTI has consistently shown widespread damage in TBI patients (Zappalà et al., 2012).

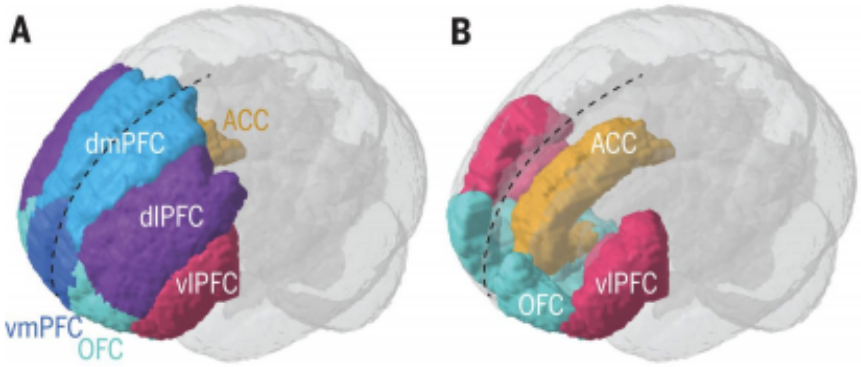


Figure 3: Classification of the frontal cortex with its sub-components. Illustration reprinted with permission from (Carlén, 2017).

Highlighted/labelled areas are regions frequently reported to be affected by focal damage following TBI.

1.6.2 Apathy-motivation

Overview

Apathy is a prevalent syndrome characterised by a profound lack of motivation or goal-directed behaviour (Ang et al., 2017). Apathy is a syndrome commonly described across neurological disorders, consisting of a loss of motivation or goal-directed behaviour. It can be further subdivided into emotional, social, or behavioural subgroups (Le Heron et al., 2018). In the absence of a diagnosed neurological or psychological condition, levels of apathy vary considerably among controls within the general population. Elevated levels of apathy are associated with lower motivation (Ang et al., 2017), a relationship that is especially pronounced in neurological conditions.

Neural correlates of apathy-motivation

Increased levels of apathy are consistently associated with disruption to the dorsal Anterior Cingulate Cortex (dACC) and ventral striatum across a range of neurological disorders (Le Heron et al., 2018), including Parkinson's Disease (PD), Fronto-temporal Dementia (FTD),

and Huntington's disease (HD). In TBI, however, little has been done to investigate the neural correlates of apathy until now. Chapter 5 of this thesis progresses on previous work I have been involved with investigating apathy and motivation after TBI.

Apathy-motivation following TBI

Higher levels of apathy in TBI patients has been corelated to disruption of the dopaminergic system (Jenkins et al., 2018). This is in line with previously reported results in patients with PD, a pathology characterised by disruptions to the dopaminergic system (Le Heron et al., 2018). Prevalence of apathy in TBI patients ranges between 20-70% (Worthington & Wood, 2018). However, it is worth noting that this variance likely relates to differences in how it is measured, and the respective definitions used. The aetiology of apathy, particularly in TBI, needs to be examined further. The lack of goal-directed behaviour may be attributed to a syndrome of apathy itself, which may arise from damage in circuits involved in motivated behaviour, including regions such as the striatum, ACC or the PFC. Conversely, apathy may also be a symptom of other syndromes such as depression.

The Lille Apathy Rating Scale (LARS) is a tool widely used by clinicians to rate apathy in PD (Sockeel et al., 2006). A useful alternative is the Apathy Motivation Index (AMI), a self-report measure validated in a large cohort of healthy controls. Using a data-driven approach, three subscales for emotional, social, and behavioural apathy have previously been derived through factor analysis (Ang et al., 2017). These measures will be used here to assess apathy and motivation following TBI in relation to neural correlates.

1.7 Emotional processing

Overview

Emotion adds affective valence and arousal to perception, affording it information regarding the importance and value of events and objects (Zadra & Clore, 2011). While it has been suggested that social cognition may be reduced to emotional processing and motivation only (Adolphs, 2003), here I consider emotional processing in conjunction with interrelated sub-processes of perception, theory of mind, contextual understanding, and affect-sharing or emotional regulation.

1.7.1 Emotional perception

Emotional perception, particularly facial processing, is an essential feature of social cognition. Emotional facial processing provides information regarding emotion or intention, which may be used to guide one's behaviour (Tarnowski et al., 2017; Vuilleumier & Pourtois, 2007). This perceptual process is the first step in towards higher-order processes such as mentalising and understanding others' mental states, also known as theory of mind (C. D. Frith & Frith, 1999; U. Frith & Frith, 2001). Theory of mind is discussed in more detail below.

Neural correlates of emotional perception

Emotional perception is primarily assessed through the processing of facial expressions or emotive scenes. Paradigms utilising facial stimuli have shown neural correlates that dissociate from emotional scenes in regions such as the fusiform and middle temporal gyrus. In contrast, emotional scenes elicited greater activation in the lateral occipital cortex and thalamus. Regions of greatest overlap in emotional processing for either stimuli type include the amygdala, medial prefrontal, and inferior orbitofrontal cortex (Sabatinelli et al., 2011).

Along with the amygdala, these frontal regions may form part of a network that attributes emotional value and modulates emotional perception (Vuilleumier & Pourtois, 2007). As frontal regions are commonly affected following TBI, the investigation into emotional perception processes is critical in informing our understanding.

Emotional perception following TBI

About a third of moderate-severe TBI patients show impairments in the emotional recognition of facial expressions, also termed facial affect recognition. Impairments in this aspect have also been correlated with reduced social participation (Neumann et al., 2014). In the presence of amygdala sclerosis or damage, accuracy in emotional perception is reduced (Calder et al., 1996; Vuilleumier & Pourtois, 2007).

Emotional affect in TBI patients measured though perception on a facial expression task shows a relationship between poorer performance and reduced grey matter in the parahippocampal gyrus, as well as reduced fractional anisotropy (FA) in the inferior longitudinal fasciculus and the inferior fronto-occipital fasciculus (Genova et al., 2015). As cited by Neumann (2016), two meta-analyses (Fusar-Poli et al., 2009; Sabatinelli et al., 2011) investigating facial affect processing have proposed its relative importance for TBI patients, as there seems to be a strong link between disrupted affect processing and emotional regulation. A network involving the PFC and areas of the limbic system, in particular the amygdala, plays an essential role in this emotional regulation. Reductions of galvanic skin response to emotionally valent facial expressions (e.g. Anger) have also been reported in TBI patients (de Sousa et al., 2011). This blunting of a psychophysical response suggests that TBI may result in disrupted interaction between visually salient information and autonomic arousal.

1.7.2 Theory of mind

Overview

The incredible ability to infer and anticipate another person's mental state and behaviour based on an understanding of their beliefs, emotions and intentions is a critical component of social cognition that separates us from other species (Gallagher & Frith, 2003). This ability is referred to as Theory of Mind (TOM).

In order to assess one's TOM, we need to consider its underlying cognitive and affective components. The classic Mind in the Eyes task (MITE) (Baron-Cohen et al., 2001) alludes to the measurement of one's understanding of another's emotion through the visualisation of only their eyes. While performance on the MITE task is among the most commonly cited measures of TOM, it has been argued that its interpretation relates to emotional processing and is highly associated with alexithymia, an inability to describe one's own emotions (Oakley et al., 2016). Other approaches include the assessment of higher-order processes such as humour, faux-pas, game theory paradigms, or perspective-taking in contextual situations (Skerry & Saxe, 2015).

Neural correlates of TOM

Among the most commonly cited regions associated with TOM are the anterior paracingulate cortex, superior temporal sulcus (STS), and temporal poles. However, these regions are not uniquely activated in mentalising paradigms and may constitute domain-general cognitive processes essential for TOM (Gallagher & Frith, 2003). While they may appear interlinked depending on specific paradigms used, emotional processing and TOM are fundamentally separable. For example, amygdala and orbitofrontal activation in TOM paradigms are potentially related to the emotional processing of stimuli used rather than the inference of

intention (Gallagher & Frith, 2003). While early work supported the amygdala as one of the three key regions of the social brain (Brothers, 1990), its involvement has not been consistently observed, potentially due to the limitations described above concerning paradigm stimuli. In contrast, the involvement of the medial PFC, OFC, STS and temporoparietal junction (TPJ) are consistently reported (Carrington & Bailey, 2009). Activation in the TPJ is also related to reorientation paradigms, this has been suggested to relate to a common process involving internal predictions of external events—or in other words, the concept of expectation (Corbetta et al., 2008). The evaluation of breaches in expectation constitutes one of the critical social cognitive paradigms, commonly measured by the utilisation of false-belief stories (Gallagher & Frith, 2003).

Notably, the above regions demonstrate considerable overlap with the DMN. While co-localisation does not necessitate shared function, the averaging of activation signals may mask subtle differences in voxel-wise distributions (Corbetta et al., 2008). It has been proposed that the network of regions commonly recruited in TOM paradigms relate more heavily to domain general processes required for TOM, rather than being TOM-specific (Rebecca Saxe & Powell, 2006; Spikman et al., 2012). Regions overlapping with the DMN can also be fractionated into components of TOM. For instance, the connection between the TPJ and the mPFC is related to the ability to mentalise or infer others' states. In contrast, the mPFC and the medial temporal lobe (MTL) are associated with affective components, and the ACC is related to functions of self-other distinction (W. Li et al., 2014).

One view of TOM breaks it down into two interrelated components: a cognitive network and an affective network. A neuroanatomical model of theory of mind proposes the following neurological correlates for each (Abu-Akel & Shamay-Tsoory, 2011)—Cognitive TOM: dorsal PFC, dorsal ACC, and dorsal striatum; affective TOM: ventromedial & orbital PFC,

ventral ACC, amygdala, and ventral striatum. These regions are known to be connected to the dopaminergic system and are commonly damaged in TBI patients.

Relation to TBI

TBI frequently results in frontal lobe damage, with the potential to disrupt OFC circuits important for social cognition (Spikman et al., 2012). As described theory of mind is not a unitary construct. Lesion studies have demonstrated fractionated deficits, findings that are informative for the development and understanding of different cognitive processes involved (Dennis et al., 2013; Hoskinson et al., 2020). As discussed throughout this thesis, inferences based solely on lesion location have limited utility in TBI, as injuries arising from DAI and secondary insults render its pathology relatively complex.

Work in paediatric TBI shows that lesions are similarly present in anatomical locations that overlap with the SN and DMN, both critical for social cognition (Dennis et al., 2013). Lesions in anatomical regions relating to these functional networks are conceivably associated with deficits in both cognitive and affective TOM, an especially pertinent concern in this cohort as TOM development is seen into early adulthood. Children with TOM impairments are at most considerable risk of adjustment issues (Hoskinson et al., 2020).

It is critical to note that deficits in TOM are distinct from executive dysfunction in TBI (Muller et al., 2010). This distinction of deficits underscores the importance of assessing this construct among others when administering cognitive tests. Following TBI, general impairment of TOM may relate to deficits in a variety of different processes, such as comprehension, working memory, or inference. This has implications for rehabilitation as well, as a comprehensive assessment of the likely causes of social impairments and targeted training of social skills, rather than general TOM training, is likely to be effective in conditions such as Autism Spectrum Disorder (ASD) (Bibby & McDonald, 2005).

Social/emotional context

The majority of measures investigating TOM use representations of emotional expressions; in other words, actors portraying expressions conventionally perceived as happiness, sadness, and anger, etc. Other paradigms include faux pas or situation understanding (Baron-Cohen et al., 1999). Our ability to infer another person's thoughts or intentions through the understanding of situational context may also be an important feature of TOM to measure (Skerry & Saxe, 2015). To this end, some work has been done to investigate the neural bases of different emotions in situational contexts in a large cohort of healthy controls. Assessing contextual understanding could be a useful approach in assessing impairments in the fine-grained understanding of subtle social appraisals. As an example, a case study of an individual with good outcomes in terms of classical neuropsychological assessments and assessments of "frontal lobe" functioning showed that they might present with ongoing impairments in social situations (Cicerone & Tanenbaum, 1997). Based on this, the implementation of tasks probing contextual understanding would be beneficial in TBI patients. Here, difficulties with incorporating information or contextual understanding of another person's emotions may occur in the absence of any deficits in emotional recognition.

1.7.3 Empathy-affect sharing

Overview

Titchener invented "Empathy" as a translation of the German word "Einfuhlung," itself a term from aesthetics meaning "to project yourself into what you observe." (Titchener, 1909), as cited by (Baron-Cohen & Wheelwright, 2004).

Beyond the ability to recognise emotions, features of empathy such as having concern or sharing the feelings of others may be affected by TBI. An operational definition of empathy

is ambiguous, as there has been much discussion over its evolution and the incorporation of both its affective and cognitive components. Practically, it is the ability to infer another person's emotional and or mental state and to respond in an appropriate manner (Baron-Cohen & Wheelwright, 2004).

Empathy requires both emotional identification (e.g. the awareness that someone is in pain) and affect sharing (i.e. concern for the state of the other). Affect sharing involves the ability to generate internal representations of another's feelings. To illustrate, we can take two cases in which an individual has a lack of empathy: Patient 'A', who mis-recognises the state of another (miss-match), and Patient 'B', who recognises their state but does not share affect (miss-bind). To differentiate these, we need to measure both an individual's accuracy in identifying a target emotion, as well as their own level of matching emotion. Without an explicit measure of affect sharing, we are unable to infer empathy; in these cases, emotional recognition is likely to be the subject of detection.

Neural correlates of empathy

fMRI studies have examined empathy across states of emotion and pain. While results tend to be paradigm-dependent, observed regions of activation frequently overlap with TOM networks. The most consistent activations are found in the anterior insula, the ACC, and the mid-cingulate cortex (MCC). Involvement of these regions are commonly cited across a range of social cognitive functions and may involve domain-general processes which help evaluate and guide responses to perceived states of others (Bernhardt & Singer, 2012).

Empathy following TBI

Empathy is known to be comorbid with factors such as negative biases in depression, apathy, and cognitive impairment, all of which are commonly reported following TBI. Research has shown that impairments in empathy may also be independent of other cognitive deficits, the severity of the injury, or psychiatric symptoms (R. Wood & Williams, 2008). This independence from injury severity or cognitive disturbance is an important consideration, as deficits in empathy, rather than cognition, are more likely to impact functional outcomes such as social relationships and wellbeing.

A comprehensive review of the various associations linking empathy and brain damage is given by (Hillis, 2014). Through dissociating the various constructs involved in empathy, we can begin to infer the preferential involvement of anatomical regions. The OFC is related to emotional contagion, defined as the ability to recognise emotional expressions; the PFC, on the other hand, is associated with affective perspective-taking and the inference of these expressions. Both of these constructs are likely to involve the right ACC, right insula, right amygdala, and the right temporal pole. Additionally, while not specific to affective processes, the TPJ also plays an important role in third-person perspective-taking. It is important to note that these are regions that are highly cited in a variety of social paradigms, and as such are important for more general processing of social information, despite being somewhat non-specific to emotional processing.

1.7.4 Emotional regulation (lability)

Overview

Emotional regulation can be defined as "the extrinsic and intrinsic processes responsible for monitoring, evaluating, and modifying emotional reactions, especially their intensive and temporal features, to accomplish one's goal" (R. A. Thompson, 1994). Affective lability, or instability, can be seen as frequent and intense changes in emotional response regardless of a positive or negative valence (R. J. Thompson et al., 2011). Emotional regulation requires a complex cognitive control process consisting of attention, appraisal and response (Ochsner et al., 2012).

Neural correlates of emotional lability

As described by the cognitive control model of emotion (Ochsner et al., 2012), the neural correlates of emotional regulation consist of several regions previously identified in other aspects of emotional processing. In the first instance, there are regions associated with emotional perception and valuation. The first two of these regions are the amygdala, considered to play a role in the perception and encoding of affective meaning to stimuli, as well as the ventral striatum, associated with learning and predicting outcome. The third is the ventromedial prefrontal cortex which, while maybe not specific to emotional processing, may integrate information from the amygdala and ventral striatum as well as historical information from the temporal lobes. The fourth region, the anterior insula, is highly cited in relation to interoception, as well as affective and motivational states.

The neural correlates described in the above sections relate to the perception and integration of emotional information. In terms of emotional regulation, further processes such as attentional control, required for focus on relevant stimuli, involve regions such as the

DMPFC. Constant monitoring of feedback from others and the subsequent matching of one's behaviour may involve the ACC. Finally, the VLPFC is essential for goal-directed behaviour. It is not presumed that these regions work in isolation; instead, they comprise a network modulating interrelated functions, with players such as the dorsal control network, which may be modulated by affective valuation and behavioural monitoring. In short, emotional regulation is a complex process involving key regions overlapping with some of those most commonly affected in TBI.

Emotional lability following TBI

Assessments of anger and irritability are equally important following TBI, as these pose a considerable threat to interpersonal relationships. A comprehensive set of measures covering these components, as well as anxiety and depression, are found in the neuropsychiatric inventory (NPI). A limitation of this single time-point clinical assessment, however, is the lack of an objective measure of frequency or severity. A close family member or friend should therefore corroborate this information to ensure its accuracy. Alternative approaches are app-based assessments of mood that allow longitudinal tracking of changes over time. At present, novel trials targeting emotional dysregulation and alexithymia through the training of emotional self-awareness are being conducted (Neumann, 2017). This emotional self-awareness ties in with the theme of metacognition discussed below. This form of training may demonstrate utility as an intervention for common emotional problems following TBI. As emotional regulation requires effective functional connectivity involving frontal regions, its disruption (often observed as higher levels of anxiety/depression) have been recorded even in cases of mild TBI, indicating an association with altered executive and salience circuits (H. J. van der Horn et al., 2017).

1.8 Metacognition

1.8.1 Overview

Metacognition is the ability to evaluate performance and confidence in one's cognitive processes (Metcalfe & Shimamura, 1994), a process that requires both internal and external error monitoring. Its role has been extensively examined, but there is much debate about whether it is a domain-specific or general function (Fitzgerald et al., 2017; Rouault et al., 2018). Metacognition can be fractionated into different levels, such as online error-monitoring, also known as emergent awareness, as well as reflection/evaluation. The former relates to real-time feedback on performance, while the latter relates to the ability to judge one's own performance accurately.

1.8.2 Neural correlates of metacognition

The medial and lateral PFC is activated during metamemory paradigms (S. M. Fleming & Dolan, 2012). Metamemory involves a judgment of accuracy subsequent to answering items on a memory test. Other evidence for levels of self-confidence in performance on memory from a meta-analysis indicates the role of the left dPFC, posterior mPFC and bilateral inferior frontal gyrus/insula. Differences were seen when contrasting prospective and retrospective judgments. Retrospective judgments saw clusters in the bilateral parahippocampal cortex and the left inferior frontal gyrus, while prospective judgments had clusters in the posterior mPFC and left dPFC. Similar results are seen for metadecision paradigms, with activity in the medial and lateral PFC, the precuneus and the insula (Vaccaro & Fleming, 2018).

1.8.3 Metacognition following TBI

The ability to self-reflect and evaluate one's behaviour is shown to be impaired post-TBI (Dockree, O'Connell, et al., 2015; S. M. Fleming & Lau, 2014; Ham et al., 2014). This lack of insight into one's own cognition or mental state is a remarkable feature and arises independently of performance accuracy (S. M. Fleming & Dolan, 2012). In terms of social impairment, this is an important avenue to investigate, as implicit evaluation of the self and explicit monitoring of others' feedback are likely vital elements of behavioural regulation and social decision-making (C. D. Frith, 2012).

One approach to identify deficits in metacognition or self-awareness following TBI is to measure discrepancies between patient and caregiver reports on measures such as the FrSBe and the Cognitive Failures Questionnaire (CFQ) (O'Keeffe et al., 2007). This approach aims to identify areas of impaired insight within particular functional behaviours, in what is referred to as metacognitive knowledge. An experimental approach towards the evaluation of metacognition involves investigation of error monitoring— Either as part of the experimental paradigm (Ham et al., 2014; O'Keeffe et al., 2007) or, alternatively, as a self-reflection/confidence judgement at the end of an experimental condition (Elmose & Happé, 2014; Hauser et al., 2017). Each of these methods is discussed in detail below.

Self-awareness

Discrepancy measures and confidence judgments of performance described above provide a good general assessment of metacognitive knowledge (Dockree, O'Connell, et al., 2015). Reduction in this index suggests an overall lack of awareness of deficits following an injury. Chronic TBI patients with a longer time since injury (10 years) show a stronger agreement between patient and caregiver responses when evaluated on the Sydney Psychosocial

Reintegration Scale (SPRS). This low discrepancy may reflect a critical role of time in the recovery of self-awareness (Draper et al., 2007), a finding supported by a longitudinal study following the recovery trajectories of TBI patients a year after injury. Here, researchers found that time since injury was the most significant predictor of recovering self-awareness (Richardson et al., 2014). This being said, an important caveat to consider in the interpretation of these studies pertains to potential differences between caregiver and patient ratings for various subscales within the measure. It has been established that caregivers tend to give lower ratings for capacity and cognitive functioning, factors strongly related to PTA duration. In comparison, patients tend to give lower ratings for measures of fatigue, anxiety and depression.

There are also reported relationships linking the impairment of self-awareness to executive dysfunction and TOM impairment (Formisano et al., 2017). Deficits in any of these processes may affect the accuracy of self-reported health outcomes, or their self-perceived quality of life, culminating in major impacts upon the rehabilitative process. Reduced self-awareness has also been linked to poor caregiver well-being (Formisano et al., 2017). Correlations between metacognitive self-awareness and executive functions suggest that the former should be targeted in rehabilitative treatments (Bivona et al., 2008).

Error monitoring following TBI

As mentioned, metacognition may consist of separate processes such as self-awareness measured by metacognitive knowledge or through online error monitoring to assess emergent awareness which can impact on the spot decision making (Dockree, Tarleton, et al., 2015). Based on assessment of online error-monitoring at baseline and follow-up, impaired self-

awareness in TBI patients was shown to be a significant predictor of reduced community re-integration (Robertson & Schmitter-Edgecombe, 2015).

Research in TBI has shown that patients' abilities to judge their own performance on memory tasks were considerably more reduced than their executive functioning abilities (Chiou et al., 2011). Similar work relates these impairments in insight into one's behaviour to lesions in the OFC (Beer et al., 2006). Reviewing studies investigating confidence judgments on memory performance (metamemory), impairments of retrospective judgment appear to be predominantly related to lateral PFC lesions. In contrast, impairments of prospective judgments (feelings of knowing) may be related to damage in the ACC (S. M. Fleming & Dolan, 2012). While this synthesis of the literature reflects a potentially interesting dissociation, further support is required by empirical evidence.

In the lab, patients identifying fewer errors showed higher discrepancies from caregiver reports of cognitive and affective difficulties (Dockree, O'Connell, et al., 2015). Interestingly, these deficits in online awareness and their relationships to metacognitive or emergent awareness in daily functioning were not related to the location of the injury. This result is potentially explained through disruptions within the frontoparietal control network following injury, rather than damage to specific anatomical locations (Ham et al., 2014). Any critical region within a neural network may be damaged, eliciting similar behavioural outcomes. The ACC has been cited as a key region for error-monitoring (Apps et al., 2015), while the DLPFC is required for the regulation or correction of behaviour. The behavioural correlates associated with these regions vary but lead to similar deficits of metacognition depending on the measure being used.

Given our knowledge of the range of functional and behavioural afflictions following TBI, it is crucial to ensure that collaborative accounts of cognitive and behavioural problems are collected within clinical practice. This information provides useful discrepancy measures between patients and their close family members. As part of a short neuropsychological battery, performance judgments can be measured across different cognitive domains to probe emergent awareness; error-monitoring tasks such as the Stop-Change task (SCT) may also be effectively implemented. In the context of rehabilitation, error-based feedback training is one potential approach that may prove helpful in ameliorating metacognitive deficits (Ownsworth, 2015(FitzGerald et al., 2019)). While still in the early stages of testing in TBI patients, this form of reflective training has been a useful tool in sports psychology among professional athletes for some time. Another potential approach is to incorporate rehabilitation of emergent awareness into cognitive or clinical rehabilitation programs.

Throughout this thesis I will cover the themes of social cognition highlighted in this introduction. I will use a combination of neuroimaging and behavioural analysis to explore deficits that may be present in patients following an injury with the hope of providing new insights into the problems faced after TBI, and guide for future directions of research.

Chapter 2 | General methods

This chapter contains the general methodological details of the studies performed as part of this thesis.

2.1 Overview

Study procedures were carried out at the Hammersmith Hospital, Imperial College London (London, UK), Charing Cross Hospital (London, UK) and St. George's Hospital (London, UK). Additional remote assessments were completed via participants' smartphones or the web. A data flow diagram is provided, detailing overlap of patients cohorts (Figure 4).

2.2 Participants

2.2.1 Data flow

The first experimental chapter of this thesis (Ch. 3 | Frontal systems) involves an analysis of legacy data of 145 patients. This data consists of a cohort of patients from (Ch. 4 | White matter) I was involved in recruiting and testing as part of a clinical trial on dopamine's role in enhancing attention and memory (DREAM), results from which have been previously published (Jenkins et al., 2018, 2019). These well-characterised patients were invited back for a follow-up visit specifically to investigate their social cognitive functioning (Ch 5 | social decision making, Ch 6 | Emotional processing). Additional patients were recruited acutely and from outpatient clinics to complete remote behavioural assessments (Ch 6 | emotional processing, Ch. 7 | metacognition). Healthy volunteers were recruited as a comparison to patients for both experimental visits and remote cognitive assessments. A data flow diagram is presented below (Figure 4).

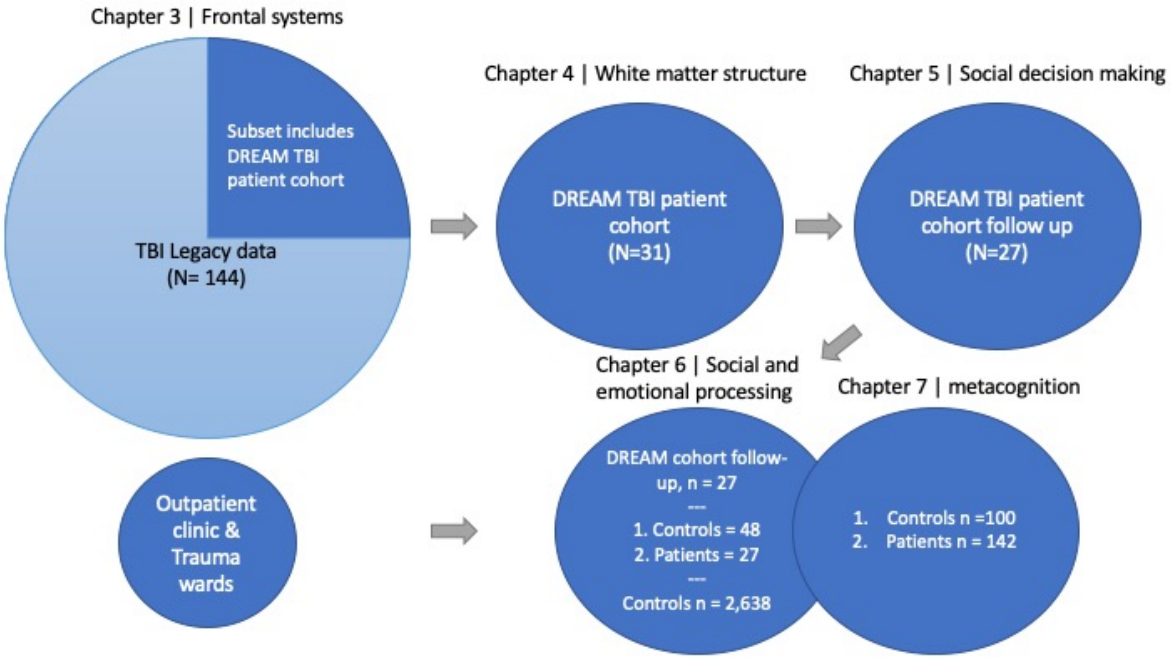


Figure 4: Data flow diagram

2.2.2 Recruitment

Patients were recruited through a specialist outpatient TBI clinic at St. Mary's Hospital, and the major trauma wards at the St. Mary's and St. George's Hospitals. All participants gave written informed consent.

Chapter 4 was approved by the West London and GTAC NRES committee (14/LO/0067). The study was registered with clinicalTrials.gov (NCT02015949).

Chapter 5-7 were approved by the Camberwell-Giles ethics committee and Imperial College London (17/LO/2066).

A set of inclusion and exclusion criteria standardised across our research group were applied as follows.

Inclusion criteria

1. Diagnosis of a moderate-severe TBI, as defined by the Mayo severity classification system (Malec et al., 2007)
    a. Chapters 3-5 patients were recruited at least three months post-injury
    b. Chapters 6-7 included acute-phase patients within 1-month post-injury who were compliant with behavioural assessments
2. Age between 20-65 years
3. Capable of giving written informed consent
4. A subjective complaint of cognitive difficulties by the participant, treating clinician or caregiver.

Exclusion criteria

1. Unwillingness or inability to follow required procedures
2. Significant neurological or psychiatric condition preceding TBI
3. Family history or first degree relative with psychotic illness
4. Use of medication or substance that, in the opinion of the investigator, would interfere with the study – psychostimulants i.e. methylphenidate, inability to withhold from nicotine, caffeine on study day.
5. A current or past history of drug or alcohol addiction
6. Contraindication to MRI scanning, assessed with standard MRI safety questionnaire

Additional exclusion criteria for patients recruited in chapter 4 as part of a clinical trial included contraindication to methylphenidate, history of drug or other allergies that contraindicates participation, positive drug screen or clinical evidence of parkinsonian motor symptoms as assessed by a neurologist.

Healthy control participants were recruited for neuroimaging analysis and behavioural assessment. They were in good general health with no history of significant illness, and ineligible if they met any of the above exclusion criteria.

2.3 Neuroimaging

2.3.1 Structural MRI

MRI was performed on a Siemens Verio 3.0 Tesla scanner using a 32-channel head coil. Each patient had standard high-resolution structural imaging, acquired with the following parameters: T1 MPRAGE (TE = 2.98s, TR = 2.3s, 1 mm isotropic voxel, 256x256 mm FOV, FA = 9, GRAPPA = 2, 5min scanning time), T2 FLAIR (TE = 395ms, TR = 5s, 1 mm isotropic voxel, 250x250 mm FOV, GRAPPA=2, 6min scanning time). Brain tissue volumes, white matter (WM), grey matter (GM), and intracranial volume (ICV) were computed for each individual using a standard morphometry pipeline on T1-weighted images with (SPM12, University College London, www.fil.ion.ucl.ac.uk/spm). The above procedures were previously described in more detail in (Cole et al., 2018).

2.3.2 Diffusion MRI

Diffusion-weighted volumes were acquired using a 64-direction protocol (64 slices, in-plane resolution=2x2mm, slice thickness=2mm, field of view = 256x256cm, matrix size=128x128, TR=9500ms, TE=103ms, b-value=1000s/mm2). Four non-diffusion weighted images were also acquired (b-value=0s/mm2).

DTI data were corrected for head motion and eddy current distortions, using linear transformations to register these images to the b=0 image. A brain mask was generated by brain extracting the b=0 image (FSL Brain extraction tool (Smith 2002)). A tensor model was

then fitted to the data using FMRIB's Diffusion Toolbox (FDT) in FSL, constrained by the brain mask. This tensor model generated voxelwise fractional anisotropy (FA) maps per participant. These maps were transformed into 1mm-resolution standard space for further statistical analysis. The mean FA image was constrained to produce a 'skeleton', depicting WM tract centres, and therefore reducing partial-volume confounds. The FA skeleton was subsequently set to a threshold >= 0.2 to suppress regions of extremely low mean FA and remove areas with substantial inter-individual variability. This was saved as a binarised mask for subsequent statistical analysis. Independent sample t-tests were run to investigate differences in diffusion metrics between patients and controls. This was done with non-parametric permutation testing (n=10,000) in FSL Randomise (Winkler et al., 2014). A threshold of $P < 0.05$ was then applied on corrected multiple comparisons results. Age was included as a nuisance regressor in TBSS analyses.

2.3.3 ^{123}I-ioflupane SPECT

Potassium iodide tablets (2x60mg) were provided to participants one hour prior to administration of ^{123}I-ioflupane in order to minimise radiation exposure to the thyroid gland. ^{123}I-ioflupane was delivered as an intravenous bolus, resulting in the mean activity of 185MBq. 180min after injection, participants were placed on a bed with a dual-head gamma camera (Symbia T16, Siemens Healthcare) at Charing Cross Hospital. Low-energy high-resolution (LEHR) collimators were used to generate SPECT images (128x128 matrix, 1.45 zoom, 128 projections, and 30 seconds per projection).

Two independent nuclear medicine consultants reported on all SPECT scans. A predefined ranking scale of normal, abnormal or indeterminate was followed. Any discrepancies between reports were resolved by consensus opinion to give a single result per scan.

T1 images were segmented into grey and white matter using SPM12 and warped to an average group template using a diffeomorphic nonlinear registration (DARTEL) (Ashburner, 2007). Templates were registered to Montreal Neurological Institute (MNI) 152 space. Individual flow-fields and template transformation from DARTEL were then applied to the SPECT images to produce MNI space images, without modulation.

The specific binding ratio (SBR) was calculated for the whole striatum and the caudate, putamen, and nucleus accumbens separately. The SBR was calculated using the formula ([region of interest counts − background counts]/background counts), where the background counts were calculated from the occipital cortex, an area of low Dopamine transporter (DaT) expression.

2.4 Neuropsychology and behavioural assessment

2.4.1 Visit assessment

Testing took place in a quiet testing room to minimise distractions. Participants completed the 30min digital battery of tasks on a Samsung (SM-T580) tablet. This included a set of cognitive tasks to test emotional processing and executive function. Participants also completed a set of standard questionnaires administered via the testing app on the tablet. Additional pen and paper assessments of the Stroop and trail making test were completed.

2.4.2 Remote assessment

Participants downloaded our app “Cognitrack” from the Android or Apple app stores. This required entering an assigned participant ID for login and consenting to take part in a study by selecting a button at the end of an information sheet. Patients recruited through an

outpatient clinic signed an additional paper consent form after going through an information sheet.

The initial version of the testing protocol required participants to complete a battery of tasks once a week. This was generally unsuccessful, resulting in a significant drop-off in participation. The protocol was amended to collect data as part of four batteries collected over a single week. Additional memory tests were available at the end of these four testing batteries. The results of the second protocol are reported here. A pre-test questionnaire was implemented at the beginning of each test battery to assess physical and mental health (PMHQ).

2.4.3 Statistical analysis

Data analysis was run with a combination of the statistical package r (Core Team, 2018 http://www.R-project.org/) and MATLAB version 2018b (MathWorks; http://www.mathworks.com/). Detailed descriptions of statistical models used are given in each of the chapters. An overview of data exploration prior to analysis is given here.

The central limit theorem postulates that given a large enough number of observations, a normal distribution should form (Zuur et al., 2010). However, this is rarely the reality of research data. Several steps can be conducted as part of data exploration prior to model testing to help guide the appropriate statistical tests to use; ones used throughout this thesis are described below.

Normal distributions are investigated with histograms and quantile-quantile (Q-Q) plots. Histograms indicate normality with a bell-shaped distribution of the sample data. A Q-Q plot

graphs a correlation between a normal distribution and the given sample, including a 45^{o} reference line. If the data falls primarily along this reference line, the assumption of normality can be inferred. Shapiro tests are also conducted. However, this is sensitive to small sample sizes, and in this thesis, normality assumptions are primarily based on visual inspection of the data.

Accounting for outliers can be contentious. Outliers have been accounted for in different ways in this thesis, each deemed the most appropriate given its context. These are outlined in each of the chapters. In general, winsorising behavioural and cognitive responses is the preferred method to avoid removing data. This method transforms the data to give outliers a lower weighting, minimising their influence on the sample. This is set at 95%, setting a value threshold at the top 2.5% and bottom 2.5% of the data. However, it is worth noting that winsorising is not always the best method. In chapter 5, three data points were removed due to abnormal responses that could be attributed to non-random noise from under-calibration of the cognitive task. In this instance, data were removed to avoid skewing results. In chapter 6, an online behavioural study was conducted. As part of the data cleaning processes, responses greater than four standard deviations were removed from further analysis. While tails in distributions may be important, for data collected in non-laboratory conditions this is an acceptable trade-off to account for participants who may not engage sufficiently with testing to improve reliability. Where data has been interpolated due to outliers, this is clearly indicated.

Chapter 3 | Reviewing a "frontal syndrome"

In this chapter, I look at measures typically associated with frontal lobe functioning in a large cohort of TBI patients with focal lesions and contrast this with patients without visible evidence of frontal lobe damage.

3.1 Abstract

Signs of executive dysfunction, such as difficulties with planning and inhibiting unwanted actions, are frequent after traumatic brain injury (TBI). The relative contributions of focal frontal injuries and diffuse axonal injury (DAI) to dysexecutive problems are unclear. I investigated whether the presence and location of focal frontal lesions predict the occurrence of dysexecutive behaviour, whether patients with focal frontal lesions show more dysexecutive behaviour than patients without focal lesions, and whether DAI was observed in dysexecutive patients both with and without focal lesions.

Patients in the chronic phase (>6 months post-injury) underwent neuropsychological assessment and MRI (n = 144 [Male = 112, mean age 41.39 ± 12.49]). Voxel-based lesion-symptom mapping (VLSM) was used to explore the relationship between FrSBe measures and lesion location (n = 102). A further group of moderate-severe TBI patients without focal lesions (n = 42) were investigated. Diffusion tensor imaging (DTI) was used to assess axonal injury across all patients using tract-based spatial statistics (TBSS).

68% of patients showed evidence of behavioural abnormality on the FrSBe. I found a clear relationship between patterns of frontal focal injury and abnormalities on the FrSBe.

However, patients without these focal injuries showed similar levels of dysexecutive behaviour. Similar effect sizes were seen for reduced FA across multiple tracts of interest in both patient groups compared to controls. Despite reduced FA in non-lesion TBI patients, a clear relationship between FA and FrSBe was not seen.

Moderate-severe TBI patients with and without focal lesions demonstrate similar levels of cognitive and dysexecutive impairment on a range of neuropsychological tests. The presence of extensive DTI abnormalities in both lesion and non-lesion groups supports the possibility that the presence of frontal lobe focal injury may not be the key pathology causing dysexecutive behavioural problems, and that the presence of focal injury may be a general marker of injury severity. One possible explanation for behavioural abnormalities in both groups is the presence of DAI that can co-exist with focal injury or be present independently.

3.2 Background

Following a traumatic brain injury (TBI), patients and caregivers commonly report disruption to executive processes including problems with inhibition, processing speed, and metacognition, as well as signs of apathy (Beer et al., 2006; Malloy et al., 1993; Stuss & Alexander, 2007). These impairments can have major implications for interpersonal relationships and return to work, impacting patients' well-being and quality of life (Formisano et al., 2017).

Disruptions to normal executive functions are often thought to stem from impairments to "frontal systems". The quintessential case of frontal systems impairment in TBI described in classical neuroscience is that of Phineas Gage. Since then, distinct behaviours have been

attributed to frontal lobe functioning (Damasio et al., 1996; J. Grace et al., 1999; Tim Shallice et al., 2008b), usually taking the form of case studies or analyses on small patient samples.

More recent work has focused on the role of frontal lobe focal lesions in larger patient groups, showing that TBI patients with lesions demonstrate impairments in executive functioning measures such as task switching, relative to controls (Baldo et al., 2001; Tim Shallice et al., 2008a). Neuropsychological assessments have been developed to measure levels of impairments relating specifically to frontal dysfunction. However, there remains a debate as to whether such impairments truly reflect the existence of a frontal system, or rather domain-general processes that involve the frontal lobes (Stuss, 2011; Stuss & Alexander, 2007). With larger sample sizes, we have been able to move away from lesion case studies and towards more technically sophisticated analyses, such as voxel-based lesion-symptom mapping (VLSM). This approach has been widely used in the stroke literature (Forkel & Catani, 2018; Meyer et al., 2016; Robinson et al., 2015; Schwartz et al., 2009). The largest VLSM studies in TBI are based on CT scans of combat veterans, and demonstrate that the presence of focal lesions may cause frontal circuit impairments that in turn associate with emotional processing deficits (Dal Monte et al., 2013; Driscoll et al., 2012). Correlations of focal lesion locations with neuropsychological assessments have also emphasised the role of specific anatomical areas in relation to these tests (Bates et al., 2003). However, without comparing performance on neuropsychological assessments to similar TBI patients without frontal lobe lesions, inference of the relative involvements of these regions is challenging. Indeed, in the absence of focal lesions, dysexecutive behaviours can still be seen following moderate-severe TBI (De Simoni et al., 2018) and mild TBI (Ozen & Fernandes, 2012),

suggesting that their importance is likely embedded within more extensive functional networks.

In some cases, patients are deemed to have good outcomes when assessed solely in terms of cognitive assessments of memory and processing speed after frontal lobe focal injuries. However, many patients performing within normal levels across cognitive domains may still face behavioural problems such as subtle impairments of social cognitive processes (Cicerone & Tanenbaum, 1997), which can ultimately lead to poor functional outcomes. Successful functional outcomes such as return to work or community reintegration are, therefore, critical metrics upon which to judge interventions following TBI. Previous research has shown that the Frontal Systems Behaviour Rating Scale (FrSBe) may be a better predictor of community reintegration following TBI than other measures of executive function (Reid-Arndt et al., 2007). The FrSBe, described in further detail in subsequent sections, is a behavioural rating scale that is filled out by either patients and their caregivers, or both. While demonstrated to be a useful tool, this scale measures behaviours that are often accepted to relate to frontal functioning, without much investigation of the neural correlates.

Neuroimaging techniques such as diffusion tensor imaging (DTI) may prove particularly beneficial in assessing cases where focal lesions may not be present. DTI has been demonstrated to be a useful tool to examine brain structure in relation to performance on neuropsychological measures and behaviour (Kinnunen et al., 2011). Such metrics provide insight into microstructural damage, thought to be related to DAI (Ghajari et al., 2017). DTI analysis has the added benefit of being an operator-independent assessment. Without this assumption of knowledge regarding the location of the injury, DTI has consistently shown widespread damage in TBI patients (Zappalà et al., 2012).

In this chapter, I aimed to examine the relationship of characteristic symptoms of dysexecutive behaviour with focal lesions and white matter damage in a large cohort of TBI patients. VLSM was used to correlate dysexecutive behaviour with lesion location. Further analysis was conducted to compare these lesion patients to a group of moderate-severe TBI patients without focal lesions. I hypothesised that in the absence of focal lesions, patients would show impairment on neuropsychological measures of dysexecutive behaviour. These non-lesion TBI patients would show damage to white matter tracts, indicative of DAI.

I investigated the following hypothesis:

- Location of focal frontal lesions are associate with elevated scores of dysexecutive behaviour;
- TBI patients classified as moderate-severe without focal frontal lesions will show similar levels of dysexecutive behaviour to patients with focal lesions;
- Widespread diffuse axonal injury will be present in patients with and without focal lesions, which will be related to dysexecutive behaviour.

3.3 Methods

3.3.1 Participant details

One hundred and two TBI patients with focal lesions [41.75(13), 21 female] and forty-two TBI patients without focal lesions [40.5(11.43), 12 female] were recruited through neurology outpatient clinics for on-going cognitive complaints. All patients were assessed as moderate-severe according to the Mayo Classification (Malec et al., 2007). This classification considers neuroimaging findings, lowest Glasgow Coma Scale score, duration of loss of consciousness, and post-traumatic amnesia. Patients were excluded based on prior history of neurological or psychological complaints or contraindication to MRI. Fifty-nine controls [41.42(12.7), 21

female] with no previous neurological or psychiatric health issues were recruited. All participants gave written informed consent. This was a legacy analysis combining TBI patients from several studies conducted in the TBI research group at Imperial College London.

3.3.2 Neuropsychological assessment

Frontal systems behaviour

The Frontal Systems Behaviour Scale (FrSBe) is commonly used in patients to evaluate subjective and objective changes in behaviour post-injury (Janet Grace & Malloy, 2001). This measure consists of a 46-item 5 point Likert scale, administered to patients and a close family member or friend. It divides up into subscales consisting of disinhibition, apathy and executive dysfunction. A normalised T-score of >65 is considered clinical impairment, while 60-64 is rated as borderline impairment. The executive dysfunction subscale indicates if an individual has difficulty with self-monitoring, mental flexibility, planning, and organisation. These may have an impact on task performance and have detrimental effects on behavioural adjustments based on real-time feedback from others (Janet Grace & Malloy, 2001).

Cognitive tests

Additional cognitive tests were run as part of a neuropsychological battery. This battery was designed to evaluate processing speed and executive function, measured by a computerised choice reaction time task (CRT), switch cost from the trail-making task (executive function), and the Delis-Kaplan Executive Function System (D-KEFS) Colour-Word Interference Test (Stroop) (Delis et al., 2001).

3.3.3 Image acquisition

Participants had high-resolution structural T1-weighted MPRAGE, fluid attenuated inversion recovery (FLAIR), and diffusion-weighted imaging (DWI). These were performed across two scanners; A Philips Intera 3T, and a 3T Siemens Magnetom Verio Syngo, using a 32-channel head coil. Physics parameters are addressed in more detail in general methods A consultant neuroradiologist reported all structural scans.

3.3.4 Lesion mapping

Semi-automated lesion segmentation, which combines high-resolution T1 and FLAIR imaging modalities, was conducted using ImSeg v1.8. Segmentation is based on an algorithm for geodesic image segmentation (Criminisi et al., 2008). These were reviewed by an experienced neurologist and revised where necessary. These lesion masks were drawn in the native T1 space and then normalised to MNI152 1mm standard space using advanced normalisation tools (ANTS) (Avants et al., 2011). Probability distribution maps and estimation of lesion volume were calculated with the FMRIB Software Library (FSL) (Jenkinson et al., 2012; Smith et al., 2004). For the primary analysis, VLSM was implemented with the non-parametric mapping toolbox in MRIcron (Rorden et al., 2007).

3.3.5 Lesion symptom mapping statistical analysis

The non-parametric mapping toolbox within MRIcron was used for VLSM. I investigated the relationship of lesions in a substantial cohort of TBI patients to a continuous measurement of behavioural functioning. The analysis was run on voxels damaged in at least 10% of the cohort using the Brunner and Munzel test with 4,000 permutations (Medina et al., 2010). Results reported are corrected for multiple comparisons with a false discovery rate (FDR) $p<0.05$.

3.3.6 Exploratory disconnectome analysis

The probability of disconnection was calculated for each lesion using the 'disconnectome map' tool from the BCBToolkit (de Schotten et al., 2020). This toolbox uses FSL native commands. Each lesion was used as a seed region in a cohort of 10 controls from the human connectome project using TrackVis. Each of the lesion tract projections derived were binarised and averaged together so that each voxel represented a probability of disconnection from 0-1. ROI tracts were based on the ICBM-81-DTI white matter atlas (Oishi et al., 2008).

3.3.7 Diffusion processing and analysis

Voxelwise analysis of white matter structure was conducted following the TBSS pipeline in FSL (Smith et al., 2004, 2006). This image analysis pipeline followed a number of steps: i) Correction of eddy current distortion; ii) fitting of diffusion tensors; iii) Registration of all images to standard MNI152 1mm space; iv) Generation of mean FA image and thresholded FA skeleton ($\geq$0.2) of white matter to remove areas of very low FA; v) Non-parametric permutation testing (10,000) with voxelwise regression of lesions. Results reported are corrected for multiple comparisons at a threshold of $p<0.05$, with age and scanner included as nuisance covariates. Predetermined tracts were selected as regions of interest (ROI) based on the ICBM-81-DTI white matter atlas, using prior work to identify regions of high test-retest reliability and sensitivity for identifying abnormality in TBI patients (Jolly et al., 2020).

3.3.8 Neuropsychology analysis

Statistical analysis of summary measures derived from neuroimaging measures and behavioural performance were analysed in the open-source software package R (R Core Team, 2018; http://www.R-project.org/). Group differences in performance were investigated

with analysis of variance using Tukey multiple comparisons of means 95% family-wise confidence level.

3.4 Results

3.4.1 Voxel-based lesion-symptom mapping

102 patients [mean age = 42.08(12.91), mean age at injury = 34.45(13.71)]. Median lesion volume 17,260mm^3 (IQR: 2,465 mm^3 – 36,150 mm^3). Independent of the mechanism of injury (Assault = 19, RTA = 43, Fall = 20, Sport = 1, Other unintentional injury = 2, Unknown = 17) the burden of focal lesions were primarily seen in the prefrontal cortex and temporal poles (Figure 5).

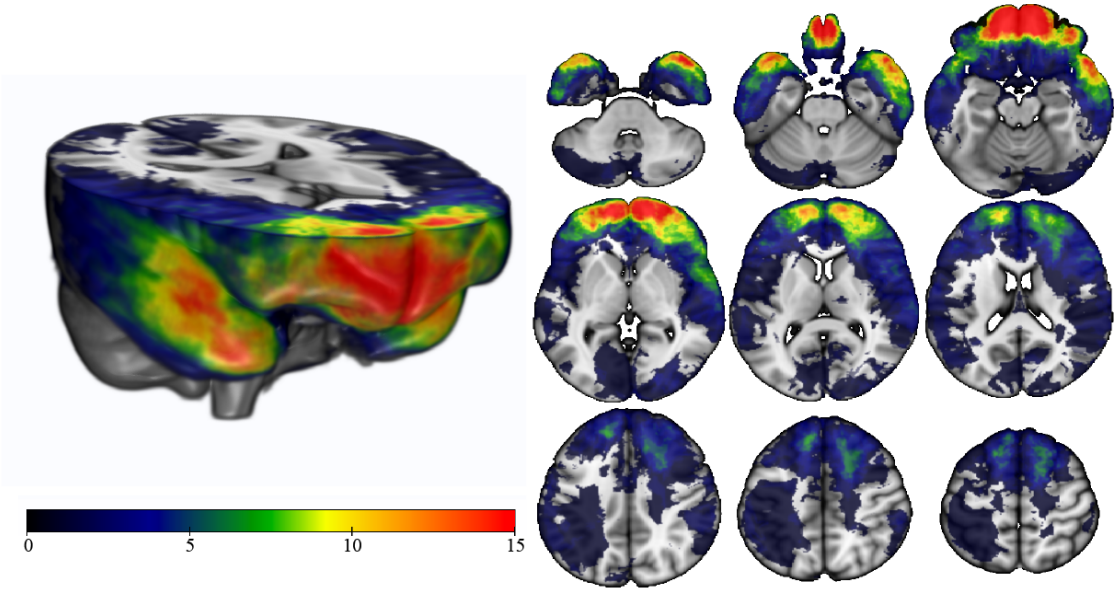


Figure 5: Frequency distribution map of lesion burden across 102 TBI patients with one or more lesions

The Frontal Systems Behavioural Rating Scale (FrSBe) was used as a continuous measure of "frontal" dysexecutive behaviour, reported by both patients and caregivers. Caregivers and patients reported similar levels of function before injury: Caregiver = 54.57(10.95), TBI = 53.15(11.67).

VLSM results indicate that self-reported total scores on the FrSBe are significantly related to right inferior frontal lobe and right superior temporal gyrus damage. Results displayed are set at a threshold between 1.5-3.0 standard deviations. VLSM analysis was also conducted for objective measures of executive functioning, including switch cost from the trail making test (B - A). Results were seen bilaterally in the medial frontal cortex, extending to a greater extent in the left cortex. The DKEFS Stroop inhibition time was associated with bilateral temporal pole and inferior orbitofrontal cortex damage (Figure 6).

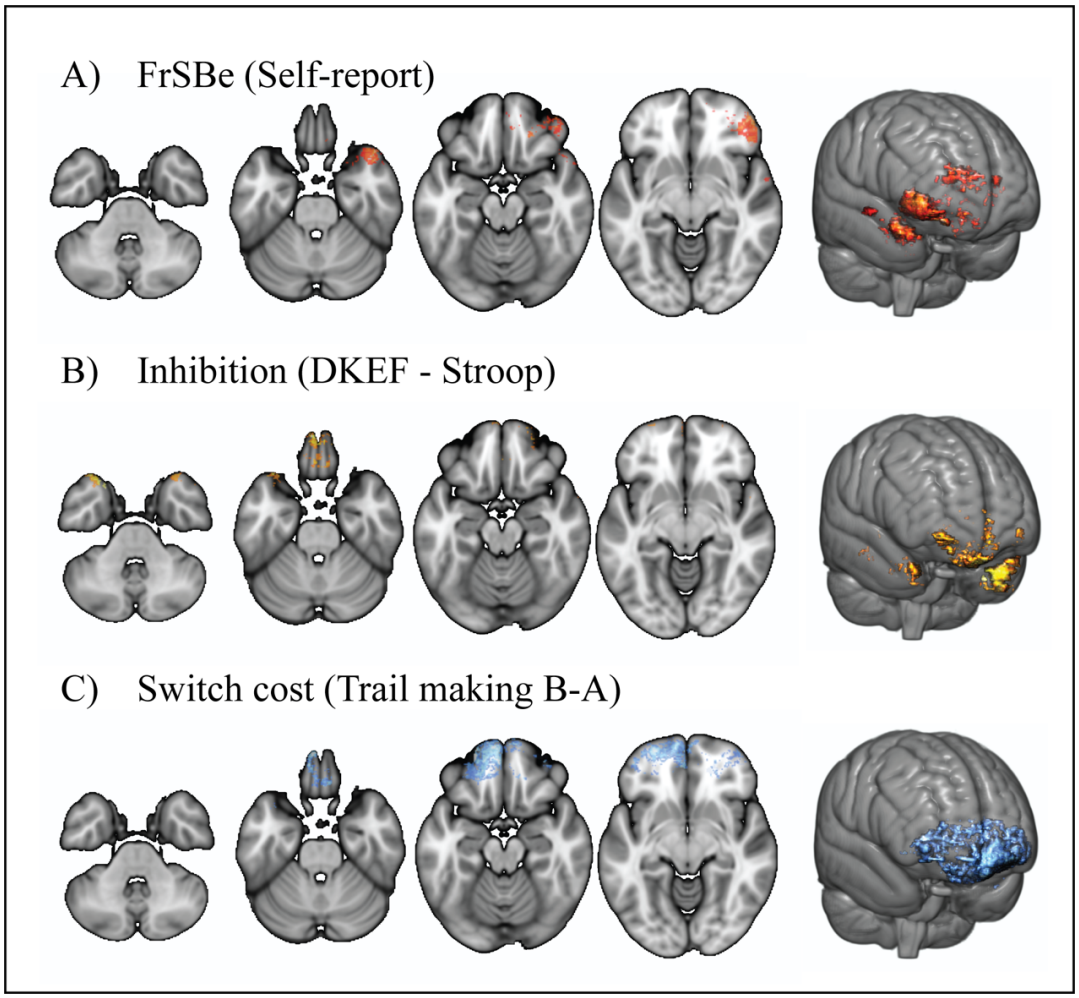


Figure 6: Voxel-based lesion-symptom mapping of 102 TBI patients on measures of executive functioning.

Corrected for multiple comparisons (FDR; $p<0.05$). Set at a threshold to only show voxels with z-scores greater than 1.5

Additional analysis looked at the three subscales from the FrSBe: apathy, disinhibition, and dysexecutive behaviour. All subscales of the FrSbe were lateralised, with a high spatial overlap in the right inferior frontal lobe. Apathy was significantly related to damage involving the superior temporal gyrus, while disinhibition was significantly associated with injury in the inferior MPFC (Figure 7).

Maintaining strict statistical thresholds, analysis was repeated for caregiver reports in a subset of patients (n=68). However, this was below the recommended sample size, and failed to pick up an effect.

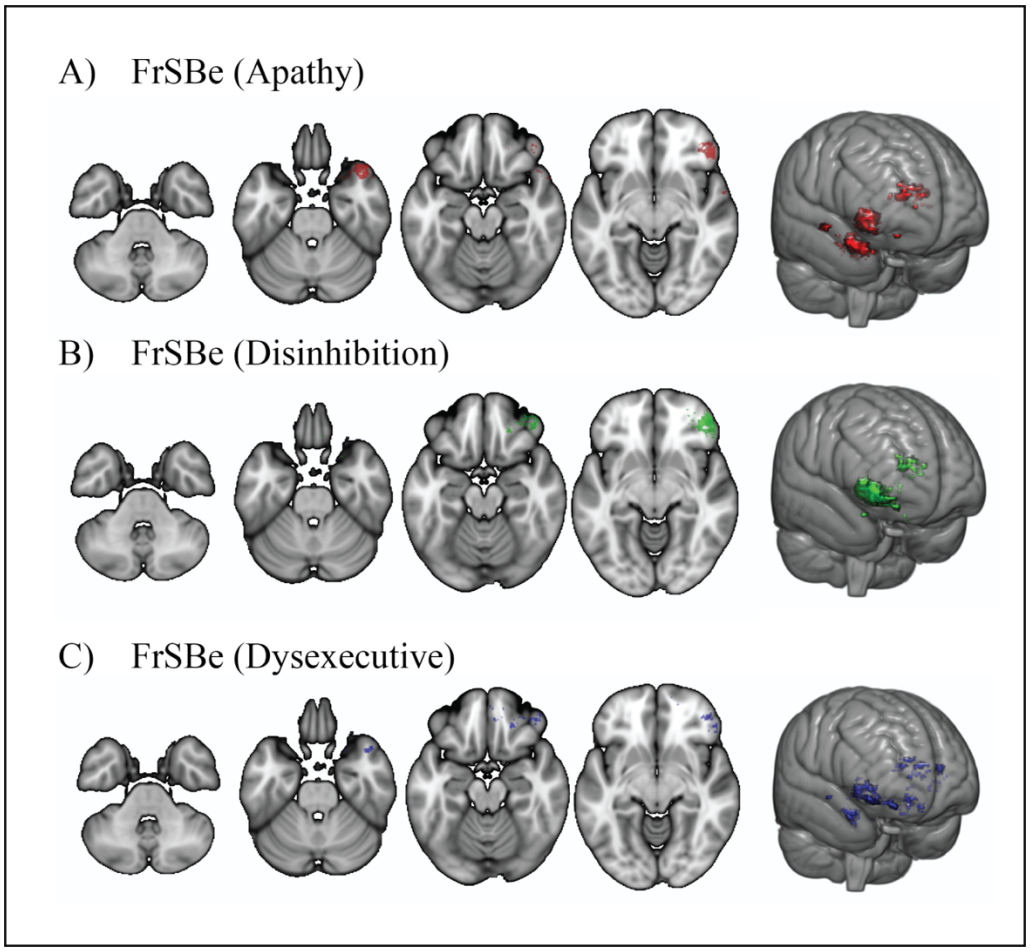


Figure 7: Voxel-based lesion-symptom mapping of 102 TBI patients with the Frontal Systems Behavioural Rating Scale (FrSBe)

Corrected for multiple comparisons (FDR; $p<0.05$). Set at a threshold to only show voxels with z-scores greater than 1.5

3.4.2 Lesion and non-lesion moderate-severe TBI patients have similar neuropsychology performance

To assess the specificity of lesion contribution to behavioural results, neuropsychological assessments of patients with lesions were compared to a group of patients without lesions using Tukey multiple comparisons of means (95% family-wise confidence level). Based on thresholds set on normalised T-scores for the FrSBe, clinical impairment was seen in 68% of both lesion and non-lesion TBI patients. Normalised T-scores for the FrSBe can be broken down to 54% clinical impairment for the lesion group and 13% for borderline clinical impairment. In the non-lesion TBI group, this was 42% clinical impairment and 26% borderline impairment. These figures reflect a non-significant difference in the FrSBe between the lesion and non-lesion patients, rejecting the hypothesis that focal lesions in the frontal lobe drive behavioural abnormalities in this patient group. Additional tests of executive functioning were carried out, including in a healthy control group. Both moderate-severe TBI patients with and without lesions performed significantly worse than controls. However, across multiple cognitive domains, no significant difference was found between moderate-severe TBI patients based on the presence of focal lesions (Table 2)

Table 2: **Analysis of variance of neuropsychology domains across the lesion and non-lesion TBI patients and controls.**

Analysis of variance (ANOVA) was conducted with Bonferroni multiple comparison correction between all pairwise means. FrSBe = Frontal Systems Behavioural Rating Scale; CRT = Choice reaction time; RT = Reaction time; s = seconds.

Domain	Neuropsychological Test	Healthy Controls Mean (+/- SD)	TBI: Lesion Patients Mean (+/- SD)	TBI: No Lesions Mean (+/- SD)	Lesion vs. Control	No Lesion vs. Control	Lesion vs. No Lesion Patient
Behavioural report	FrSBe: Self Total Now	-	68.35(15.84)	67.05(14.51)	-	-	0.65
(Tscore)	FrSBe: Other Total Now	-	65.74(17.07)	65.75(17.18)	-	-	0.99
	FrSBe: Self Apathy	-	71.15(20.22)	68.19(18.8)	-	-	0.42
	FrSBe: Self Dysexecutive	-	73.09(19.16)	73.71(17.26)	-	-	0.85
	FrSBe: Self Disinhibition	-	62.85(14.36)	62.40(15.5)	-	-	0.87
Processing speed	Trail Making Test A (s)	21.33(9.04)	31.67(14.26)	29.04(11.22)	<0.001	<0.01	0.48
	Trail Making Test B (s)	48.63(24.37)	71.56(36.76)	65.65(30.87)	<0.001	0.02	0.59
	Stroop Colour Naming & Word Reading Composite Score (s)	33.6 (8.0)	39.25 (10.98)	36.89(9.11)	<0.001	0.22	0.39
	CRT Median RT (s)	0.41(0.07)	0.44(0.08)	0.45(0.07)	0.009	0.03	0.98
Executive Function	Trail Making Test B-A (s)	26.97(19.1)	40.04(29.49)	36.94(23.29)	0.005	0.13	0.79
	Stroop Inhibition (s)	47.04 (17.9)	60.3 (17.8)	58.9 (15.66)	<0.001	0.002	0.91
	Stroop Inhibition-Switching (s)	55.8 (15.2)	71.2(19.24)	69.9(19.53)	<0.001	<0.001	0.92
	Stroop Inhibition-Switching vs. Baseline Contrast (s)	29.6(18.33)	36.0(19.02)	37.1 (20.04)	0.10	0.13	0.95

3.4.3 Exploring a disconnectome

An exploratory analysis was conducted to identify tracts most likely to be disconnected following a focal lesion following TBI. Disconnection is defined here as a tract which is directly connected to the site of the focal lesion. Regions with the highest probability of disconnection (> 50%) include the genu of the corpus callosum, bilateral anterior corona radiata, inferior fronto-occipital and thalamic projections.

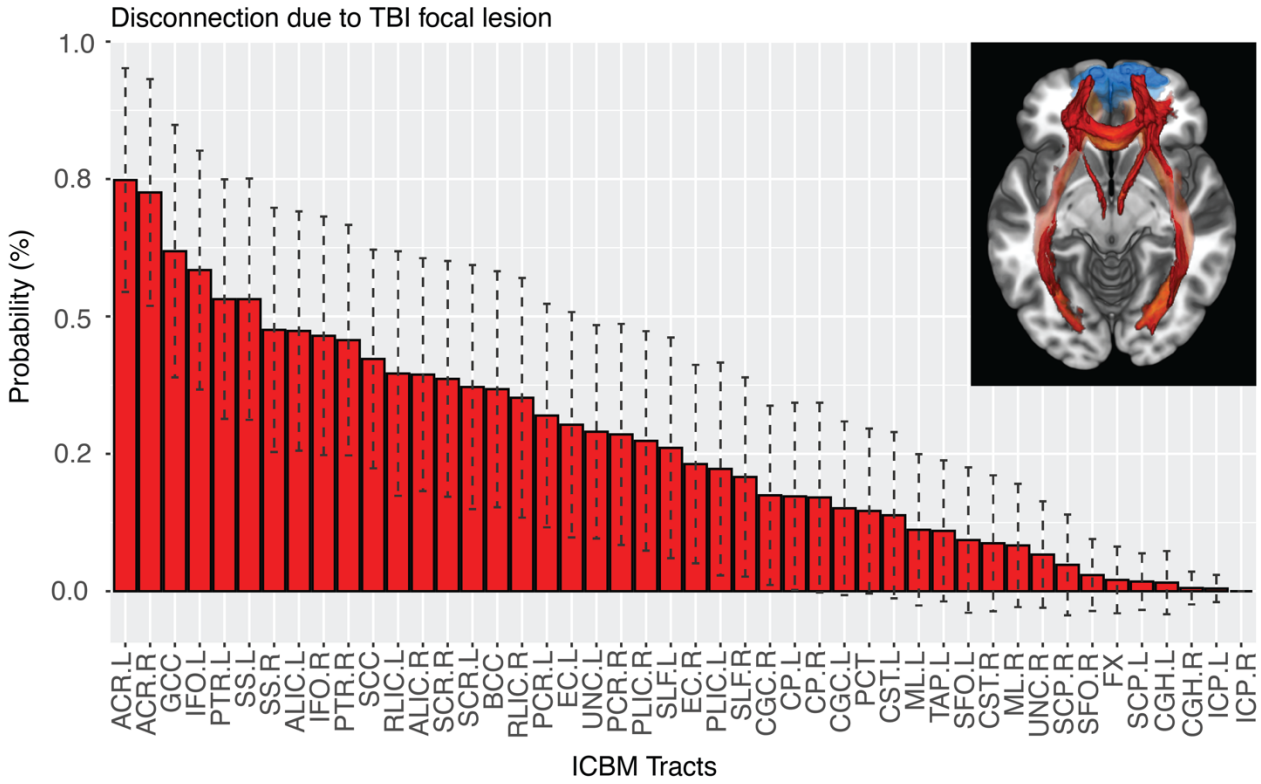


Figure 8: White matter tracts with the highest probability of disconnection following focal lesion in TBI patients.

A sample of 102 TBI patients with focal lesions. A | Probability of tract being disconnected due to the presence of a focal lesion. B | Blue: Region of highest lesion probability in TBI patients. Red: tracts disconnected due to focal lesion (threshold: >50%), indicating widespread network disruption distal to the site of the lesion.

3.4.4 Diffusion analysis

Levels of white matter damage were similar across both lesion and non-lesion moderate-severe TBI patients. A voxel-wise analysis was conducted, regressing out the effects of individual participants' lesions to examine the relative contributions of group differences between the lesion and non-lesion patients. Compared to controls, widespread decreases can be seen across the whole brain white matter skeleton for TBI patients with focal lesions. To a lesser extent, similar widespread reductions are seen with non-lesion TBI patients compared with controls. As previously indicated with the lesion probability distribution map, an examination of the lesion and non-lesion patients shows that tracts in the anterior part of the brain are more susceptible to focal damage. Interestingly, little difference can be seen

between lesion and non-lesion TBI patients across the majority of the white matter tracts. This is in line with my findings from the neuropsychological examination, where both lesion and non-lesion patients are impaired relative to controls but show little difference between each other (Table 2).

Effect sizes are displayed for both patient groups compared to controls across a range of white matter tracts (Figure 9). These effects were calculated using Cohen's d, a normalised score comparing the mean difference and standard deviation of the patient group to controls. Results were mostly similar across both lesion and non-lesion patients. Following a voxelwise regression of individual lesions, the genu of the corpus callosum was the only ROI that showed a distinction between the lesion and non-lesion TBI groups. Non-significant effects were observed in the corticospinal tracts for lesion patients compared to controls, while a small to moderate effect size was seen in non-lesion patients for the same region. The superior longitudinal fasciculi were the least sensitive tracts of interest for effects across both lesion and non-lesion patient groups compared to controls.

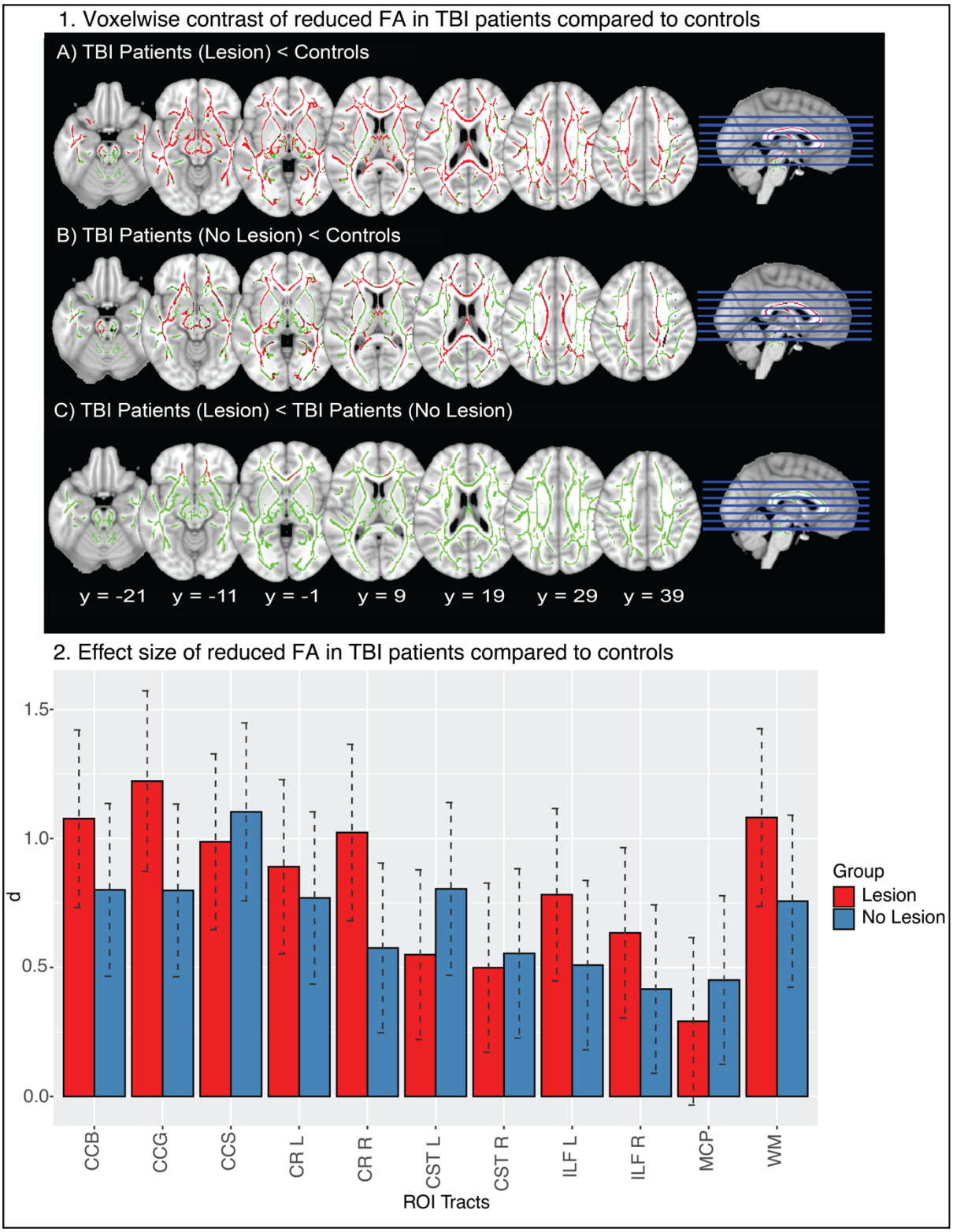


Figure 9: Voxelwise comparison of FA between lesion and non-lesion TBI patients and healthy controls

1 | The results of an ANOVA investigating FA changes across lesion, non-lesion, and control groups, controlling for scanner effects. Red indicates regions of significantly lower FA across group comparisons. The comparison of the lesion and non-lesion TBI patients included voxel-wise regression of the effects from individual lesions. 2 | Effect sizes of reduced FA across white matter tracts of interest for lesion and non-lesion TBI patients compared to controls.

3.4.5 Relationship between disconnection and cognitive neuropsychological measures

No relationship is seen between the Stroop or trail making task and any of the tracts identified as likely candidates for disconnection. There is a significant relationship between the FrSBe self-total now and the left anterior corona radiata ($r = 0.3$, $p_{unc} = 0.006$), the genu of the corpus callosum ($r = 0.2$, $p_{unc} = 0.02$), left inferior frontal-occipital ($r = 0.2$, $p_{unc} = 0.03$). Following Bonferroni correction only the relationship with the left anterior cornona radiata survives ($p < 0.03$), indicating increasing behavioural symptoms with increased probability of disconnection of this tract.

3.4.6 Relationship of Frontal systems behaviour with diffusion measures

Contrasting lesion and non-lesion TBI patients, no significant group differences were found with a voxelwise analysis of FA in relation to the FrSBe self-report total. A higher total score as reported by caregivers was correlated with lower FA in the posterior section of the inferior longitudinal fasciculus at the intersection of the posterior thalamic radiation.

A discrepancy score between caregiver and patient was calculated by subtracting patients' self-report from caregiver assessment, as a measure of metacognition. A significant negative main effect was found in the body of the corpus callosum, with caregivers reporting more impairments compared to patients (Figure 10).

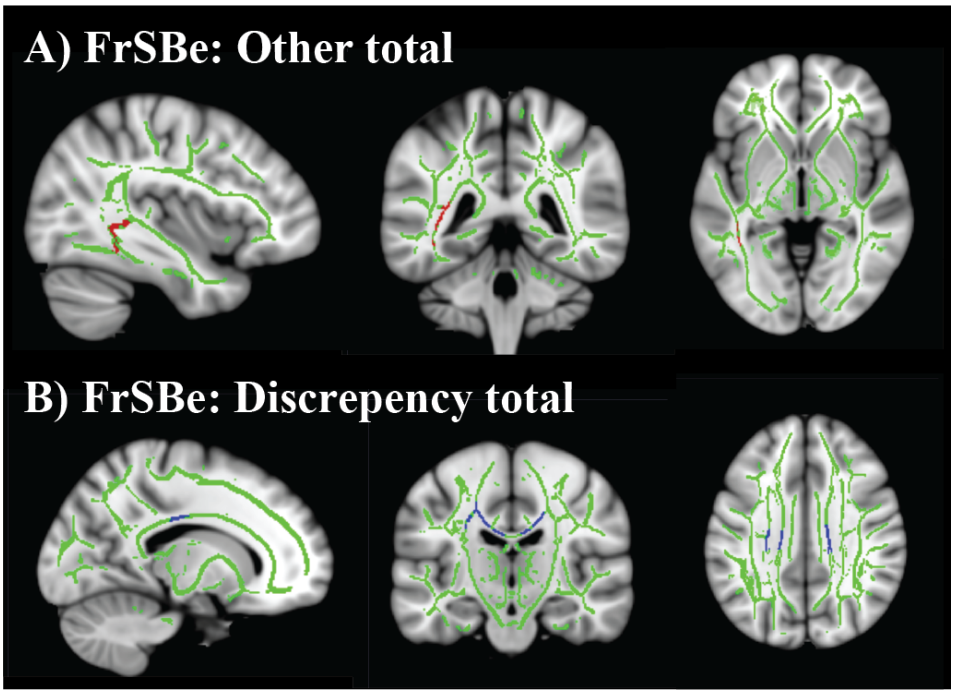


Figure 10: Main effects of voxelwise FA results for FrSBe

A | FrSBe caregiver total; red indicates regions of higher reported symptoms, corresponding to lower FA. B | FrSBe discrepency score (caregiver reporting more symptoms compared to patients), where blue indicates an association with lower FA.

3.4.7 Relationship between FA and cognitive neuropsychological measures

The analysis was extended to include objective measures of executive functioning and processing speed to investigate potential differences between the lesion and non-lesion moderate-severe TBI patients. No effects between inhibition (DKEFS-Stroop), switch-cost (Trails B-A), or processing speed (CRT) were observed with FA.

3.5 Discussion

The understanding of factors affecting functional outcomes of TBI patients is essential in order to inform optimal investigations and interventions in a clinical context. Here I focus on executive behaviour commonly attributed to frontal lobe function. In a large cohort, I explore the relationship of these behaviours with patients that have focal lesions and further contrast that to moderate-severe TBI patients without visible focal lesions. This combination of voxel-based symptom lesion mapping, diffusion analysis, and examination of executive functioning is a novel approach to the examination of moderate-severe TBI patients. Using this approach, I first demonstrate a relationship between frontal lesions and behavioural traits assessed by widely used and validated neuropsychological instruments. In particular, these results highlight the importance of the right inferior frontal lobe and right temporal pole in effective executive functioning.

While relationships between dysexecutive behavioural traits and frontal lobe functioning have previously been reported and used as evidence to support the "frontal" nature of TBI, this notion has largely been established through case studies and small samples. I conducted an exploratory disconnectome analysis to investigate which white matter tracts may be commonly affected distal to site of focal lesions, and if these could in turn explain behavioural performance in non-lesion TBI patients. Results from this exploratory analysis highlight several tracts most likely affected by disconnection, as well as a relationship between damage to the left anterior corona radiata, that survives correction for multiple comparisons. I further revisit this hypothesis of 'frontal' symptoms by contrasting results from lesion and non-lesion patients of moderate-severe TBI, showing that similar behavioural problems may present even in the absence of visible focal lesions in the frontal lobes. When analysed in conjunction with FA measurements, results from non-lesion TBI patients

indicated similarly widespread white matter disruption to those with focal lesions. Voxelwise correlations were seen between white matter structure and the FrSBe, However, despite clear FA reductions in non-lesion TBI patients, this did not fully account for observed behavioural impairments in this group.

Lesion-symptom mapping has been used as a method to explain brain function long before the current statistical approaches were available. The historical approach would infer that region X was responsible for a particular behaviour Y if, after damage to region X, Y could no longer be performed. VLSM improves on this case study approach by examining continuous behavioural scores on a voxel-by-voxel basis across patients. This work could be further developed with consideration of a connectome-based lesion-symptom mapping approach (Gleichgerrcht et al., 2017). In the case of TBI where damage is likely to extend beyond apparent lesions (e.g. diffuse axonal injury), interpretations must consider alternative explanations for symptom presentation, such as widespread network damage from subtle microstructural damage to white matter or neurotransmitter dysfunction.

Given the bilateral distribution of injury (Figure 5), behavioural impairments measured by the FrSBe appear to be associated with lesions lateralised to the right. This is consistent with previous work on executive function, specifically in an objective task of inhibition that highlighted the role of the right inferior frontal gyrus in task performance (Hampshire et al., 2011). Results from the trail making test were seen bilaterally in the frontal poles, extending over a larger area of the left medial frontal cortex in particular. This observation is also in line with previous literature (Varjacic et al., 2018).

A fundamental limitation of VLSM is a bias towards higher power in regions with greater lesion overlay, which is mainly the case in smaller sample sizes. In response to this, several

features have been recommended to address the limitations of previous lesion mapping studies, and include a requirement of larger sample sizes, along with more rigorous analysis. Following recommendations (Kimberg et al., 2007; Medina et al., 2010; Rorden et al., 2007; Seifert et al., 2016), the Brunner-Munzel test statistic was used here, alongside a lower limit for damaged voxels, and a non-parametric permutation testing approach, as adapted from fMRI analysis. This more rigorous approach to lesion mapping minimises type 1 error and can provide more robust insight into brain structure and function.

Diffuse axonal injury is a widely accepted facet of TBI, occurring as excessive shearing forces are applied to tissues, resulting in high strain rates (Ghajari et al., 2017). This can happen in the absence of focal lesions, yet result in a similar clinical profile of behavioural and cognitive impairment. I hypothesised that lesion location would be related to neuropsychological measures of executive functioning. In the absence of visible damage on high-resolution structural MRI scans, I hypothesised that TBI patients would present with widespread white matter abnormalities which would in turn correlate with behavioural impairments.

Both lesion and non-lesion TBI patients showed significant reductions in FA compared to healthy controls. Contrasting lesion and non-lesion moderate-severe TBI patients showed little difference between groups. While widespread decreases in FA were seen for both lesion and non-lesion TBI patients, no significant relationships were seen with the cognitive assessments when accounting for effects of age and scanner. A main effect was seen with reduced FA and a higher FrSBe caregiver total in the right temporal-parietal junction, previously identified as a critical region for theory of mind (R. Saxe & Kanwisher, 2003). The body of the corpus callosum also showed reduced FA, correlated with increased

discrepancy between patients and caregivers. Here, caregivers rated executive problems more highly than patients did in their self-reports.

The focus of this work was to examine the link of "frontal behaviours" from a well-established neuropsychology measure, the FsBe and TBI lesions. This included additional objective assessments of executive functioning associated with frontal lobe functioning, where the highest lesion burden is seen. Given the prevalence to which temporal poles are also affected by lesions following TBI, further work could focus on assessments of memory. This was not feasible in the current work as consistent assessments of memory function were not available in the current legacy analysis. It would be hypothesised that temporal pole lesions would be associated with impaired memory functioning.

Multi-centre imaging comes with the issue of scanner variability when conducting quantitative analysis such as DTI. Scanner effects were therefore included as a factor in my voxelwise diffusion analysis to account for this variability. While the primary outcome measure (FrSBe) has been well validated, I attempted to address the limitation of the self-report format by supplementing it with responses from caregivers.

The frontal and anterior temporal lobes are evidently susceptible to damage following TBI. Models of frontal lobe function have been used to investigate behaviour (Stuss, 2011). Considering that no behavioural differences were observed between moderate-severe TBI patients with and without focal lesions, these models may be insufficient to explain behaviour. Instead, disconnection of distal anatomical regions from the site of focal injuries or the presence of diffuse axonal injury following TBI may contribute to observed behaviour. The exploratory analysis of disconnection in the current work illustrates the broader effects of

communication on regions distal from the site of a lesion. This disconnectome approach is quickly gaining traction, and can be further developed (de Schotten et al., 2020; Foulon et al., 2018). In a similar vein, the incorporation of other modalities such as resting-state fMRI would allow the investigation of functional dysconnectivity based on focal lesions. This may be approached using constrained ICA on a lesion probability distribution, much like the one presented here; this would generate functional components that can be back-projected onto a group of healthy independent controls to derive functional networks. In theory, these functional components could be used to identify probable functional disconnection due to lesion location.

Behavioural impairments can stem from a variety of causes, particularly following TBI. Issues we need to consider are how behavioural impairments may manifest from disruption to a complex neural system through focal lesions, abnormalities in white matter microstructure, or disruption to the dopaminergic system. While measures of dopamine are not discussed in this analysis, we have previously shown disruption to the dopaminergic system following TBI and its relationship with independent measures of self and caregiver reports of apathy (Jenkins et al., 2019). Dopamine modulates cognitive performance and behaviour that is typically represented by the frontal lobes (Frank & O'Reilly, 2006). Metrics from each of these potential pathological mechanisms may show correlates to important functional outcome measures. Focal lesions to the RIFG may cause difficulties with inhibition or produce apathetic behaviour, as may disruption to projections from the dopaminergic system or white matter tracts to the same region (De Simoni et al., 2018).

3.6 Conclusion

While lesion location can inform us of regions important for particular behaviours, these should be considered as nodes within a network. Beyond focal lesions, other mechanisms of damage such as disruptions to white matter connections are common in TBI patients. Results from a combined approach utilising VLSM and diffusion analysis indicate the need to consider different mechanisms that may contribute to varied patterns of structural damage, ultimately resulting in similar behaviour phenotypes. Future studies may benefit from a multimodal approach incorporating functional imaging to look at the structural and functional disconnectome in an attempt to understand the complex nature of behavioural impairment following TBI.

Chapter 4 | Differentiating features of white matter damage following traumatic brain injury: a comparison of neurite density, orientation dispersion, DTI, and volumetric alterations

In this chapter, I look at various measures for assessing white matter microstructure, including metrics from multi-shell diffusion imaging, conventional DTI measures, and volume. These are looked at with respect to cognitive performance following TBI.

4.1 Abstract

Cognitive impairment following traumatic brain injury (TBI) remains hard to predict. This is partly because axonal injury, which is of fundamental importance, is difficult to measure clinically. Advances in magnetic resonance imaging (MRI) allow axonal injury to be detected after TBI, but the breadth of tools available in this field can render the most sensitive approach to take unclear. Here I compare the performance of diffusion tensor imaging (DTI), neurite orientation dispersion and density-imaging (NODDI), and volumetric measures of brain atrophy in the identification of white matter abnormalities after TBI.

Thirty patients in the chronic phase of moderate-severe TBI and twenty-one age-matched controls underwent T1-weighted and diffusion MRI. Neuropsychological tests of processing speed, executive functioning and memory were used to detect cognitive impairment.

Using NODDI, extensive abnormalities in neurite density index (NDI) and orientation dispersion index (ODI) were observed, each with distinct spatial patterns. From DTI results, fractional anisotropy (FA) and mean diffusivity (MD) also indicated widespread abnormalities of white matter structure. Processing speed was significantly correlated with NDI; slower processing speed was also related to higher MD in the cortico-spinal tracts. Lower white matter volumes were seen following brain injury, with larger effect sizes compared to diffusion metrics. However, volume was not sensitive to changes in cognitive performance.

Volume was the most sensitive at detecting change between groups, but was not specific for relationships with cognition. Abnormalities in FA and MD were the most sensitive diffusion measures; however, NDI and ODI may be more spatially specific. Lower NDI may be a useful metric for examining changes in processing speed.

4.2 Background

Outcomes after traumatic brain injury (TBI) are often poor and remain hard to predict, largely because the degree of underlying structural damage can be difficult to determine (Maas et al., 2017). As discussed previously, diffuse axonal injury (DAI) plays a crucial role in the pathophysiology of TBI, but is difficult to measure clinically. Conventional diagnostic imaging approaches often underestimate the severity of DAI, causing diagnostic confusion. Significant advances have been made over the last decade in the use of magnetic resonance imaging (MRI) to quantify post-traumatic axonal injury. Amidst this abundance of new methodology, it is necessary to establish which may be the most appropriate to use for aspects of injury within this clinical population.

Diffusion MRI has been widely used to assess white matter (WM) structure following TBI (Kinnunen et al., 2011; Mac Donald et al., 2007). As the name suggests, diffusion techniques rely on the diffusion properties of water molecules within WM tracts to provide information about its structure. Among these, diffusion tensor imaging (DTI) is most commonly used; this method fits a tensor model at each voxel, allowing the calculation of a range of metrics such as fractional anisotropy (FA), reductions in which are frequently used as a marker of white matter disruption (Mac Donald et al., 2007).

The inherent complexity in tissue microstructure exceeds what a single value measurement from a given voxel can inform (ie. FA; (Jones et al., 2013). FA highlights axon directionality, giving information to map white matter structure (P J Basser & Pierpaoli, 1998; Peter J. Basser & Pierpaoli, 1996). This however comes as a challenge for the interpretation of DTI data as the same finding (ie. FA alterations) can potentially originate from different pathological variations, all arising from traumatic brain injury. For example, a reduction in

FA can be caused by demyelination, edema, inflammation, or increased white matter fiber dispersion. Regions of high crossing fibres also have a lower FA value, which can confound result interpretations even further (Alexander et al., 2007). With advancing multi-shell scanning acquisitions it is proposed this biological complexity associated with white matter damage can be more accurately depicted by the introduction of multi-compartment diffusion models, as these allow a more complex description of the underlying white matter properties. The Neurite Orientation Dispersion and Density Imaging (NODDI) framework (Zhang et al., 2012a) estimates changes in tissue properties with a three compartment model rather than a single tensor. Three components are proposed per voxel: two tissue compartments (intra-cellular and extra-cellular) and a cerebral spinal fluid (CSF) compartment, each providing a signal that can be measured individually. This culminates in greater biophysically meaningful results with *in vivo* imaging (Tariq et al., 2016). This model has recently been applied to a variety of disease states, but as of yet has not been investigated in moderate-severe TBI patients.

Lastly, volume measures are also frequently used when investigating clinical populations. Structural MRI allows the quantification of progressive white matter atrophy in the chronic phase of injury following TBI, providing a sensitive measure of neurodegeneration (James H. Cole et al., 2018). In this population, volumetric measures of white matter structure may be considered a proxy indicator of previous DAI, albeit a somewhat non-specific one.

In this chapter, I conducted a direct comparison of DTI, NODDI, and volumetric measures in the identification of white matter abnormalities after moderate-severe TBI. I tested whether lower NDI and higher ODI are seen in TBI patients compared to healthy controls. I then compared the sensitivity of NODDI metrics to FA, a standard measure of diffusion MRI, and to volumetric measures of white matter structure. I then assessed whether the spatial patterns

of alterations in each of the three modalities are distinct from each other. Finally, I investigated how NODDI metrics relate to cognitive function, and compared their sensitivity for detecting cognitive impairment with that of FA.

4.3 Methods

4.3.1 Study participants

Thirty-one patients with moderate-severe TBI (26 male, mean age ± SD = 38.5 ± 10.1) and 21 age-matched controls (16 male, mean age ± SD = 38 ± 10.5) were recruited. One patient was excluded due to motion artefacts, leaving 30 patients for further analysis. Mechanism of injury varied across participants: Road traffic accident (16), assault (7), falls (5), and other (2). All patients were recruited in the post-acute/chronic phase (median time since injury 34 months, range 6–360 months) and scanned at the Clinical Imaging Facility at Imperial College London. Patients were recruited through specialist TBI outpatient clinics in London or referred from their local brain injury services based on on-going cognitive impairments. Details about consent procedures, injury classification and inclusion criteria were discussed previously in Chapter 2, General Methods. The study was approved by the West London and GTAC NRES Committee (14/LO/0067).

4.3.2 Neuropsychological assessment

Participants completed a standard neuropsychological battery to investigate cognitive domains commonly associated with dysfunction following TBI, selected based on previous work from the TBI research group at Imperial College London (Kinnunen et al., 2011). Specifically, these measures included ones of i) processing speed, measured by a computerised choice reaction time (CRT) task and the baseline verbal recall on the Stroop task; ii) alternating switch cost index, calculated from the trail making task as the difference

between the alternating letters and numbers condition and the numbers only condition; iii) the Delis-Kaplan Executive Function System (D-KEFS) Colour-Word Interference Test (Stroop; Delis et al., 2001); iv) the people subsection of the Doors and People Test for immediate and delayed memory recall (Wechsler, 1945). As intellectual ability diverges from specific cognitive domains and is often spared following TBI, previous findings suggest that estimates of pre-morbid ability can be ascertained through measures of matrix reasoning (Donders et al., 2001).

4.3.3 Image acquisition

MRI was performed on a Siemens Verio 3.0 Tesla scanner using a 32-channel head coil. Each patient had standard high-resolution structural imaging, acquired with the following parameters: T1 MPRAGE (TE = 2.98s, TR = 2.3s, 1 mm isotropic voxel, 256x256 mm FOV, FA = 9, GRAPPA = 2, 5min scanning time), T2 FLAIR (TE = 395ms, TR = 5s, 1 mm isotropic voxel, 250x250 mm FOV, GRAPPA=2, 6min scanning time). For diffusion MRI, the NODDI multi-shell protocol included one shell with 30 gradient directions and $b = 700$ s/mm^2 and another with 60 directions and $b = 2000$ s/mm^2. The protocol also contained 9 images without diffusion weighting ($b = 0$ s/mm^2) and a single reversed-phase encoding image without diffusion weighting. The EPI multiband readout (multiband factor = 3, TE = 105.2ms, TR = 5s) used a matrix size of 128 × 128 over a field of view (FOV) of 256 × 256 mm^2 and slice thickness of 2 mm, resulting in isotropic voxels of 2 mm^3. A total of 66 contiguous slices were acquired for whole-brain coverage. The total scanning time for the NODDI protocol was 10 min. An additional single-shell acquisition (64 directions, $b = 1000$ s/mm^2) was acquired for comparison.

4.3.4 Image processing and analysis

Image processing and analysis were performed using a variety of packages, partially implemented through a NIPYPE (Neuroimaging in python) pipeline to automate the process and ensure reproducibility. A high-level overview of the analysis pipeline can be seen in (Figure 11). NIPYPE is an open-source, community-developed Python project that provides a uniform interface to existing neuroimaging software and facilitates interaction between these packages within a single workflow. The pre-processing NIPYPE pipeline included segmentation of structural T1-weighted data and removal of non-brain voxels using Freesurfer; correction of susceptibility induced distortions, eddy current distortions, and rigid-body head motion in diffusion-MRI data were performed using the tools Topup and Eddy from FSL (Smith et al., 2004; Woolrich et al., 2009). dMRI data were then analysed to extract standard DTI metrics (FA, MD) using the FSL tool DTIFIT (Behrens et al., 2003) from both the multi-shell and single-shell data. NODDI modelling and DTI analysis were run in parallel on the multi-shell DWI. Tensor-based registration using DTI-TK (Zhang et al., 2006) was performed on the processed dMRI data from NIPYPE to generate DTI metrics (FA, MD). Tract Based Spatial Statistics (TBSS) were then performed, as per previous work from our lab (Bonnelle et al., 2012). NODDI modelling was performed using the Accelerated Microstructure Imaging via Convex Optimization (AMICO) framework (Daducci et al., 2015), which accelerates the modelling fit by up to four orders of magnitude by re-formulating the model as a linear system, preserving accuracy and precision in the results. The output of this modelling produces NDI, ODI and ISOVF images which were then moved into the standard space for voxel-wise analysis.

Brain tissue volumes, white matter (WM), grey matter (GM) and intracranial volume (ICV) were computed for each individual using a standard morphometry pipeline on T1-weighted images with SPM (SPM12, University College London, www.fil.ion.ucl.ac.uk/spm), previously described in more detail in (J H Cole et al., 2018).

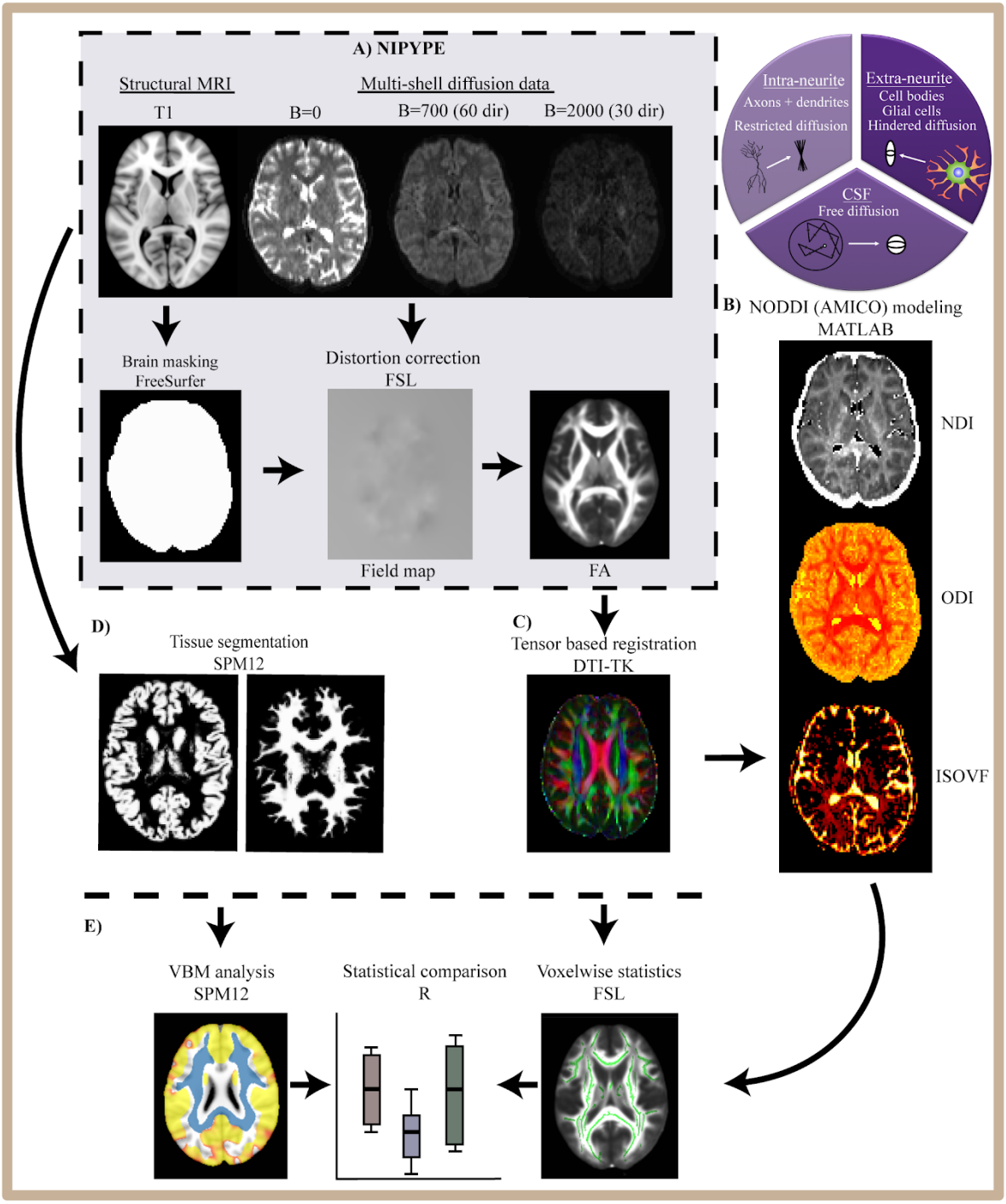


Figure 11: **Neuroimaging analysis pipeline.**

A | An automated NIPYPE pipeline extracted structural and diffusion data from XNAT and ran pre-processing steps, including FreeSurfer segmentation for structural T1 and eddy, topup distortion correction for diffusion-weighted images. Standard DTI metrics are generated with FSL within the NIPYPE framework. B | NODDI modelling of diffusion data was performed using MATLAB. NODDI produces measures of three compartments: intra-neurite (axons and dendrites), characterised by restricted diffusion; extra-neurite (cell bodies and glia), characterised by hindered diffusion, and cerebrospinal fluid (CSF), characterised by free diffusion. C | Registration is performed with DTI-TK. D) Voxel-based morphometry analysis was conducted with SPM12, segmenting T1-weighted images into grey and white matter probability maps. These are normalised and smoothed (8mm). E | Finally, voxel-wise statistical analysis was carried out using FSL TBSS. Summary measures were exported into R for statistical analysis.

4.3.5 Statistical analysis

Voxel-wise analysis of the NODDI metrics (NDI, ODI, ISOVF) and multi-shell derived DTI measures (FA, MD) were performed using TBSS in FSL (Smith et al., 2004, 2006). The mean FA image was constrained to produce a 'skeleton', depicting WM tracts centres and therefore reducing partial-volume confounds. The FA skeleton was subsequently set to a threshold >= 0.2 to suppress regions of extremely low mean FA and remove areas with substantial inter-individual variability. This was saved as a binarised mask for subsequent statistical analysis. Equivalent steps for processing non-FA images were then performed to derive the MD and NODDI images. Independent sample t-tests were run to investigate differences in diffusion metrics between patients and controls. This was done with non-parametric permutation testing (n=10,000) in FSL Randomise (Winkler et al., 2014). A threshold of $P < 0.05$ was then applied on the results after correcting for multiple comparisons. Age, gender, and ICV were included as nuisance regressors in all TBSS analyses. Analysis of the single-shell DWI acquisition followed the same analysis pipeline. The same permutation testing was applied to measures of white matter volume derived from SPM12. Neuropsychological test results were included in a General Linear Model (GLM) with imaging data to assess differences in relation to WM structure. Analysis of behavioural tests and summary dMRI measures was conducted using the R statistical environment (R Core Team, 2018; http://www.R-project.org/).

4.3.6 Lesion segmentation

Semi-automatic segmentation was conducted using IMSEG v1.8 to delineate brain areas with focal lesions. Segmentation is based on an algorithm for geodesic image segmentation as described in (Criminisi et al., 2008). T1-weighted and FLAIR images were imported into the software and co-registered. Lesion maps were drawn as overlays on the T1-weighted images,

using FLAIR to improve contrast for accuracy. A lesion probability distribution map was generated. Binary lesion masks were transformed to MNI standard space using Advanced Normalisation Tools (ANTS; Avants et al., 2011), followed by a concatenation of masks to display regions of increasing lesion burden using FSL lesion tools.

4.4 Results

Focal brain lesions were seen in 83% of the patients (Figure 12). The highest areas of overlap between patients were seen in the orbital frontal cortex, superior parts of the medial prefrontal cortex, and the temporal poles. A comparison of the moderate-severe lesion and non-lesion TBI patients showed no group differences for measures of reaction time and delayed memory recall. Cognitive performance is discussed in more detail in relation to diffusion measures below.

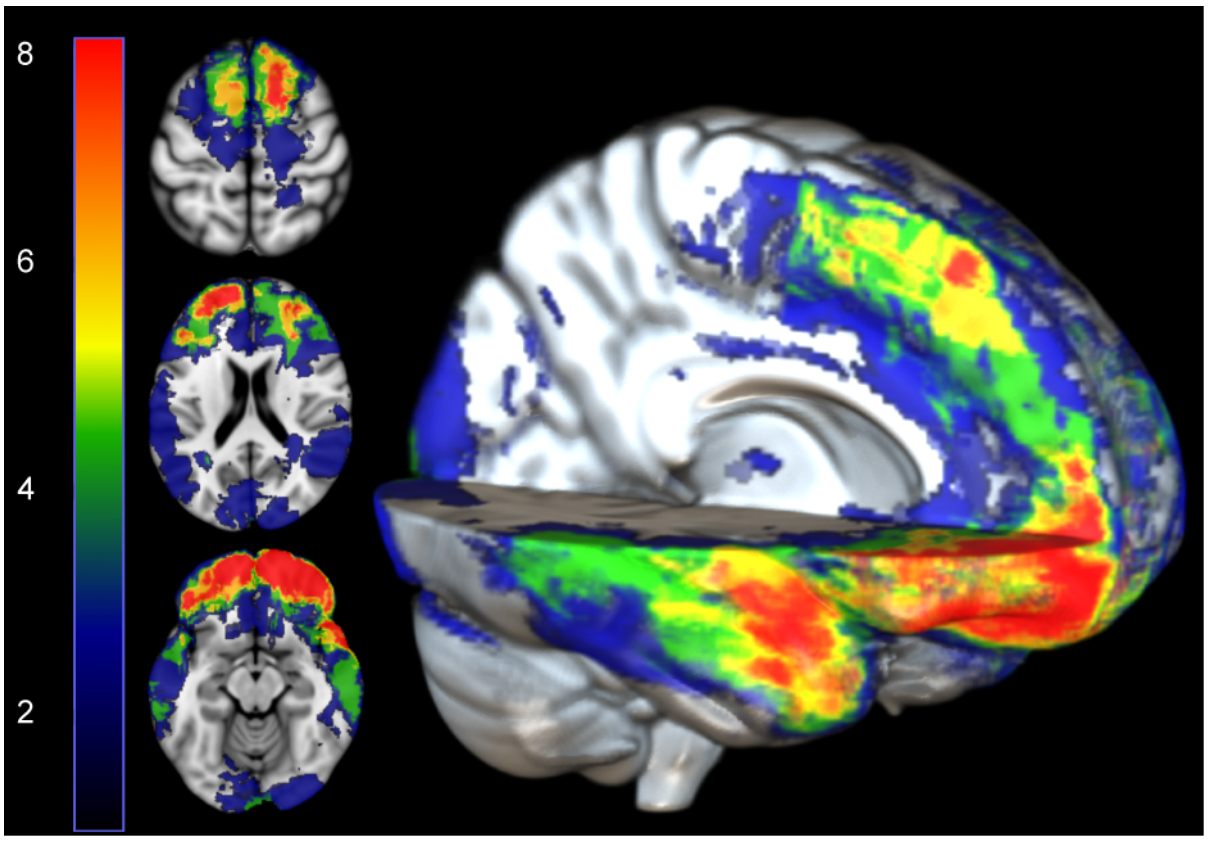


Figure 12: **Lesion distribution map**

Regions indicating greatest lesion burden are in red. Numbers on the colour bar represent the number of TBI patients with a lesion at that voxel.

4.4.1 Abnormalities in Neurite Density Index (NDI) and Orientation Dispersion Index (ODI) after TBI

Widespread abnormalities were observed in the diffusion measures produced by NODDI modelling. Reductions in NDI were seen in a large number of WM tracts (Figure 13A), including the genu and splenium of the corpus callosum and the bilateral inferior longitudinal fasciculi. ODI showed the reverse pattern, with higher values in TBI patients compared with controls (Figure 13B). Abnormally high ODI was seen bilaterally in the corticospinal tracts and in the body of the corpus callosum, with further reductions seen in the splenium and genu of the corpus callosum and the bilateral inferior longitudinal fasciculi. ISOVF showed higher values in TBI patients in all sections of the corpus callosum, as well as in anterior parts of the fronto-occipital tracts. No WM tracts showed higher NDI or lower ODI or ISOVF in the patient group.

4.4.2 Diffusion tensor imaging abnormalities

DTI results presented are from the same multi-shell acquisition as the modelled NODDI data. As expected, lower FA was seen in patients following TBI compared to age-matched controls in widespread WM regions (Figure 13D). Reductions were observed in the inferior longitudinal fasciculi, inferior frontotemporal occipital fasciculi, corticospinal tracts, and all parts of the corpus callosum. Also in line with my hypotheses, MD was higher in patients, showing a similar spatial pattern to that observed with FA (Figure 13E). No WM tracts showed higher FA or lower MD in the patient group compared to the control group.

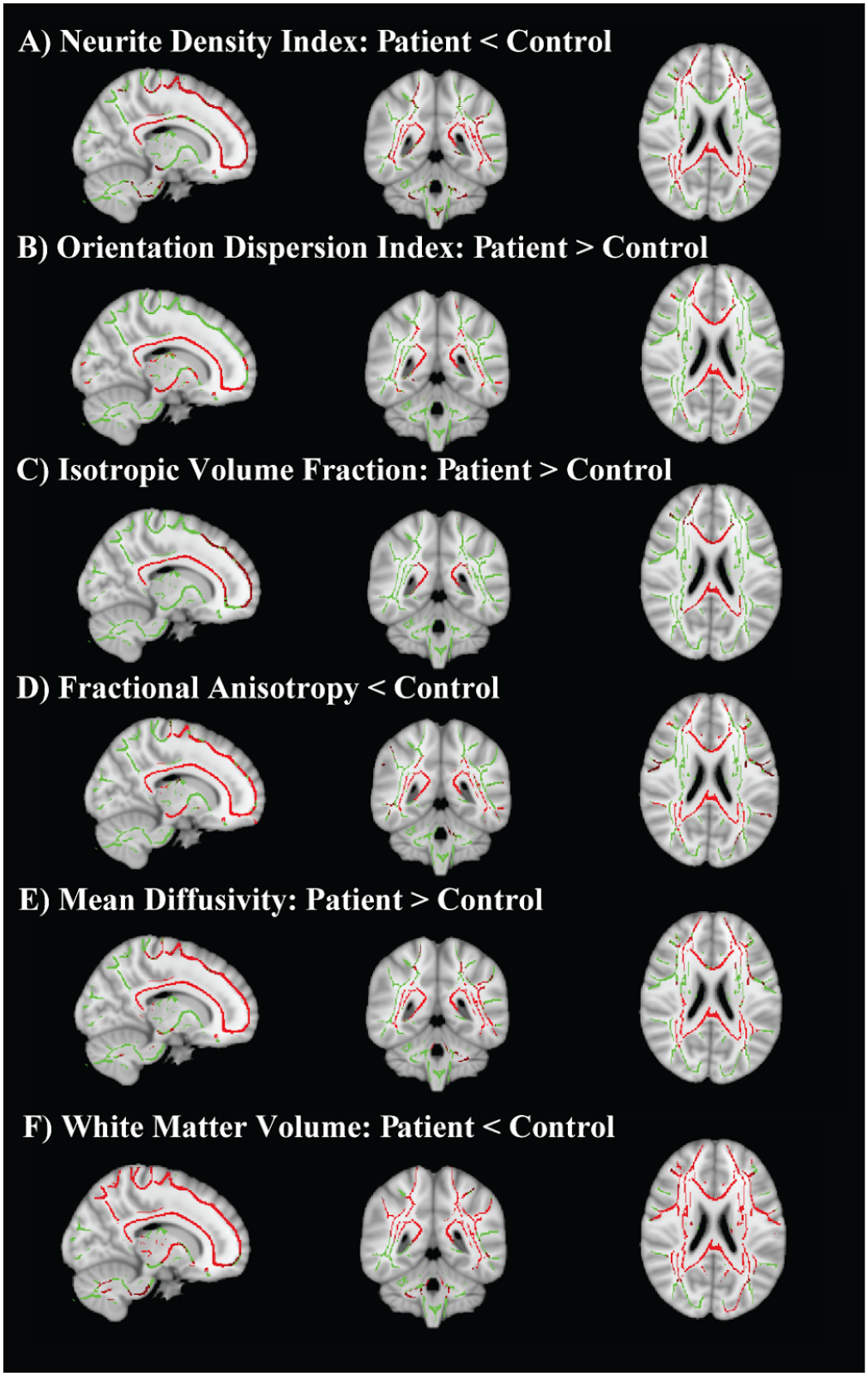


Figure 13: **Widespread white matter disruption in imaging measures following traumatic brain injury**

Whole-brain TBSS contrasts between traumatic brain injury patients and controls. Red: indicates voxels with significant differences between patients and controls. Contrasts are overlaid on the mean FA skeleton (green) and are adjusted for age, gender and intracranial volume (TFCE: $p<0.05$, corrected for multiple comparisons).

4.4.3 Volumetric analysis

There was markedly reduced total WM volume in the TBI group (mean = 0.435 (0.06)) compared with controls (mean = 0.497 (0.06)), t = 4.115, p <0.001. When analysing WM tracts individually (Figure 14A), lower volumes were apparent across all sampled tracts, including the corpus callosum and the bilateral superior and inferior longitudinal fasciculi for patients compared with controls. The voxel-wise analysis showed evidence of lower white matter volume (atrophy) across most of the white matter (Figure 14B).

4.4.4 Effect sizes for white matter abnormality detection

I next compared the effect sizes for the ability of diffusion and volumetric measures to discriminate between patients and controls, using Cohens *d*. Medium and large effect sizes were observed with varying patterns across NDI, ODI, FA, MD, and volume (Figure 14C). The splenium of the corpus callosum had similarly large effect sizes (d > 0.8) across all diffusion metrics and volume, as did the bilateral inferior fronto-occipital fasciculi. Significant effects were detected in the body of the corpus callosum by all diffusion and volumetric measures, with the exception of NDI. The largest effect sizes were seen for volumetric measures. All tracts showed significant reductions in volume, including tracts that showed no change using any of the diffusion measures. This was particularly apparent for the superior longitudinal fasciculi, where large effect sizes for volumetric reduction were accompanied by no significant differences in any diffusion MRI measures. Large effects for volume reduction were seen in the corticospinal tracts, accompanied only by increased MD. Comparative analyses of DTI metrics with diffusion data acquired with a single shell for these participants showed comparable effect size patterns across tracts for single-shell FA and MD to the multi-shell results.

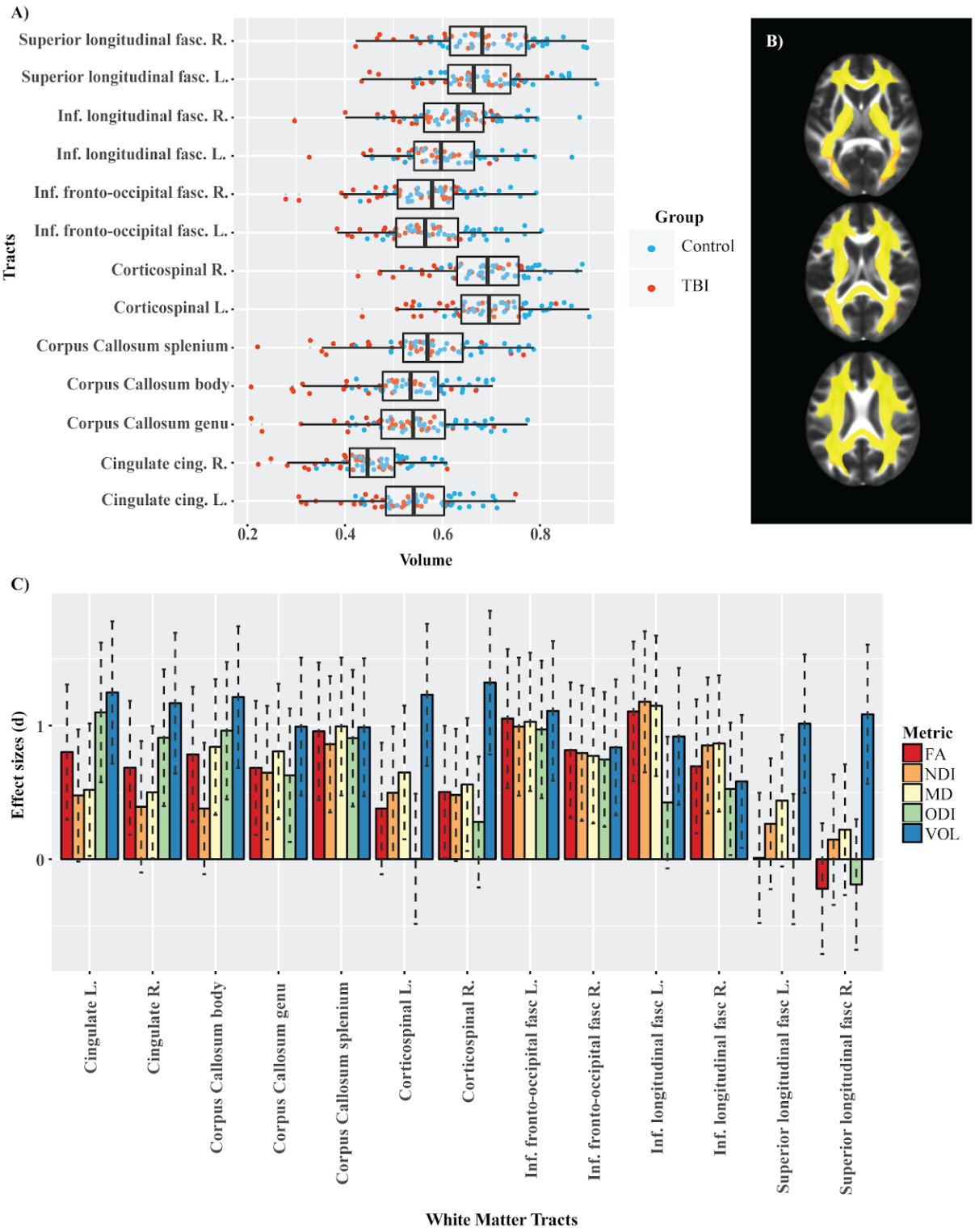


Figure 14: **Effect size across white matter measures.**

A | White matter volume. B | Voxels showing significantly lower WM (yellow-red) volume in patients compared to controls. C | A plot of effect size between patients and controls across metrics for different tracts. FA = red, NDI = orange, MD = yellow, ODI = green and volume = blue.

4.4.5 Relationship between neuroimaging measures

Correlations were generally robust between diffusion and volumetric measures, calculated from the whole white matter skeleton (Figure 15). There was a strong positive correlation between NDI and FA (r = 0.83, p <0.001) and a strong negative correlation between ODI and FA (r = -0.72, p <0.001), as well as between ISOVF and FA (r = -0.39, p <0.001). These relationships suggest that the FA signal consists of both elements of neurite density and fibre orientation. MD was also negatively correlated with both FA (r = -0.88, p <0.001) and NDI (r = -0.95, p <0.001). There were also significant positive correlations between WM volume (WM_{vol}) and NDI (r = 0.42, p <0.001) and WM_{vol} and FA (r = 0.63, p <0.001), with negative correlations between WM_{vol} and ODI (r= -0.65, p <0.001), WM_{vol} and ISOVF (r = -0.39, p <0.001) and WM_{vol} and MD (r = -0.50, p <0.001).

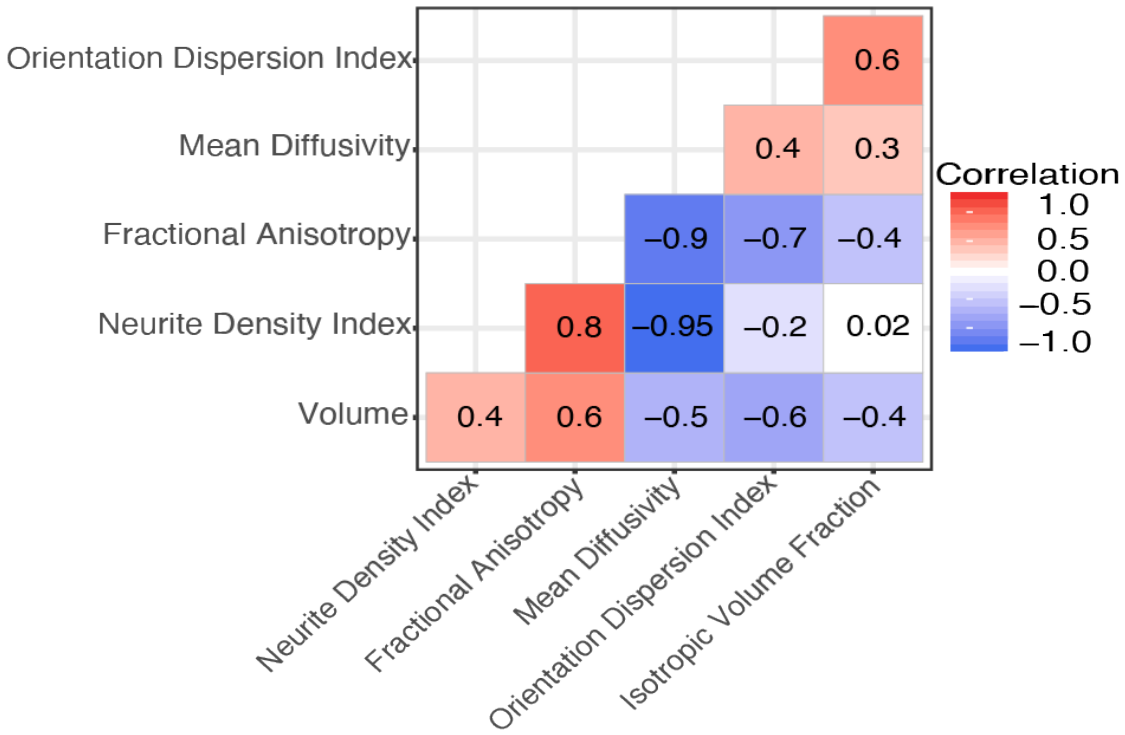


Figure 15: Correlation matrix of diffusion metrics and white matter volume

Red: positive correlation, Blue: negative correlation, White: not significant. The y-axis is ordered based on hierarchal clustering with increasing correlation coefficients.

4.4.6 Relationships between neuroimaging measures and cognitive function

There were significant relationships between diffusion measures and neuropsychological performance (Figure 16). NDI significantly correlated with processing speed, as indexed by CRT response, in extensive WM regions. Increasing reaction times on the CRT (i.e., worse performance) were associated with reductions in NDI within large parts of the white matter, including the corpus callosum, cingulum and the inferior longitudinal fasciculi. This relationship was not seen for ODI or ISOVF. There were no significant relationships between other neuropsychological measures and either ODI, NDI or ISOVF. CRT performance also correlated positively with MD, primarily within the corticospinal tracts. FA and MD were correlated with delayed recall for associative memory. Lower FA values were indicative of poor memory recall across both patient and control groups, while patients were further along with the distribution with lower scores. Significantly lower FA was seen within the body of the corpus callosum and the cingulate. Higher MD was also seen in these tracts. Similarly, an inverse relationship for MD was present, with lower scores of memory recall associated with higher MD. Significant relationships were not observed between other neuropsychological results and either diffusion or volumetric measures.

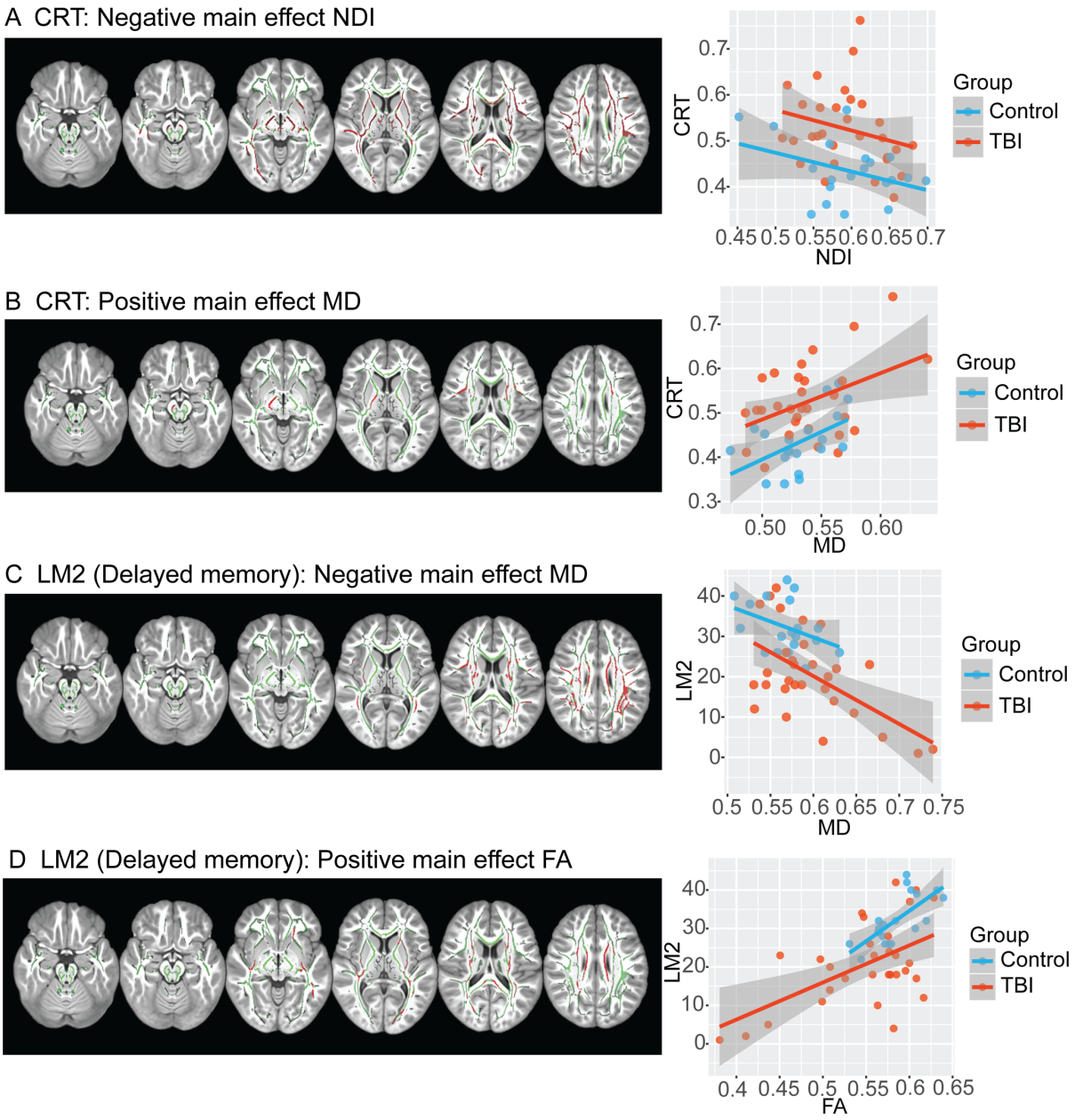


Figure 16: Correlation of neuropsychological assessment with MRI measures of white matter

A | Voxels with a negative correlation between neurite density index and choice reaction time (Red); B | Voxels with a positive correlation between mean diffusivity and choice reaction time; C | Voxels with a negative correlation with delayed recall on the peoples test; D | Voxels with a positive correlation and delayed recall on peoples test. Contrasts are overlaid on the mean FA skeleton (green) and are adjusted for age, gender and intracranial volume (TFCE: $p<0.05$, corrected for multiple comparisons).

4.5 Discussion

Advances in magnetic resonance imaging provide new ways to investigate axonal injury after TBI, but the advantages of each remain unclear. In this chapter, I applied a neurite orientation dispersion and density-imaging model in patients with persistent neurological problems after TBI, alongside two widely used measures of white matter structure: diffusion tensor imaging and volumetric measures of brain atrophy. Widespread abnormalities were observed across all three methods, particularly in midline structures such as the corpus callosum known to be particularly affected by diffuse axonal injury (Ghajari et al., 2017). Reductions in brain volume were most sensitive in identifying abnormality following TBI. In patients, this non-specific measure showed abnormalities across all of the major white matter tracts investigated, with consistently large effect sizes across all the tracts. Medium-to-large effect sizes were also seen for the diffusion measures in most of the white matter tracts studied.

DTI has been widely used to study axonal injury after TBI. Though sensitive to WM abnormalities, FA lacks specificity; it reflects a combination of axon density, axon distribution, gliosis, oedema, and degree of myelination. This lack of specificity significantly limits the interpretations that can be made about pathological mechanisms underlying axonal injury and associated cognitive deficits after TBI. Histological analysis of animal models suggests that the NODDI metrics NDI and ODI may provide a better representation of the biological microstructure than FA (Jespersen et al., 2010; Jones & Cercignani, 2010; Sepehrband et al., 2015). In the current study, widespread abnormalities were found using ODI and NDI in a moderate-severe TBI group. Distinct spatial abnormalities were seen across different tracts and diffusion metrics. An increase in ODI in the corpus callosum, an area which is protected from the effects of a direct impact, might be associated with the high strain rates caused by the biomechanics of TBI (Sato et al., 2017). Widespread relationships

between lower neurite density and slower processing speed suggest that the loss of neuronal elements may be particularly important for characteristic impairments in processing speed following TBI. These results indicate that NODDI can be used to clarify the location and extent of WM damage, in a way that is relevant to improving our understanding of post-traumatic cognitive impairment.

Cerebrospinal fluid contamination can produce errors in diffusion metrics, causing FA to be underestimated and reducing tissue characterisation accuracy by as much as 60% (Grussu et al., 2017). One advantage of NODDI over DTI is that CSF is accounted for and modelled as a separate compartment of the signal. An increase in CSF contribution to the signal would result in an increase in the ISOVF, leaving the other two metrics (NDI and ODI) unaffected (Viano et al., 2005). In this way, partial volume effects from CSF may be less influential on NODDI metrics, which might be particularly beneficial in investigations of brain atrophy (J H Cole et al., 2018). By combining NODDI with the "skeletonisation" process in TBSS, the impact of partial volume effects is further limited.

A consideration during the development of NODDI was its potential clinical feasibility (Zhang et al., 2012). Since then, however, multi-shell acquisition has become increasingly accessible, and comes with little extra time cost compared with traditional single-shell acquisitions. Furthermore, optimised NODDI processing means a single brain can be analysed in under ten minutes (Daducci et al., 2015). As more information can be gathered from the diffusion properties of different brain tissues via a multi-shell acquisition, it holds promise as a useful tool in clinical settings.

A limitation of the NODDI model is that it does not account for multiple crossing fibres. This has previously been highlighted as an issue for other DTI metrics such as FA. While this is a potential confound for ODI, NDI should remain unbiased. Another factor to consider is that diffusion metrics are known to be spatially heterogeneous across brain regions, with the highest signal-to-noise ratio in medial parts of the brain (Jones & Cercignani, 2010). This would be expected to impact on the sensitivity of diffusion measures to pathology, which is often assumed to be uniform. Hence, diffusion metrics from lateral parts of the brain may show reduced sensitivity to pathology. T1 structural scans are acquired at a higher resolution ($1mm^3$) to diffusion MRI ($2mm^3$), which potentially offers more power to pick up group differences.

While the multitude of novel neuroimaging measures allows for exciting new inferences to be made in vivo, their very nature also implies that direct comparisons with underlying histological measures are challenging. Hence, caution is needed in the interpretation of NDI and ODI, as their exact relationships with underlying biology remain uncertain. While some histopathological evidence has been provided to validate the assumptions of advanced diffusion metrics using animal models, this remains limited; there is scope for further clinical and preclinical work in this area.

4.6 Conclusion

Volume changes were the most sensitive marker of structural abnormalities following TBI, indicating their utility as targets for interventions. However, observed abnormalities in NODDI metrics after TBI were decomposed into partially overlapping changes, each demonstrating specific relationships with cognitive performance. Compared to other diffusion metrics, ODI appeared to provide a more distinct measure, which may potentially provide additional estimates of the underlying neuropathology seen after TBI. Neurite density shows a strong relationship with processing speed, a useful measure of cognitive function following TBI. Advances in neuroimaging acquisition and analysis such as multi-shell diffusion imaging may help disentangle the biological mechanisms underlying DAI and the relationship of brain structure with cognitive performance.

Chapter 5 | Apathy & social decision making following traumatic brain injury

In this chapter, I follow up with TBI patients from the previous chapter investigating white matter structure to look specifically at measures of apathy and social processing. This cohort of patients have previously exhibited higher levels of apathy and lower levels of striatal dopamine compared to healthy controls. A reward discounting paradigm with a social condition is used to investigate social decision making and its link with apathy in TBI patients.

5.1 Abstract

Social impairments and disruption to interpersonal relationships are common sequelae of TBI. Apathy and executive dysfunction are contributory factors to this phenomenon, both impacting on engagement with rehabilitation, normal social functioning, and return to work. Following previous work identifying neural correlates of apathy in TBI patients, further investigations on social decision making were conducted using a reward discounting paradigm. This paradigm requires patients to make choices of varying reward and effort levels for themselves or another participant (confederate). To negate superficial choices, physical effort was required to attain rewards using a hand dynamometer.

Twenty-eight TBI patients (mean age = 45(11.95)) described in the previous chapter attended a follow-up visit 1.5-2 years after completion of the previous study. Twenty-four healthy controls (mean age = 35.18(12.11)) with no history of neurological or psychiatric illness were recruited as a comparison group.

Patients failed to differentiate between self and other conditions in reward discounting choices compared to controls. In energising action for these choices, as reward level increased controls put in significantly more effort for self than other, while patients showed no difference. Additionally there was an interaction between reward and effort for controls, whereby as effort increased, sensitivity to reward decreased. This reduced sensitivity to reward with increasing effort levels was not seen for patients. While apathy remained a significant problem in this TBI group, no link was seen between reward discounting and apathy.

While reporting higher levels of apathy related to self-initiation or goal-directed behaviour and poorer social functioning, TBI patients showed lower levels of reward discounting compared to controls, reflecting a different process to apathy in the current context. Reduced reward discounting and failure to integrated social information has an important implication for TBI patients behaviour, as it may impact valuation judgment leading to poor decision making or lead to inappropriate pro-sociality, resulting in increased vulnerability to being manipulated and taken advantage of.

5.2 Background

As discussed in the general introduction, social outcomes of TBI patients can pose a crucial challenge on many levels, whether on the individual or those around them, or on society (May et al., 2017). Apathy can have a significant impact on engagement with rehabilitation, social relationships, and return to daily life and work. Reduced motivation, or apathy, has been commonly reported among patients with TBI, ranging from 20-71% (Worthington & Wood, 2018). The authors highlight the dearth of work relating this prominent deficit and the neural correlates in TBI patients.

5.2.2 Description of apathy as a clinical syndrome

Apathy is a syndrome common across neurological disorders and has been described to consist of a loss of motivation or goal-directed behaviour which can be subdivided into emotional, social, or behavioural subgroups (Le Heron et al., 2018). In the absence of a diagnosed neurological or psychological condition, controls from the general population vary considerably on levels of apathy. Elevated levels of apathy are associated with lower motivation. However, this relationship is more pronounced in neurological conditions (Ang et al., 2017). TBI patients have higher levels of apathy, which is correlated to reduced DaT, implying disruption of the dopaminergic system (Jenkins et al., 2018). Similar results have been seen in patients with Parkinson's disease, who suffer characteristic disruptions to their dopaminergic systems (Le Heron et al., 2018). While reduced dopamine may play an important role in the presentation of apathy, this is by no means the only neural feature that is related to the behavioural presentation. Results from my earlier VLSM analysis indicated damage to the RIFG was also related to symptoms of apathy, supporting the idea of a network of processes that may be affected following an injury.

An important consideration when viewing apathy as a clinical syndrome among neurological patients is the potential differences in neural substrates leading to that behaviour. A review on apathy in Parkinson's disease states that reduction in goal-directed behaviour may be due to a reward deficiency syndrome, emotional distress, executive dysfunction, or akinesia— each with different neural pathways and optimal intervention options (Pagonabarraga et al., 2015). Various mechanisms of neural damage may occur, disrupting a circuit comprising the amygdala, ventral striatum and prefrontal cortex. These are regions at high risk of damage following TBI (De Simoni et al., 2018; Jenkins et al., 2019). Disruption to these circuits may present in the form of different apathetic syndromes (affective, executive, auto-activation).

The link between apathy and TBI-related pathology is supported by well-documented case studies, and was previously explored using voxel-based lesion-symptom mapping on a large cohort of TBI patients in chapter 3.

5.2.3 Description of motivation & decision making

Motivation and the willingness to exert effort for both self and others are key features of human social behaviour. The motivation for action has been theorised to comprise two levels: the first evaluates the cost-benefit prior to an action; the second occurs when an action has been chosen, and initiates the action that must be performed in order to achieve the desired outcome. Human decision making plays a large role in behavioural economics and is influenced to a large degree by many facets of social cognition (C. D. Frith, 2008). Choices are based on moral and economic information and influenced by social and emotional information. Computations of cost-benefit, risk-reward guide decisions made. TBI patients have previously shown impairments on a social decision-making task where participants had to learn who are the "friendly" players in order to guide future decisions in a game of toss (M. Kelly et al., 2014). In this paradigm participants were rewarded by inclusion more frequently when making good decisions by passing to "friendly" players, while punished by exclusion when passing to "unfriendly" players. This structure resembles the IOWA gambling task based on a social condition rather than monitory rewards. Patients made poorer choices compared to controls overall on who to pass to. Patients were slower to learn the "good" social options.

5.2.4 Effort based reward discounting

Individuals devalue reward to a greater extent with increasing levels of cognitive or physical effort (Białaszek et al., 2017). Evaluation of computational models of behaviour indicate when choices are being made for self, compared to other, healthy controls show a self-benefiting bias when it comes to reward discounting (Lockwood et al., 2017). That is, for low effort costs, they are willing to put in effort for both self and other. However, as the effort cost increases, their likelihood to choose to put in the effort decreases. This decrease has a steeper curve for others than for self, indicating that individuals are willing to put in more effort for themselves than for others. Reward discounting is important to examine in TBI patients, as it provides insights into the internal economic evaluation that guide decisions being made (Białaszek et al., 2017). Decisions are constantly been driven by these internal evaluations of cost and benefit. Reward discounting in TBI patients has not been previously investigated using an effort-based paradigm. This paradigm may provide novel insights into a link between self-reported apathy and social dysfunction in TBI patients.

Various high-level social behaviours may be affected following TBI. There is an extensive literature on the structure and function of the anterior cingulate cortex (ACC) (Botvinick et al., 2004; Bush et al., 1999; Margulies et al., 2007; Stevens et al., 2011). One of the key functions suggested of the ACC has been for effective decision making (Chudasama et al., 2013). More recently, the ACC gyrus (ACCg) has been highlighted as an important region when evaluating costs and benefits relating to another person rather than self. Empathy and prosocial behaviour are linked with selective responses in the sub genual ACC (sgACC) (Apps & Ramnani, 2014; Lockwood et al., 2016). This distinguishable system for processing socially relevant information independent of the self may be a key feature to explain social cognitive deficits in TBI patients. Previous work has shown disruption in structural and

functional connectivity with the ACC following TBI, associated with a range of cognitive deficits (De Simoni et al., 2018).

In this section, effort and reward processing are investigated in TBI patients and healthy controls with a social effort paradigm. Here, participants make decisions on a monetary reward: i) with respect to varying levels of physical effort that must be exerted in order to attain the reward; and ii) for either themselves or another participant. Computational modelling of these decisions allows estimates of reward discounting based on varying effort and reward levels. Results of this paradigm are looked at in relation to behavioural reports imaging measures of volume, DTI, DaT, and presence of focal lesions to assess possible neural correlates across multiple imaging modalities. Specific regions of interest including the ACC, TPJ, and DMPFC are selected for analysis based on previous social cognition literature relating to value judgments and decision making.

Hypotheses were based on previous work linking TBI and reward discounting with reduced dopamine intake and disrupted striatal connectivity (De Simoni et al., 2018; Jenkins et al., 2018, 2019; Lockwood et al., 2017). These were as follows:

1. TBI patients will show an alternative pattern of reward discounting compared with healthy controls
2. Reward discounting in TBI patients will relate to self-reported measures of apathy
3. Reduced striatal dopamine and structural connectivity will be associated with increased reward discounting in TBI patients

5.3 Methods

5.3.1 Participants

Patients from a previous study investigating the role of dopamine following TBI were invited for a follow-up visit 1.5-2 years after completion (as described in chapter 4). These patients have been very well characterised previously (Jenkins et al., 2018). The mean age was 45(11.95). Twenty-eight out of the original forty-two patients attended a follow-up visit. Three patients were excluded due to under-calibration of the main experimental paradigm. Of the original cohort which reported 14/42 having abnormal levels of DaT, thirteen of these patients returned for follow up. Fourteen patients had focal lesions, primarily in the frontal and anterior temporal lobes. These lesions were masked out in further neuroimaging analysis. All participants provided written consent to participate in the current study, approved by Camberwell-Giles ethics committee.

Twenty-four healthy controls (mean age = 35.18(12.11)) were screened for exclusion criteria, including neurological or psychiatric disorders (based on self-reports by participants). One control was excluded from further analysis following an incidental finding on MRI. Participants received £50 financial reimbursement for their time. Participants were instructed of an additional financial reward as part of the task. They were informed that this reward was available for themselves as well as for the confederate participant, and that their obtainment of the amount was contingent on their task performance. Upon completion of the task, all participants received an additional £10 and were debriefed that everyone received an equal reimbursement, regardless of task performance.

5.3.2 Design

The design and modelling of the social effort task were described previously (Lockwood et al., 2017). The task consists of 5 blocks of 30 trials (150 trials in total), in which participants complete 75 decisions for themselves and 75 decisions for another participant (confederate). Between each block, participants were given the opportunity to rest in order to avoid fatigue. Trials involved a choice between a baseline option that provided a single credit for no effort, or an alternative 'offer' which could be attained with a varying amount of required effort (30, 40, 50, 60 or 70% of participants maximum voluntary contraction (MVC)) and a varying level of reward (2, 4, 6, 8 or 10 credits; Figure 17).

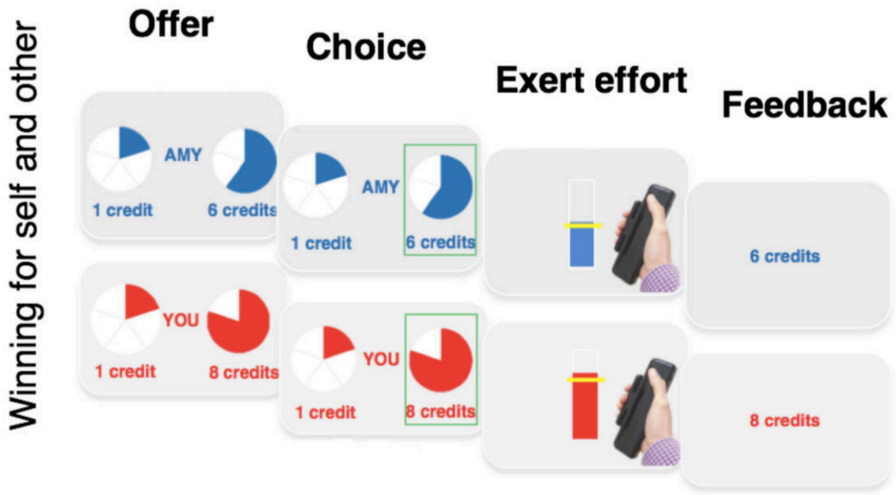


Figure 17: **Schematic diagram of paradigm, reprinted from (Lockwood et al., 2017)**

5.3.3 Equipment

MATLAB version 2011b (MathWorks http://www.mathworks.com/) and Psychtoolbox version 3 (http://psychtoolbox.org/) were used to program stimulus presentations. To measure effort, an applied force was recorded on a hand-held dynamometer (TSD121B-MRI BIOPAC Systems). Real-time visual feedback was provided to participants on the force they were exerting. The paradigm was run on a Lenovo IP020S i5 laptop operating Windows 10.

5.3.4 Procedure

Participants filled out a reimbursement form immediately before participating in the task in order to reinforce the idea of real financial incentive. To ensure participants believed they were making choices for another person, they were instructed of their anonymised participant ID and told for data protection reasons that they would not be able to see the other participant. The computer would display an anonymised ID on the screen of another participant they would make choices for.

5.3.5 Task

Prior to the main task, participants held a hand-dynamometer and were instructed to squeeze with as much force as possible. This calibration step measured the maximum voluntary contraction (MVC). This allowed the task to be adjusted relative to the MVC to account for varying strength across individuals. Subject-specific thresholds were set for effort levels based on this calibration. Participants were then provided with training trials consisting of 18 trials of each possible effort level (30, 40, 50, 60 or 70% MVC). Effort levels were indicated as segments on a pie chart.

The main experimental task requires participants to choose between a low effort baseline option (0% MVC) that provided 1 credit if the baseline condition was chosen and a variable offer in which more credits (2, 4, 6, 8, 10 credits) were available but also involved more force (30, 40, 50, 60 or 70% MVC). These were illustrated as segments on a pie chart. Effort and reward levels varied independently across trials, with each reward-effort combination sampled three times for each agent. After making their selection of the baseline or higher effort choice, participants were required to exert a force higher than the required MVC level for a total of 1s in a 3s window. Failure to apply sufficient effort or the failure to select either

option resulted in 0 credits being awarded. Participants had a high chance of reward based on their choices, by setting the maximum effort level to 70% MVC to minimise failure. Thereby excluding the possibility of risk aversion, which may interact with effort discounting. Comparisons of MVC were made across groups to examine compliance with the experimental paradigm.

5.3.6 Behavioural modelling

Following previous work from (Lockwood et al., 2017), the behavioural data was modelled with distinct parameters evaluating the degree to which reward was devalued by effort (K). This included varying noise parameters for stochastic/random choices (beta): These included the function that characterised reward discounting by physical effort (parabolically, linearly, hyperbolically), as well as a comparison of models that investigated if there was differential discounting of reward by effort for self and other trials. In other words, whether participants discounted reward similarly for themselves and others, or whether their responses differed based on the agent being played for. These factors formed subclasses of models evaluating parameters that best explained behaviour.

$$SV = R - KE2$$

Subjective value = Reward – (Discount Parameter X Effort^2), where the discount parameter was different for self and others.

The discounting model assumes that for each trial, the subjective value (SV) is determined by the effort level (E). Effort level is scaled in proportion to the individual participant's MVC, the reward level (R), and the subject-specific discounting parameter describing the steepness of each individual's devaluation of rewards by effort.

High K values (discount parameters) suggest that reward is discounted by effort to a greater degree. K was modelled as being different for self and other trials or the same for self and other trials depending on the model parameters set. Discounting functions for each individual is referenced to the SV of the baseline offer, which is always 1, corresponding to 1 credit and no effort. To avoid overfitting by adding additional parameters, the best model was chosen using the Bayesian Information Criterion (BIC), which imposes a penalty for the number of parameters in the model.

5.3.7 Subsidiary analysis (bias testing)

A secondary analysis was run to investigate potential biases in the results. Levels of success at achieving the reward were compared across groups to exclude the possibility of risk aversion. There was no significant difference in success rates between patients and controls. Controls (n = 22) = 94%, SD = 1%, patients (n = 25) = 97%, SD = 3%. On almost every trial, participants achieved the required amount of force in order to attain the reward. This high probability of reward attainment for the given options is thought to mitigate the chances of risk avoidance (Lockwood et al., 2017).

During a debrief following the study visit, participants were asked to indicate the believability of the experimental condition; in other words, whether they thought they were actually playing for another real individual. With the exception of one patient, all subjects indicated that they did not suspect deception during the experimental paradigm. The analysis was rerun with the exclusion of this subject to examine any potential influence on the results. Additionally, as age effects have recently been reported to play a significant role in prosocial behaviours, this was also investigated to see what influence, if any, this had on the data. No effects were observed on the results reported below.

5.3.8 Measures of wellbeing

Participants completed self-reported measures of wellbeing. These were standardised paper assessments adapted for use on a digital interface (i.e., tablet, smartphone, or webpage). In this study, participants completed the set of questionnaires on a Samsung (SM-T580) tablet.

Questionnaires (15-20 min):

1. Mayo-Portland Adaptability Inventory (Malec et al., 2007)
2. Beck Depression Inventory (Beck et al., 2011)
3. Visual Analogue Fatigue Scale (Tseng et al., 2010)
4. Apathy-Motivation Index (Ang et al., 2017)
5. Social Network Index (Cohen, 1997)
6. Short-Form (36) Health Survey (SF-36; Lins & Carvalho, 2016)
7. Frontal Systems Behaviour Rating Scale FrSBe (Grace & Malloy, 2001)

Following the series of questionnaires, an effort test of memory and malingering was also conducted. This was a novel digital adaptation of a classic pen and paper task. In this task, a sequence of 50 items is presented to the participant. A choice of two images is then presented, and participants are required to select the one they saw from the original list. In control populations, a very high accuracy is expected for this sort of recognition task. Previously collected apathy data in this cohort from the Lille Apathy Rating Scale (LARS) was investigated in relation to structural MRI measures. A surrogate marker of self-awareness was taken by calculating a discrepancy measure between patient and caregiver on the LARS during their initial visit.

5.3.9 Neuroimaging analyses

Multiple neuroimaging modalities have been previously collected on this cohort of patients. Acquisition parameters for MRI and SPECT are described in the general methods.

The discounting parameter (K) was evaluated in association with striatal DaT, the presence of a focal frontal lesion, and voxelwise analysis of white matter FA and volume. Regions of interest were selected based on their associations with apathy and executive functioning, and included nigrostriatal FA and volume in the sgACC, ACCg, DMPFC and TPJ.

5.3.10 ROI analysis

Region of interest (ROI) analysis was performed on grey matter volume for regions commonly associated with social cognition (Figure 18). These included the ACCg, sgACC, DMPFC, and the TPJ. MNI coordinates were selected from an amalgamation of previous papers. ACCg: *x = 2, y = 24, z = 17.5* (Apps et al., 2015; Apps & Ramnani, 2014; Lockwood et al., 2015). DMPFC: *x = 2.5, y = 40, z = 41*(Hampton et al., 2008; Izuma & Adolphs, 2013; Nicolle et al., 2012; Sul et al., 2015; Suzuki et al., 2012; Wittmann et al., 2016). sgACC: *x = -3.5, y = 8, z = 11* (Diaconescu et al., 2017; Lockwood et al., 2016). TPJ: *x = 55, y = -52, z = 15* (Diaconescu et al., 2017; Hampton et al., 2008).

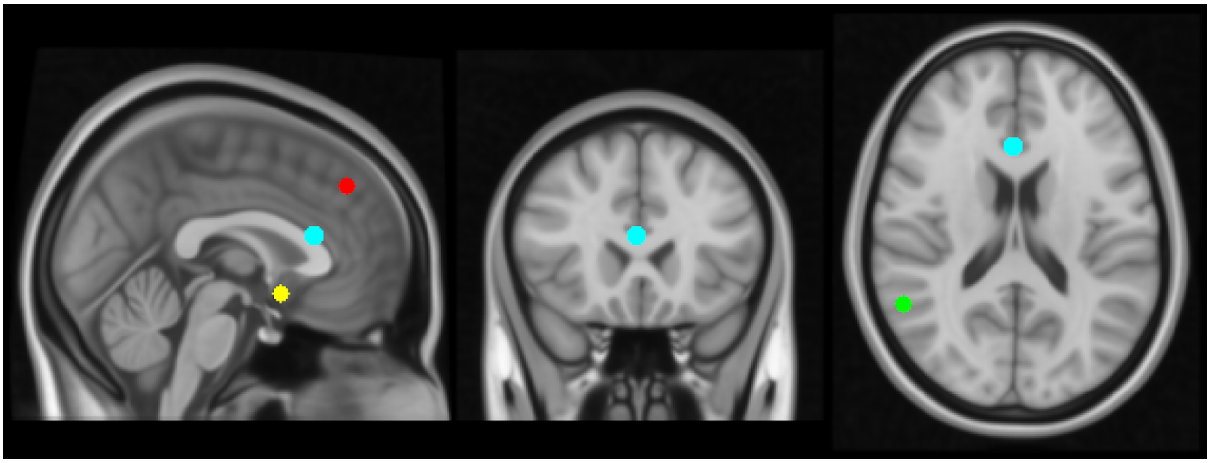


Figure 18: **Region of interest (ROI) for grey matter volume**

Red = DMPFC; Blue = ACCg; Yellow = sgACC; Green = TPJ

5.3.11 Statistical analysis

Behavioural and questionnaire data and summary measures from MRI and DaT were analysed within the R statistical environment (Core Team, 2018; http://www.R-project.org/). Recorded force data exerted on the hand dynamometer was standardised to compare differences in relation to reward and effort across participants. This was measured as the area under the curve using the MATLAB 'trapz' function, which calculates the Y integral with respect to X using the trapezoidal method. This value was calculated in relation to an individual's MVC to account for different baselines across participants.

Differences between choice conditions for effort and reward between "self" and "other" were conducted by running a generalised linear mixed effects model, testing significance with a type II Walds. Comparison of the discounting rates (K) extracted from the model for self and other were analysed using robust regression for non-normally distributed data.

5.4 Results

Results of self-report assessments of wellbeing are presented in (Table 3). Overall, TBI patients in the chronic phase of injury present ongoing impairments measured on the Mayo-Portland Adaptability Inventory, which was significantly greater than controls ($mean_{pat}$ = 30.11 (22.98), W = 28.5, $p_{fdr} < 0.001$). Subjects within the patient group reported symptoms of depression, which were significantly greater than controls ($mean_{pat}$ = 12.52 (13.31), W = 162, $p_{fdr} = 0.02$), self-initiation apathy ($mean_{pat}$ = 1.9 (0.87), W = 412, $p_{fdr} < 0.04$), fatigue ($mean_{pat}$ = 43.41 (22.27), W = 157.7, $p_{fdr} = 0.02$) and deficits in physical functioning ($mean_{pat}$ = 70.1 (29.86), W = 463 $p_{fdr} < 0.01$). The SF-36 reported lower social functioning in TBI patients compared to controls ($mean_{pat}$ = 67.91 (28.59), W = 469 $p_{fdr} < 0.01$), while the SNI

indicates no significant difference in the number of regular contacts ($mean_{pat}$ = 14.16 (9.52), W = 366 p_{fdr} = 0.24).

Table 3: Neuropsychology measures of wellbeing

Independent sample t-tests were conducted with the Wilcoxon rank sums, with FDR multiple comparison correction between all pairwise means.

Behavioural measure	Domain	Healthy Controls Mean (+/- SD)	TBI Patients Mean (+/- SD)	W	p-uncorrected	p-FDR corrected
Mayo Portland Inventory	Ability	1.13 (2.37)	13.19 (8.97)	31.5	<0.001	<0.001
	Adjustment	1.52 (2.39)	13.42 (12.30)	50.5	<0.001	<0.001
	Participation	0.86 (1.28)	7.30 (8.82)	61.5	<0.001	<0.001
	Total	3.34 (4.83)	30.11 (22.98)	28.5	<0.001	<0.001
Beck Depression Inventory	Depression	4.69 (6.53)	12.52 (13.31)	162.0	<0.01	0.02
Fatigue	VAS-Fatigue	26.46 (17.26)	43.41 (22.27)	157.5	0.01	0.02
Apathy Motivation Index	Emotional	1.28 (0.56)	1.7 (1.02)	386.0	0.08	0.12
	Social	1.52 (0.73)	1.82 (0.87)	356.0	0.26	0.31
	Behavioural	1.25 (0.63)	1.9 (0.87)	412.5	0.02	0.04
Social Network Index	Number of high contact roles	4.45 (1.53)	4.36 (1.84)	313.5	0.79	0.79
	Number of people	18.79 (13.70)	14.16 (9.52)	366.0	0.18	0.24
	Embedded networks	1.4 (1.31)	1.24 (1.20)	318.5	0.70	0.74
SF-36	General Health	82.43 (15.86)	60.19 (23.94)	466.0	<0.001	<0.01
	Physical Functioning	93.69 (14.94)	70.10 (29.86)	463.0	<0.001	<0.01
	Emotional Wellbeing	79.56 (13.60)	69.68 (19.30)	402.5	0.03	0.06
	SF-36 Social Functioning	91.96 (14.88)	67.91 (28.59)	469.0	<0.001	<0.01
	SF-36 Energy/Fatigue	70.36 (15.94)	59.46 (24.92)	374.0	0.13	0.18
	Pain	93.36 (17.33)	82.21 (24.84)	387.0	0.05	0.08
TOMMS	Malingering	46 (4.42)	43 (9.67)	292.0	0.48	0.53

5.4.1 Apathy-motivation

During the initial visit patient reports of apathy were compared to caregivers. Welch's two-sample t-tests were conducted. After correcting for family-wise error (Bonferroni), the only domain in which this difference was found was the self-awareness subscale itself, where caregivers (M = -1.72, SD = 2.22) rated patients as significantly more apathetic than patients (M = -3.09, SD = 1.17) rated themselves $t(77.07)$ -4.25, $p = 0.0003$, thus indicating higher levels of self-awareness problems rated by caregivers compared to patients.

During the follow-up visit, pair-wise comparisons showed patients (M =1.81(0.87)) continued to report significantly higher levels of apathy and poor motivation compared to controls (M = 1.24(0.64)) on the behavioural subscale subtype $t(117)= 2.4$, $p = 0.02$ (Figure 19), as measured by the Apathy Motivation Index. While no significant differences were seen in the social $t(117) = 1.3$, $p = 0.1$ and emotional domains $t(117) = 1.6$, $p = 0.09$). The behavioural activation subscale targets propensity for self-initiation and goal-directed behaviour (Ang et al., 2017).

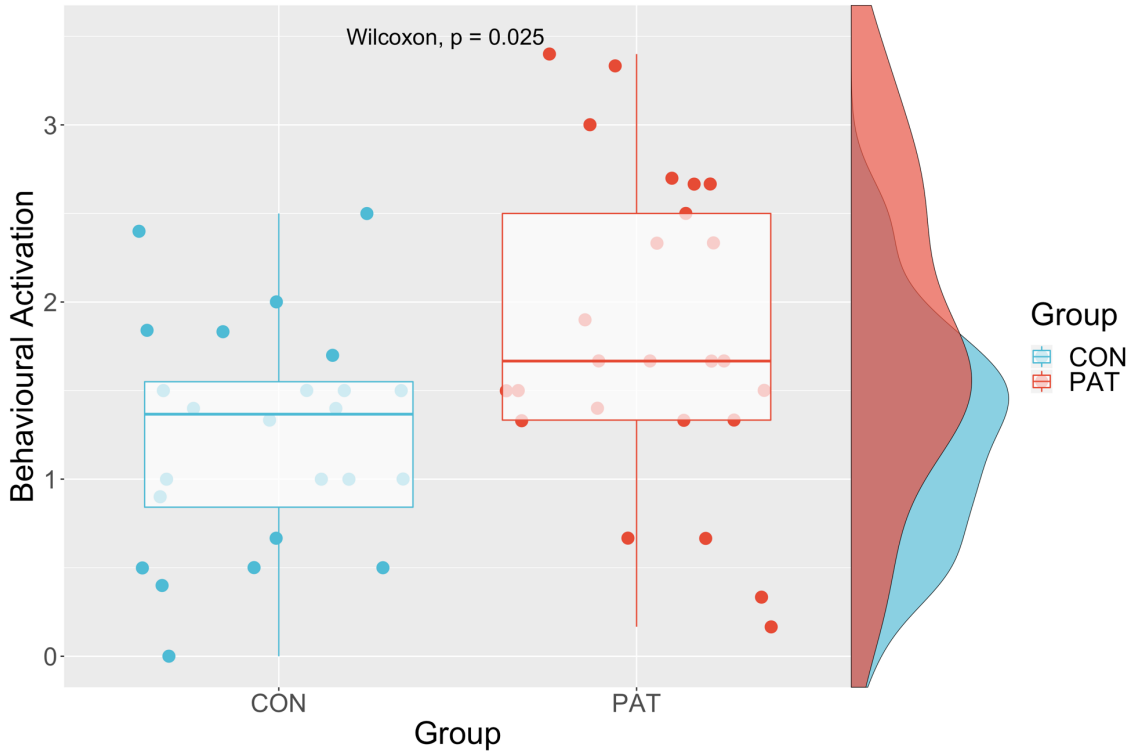


Figure 19: Plot of behavioural activation (apathy relating to self-initiation) between TBI patients and controls

5.4.2 Social decision-making paradigm

Choice

Choice data was investigated with generalised linear mixed effects model with participant as a random effect. Choice was coded as a binary outcome measure and included group, recipients (agent), reward level and effort level as fixed effects along with their interactions. A type two Wald chi-square revealed a significant two-way interaction between Group*Agent ($X^2_{(1)} = 45.34, p < 0.001$)(Figure 20), marginal effects from the interaction were extracted with Tukey multiplicity adjustment. Overall there was a significant effect of agency within the control group t(405) = -8.12, p <0.001, and in patient group t(405) = 02.45, p = 0.01 (Figure 22). Between groups a significant effect was seen for other-agency between patients and controls t(55) = -4.12, p < 0.001, while for self-agency no significant effect was seen between patients and controls t(55) = -1.52, p = 0.13.

There was also a two-way interaction for Group*Effort ($X^2_{(4)} = 4.28, p = 0.03$), whereby patients put in more effort compared to controls across all effort levels (p<0.01) (Figure 22; Supplementary: Table 4). There was also a significant 2-way interactions for Agent*Reward ($X^2_{(4)} = 22.93, p < 0.001$), marginal effects from the interaction showing that participants favour self to other across all reward conditions (p<0.01). Main effects of p<0.01 were seen in all conditions (Group, Agent, Effort, Reward).

Finally a significant three-way interaction was seen for Agent*Effort*Reward ($X^2_{(16)} = 38.04, p = 0.001$). With increasing levels of effort and reward a significant difference in agency, favouring self was seen for level 2 (z = 1.9, p = 0.04) and 3 (z = 3.1, p<0.01) (Figure 20, 21).

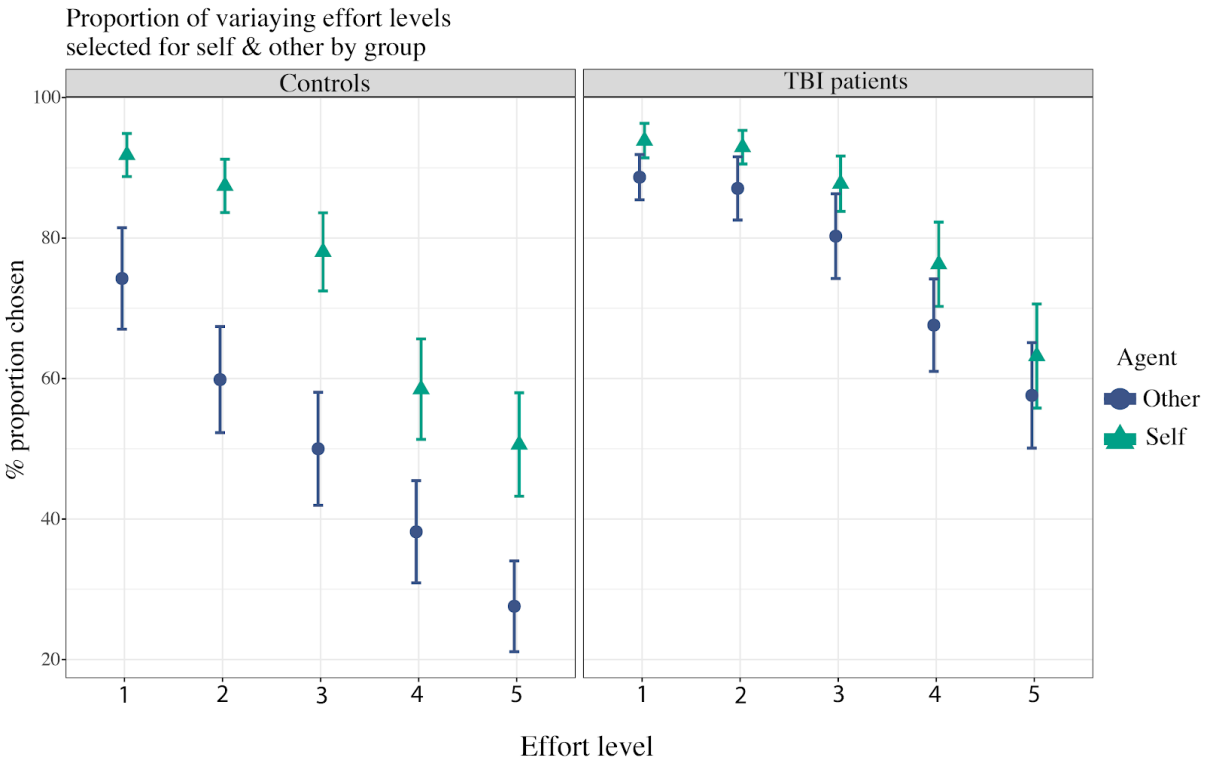


Figure 20: Proportion of varying effort levels selected for self & other by group

Effort levels 1-5 correspond to 30%, 40%, 50%, 60% or 70% of the participants maximum voluntary contraction (MVC)

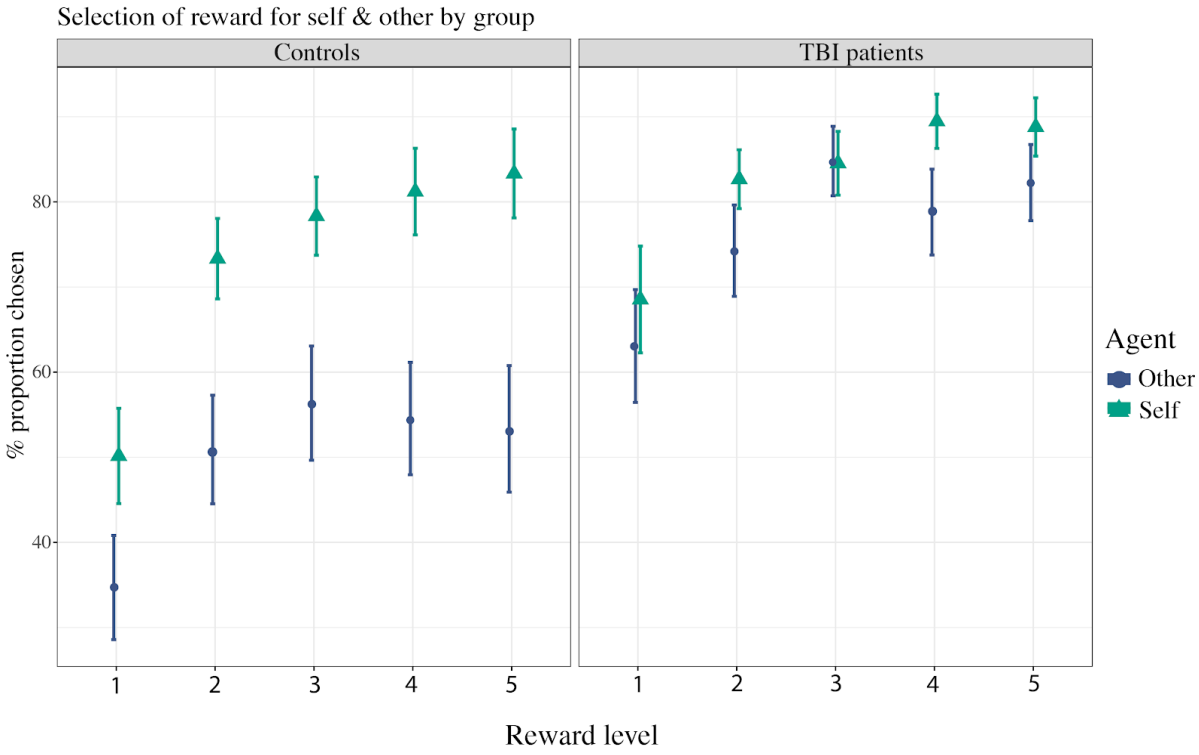


Figure 21: Proportion of effortful choices accepted by reward level for self and other in both TBI and control groups

Reward levels 1-5 correspond to 2, 4 ,6, 8, or 10 credits. The choice of these rewards involves variable levels of effort to attain and are in contrast to a single credit available that involves no effort to attain.

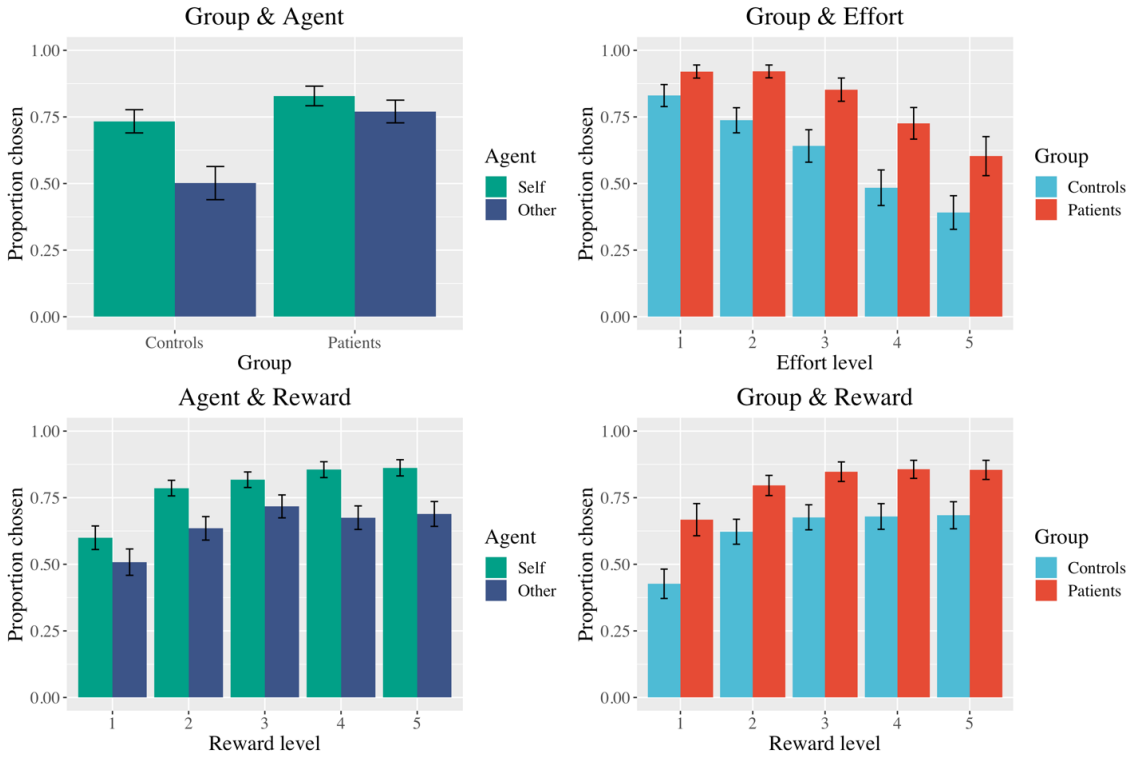


Figure 22: Two-way interactions for choice data

Force

Further to choice analysis I investigated to what extent do participants energise their actions, to account for the possibility of superficial choices being made. To account for between subject variability force was normalised to each participants maximum voluntary contraction. A significant three-way interaction was seen for Group*Reward*Agent $X^2_{(16)} = 14.02$, $p = 0.007$ (Figure 23, 24), post-hoc analysis indicated significant differences in force were applied for reward for self, compared to other in controls ($z = -5.9$, $p<0.001$), but not for patients ($z = -0.8$. $p = 0.42$). Another significant three-way interaction was seen for Group*Effort*Reward $X^2_{(4)} = 11.55$, $p = 0.02$, post-hoc analysis show significant effects for higher reward and effort levels 3-5 ($p<0.01$) with less force applied by controls compared to patients. A final significant three-way interaction was seen for Effort*Reward*Agent $X^2_{(16)} = 81.84$, $p< 0.001$, post-hoc analysis indicating as reward and effort increase less force is applied for other compared to self (Figure 23, 24). Further significant two-way and main effects were seen across all conditions $p<0.01$ (Supplementary figures in Appendix 1).

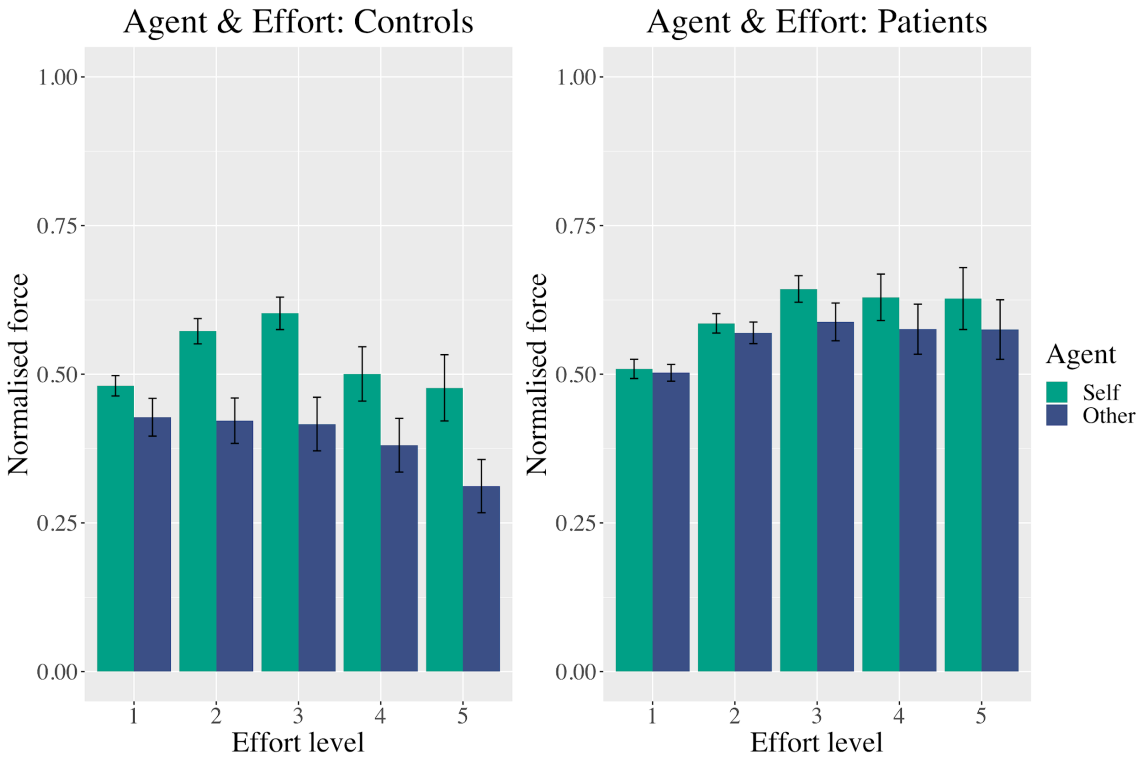


Figure 23: **Normalised force exerted across each effort level for self and other conditions**



Figure 24: **Normalised force exerted across each reward level for self and other conditions**

Computation modelling results

Further to mixed effects models of behavioural data, computational modelling was applied to characterise the subjective influence of effort on rewards for self and other. A range of computational models were explored to describe how reward is devalued by the amount of effort required (K). These models varied by investigating single or separate reward discounting parameters for self and other, as well as single or separate noise parameters (β), with parabolic, linear, or hyperbolic discounting functions.

1. Parabolic, single discounting parameter, single noise parameter
2. Linear, single discounting parameter, single noise parameter
3. Hyperbolic, single discounting parameter, single noise parameter
4. Parabolic, single discounting parameter, separate noise parameter
5. Linear, single discounting parameter, separate noise parameter
6. Hyperbolic, single discounting parameter, separate noise parameter
7. Parabolic, separate discounting parameter, single noise parameter
8. Linear, separate discounting parameter, single noise parameter
9. Hyperbolic, separate discounting parameter, single noise parameter
10. Parabolic, separate discounting parameter, separate noise parameter
11. Linear, separate discounting parameter, separate noise parameter
12. Hyperbolic, separate discounting parameter, separate noise parameter

Replicating previous findings in healthy controls, the winning model of control participants was a parabolic discounting model with separate parameters devaluing reward (K) for self and other with a single noise parameter (β). TBI patients showed a contrasting best fit model to explain reward devaluation with effort, where behaviour was best explained by a parabolic

model with a single parameter for devaluing reward (K) with a single noise parameter. Thus explaining behaviour as treating self and other conditions the same. The winning model in patients had the lowest BIC score seen in the majority of the group 79% compared to a similar performing model with two noise parameters 21% (Figure 25).

The pooled data of controls and patients indicated the overall winning model to be a parabolic discounting model with separate parameters devaluing reward (K) for self and other with separate noise parameter (β). This was based on the lowest Bayesian Information Criterion (BIC) score when contrasting with 12 other possible models (model 10: Figure 25).

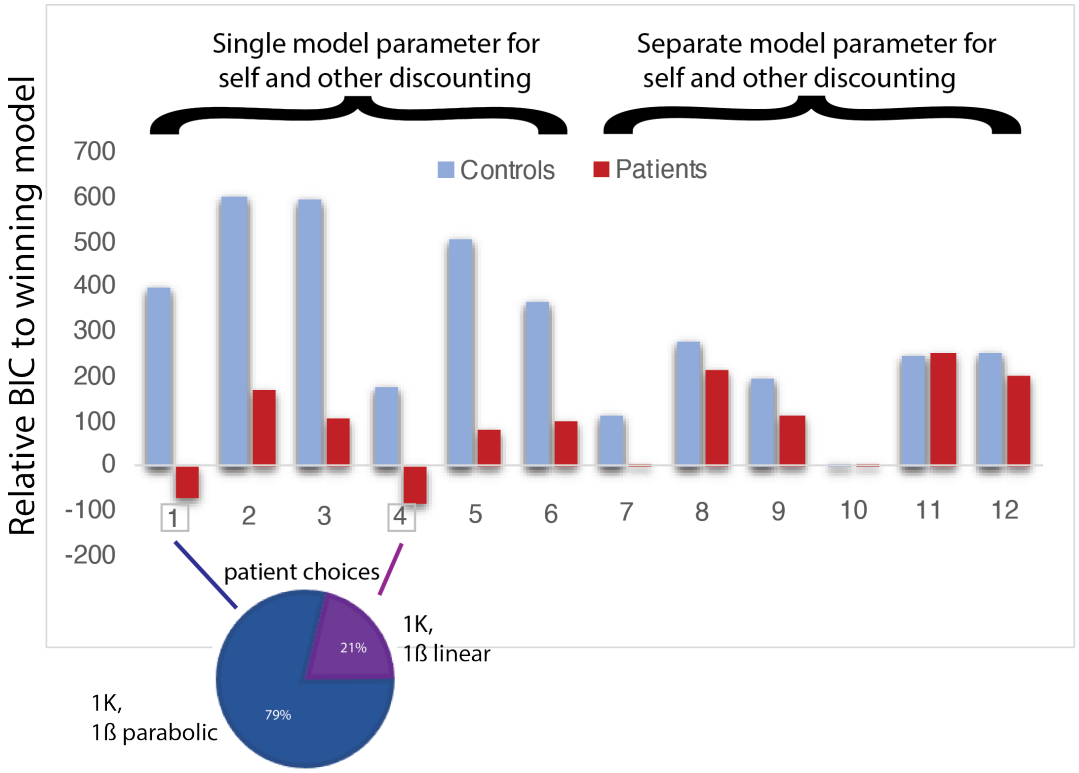


Figure 25: TBI patients discount rewards less by effort compared to controls, particularly for others.

A model comparison of single (models 1–6) discount parameters and separate discount (K) parameters (models 7–12) for self and other. Split into parabolic, linear and hyperbolic discounting functions with single or separate noise (β) parameters for self and other

A parabolic model with separate parameters for self and other discounting and noise parameter, best explained behaviour in the majority of subjects in both groups (model 10), which was determined by this model having the lowest summed BIC score, in combination with explaining behaviour in the highest proportion of participants. The pie chart shows the proportion of participants that the winning parabolic model for patients explains behaviour for (blue) compared with a linear model with separate noise parameters (purple). Graph displays relative BIC to overall winning model for both groups (10).

Following from the behavioural results, to examine if patients differentiated between self and other trials, I compared the reward discounting parameters from the computational modelling separately in each group. Wilcoxon signed rank tests showed controls distinguished between self and other trials (W = 121, p <0.001, 95% CI = [-0.23, -0.03]), replicating previous findings, where controls had significantly higher reward discounting for other compared to self (Lockwood et al., 2017). While patients did not distinguish between self and other trials (W = 128, p = 0.54, 95% CI = [-0.05, -0.01]). Furthermore differences between groups can be seen for Other K (W = 419, p <0.01, CI = [-0.02, 0.51), but not Self K (W = 306, p = 0.5, CI = [-0.02, 0.06]) (Figure 26).

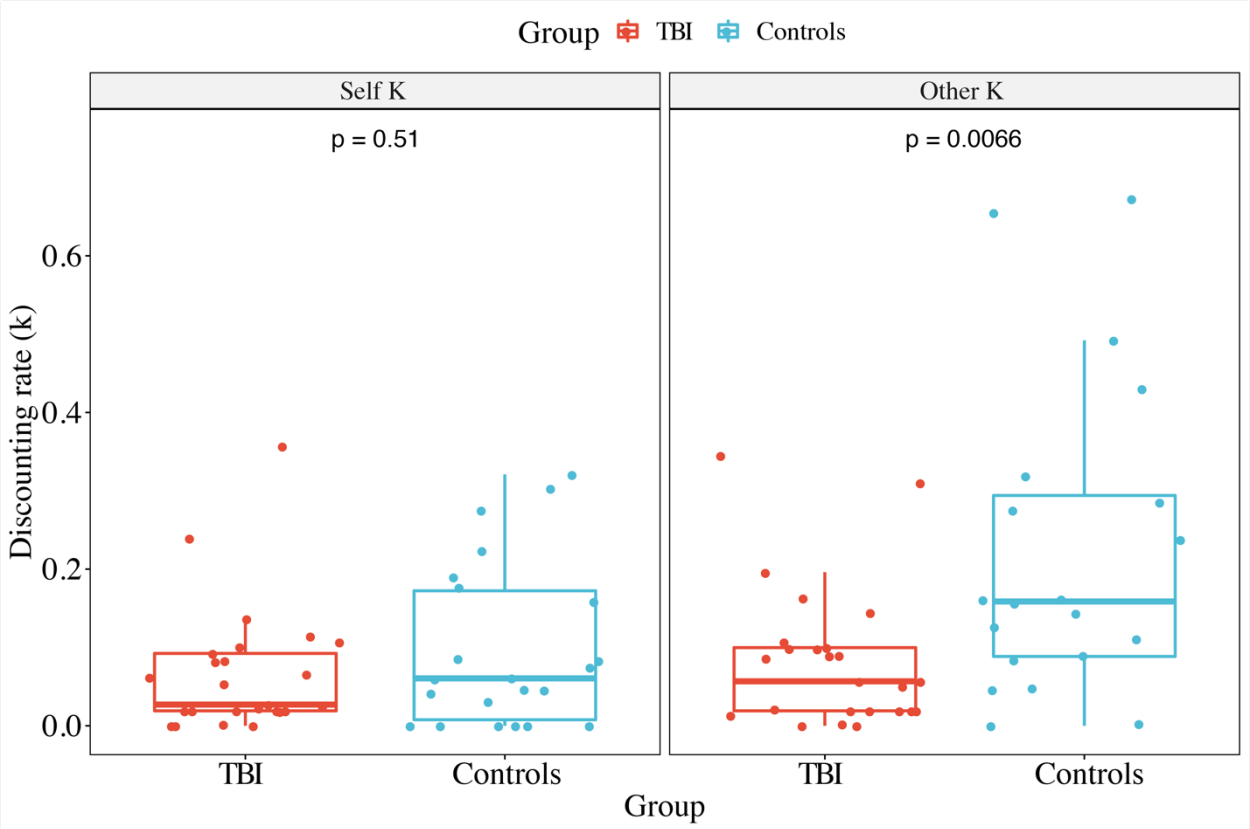


Figure 26: Discount rate (K) for self and other across groups

Differences in reward discounting between TBI patients and controls can be seen for other condition, while similar levels of reward discount are present for self.

5.4.3 Reward discounting and apathy-motivation

I next investigated the hypothesis linking higher levels of apathy and increased reward discounting in TBI patients. There was no relationship found for Self K ($r^2 = 0.3$, $p = 0.11$) and Other K ($r^2 = 0.35$, $p = 0.085$).

5.4.4 Neural correlates

Patient summary measures

Focal frontal lobe lesions were present in twelve TBI patients ($mean_{vol} = 26{,}230mm^3$, range = [$128mm^3$ - $307{,}736\ mm^3$]), four of which extended into the striatum. In addition 3 patients without focal lesions had evidence of microbleeds. The SBR for striatal DaT was abnormal in thirteen TBI patients based on clinical reporting and quantitative analysis of >1SD below a comparative control group ($mean_{SBR} = 2.36(0.5)$, range = [1.37 – 3.37]).

There was a significant group difference between patients (mean = 0.38(0.05)) and controls (mean = 0.43(0.02)) for white matter FA ($W = 346$, $p < 0.001$), while there was no significant difference between patients (mean = 0.46(0.07), $p = 0.07$) and controls (mean = 0.48(0.06)), $p = 0.06$ for white matter volume ($W = 304$, $p = 0.36$)(Figure 27). From the selected ROIs, only the sgACC was significantly reduced in volume for patients (mean = 0.47(0.05)) compared to controls (mean = 0.51(0.05)), $t = 2.5$, $p = 0.01$. None of the other ROIs showed a significant group differences; DMPFC ($W = 328$, $p = 0.15$), ACCg ($W = 248$, $p = 0.76$), TPJ($W = 311$, $p = 0.29$).

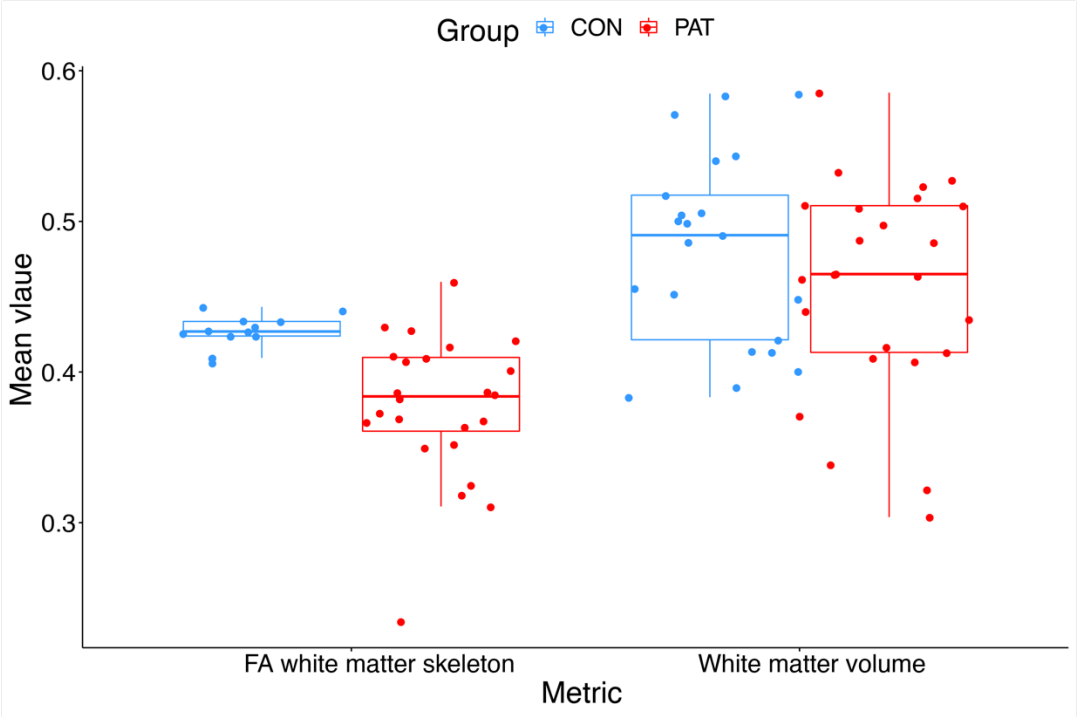


Figure 27: Estimates of white matter structure

Apathy

Previous caregiver and self-reports in this patient cohort indicated that levels of apathy are greater in patients with TBI compared to controls, with a strong relationship to caudate DaT levels (described in Jenkins et al., 2019). This association with care-giver reports of apathy can also be seen with lower DaT in the nucleus accumbens (adj-$R^2 = 0.27$, $p = 0.01$)(Figure 28).

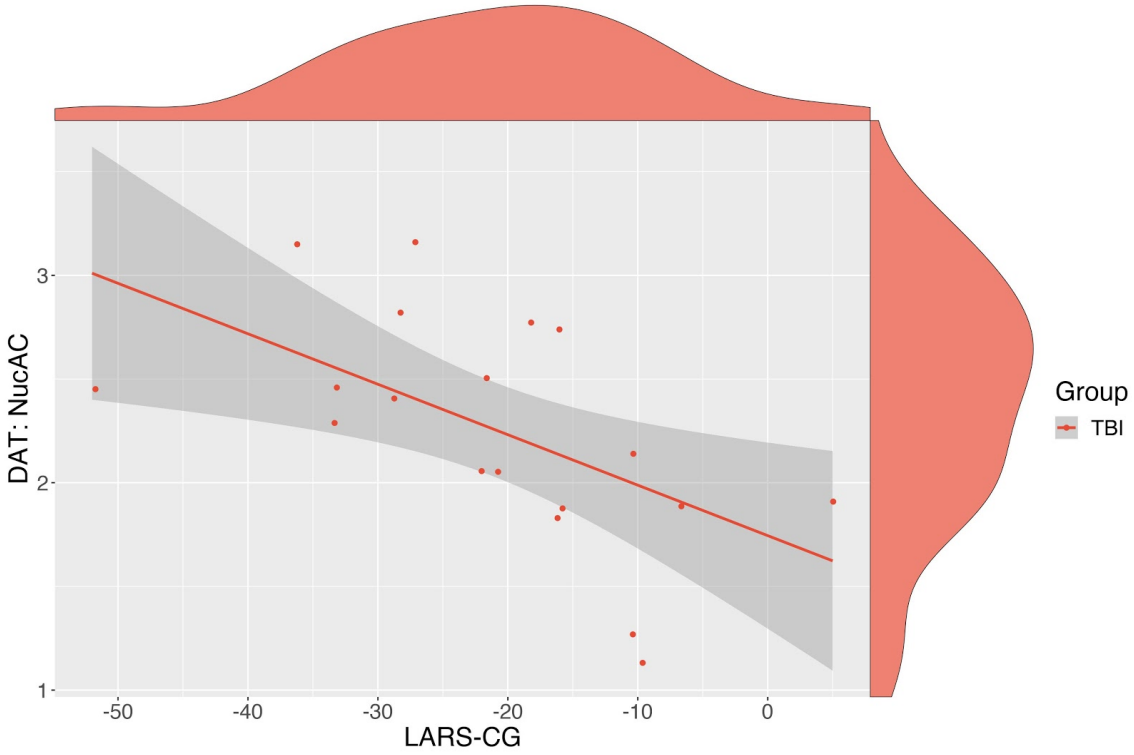


Figure 28: **Plot of LARS-Care Giver with DaT in the Nucleus accumbens**

Further investigations of neural corelates of white matter structure for caregiver reports of apathy in TBI patients did not show significant relationships. Further exploratory analysis with discrepancy scores between patient and caregiver also showed no relationship with white matter structure.

Follow-up assessments of apathy showed behavioural activation was significantly related with white matter volume (adj-$R^2 = 0.22$, $p = 0.01$) and FA (adj-$R^2 = 0.20$, $p = 0.02$) in both patients and controls (Figure 29, 30).

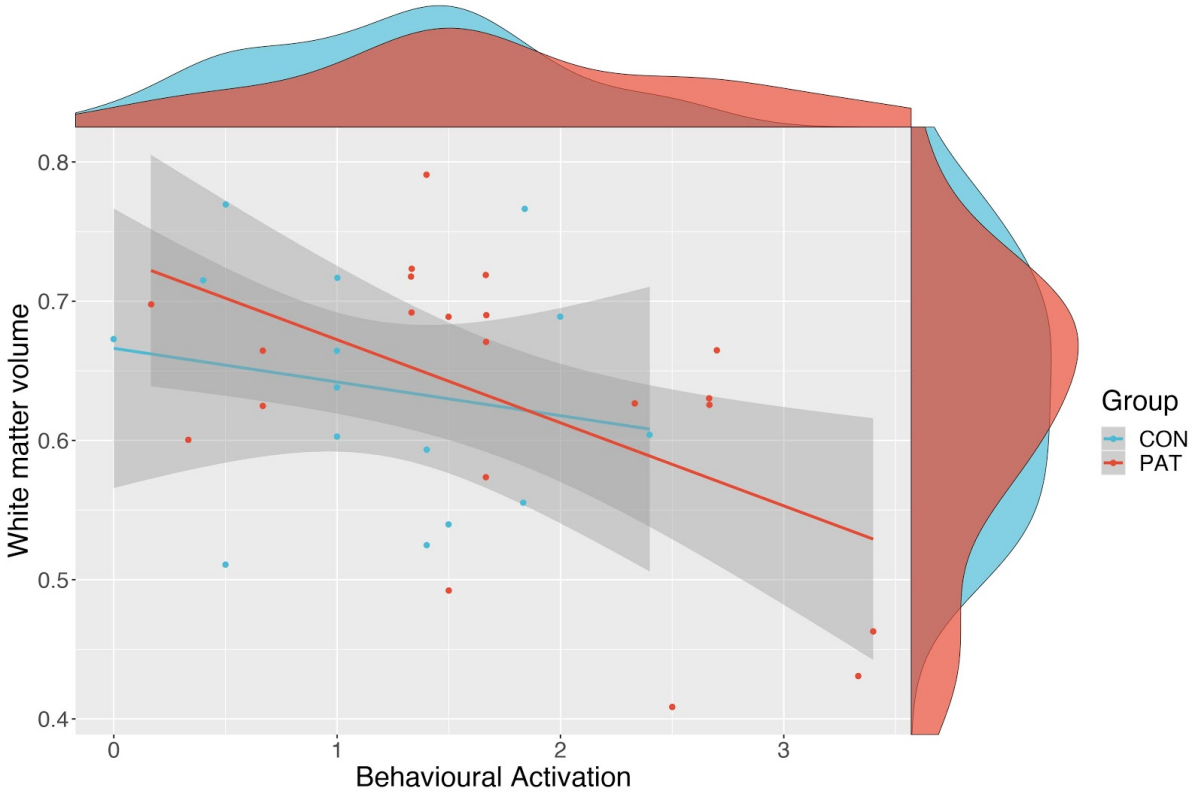


Figure 29: **Plot of behavioural activation (apathy relating to self-initiation) and white matter volume**

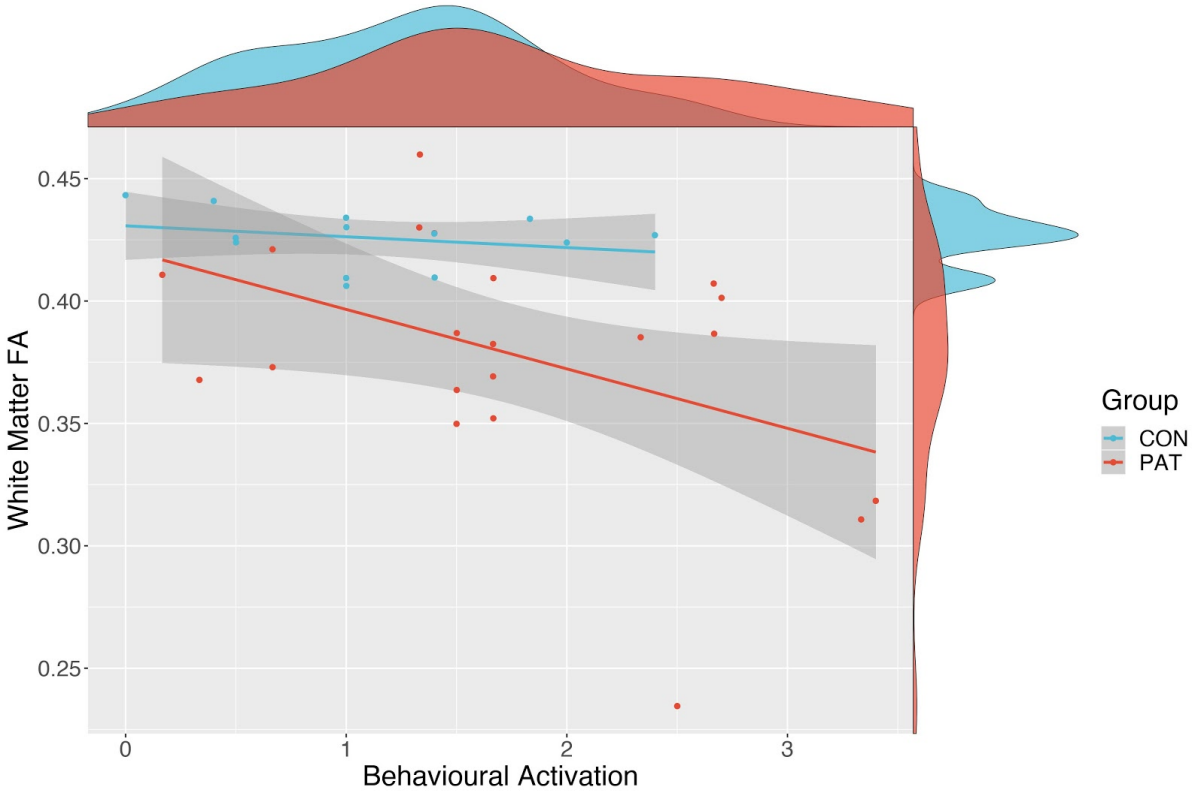


Figure 30: **Plot of behavioural activation (apathy relating to self-initiation) and white matter fractional anisotropy (FA)**

Reward discounting

No significant difference was seen for reward discounting between patients with and without focal lesions $F(1, 23) = 0.73$, $p = 0.4$. No significant relationship was seen for reward discounting and striatal DaT in TBI patients for Self K ($r = 0.19$, $p = 0.36$) or Other K ($r = 0.11$, $p = 0.44$). Additionally voxelwise analysis of FA and volume showed no significant relationship to white matter structure in relation to reward discounting (K) (Figure 31, 32). Further ROI volume analysis investigated the relationship of ROI and group to Other K. No significant interaction was seen for sgACC and group for other K, $F(1, 42) = 0.14$, $p = 0.7$, nor main effect $F(1, 42) = 0.31$, $p = 0.58$ and group $F(1, 42) = 0.01$, $p = 0.91$. No significant interaction was seen for ACCg and group for other K, $F(1, 42) = 0.33$, $p = 0.56$, nor main effect $F(1, 42) = 0.80$, $p = 0.37$ and group $F(1, 42) = 0.03$, $p = 0.84$. No significant interaction was seen for DMPFC and group for other K, $F(1, 42) = 0.05$, $p = 0.82$, nor main effect $F(1, 42) = 0.11$, $p = 0.73$ and group $F(1, 42) = 0.45$, $p = 0.50$. No significant interaction was seen for TPJ and group for other K, $F(1, 42) = 0.01$, $p = 0.91$, nor main effect $F(1, 42) = 0.002$, $p = 0.96$ and group $F(1, 42) = 0.05$, $p = 0.80$.

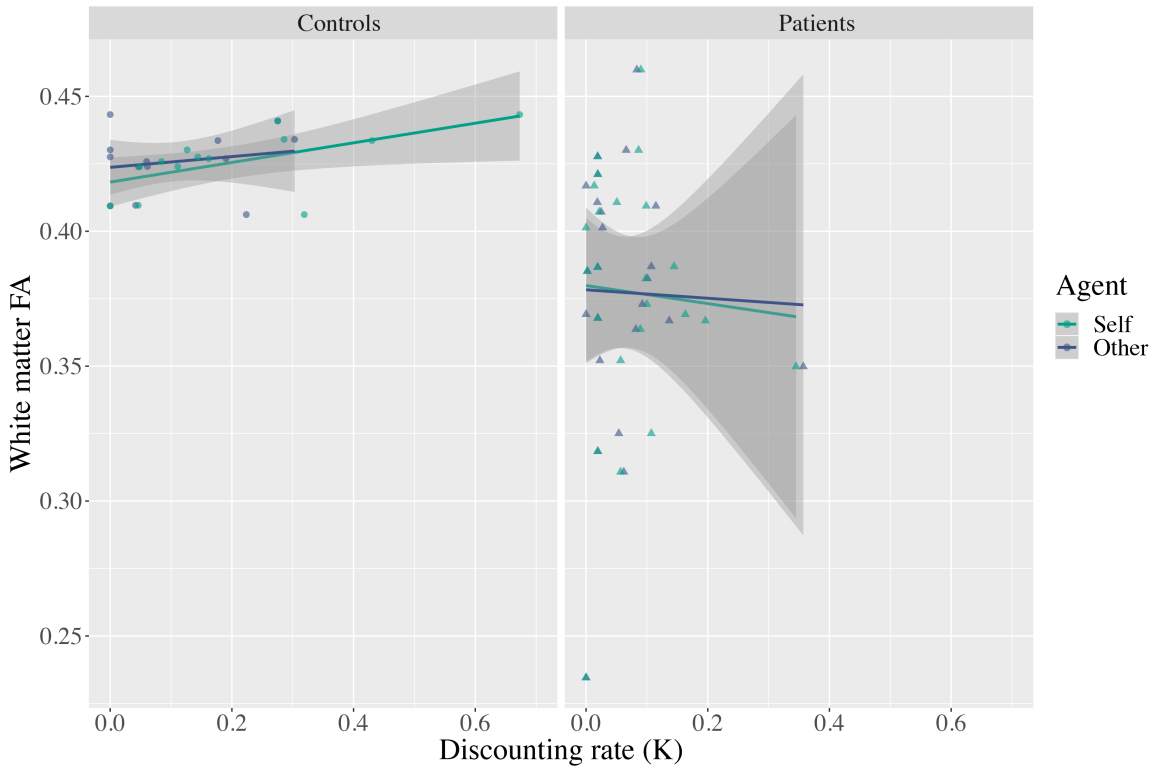


Figure 31: White matter FA & discounting rate (K) across patient and control groups

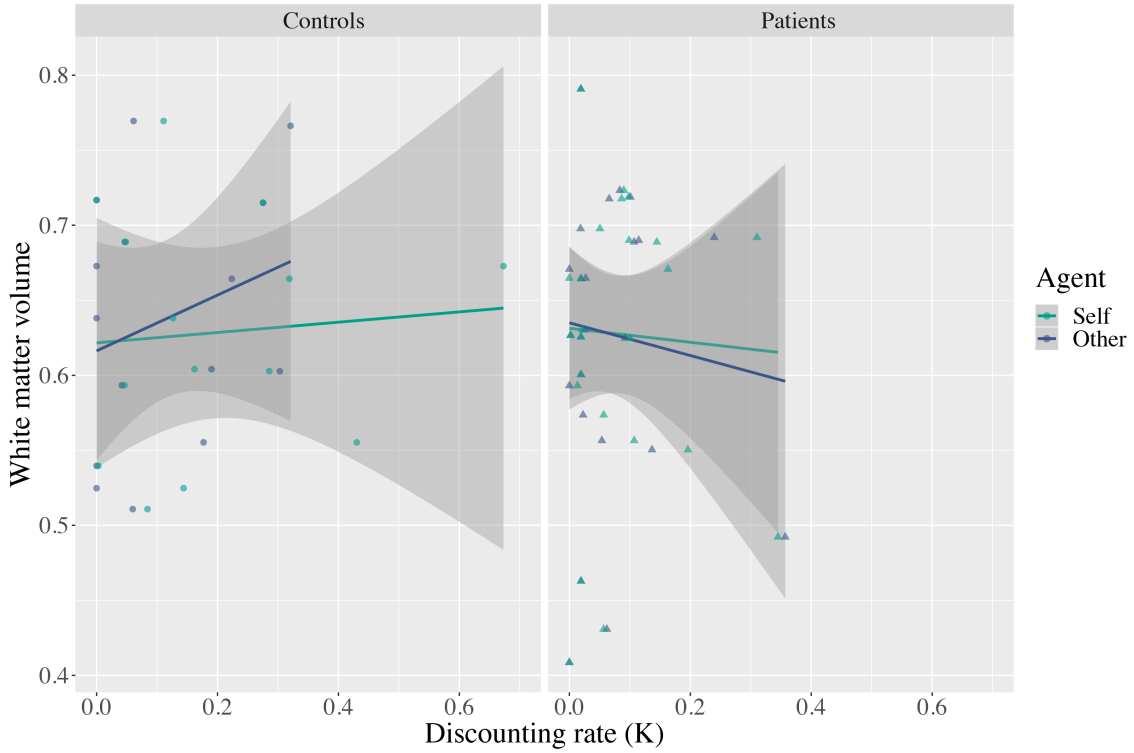


Figure 32: White matter volume and discounting rate (K) across patient and control groups

5.5 Discussion

Valuation and motivation to exert effort is an important feature in decision making. Here I show that higher levels of apathy are correlated with reduced DaT in the nucleus accumbens. Counter to my original hypothesis, while apathy continues to be a significant feature at follow-up of TBI patients, this was not related to aberrant social decision making in a reward discounting paradigm. Application of computational modelling and mixed effects models show that TBI patients did not discriminate between self and other when making choices and failed to discount rewards by effort, thus choosing more effortful acts more frequently overall compared to controls. This lack of self-bias in TBI patients was not only present for decision making but was also seen in energising action. Patients applied a similar level of force to attain reward for both self and other and no interaction was seen between effort and reward for force applied in the patient group. While strong behavioural results are seen, no direct neural correlates were observed for reward discounting.

Overall, these results show that over time apathy continues to be an enduring sequalae following TBI with neural correlates relating to white matter structure and reduced DaT. Despite self-reported behavioural apathy, patients performed similarly to controls in a reward discounting paradigm playing for self. Unlike controls, patients did not differentiate in reward discounting when playing for someone else. This divergence in social behaviour could be important for assessing risks and vulnerabilities due to decision making in TBI patients, where there may be a lack of integration of social information. This may result in abnormal pro-sociality, putting patients at increased risk of scams.

This work extends research in the area of motivation and reward processing in a social context, and constitutes the first time such a paradigm has been run in patients with

moderate-severe TBI. An important strength of this experimental design is the ability to distinguish between superficial choices in behaviour and actual effort provided. Previous behavioural economic research has shown that without an actual cost associated with their decisions, participants' choices alone can appear superficially prosocial (Lockwood et al., 2017). Importantly the results in both choice and energising of action indicate a significant difference between TBI patients and controls when it comes to reward discounting for self and other. The paradigm I used to investigate patients is relatively straightforward and lack of understanding of the task is unlikely to explain behavioural results in the patient group. Patients were compliant with the task instructions and showed similar reduced choices at higher effort costs to controls. Success rates for attaining rewards based on choices did not vary significantly between groups. In addition, when looking at the normed forces across effort levels this tracked in line with expected increasing force required for increasing effort levels, suggesting sufficient effort being applied. These results highlight the importance of investigating reward, motivation and effort independently to understand how they may interact in shaping decision making and behaviour in this patient group.

Behaviour in this cohort of patients for reward discounting may be explained by a change of executive functioning in which they incorrectly judge the value of effort and reward or fail to distinguish value between agents, rather than apathy. In other words, patients inappropriately don't discount reward irrespective of agent. Impaired reward processing has been described previously in the TBI literature (Cotrena et al., 2014). Influence of reward and effort on decision making for TBI patients could be explored in much finer detail. If patients demonstrate high sensitivity to reward, this could be a target of reward-based learning within the domain of cognitive rehabilitation. Recent work has even shown that reward can reduce cognitive fatigue during task completion (Dobryakova et al., 2020).

In a response to a BMJ article discussing accepting gifts from patients, it highlighted a number of factors that may contribute to abnormal pro-sociality, including head injury resulting in significant financial and social burden for patients and caregivers (Davies, 2015). While there is anecdotal evidence to support this claim, little empirical evidence can be found. There are references to a case study following a left lenticular stroke of pathological generosity resembling an impulse control disorder (Ferreira-Garcia et al., 2014). Additionally case reports on fronto-temporal dementia patients show a group with personality changes characterised by social disinhibition resulting in acquired extroversion (Mendez & Shapira, 2011). The current findings may suggest an important clinical presentation of abnormal pro-sociality in TBI patients, or a lack of differentiation between self and other leading to poor economic choices. Such a deficit may lead patients be susceptible to being taken advantage of, such as phishing scams or inappropriately trusting of strangers

While no link between apathy and reward discounting was seen in the current work, it remains an important sequala following TBI. A discrepancy between caregiver and patient reports was also seen for measures of apathy. The importance of such self-awareness assessments is discussed later in the chapter on metacognition. Taking a multidimensional perspective to apathy in clinical disorders, we should note that previous work has shown that behavioural and social apathy is increased in PD patients while emotional apathy is preserved (Ang et al., 2018). The authors highlight the importance of investigating these distinctions across neurological and psychiatric disorders in order to better target and evaluate interventions. Importantly, the results in my current work suggest that deficits in social apathy may not be present following TBI; however, patients still reported significant reductions in social functioning. Further work is required to investigate factors relating to the

reduction of social functioning in the absence of apathy in TBI patients, such as depression or other cognitive or physical impairments.

Apathy has been described as clinical syndrome separable to depression and a common in a range of neurological disorders including TBI, with a basis in fronto-striatal connectivity (Ang et al., 2017; Le Heron et al., 2018). An important consideration is classification of apathy typically has been difficult to dissociate from depression due to a high level of symptom overlap. Clinical distinction between apathy and depression is often based on reduced motivation by identifying the emotional component (Di Santo, 2019; Iacobacci, 2017). Depression is an affective disorder characterized by extreme low levels of mood and or negative thinking, impacting on daily function while apathy is a disruption of goal-directed behaviors, that may include emotional blunting. This judgement may be made clinically but still poses a difficulty interpreting measures in a research context.

With large enough samples mediation analysis may provide a useful way to distinguish between measures of apathy and depression on cognition (Funes et al., 2018). This would be a useful direction in future work investigating the relationship with social decision making. Limitations of this approach include shared symptoms being reported in each measure for apathy and depression. In the current work the BDI provides a single score as a measure of depression. Consideration of deriving subscales through factor analysis in further work could dissociate clusters of symptoms. Previous work has identified two factors from the BDI, Cognitive-affective and Somatic (Whisman et al., 2000). This study did not consider apathy symptoms of depression and may not have been the optimal solution. A similar approach previously used in a sample of Parkinson's patients combined an apathy scale and the BDI in a factor analysis to derive separable apathy, depression, overlapping symptoms and somatic

symptoms (Kirsch-Darrow et al., 2011). Alternatively measures of depression and apathy from the NPI do not share overlapping symptoms (Levy et al., 1998).

No neural correlates associated with the reward discounting parameter (K) were seen. This may reflect limitations of sample size and availability of patient imaging data. The nature of patient responses for reward discounting resulted in the groups responses clustering around zero, making relationships difficult to detect with the current sample. However the presence of apathy was related to global white matter impairment and reduced DaT in the nucleus acumbens. This could have important implications for identifying TBI patients who may be at greater risk of apathy disorders following injury.

5.6 Conclusion

Apathy is a consistent issue following traumatic brain injury. Evidence from the current work along with results across a range of neurological conditions indicate the importance of striatal dopamine on levels of apathy. Despite higher levels of apathy, TBI patients' reward discounting behaviour showed unexpected patterns. Patients exhibited lower levels of reward discounting for others compared to healthy controls. Taken together, we may conclude that the results of this paradigm were likely unrelated to reported apathy in patients, but may be due to altered reward processing relating to valuation of self and other. Further work is required to investigate how this altered social processing may impact on everyday functioning in TBI patients.

Chapter 6 | Testing a novel app-based assessment of emotional processing via the web, face to face and remotely by smartphone in TBI patients and healthy subjects

In this chapter, I look at newly developed digital assessments of emotional processing. This is conducted through a large-scale online study in the general population, a face to face assessment of TBI patients and healthy controls as well as a remote assessment via smartphone with a new cohort of TBI patients and controls.

6.1 Abstract

Evaluation of social and emotional deficits following TBI is relatively sparse in comparison to "cold" cognitive functions such as processing speed or memory. This may be attributed to the relative challenges of evaluating social and emotional difficulties experienced by patients following an injury. This includes a lack of freely available measures of social and emotional functioning. Digital assessments are a convenient and reliable way to assess cognitive functioning, with potential clinical utility and the added benefit of easier record-keeping and continuity.

The current chapter utilises a novel digital platform to evaluate cognitive function, with a focus on social and emotional processes. This digital platform is app-based and can be delivered in person via a tablet or remotely by smartphone or the web. Three studies are reported: A large-scale, web-based population study (n = 2,683), a face to face assessment

using a tablet device to assess emotional processing in TBI patients (n = 27) and healthy controls (n = 24), and finally a remote smartphone app based assessment on an independent cohort of TBI patients (n = 26) and healthy controls (n = 53).

The online web study provided useful age and gender curves on a large scale, which may be used as normative data. It has also demonstrated the efficacy of large scale cognitive testing online. The tablet and remote smartphone assessment highlights difficulties TBI patients may experience with recognising emotional expressions. Together these three studies demonstrate the utility of digital assessments for emotional processing in both face to face settings and remotely via smartphone or the web.

6.2 Background

Emotional processing, or the ability to recognise emotions in others, is one of three key components of social cognition, along with social understanding and social decision-making. While not the only source of information for social decision-making, facial processing plays a vital role in our judgments (Winston et al., 2002). The ability to ascribe value to events has been described previously as an evolutionary advantage for value-dependent learning (Friston et al., 1994). It can also be thought of in terms of learning from social and emotional situations. In short, emotions have an intrinsic value which influences our behaviour and other aspects of perception and cognition (Dolan, 2002).

As discussed in the introduction of this thesis, emotional problems are common in TBI patients. Impacts of these issues include negative ramifications on interpersonal relationships and high economic cost to society (May et al., 2017), reflecting an urgent need to develop assessments of emotional processing that can be easily implemented. Freely available

standardised measures of social cognitive functioning are scarce. Cognitive testing platforms like CANTAB (www.cambridgecognition.com) have become widely used, and include an emotional recognition test. The lack of a broader set of social and emotional tests is limiting. In addition restrictions on hardware to run the paradigms and associated costs limit the utility of this platform. Other batteries of tests including EMOTICOM are better suited to investigate social cognition, covering functions such as emotional processing, motivation, and impulsivity (Bland et al., 2016). While this battery is undoubtfully beneficial, and paves the way for a standardised test for social cognition, it is limited in delivery as it requires substantial user setup and installation of third party software PsychoPy (Peirce et al., 2019). In laboratory settings, with a researcher controlled setup, this works well and allows for a relatively easy environment to develop and test new paradigms. However it's translational value is somewhat limited, as it is a rigid structure. A move to self-contained app based technology has arisen to address the issue of cross platform compatibility (e.g. iOS, Android, Safari, Chrome). Development of software in this way provides more flexible delivery that can be run consistently across many platforms.

The ability to attain large amounts of data from the general public via the internet is a valuable asset to cognitive neuroscience. Aside from large sample sizes, it affords the opportunity to easily test new paradigms, alter parameters and evaluate measures that may be useful in other research or clinical settings. Previous work with web-based studies has focused on cognitive functions such as memory, processing speed or executive functioning (Hampshire et al., 2019; Owen et al., 2010). Newly developed batteries looking at social and emotional functioning, adapting gold standard psychological assessments and development of novel paradigms have been conducted. I will focus on a novel assessment of emotional

discrimination applied online in a large scale study of the general public as well as conducted face to face and remotely via smartphone with TBI patients and healthy controls.

There are increasing demands on resources available within healthcare and community rehabilitation systems. The aim of the current work is to assess emotional functioning on a novel digital platform, currently available as a clinical tool on a tablet, or remotely via mobile phone or the web. This is presented as three studies, each consisting of separate cohorts of participants (Figure 33).

The online web study in the general population is mainly hypothesis-free, with a data-driven approach. Its aim was to collect large samples of responses, evaluate the age and gender differences across a range of social and emotional tasks, and assess their potential utility in clinical research. For the following studies in TBI patients, I focus on one emotional processing task delivered in the web-based study. My hypotheses were as follows:

1. TBI patients will show reduced accuracy for emotional recognition and processing compared to healthy controls using novel digital assessments.
2. In TBI patients, there will be increased reaction time during the processing of incongruent emotional stimuli
3. Performance on these tasks will be associated with reported measures of emotional and social well-being. Patients are expected to show higher levels of deficits compared to controls.

6.3 Methods

The web-based study includes new tasks and questionnaires relevant to social and cognitive functioning with potential utility for future clinical studies, including emotional processing discussed here. The first patient study is a face to face assessment on a tablet device. The second cohort of patients and healthy controls completed assessments remotely on a smartphone app (Figure 33).

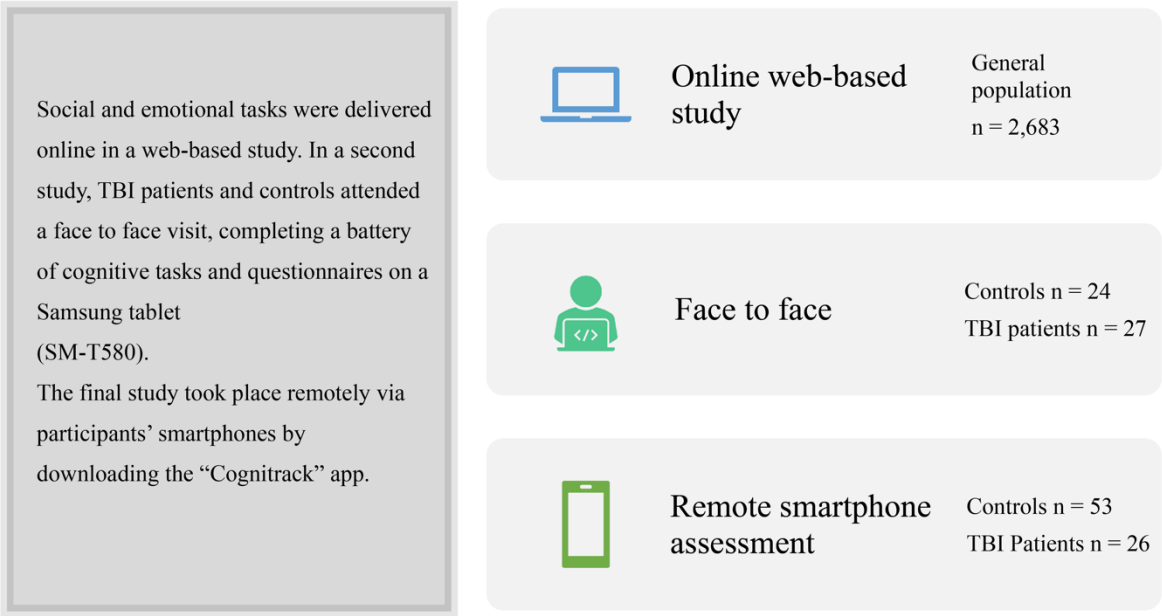


Figure 33: **Data flow diagram for studies presented in the chapter 6.**

Study 1 = Web-based study (BBC Collective Intelligence); Study 2 = Face to face;

Study 3 = Smartphone app (Cognitrack)

6.3.2 Participants and testing procedure

Web-based study participants and testing procedure

Data collection was performed between June and September 2019 via a website advertised in conjunction with the BBC's TV quiz show, "The Family Brain Games". All participants gave informed consent on the website by clicking a button before being able to access the

cognitive tasks. Assessment of data quality is vital for online sample testing. In the current study, performance feedback in relation to the distribution of the population was provided at the end of each task, updated in real-time. The aim of this feedback was to motivate participants to continue with the battery of tasks. Demographic information was collected at the end of testing. This was used as a filtering measure, as accurate demographic information is more reliably gathered from participants who went to the effort of completing all tasks. The first pass at data cleaning was to remove participants with no demographic information. Out of the 5,347 who logged on to attempt these tasks, 2,914 completed the entire testing battery. Participants with ages below 10 or above 80 were excluded from the analysis. Additionally, to deal with extreme or nonsensical scores, data beyond 4 SD were removed. After data-cleaning, 2,638 participants with complete demographic information were included in further analysis.

Face to face participants and testing procedure

Participants completing the social decision-making paradigm in the previous chapter were also evaluated in this chapter on the basis of their performance on cognitive tests implemented on our novel digital platform. Patients n = 27, mean age = 45(12.13), controls n = 23, mean age = 35.87(12.29). Further detail of clinical characteristics can be found in (Jenkins et al., 2018). All participants provided written consent to participate in the current study, approved by Camberwell-Giles ethics committee. Controls were recruited through Imperial College London's clinical research facility database. Exclusion criteria for controls included a previous or current history of psychiatric or neurological disorders. Additionally, controls underwent an MRI scan during their visit; thus, any contraindication was included as an exclusion criterion.

Testing took place in a quiet testing room to minimise distractions. Participants completed the 30min digital battery of tasks on a Samsung (SM-T580) tablet. This wider battery included a set of cognitive tasks to test emotional processing and executive function, only results of emotional discrimination will be discussed here. Participants also completed a set of standard questionnaires including the Beck Depression Inventory (BDI) and Social Network Index (SNI)(Beck et al., 2011; S. Cohen, 1997) (Table 3).

Remote smartphone app participants and testing procedure

Twenty-six patients aged between 23-71 years old, mean age = 40.07(12.56), 6 females took part in this study. Time since injury (months): mean = 16.91(25.88), range 0 - 101 months; 12 patients were in the acute phase, <= 6 months since the injury, 10 were in the chronic phase > 6 months since the injury. There was no reliable information on the remaining 5 patients on time of injury. The current analysis pools acute and chronic patients into a single group. Future work will investigate acute and chronic patients separately when larger sample sizes are available. Mechanisms of injury included RTA = 12, Home/domestic = 2, Sport/recreation = 6, Workplace = 1, Unknown = 6. Patients were recruited through trauma wards at the St. Mary's and St. George's Hospitals, as well as a specialist TBI outpatient clinic at St. Mary's Hospital. Forty-eight controls aged between 17-62 years old, mean age = 34.62(13.17), 27 females participated in the study.

Participants downloaded our app, named "Cognitrack", from either the Android or Apple app stores. This required entering an assigned participant ID for login and consenting to take part in a study by selecting a button at the end of an information sheet. Patients recruited through the outpatient clinic signed an additional paper consent form after going through an

information sheet. The study was approved by Camberwell-Giles ethics committee and Imperial College London.

6.3.3 Cognitive assessments of emotional processing

Emotional discrimination

Two facial stimuli are presented and participants are instructed to indicate if the expressions on these faces are the same or different (Figure 34). The task consists of 50 trials of emotional pairs, with randomisation balancing for emotional combinations. Stimuli used in the task were from the Chicago face database and consisted of happy, angry, fearful, neutral expressions (Ma et al., 2015). An effort was also made to balance stimuli across sex and ethnicity. Following the task participants are required provide a metacognitive judgment on their own performance (discussed in the following chapter). Incongruency accuracy and reaction time were calculated from the difference between congruent (same emotion stimuli) and incongruent (different emotion stimuli) conditions.

Task description for participants:

"Identifying and being able to discriminate between different emotions is important for normal social interactions. Test your ability to identify if two people have the same or different emotional expressions."

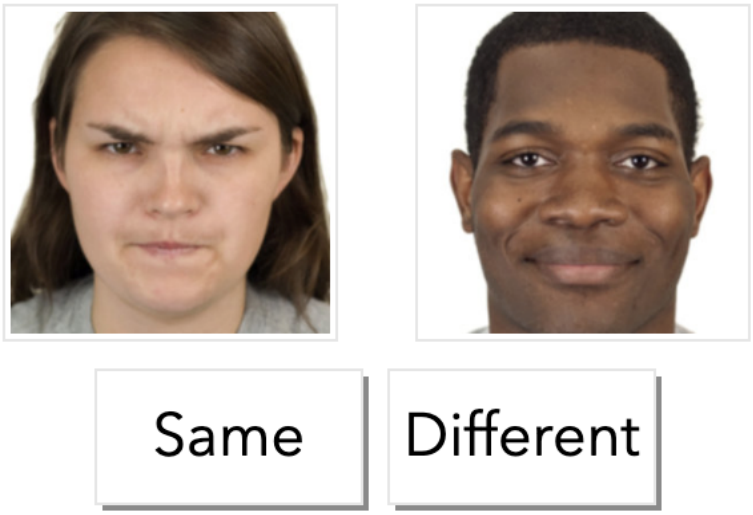


Figure 34: **Example trial of emotional discrimination task**

6.3.4 Statistical analysis

Behavioural data were analysed with the statistical package r (Core Team, 2018; http://www.R-project.org/). For measures of social functioning and well-being, group differences were investigated with separate Wilcox tests using FDR multiple comparisons correction. To assess the task design, accuracy and time costs were calculated by subtracting the respective measures under congruent stimuli conditions from those under incongruent stimuli conditions. A t-test comparing the sample to 0 was run for these cost measures. Group differences for total correct and cost scores were calculated with Wilcoxon sum ranks test due to non-normality of the data evaluated with a visual inspection of histograms and Q-Q plots. A description of general data exploration is given in general methods, following guidance from (Zuur et al., 2010). To explore potential relationships between the objective emotional processing measures and reported well-being across groups, mixed effect linear models were run. These comparisons were based on a priori hypothesis.

6.4 Results for digital assessments of emotional processing

6.4.1 Emotional discrimination: Web-based study

Analysis was conducted on 2,638 participants who had the complete task and demographic data. Women (n = 2,037) mean age = 39.33(15.54) consisted of the majority of the subject group, whereas the number of male participants made up about a quarter of the total (n = 601) mean age = 37.22(14.13) (Figure 35).



Figure 35: Distribution of age and gender on the completed data (web-based data)

Females (mean = 44.34(3.27)) showed overall higher accuracy than males (mean = 43.34(3.79)) , $t(2623) = 5.84$, $p < 0.001$. An overall significant difference was seen between congruent (mean = 0.91(0.08)) and incongruent conditions (mean = 0.86(0.09)), $t(2623) = -20.25$, $p = 0.001$. A linear model to explore the effects of age and gender on emotional discrimination incongruency cost showed no significant age $F(6, 2623) = 1.32$, $p = 0.24$, and gender $F(6, 2623) = 0.76$, $p = 0.38$ effects, with no significant age*sex interaction $F(6, 2623)$

= 1.73, p = 0.1. Across all participants, responses for incongruent stimuli (mean = 1866.20(466.17)) were significantly slower than those for congruent stimuli (mean = 1714.67(439.19)), t = -12.15, p < 0.005 (Figure 32). A linear model was run to examine the cost effect between congruent and incongruent conditions in relation to age category and sex. No significant age F(6, 2623) = 1.67, p = 0.12, sex F(1, 2623) = 3.17, p = 0.05 or interaction F(6, 2623) = 1.41, p = 0.21 effects were seen (Figure 36, 37).

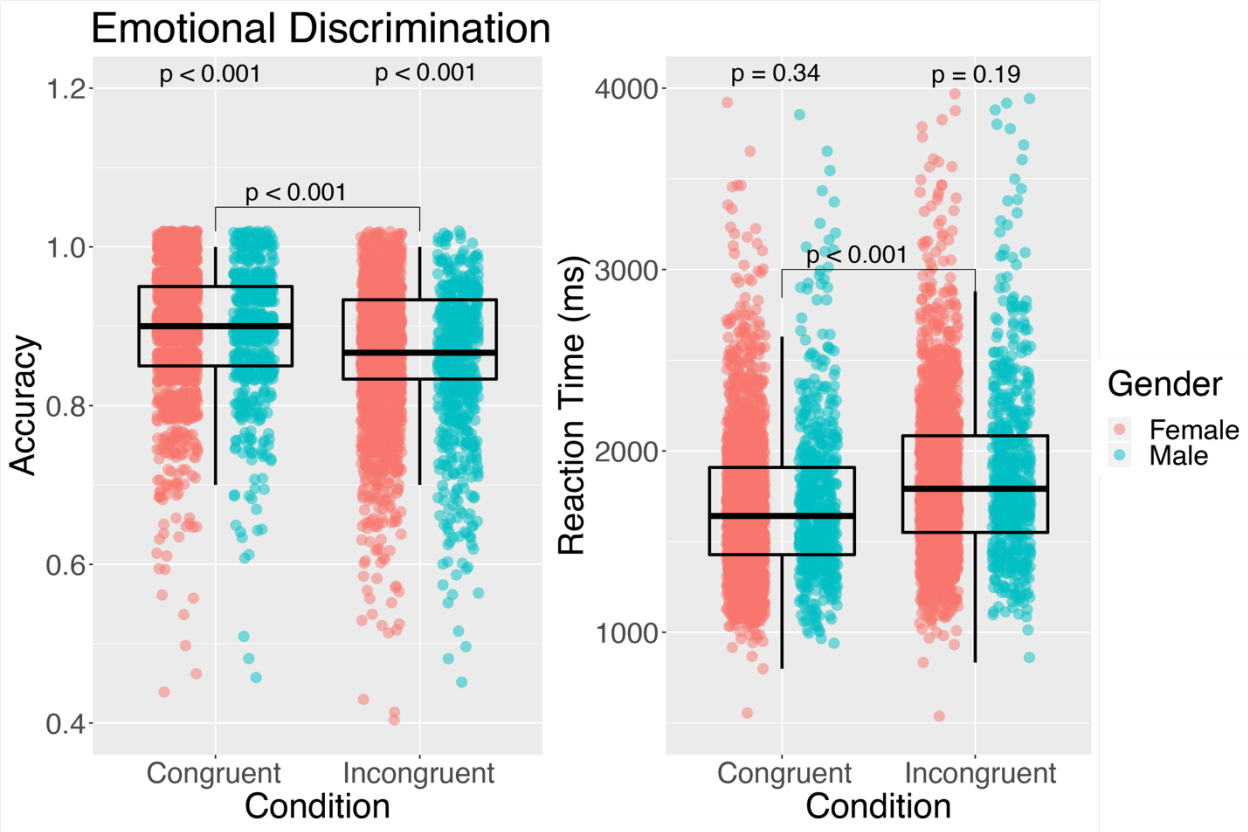


Figure 36: **Emotional discrimination accuracy and reaction time for congruent and incongruent conditions (web-based data)**

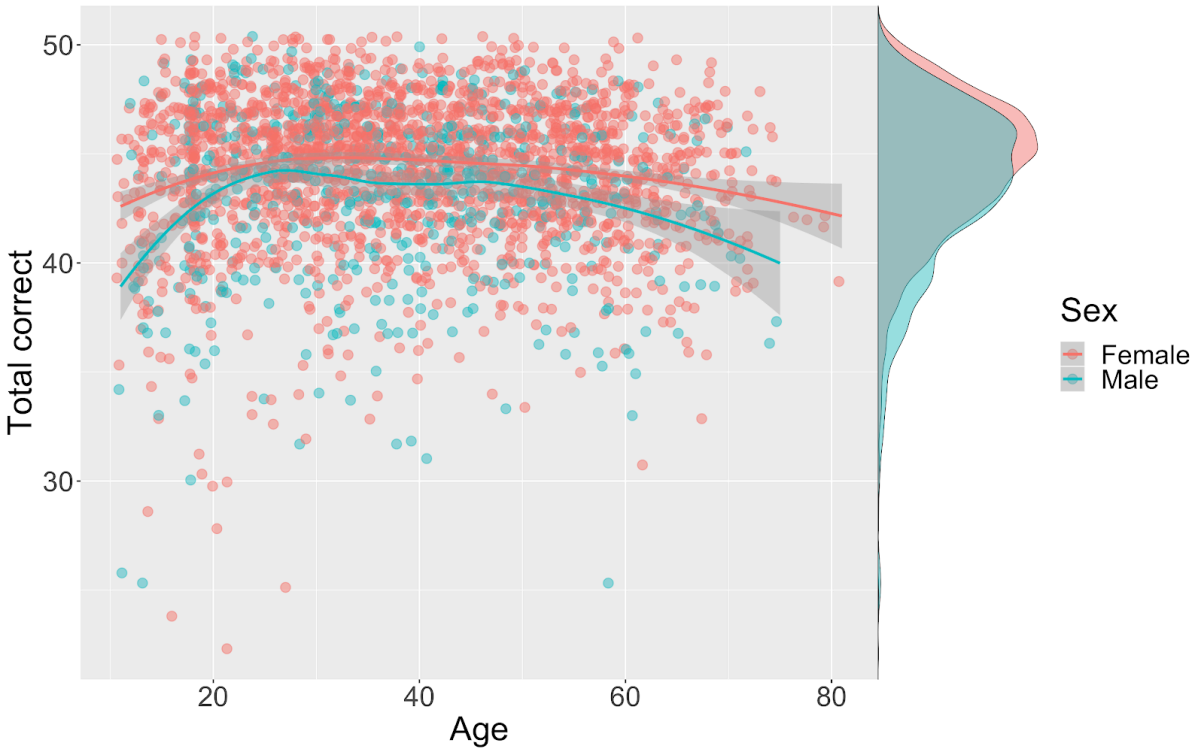


Figure 37: **Emotional discrimination total correct distribution between sex, across the total age range *(web-based data)***

6.4.2 Emotional discrimination: Face to face

No significant difference was seen for total correct between controls (mean = 43(3.96)) and patients (mean = 41.42(4.21)), (W = 337, p = 0.17)(Figure 38). A significant main effect was seen for accuracy cost (the difference between congruent and incongruent conditions) between patients (mean = -0.11(0.16)) and controls (mean = 0.01(0.08)), (W = 355, p = 0.042) (Figure 39)

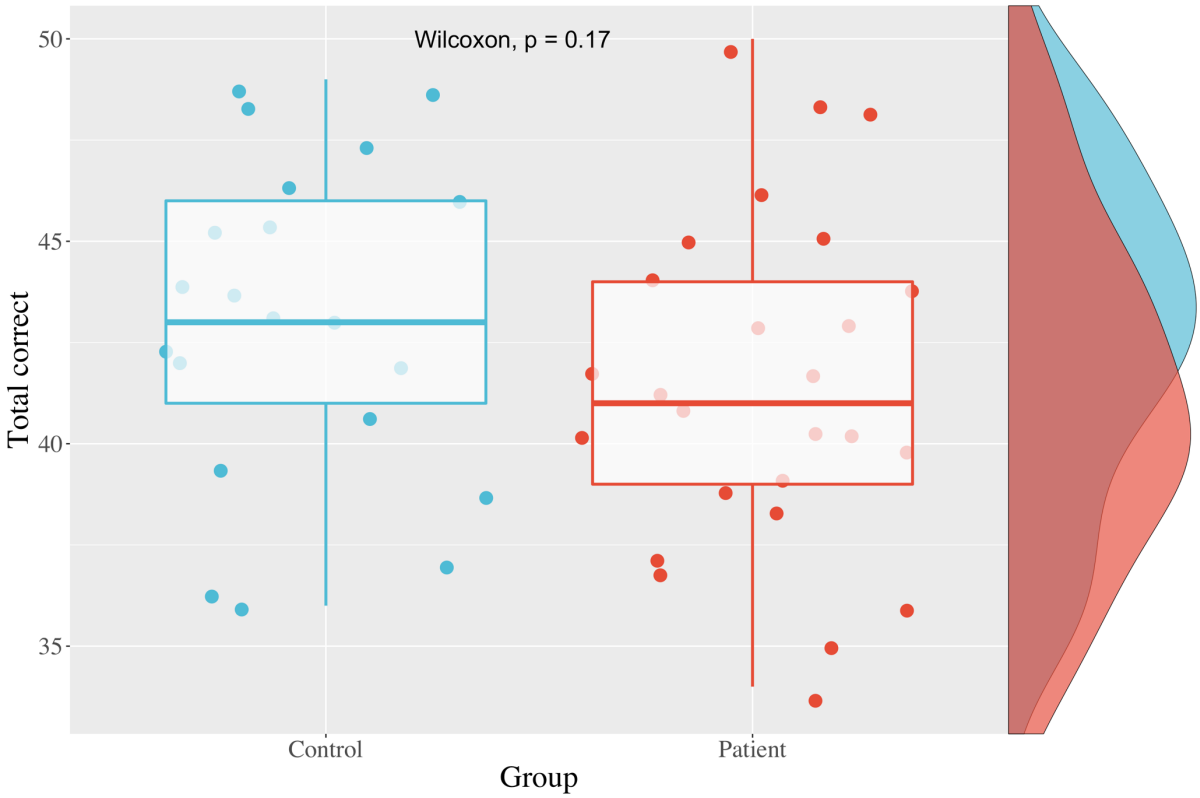


Figure 38: Emotional discrimination total accuracy (Face to face)

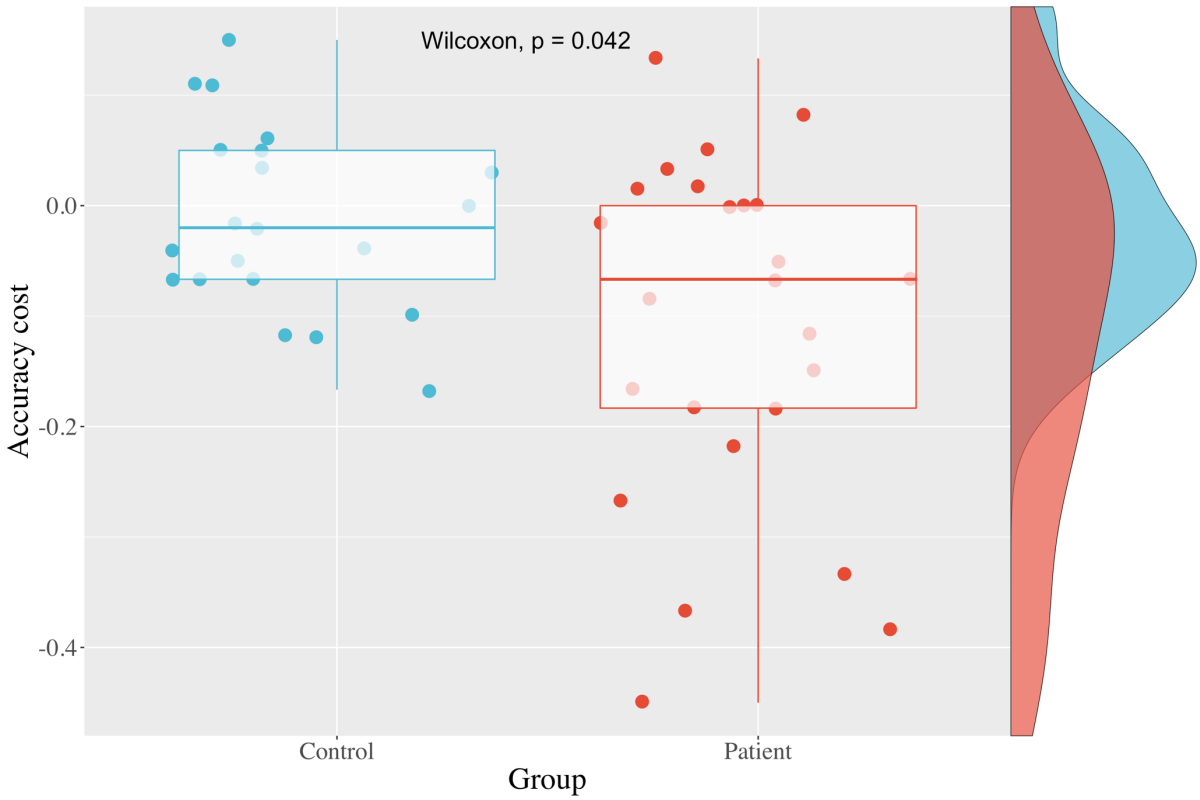


Figure 39: Emotional discrimination accuracy cost (Face to face)

The difference in accuracy between congruent and incongruent emotional expressions

On average, there was a significant reaction time cost for incongruent compared to congruent conditions (mean = 231.71(231.71), range = [-303.5; 646]), t(46) = 3.251, p = 0.002. A significant difference was seen between the patient (mean = 289.9(212.23)) and control (mean = 143.95(174.69)) groups for reaction time cost (W = 113, p = 0.03), with patients having a longer reaction time during incongruent conditions.

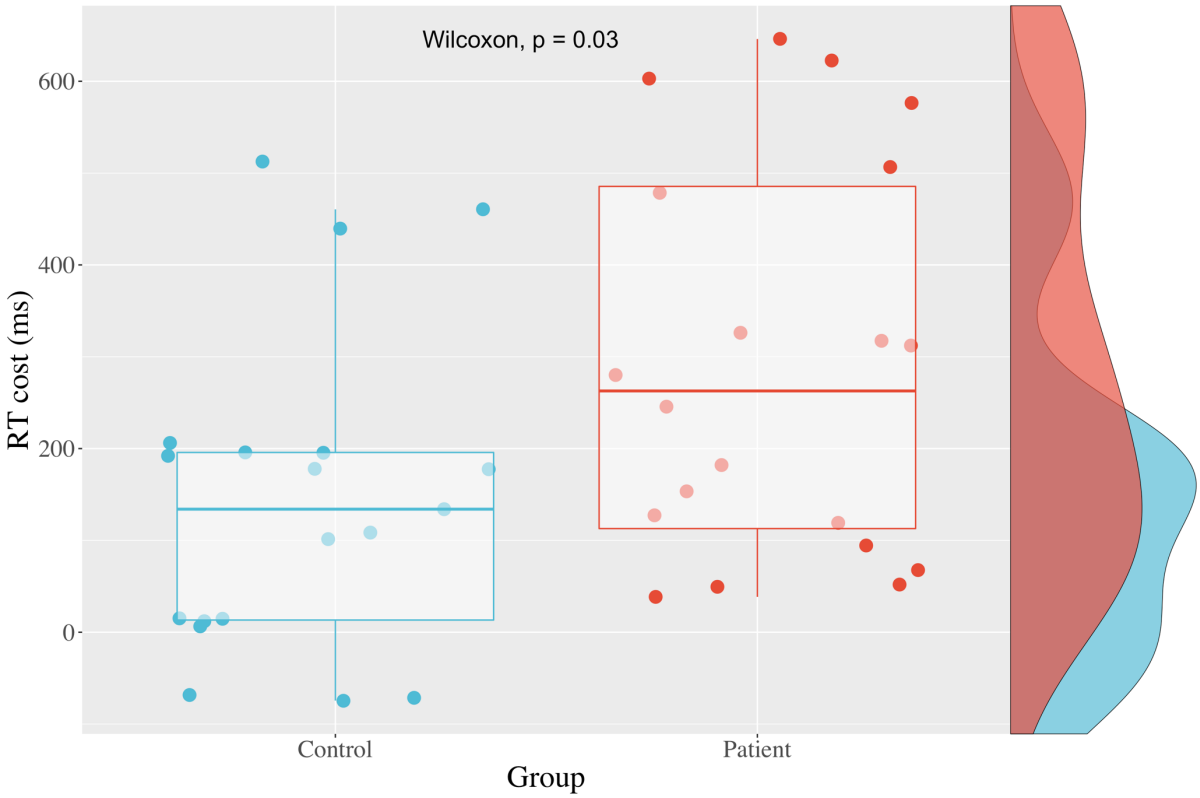


Figure 40: Emotional discrimination reaction time cost (Face to face)

6.4.3 Emotional discrimination: Smartphone app

Following multiple comparison corrections, no significant differences were found for accuracy between patient and control groups across emotional conditions F(1,300) = 0.09, p = 0.75 (Figure 41). A borderline effect was seen towards a difference in accuracy cost between congruent and incongruent conditions for TBI patients and controls F(1,75) = 3.96, p = 0.05.

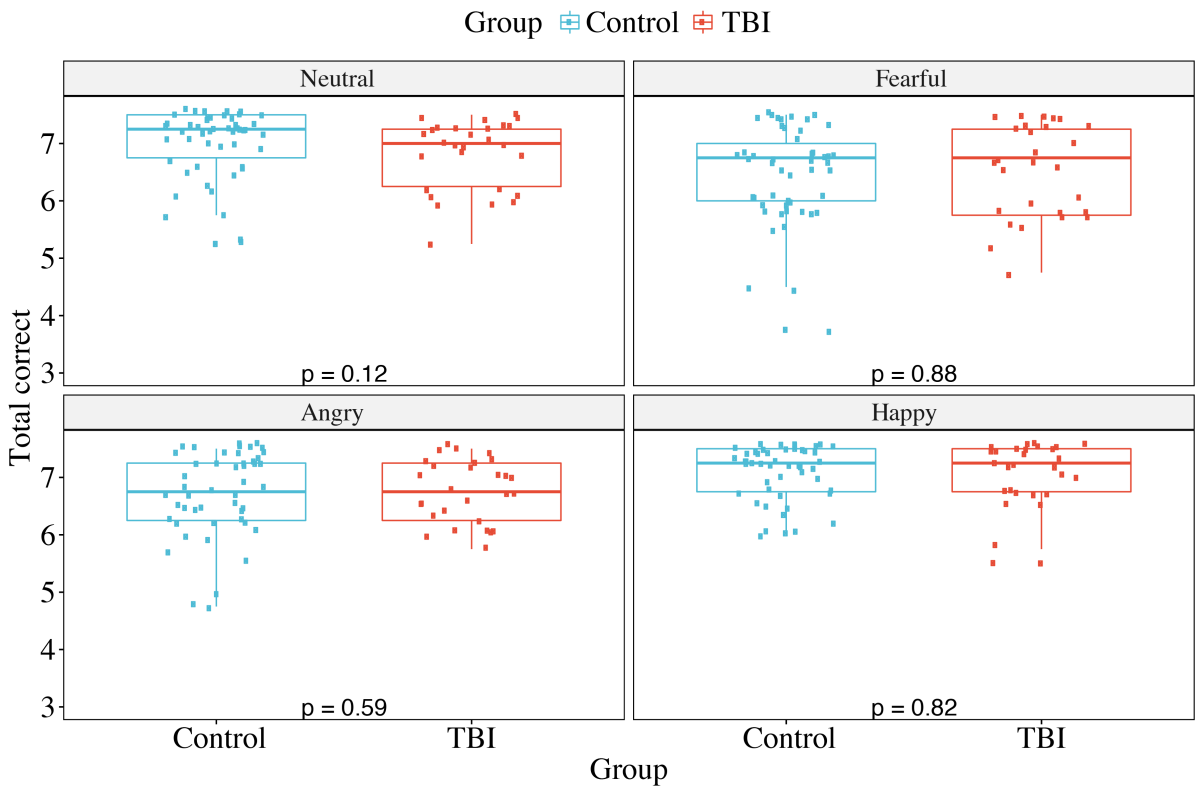


Figure 41: Emotional discrimination accuracy (Remote smartphone assessment)

Patients were significantly slower at identifying the correct emotion compared to controls $F(1,300) = 21.02$, $p < 0.001$. Pairwise comparisons with Tukey adjustment indicate these differences were seen for fearful (t-ratio = -3.12, p = 0.002), angry (t-ratio = -2.27, p = 0.02) and happy (t-ratio = -2.68, p = 0.007) expressions (Figure 42). No significant differences were found for neutral expressions (t-ratio = -1.09, p = 0.27). No reaction time cost was seen between groups for emotional discrimination $F(1,69) = 0.07$, $p = 0.78$.

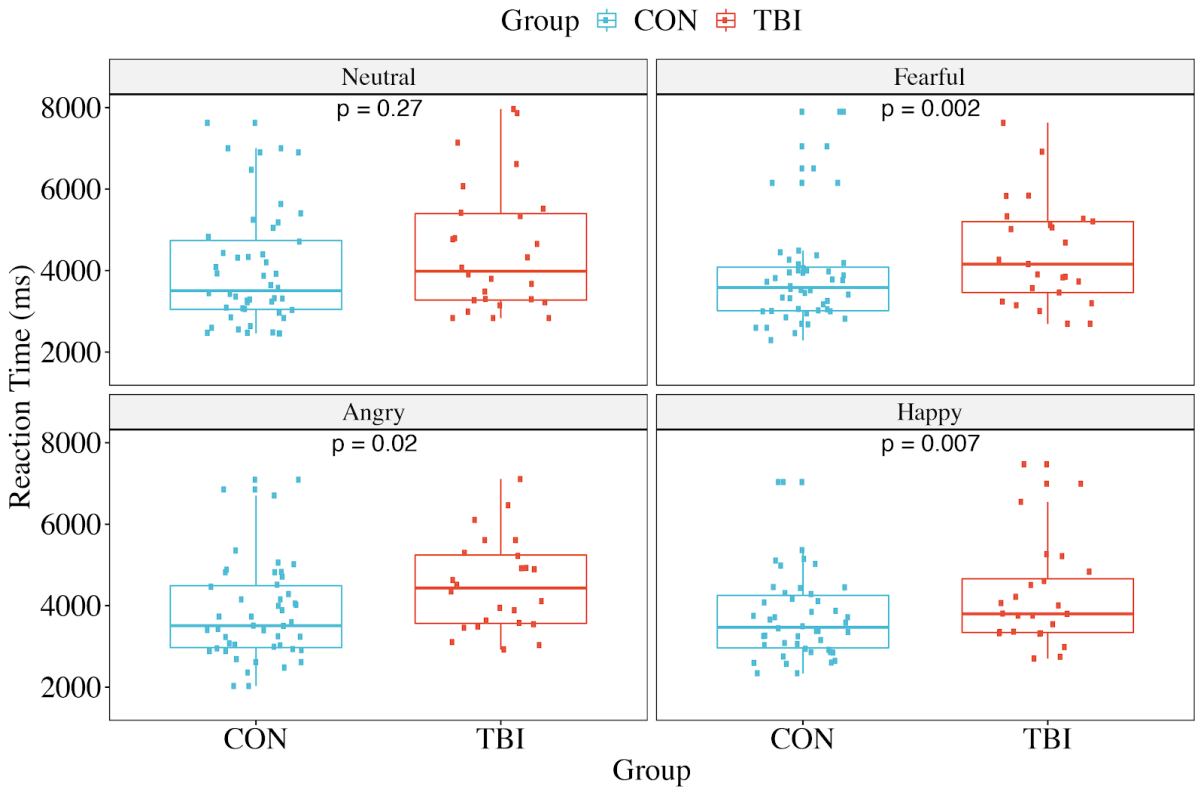


Figure 42: **Remote smartphone assessment of emotional discrimination reaction time** ***(Remote smartphone assessment)***

Overall, patients showed slower reaction times across emotional conditions compared to controls, with no significant differences for neutral conditions

6.4.4 Relationship of emotional processing to self-report measures (face to face)

A linear mixed effects model showed a significant interaction between accuracy for emotional discrimination, the BDI and group (Figure 43), with a link between lower accuracy and higher reported depression symptoms X^2 (1, N = 52) = 7.99, $p < 0.01$; similarly a significant relationship was found between accuracy for emotional discrimination and social network size, with lower accuracy relating to a reduced number of close contacts X^2 (1, N = 52) = 243.34, $p < 0.001$, no significant effect of group was seen X^2 (1, N = 52) = 2.6, p = 0.1, or interaction between group and number of close contacts X^2 (1, N = 52) = 0.85, p = 0.35 (Figure 44). A main effect of higher BDI was also significantly correlated with a smaller social network (r = 0.39, p = 0.005), while no interaction effects were seen with group from a linear

mixed effects model X^2 (1, N = 52) = 2.65, p = 0.1 (Figure 45). Full details of wellbeing measures collected through the app can be seen in chapter 5, Table 3.

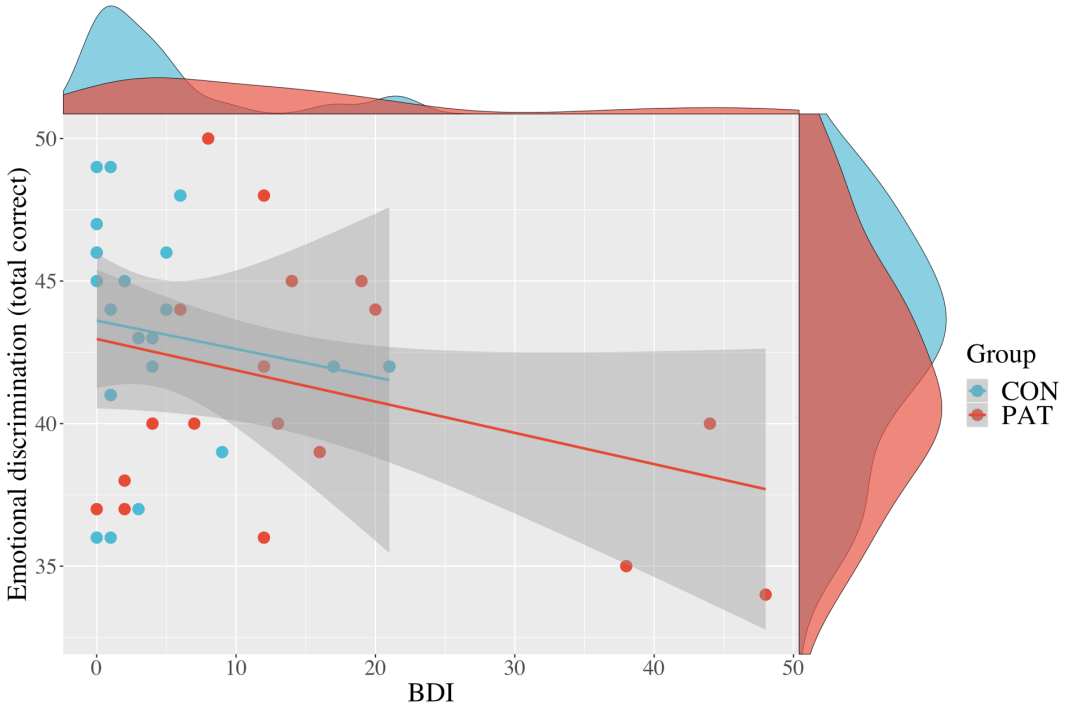


Figure 43: Emotional discrimination total correct and Beck Depression Inventory (BDI) (Face to face)

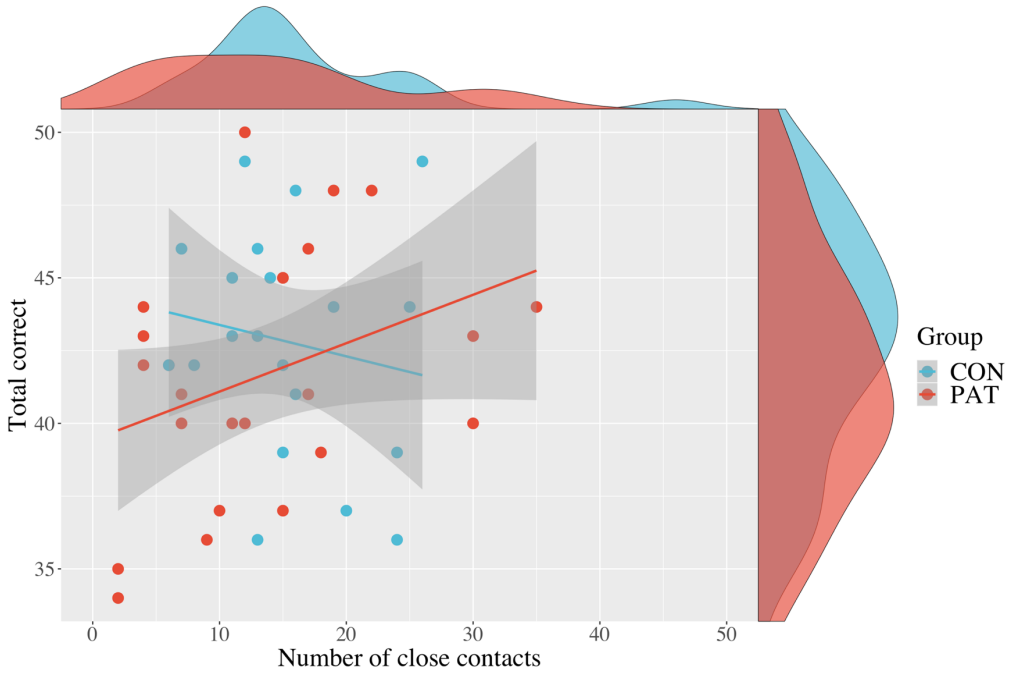


Figure 44: Emotional discrimination total correct and number of close contacts (Face to face)

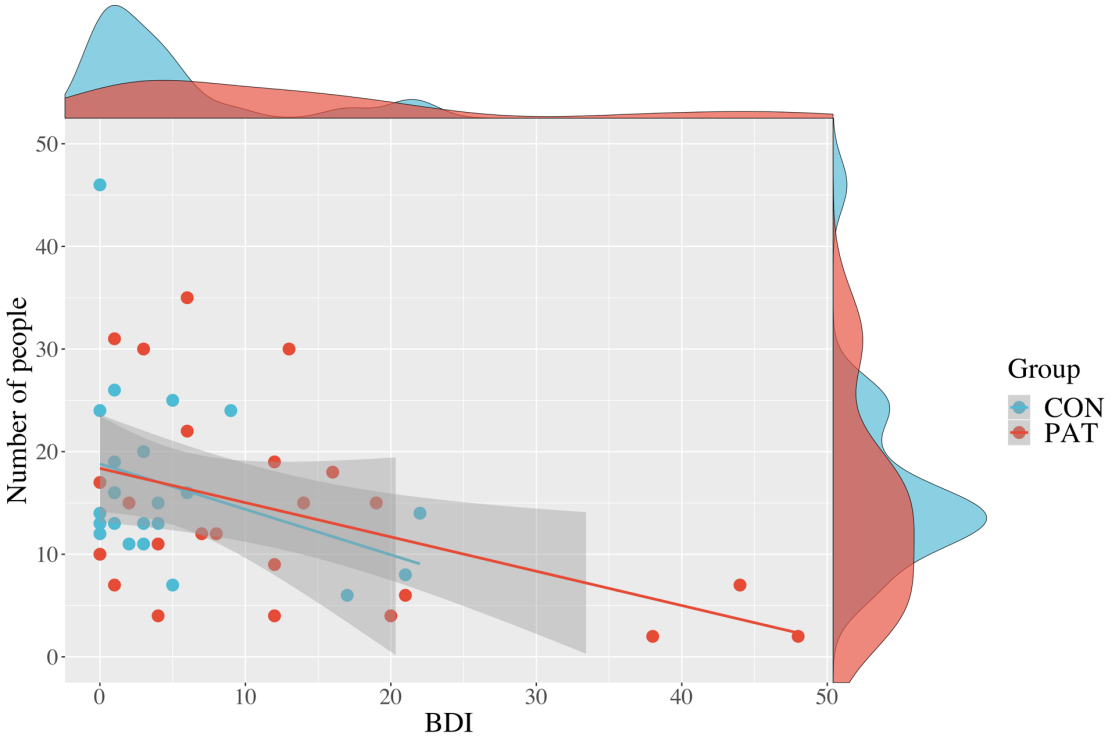


Figure 45: Number of close contacts and beck depression inventory (Face to face)

BDI = Beck Depression Inventory. A number of close social contacts was measured with the social network index (SNI).

6.5 Discussion

The overarching aim of these three studies was to implement novel social and emotional paradigms through a new digital platform: online through a large-scale web-based study, face to face via a tablet app and remotely with a mobile app.

Here I demonstrate:

1. The feasibility of delivering social cognitive paradigms via a testing app across multiple digital platforms.
2. TBI patients have lower levels of accuracy and slower processing speed on emotional recognition paradigms.
3. Reduced ability of emotional recognition is correlated with worsening depression symptoms on the BDI and smaller social network size.

In the emotional discrimination paradigm, an overall cost effect was seen between congruent and incongruent stimuli for both accuracy and reaction time, with lower accuracy in the incongruent condition along with slower reaction time for correct responses. Overall, females performed better than males, with no interaction seen for cost effects across age or sex. The face to face assessment of emotional processing demonstrated that TBI patients may struggle with the processing of conflicting emotional expressions. Accuracy on the emotional discrimination task was correlated with levels of depression symptoms, as well as social network size. This highlights an important link of everyday functioning to emotional processing performance. In the final remote smartphone study there were no significant differences seen for accuracy across any of the emotional conditions after correcting for multiple comparisons. Similarly, no cost effects were seen between congruent and incongruent conditions. However, patients were significantly slower than controls for happy,

fearful and angry conditions on the emotional discrimination paradigm, with no differences seen for the neutral condition.

The use of digital technology to probe cognition and well-being allows for the unique advantage of remote monitoring. It potentially reduces confounds such as social desirability, which may result from the presence of a researcher. On the other hand, however, large sample sizes are initially required in order to ascertain a reliable assessment of the validity of such a measure. The online web-based study provide insights into how demographics such as age and sex may contribute to variation in task responses. It also demonstrates the feasibility of delivering large scale cognitive tests to the general population, which otherwise would not be possible. The face to face study also demonstrated the efficacy of digital app-based data collection off a commercially available tablet. It negated several common sources of error from paper data, including reducing missing responses by having forced choices and potential transcription error by researchers. Following the initial time cost of setting up, it streamlines the process of collecting and analysing data in a flexible way. Remote app assessments may have their place as useful screening tools going forward, or to track well-being through short surveys. In situations where direct face to face contact is not feasible this is a potential alternative.

A few necessary caveats should be noted in the web-based study. First, the sample of participants completing this battery was heavily skewed towards females. Second, this study was run with a large sample size. Plotting the number of observations per task in order of completion shows a steady drop off rate of participants, among which around half the number of people who began the tests completed the full battery of tasks, including the demographics questionnaire at the end. This may result in selection bias of those completing the tasks. Self-

selection bias is a known issue for most studies requiring volunteers to give their time; however, it may be argued that online studies like this are inherently valuable despite this shortfall, as they enable the sampling of a broader range of the general population than would otherwise be possible. Despite this, complete observations were extracted from a total of 2,638 subjects. Due to large sample sizes, it must be considered that statistical significance may be reached with very small effect sizes (Hampshire et al., 2019; Owen et al., 2010).

A limitation of the face to face study is the relatively narrow scope through which components of emotional processing were explored. Beyond the recognition of emotional faces, patients may experience difficulty with affect sharing or understanding the feelings of others, aspects that were not addressed during this study.

Lack of environmental control of remote assessments, particularly when looking at group comparisons is a considerable point to note. There is a trade-off between rigorously controlled experimental settings and convenience and scalability of remote assessments. For population studies, large enough samples may negate the former issue to a degree. However in the context of group comparisons of clinical populations a combined approach is required to provide a reliable assessment.

Additionally the stimuli set used from the Chicago face database for the emotional discrimination task did not include any sad stimuli. Future work would benefit from the inclusion of new stimuli sets with a sad condition. The setup of this task and platform should make the alteration of stimuli sets a relatively trivial job.

While emotional processing paradigms using canonical facial expressions have been widely investigated, this may be limited by emotional labels assigned by researchers (Barrett et al., 2019). Aside from explicit labelling of static facial expressions, alternatives for emotional recognition include the usage of naturalistic or dynamic expressions, which can elicit a stronger response (Holland et al., 2019). Additionally, emotional processing is by no means restricted to the identification of facial expressions. For the online study, I put together a context task which required participants to understand the emotion someone may be feeling given a particular situation. It is likely that a combination of approaches is required to understand emotional processing, and this task, in particular, provides a good starting point to understanding this complex process. Going forward, the evaluation of emotional processing in patients should consider the recognition of expression, the understanding of how another person may feel, as well as reports of emotional/behavioural expression, preferably from a close friend or partner.

6.6 Conclusion

There is utility in using digital technology via tablet/phone app and the web to assess social and emotional functioning. In these studies, TBI patients consistently showed impairments in the processing of emotional expression stimuli. These quick assessments are flexible in design, can be done in-person or remotely, and could be informative for clinical practice as targets to consider for potential interventions

Chapter 7 | Dissociable impairments in metacognition across cognitive domains after TBI

In the final experimental chapter, I will look at measures of metacognition collected as part of a remote digital assessment (Cognitrack), previously discussed in chapter 6.

7.1 Abstract

The ability to monitor one's behaviour may be impaired following TBI, impacting on patients' rehabilitation and resulting in poor functional outcomes. This can be measured as deficits in metacognition, or in other words, inaccuracies in the judgement or self-reflection upon one's performance. How metacognition varies across cognitive domains is unclear.

In the current work, metacognition is measured through prospective evaluation of memory and attention, and retrospective confidence judgements of performance on cognitive tasks completed remotely via smartphone. Metacognitive insight was calculated from the difference between confidence judgement of task performance and actual performance, normalised as a percentage of maximum possible. The full cohort of participants consisted of 100 controls and 142 TBI patients, with individuals completing different subsets of tasks collected as part of a broader scope of cognitive data collection.

Controls' prospective judgement of their memory and attention functioning was significantly related to subsequent task performance in these domains. TBI patients showed no such relationship. On retrospective judgements of task performance TBI patients overestimated

their task performance compared to controls overall. Accuracy in judging performance varied across cognitive tasks. TBI patients did not show a significant relationship between performance and retrospective judgement for working memory, while controls did. There were significant relationships between performance and retrospective judgements in both groups for attention, executive functioning and emotional processing. Both groups showed no relationship between performance and confidence for processing speed. Furthermore, pooled metacognitive insight showed a significant relationship with self-reported levels of mood and anxiety.

Metacognition is a complex construct in which TBI patients may show dissociable impairments across cognitive domains. Overall TBI patients demonstrate an overestimation of cognitive performance compared to controls. Disassociations between performance and metacognitive judgements across cognitive domains have important theoretical and practical implications for evaluation of metacognitive impairment in TBI patients.

7.2 Background

The ability to self-reflect or accurately evaluate one's behaviour is frequently impaired following TBI (Dockree, O'Connell, et al., 2015; S. M. Fleming & Lau, 2014; Ham et al., 2014). Clinically, this lack of insight can severely impact the efficacy of rehabilitation interventions (T. Hart et al., 2005; Prigatano, 2005; Robertson & Schmitter-Edgecombe, 2015), and is often associated with poor functional outcomes (M. Kelly et al., 2014; O'Keeffe et al., 2007; Ownsworth & Fleming, 2005; Robertson & Schmitter-Edgecombe, 2015). Curiously, there is a frequently cited discrepancy in emotional distress following TBI, whereby milder patients report more significant psychiatric problems than more severe ones (Bigler, 2001). This phenomenon potentially relates to a reduced sense of self-awareness in more severe cases with relatively widespread damage. Various methods to estimate self-awareness have been established, including objective online error monitoring paradigms (Ham et al., 2014), in which participants have to correct errors made in the task. Another method uses discrepancy scores: Discrepancy measures in reported symptom severity between patients and their caregivers, discussed here in previous chapters. Discrepancy scores have been a useful method of establishing metacognition in TBI patients (J. M. Fleming et al., 1996; O'Keeffe et al., 2007). Other work has compared participants' performance with semi-quantified verbal reports of how they believed they did on the task (T. Hart et al., 1998). Here I will focus on global estimates of metacognition, a self-reflective judgement on performance.

The neural correlates of impaired awareness following TBI is addressed in the general introduction. In addition to the general introduction, work described in previous chapters of this thesis highlight some issues of metacognition in TBI patients. In chapter 3, voxelwise DTI analysis showed that increased discrepancy scores on the FrSBe were significantly

correlated with reduced FA in the Corpus Callosum. Chapter 3 also highlights the high probability of focal damage in the frontal lobes following TBI. Lesions in the OFC have previously been linked with impairments in judging one's own performance (Beer et al., 2006). However, as discussed, there is likely a control network that is affected, in which a multitude of tracts or functional connectivity may be impaired, resulting in reduced awareness (Dockree, O'Connell, et al., 2015; Ham et al., 2014). Chapter 6 saw caregivers reporting higher levels of self-awareness problems in patients than patients rate themselves, as measured on the LARS.

Metacognition is complicated and can be viewed as a sub-component of self-awareness itself, separable from other facets such as emergent awareness. Within metacognition itself, from an early definition from developmental and educational psychology this processes can be divided into three subcomponents of metacognitive knowledge, metacognitive regulation and metacognitive experiences (Flavell, 1979). A main focus of cognitive neuroscience has been on metacognitive knowledge, evaluating ones cognitive performance or ability in the form of cognitive judgements. Furthermore, metacognitive judgments may be performed at various temporal stages, prospectively, concurrently and retrospectively (Hacker et al., 2009). Retrospective judgments provide a global response following completion of a test, rather than individual items as would be with concurrent judgments, sometimes referred to relative metacognitive judgments (K. J. Kelly & Metcalfe, 2011). Metacognition is frequently investigated with concurrent judgements using signal detection theory (Allen et al., 2017; Siedlecka et al., 2016).

Assessment of metacognition has been approached from multiple directions, and it is not clear where metacognition fits into current models of cognition. There is a question of

whether metacognition is domain-specific or a general function (Rouault et al., 2018). Indeed, some models include working memory and self-monitoring as sub-processes under the umbrella of executive functioning (T. Shallice & Burgess, 1996). While this is a sensible heuristic for testing cognitive functions, it fails to address the plethora of interactions across cognitive domains, including executive functioning itself. Evidence has emerged that metacognition may dissociate into domain-specific functions across three tasks of online awareness, perception and memory (Fitzgerald et al., 2017). Other work indicates that efficacy varies across domains in the presence of spatial variation of focal lesions, suggesting metacognition may be domain specific (S. M. Fleming et al., 2014). More recently there has been an argument for a "metacognitive g factor", and that metacognition is a domain general function (Mazancieux et al., 2020). From the existing literature metacognition is not only likely to dissociate across cognitive abilities, but can also be subcategorised into different processes such as prediction, online monitoring and retrospective self-reflection/judgment.

Here I use a semi-quantitative approach to evaluate metacognition through completion of cognitive tests performed remotely via their smartphone; this requires participants to complete a battery of tests across multiple cognitive domains including processing speed, attention, working memory and emotional processing. Following completion of each task they are required to rate their performance on a sliding scale. Metacognitive insight is the difference between retrospective confidence judgments (CJ) in performance and actual performance. These CJs are with respect to the performance of the associated cognitive task. This reflection provides a measure of metacognitive awareness across several cognitive domains without the interference of task designs, including assessments where accuracy is not the primary outcome measure. Metacognitive accuracy, the relationship between CJ and performance is then investigated.

In addition, prospective judgements on memory and attentional function, two commonly reported complaints following TBI will be collected as part of a questionnaire prior to the completion of cognitive tasks. These judgements will be looked at in relation to participants task performance.

My hypotheses are:

1. TBI patients will have reduced predictive insight into attention and memory compared to controls
2. Global retrospective metacognitive insight of performance will vary across cognitive tasks, with patients overestimating their performance.
3. Patterns of reduced global metacognitive insight will be related to self-reported levels of wellbeing

7.3 Methods

7.3.1 Participants

Participants took part in a remote assessment via their smartphone. The number of participants varies across tasks, depending on the measures they completed. For individual analysis varying n for each task are reported along with the results of each measure. Patients were recruited from a specialist outpatient TBI clinic at St Mary's Hospital, as well as from the major trauma wards at the St. Mary's and St. George’s Hospitals. Exclusion criteria included any previous neurological or psychiatric illness. Inclusion criteria involved participants with a smartphone capable of downloading apps. All participants gave consent to partake through a checkbox on an information screen when they downloaded the app.

The full cohort consisted of 100 controls [44 male; mean age = 33.69(13.88)] and 142 patients [104 male; mean age = 45.44(15.12)]. Controls' highest reported completed education was University = 72; high school = 21; Unknown = 7. Patients' highest education level was University = 69; High school = 31, primary = 3; unknown = 29. The mean time since injury was 36.61 months, ranging from 0-778 months. Mechanism of injury included: Home/domestic = 21; RTA = 60; Sport 16; Workplace accident = 10; Unknown = 29; Other = 2. Self-reports of loss of consciousness (LOC): <1min = 2; 1min-30min = 32; 1h-24hr = 5; 24hr-7days = 2; more than 7 days = 7; unknown = 62; no LOC = 8.

7.3.2 Tasks

Before cognitive assessments, participants completed the physical and mental health questionnaire (PMHQ), which includes questions on memory, attention and wellbeing. Participants completed the cognitive tasks covering domains of processing speed, memory, executive functioning, attention and emotional processing. Prospective ratings of general memory and attention were looked at in relation to subsequent task performance in those domains.

Processing speed:

Motor control (MC) requires participants to select targets (n = 30) appearing on the screen in random locations as quickly and accurately as possible. Simple reaction time (SRT) involves tapping on the screen as quickly as possible when a target appears (n = 60). Choice reaction time (CRT) requires selection of one of two arrows as quickly and accurately as possible (n = 60). If a target arrow appears pointing left, the participant needs to select left; if the target arrow points right, the participant needs to select right.

Attention:

In the target detection (TD) task, a target stimulus is provided. In a field of changing shapes, the participant must identify and select the target stimulus (n = 120). Each stimulus is presented for 1,000ms before disappearing. The total number of correct selections are counted.

Executive functioning:

The trail making task is a response based task modelled from the classic pen and paper assessment of the same name. The switch cost from trail making task (Trails) involves two levels. The first a set of sixteen numbers are dispersed across the screen. Participants are required to select each number going up in ascending order (e.g. 1-2-3-4...). The second level involves numbers and letters. Participants must switch between these also going up in ascending order. (e.g. 1-A-2-B-3…).

Working memory:

Paired associates learning (PAL) is a working memory task, where participants are required to remember both an image and the location on a grid. Stimulus duration is 2,000ms for each association. Following each correct trial an additional stimulus is added, increasing the difficulty. The task ends after 3 consecutive incorrect trials. The outcome measure is the maximum number of correct associations.

Emotional processing:

Emotional discrimination (EMD) is a response based task presenting 50 trials of two faces with emotional expressions. The task is balanced for emotional pairing containing stimuli from the Chicago face database, including varying sex and ethnicity(Ma et al., 2015). The aim is to identify if the faces are exhibiting the same or different emotions. The total number of correct responses is calculated.

Following each task, participants were asked to provide a retrospective confidence judgement (CJ) on their task performance. This was given in the form of a slider ranging from 0-100, with 100 being very confident on task performance. Data from participants was filtered to take only the first time point a task was completed. I investigated overall performance across a range of tasks, the confidence of performance for each task and assessments of metacognition. An index of global metacognitive insight was calculated by the difference between confidence and performance in a given task. This measure reflects a participants' overall under or overestimation of their performance. Scores >0 indicate overestimation, while scores <0 indicate underestimation. Additionally, an estimate of metacognitive performance was calculated by the correlation of performance and confidence. This is taken as a global estimate rather than trial-by-trial judgments.

7.3.3 Statistical analysis

Data analysis was run with the statistical package r (Core Team, 2018; http://www.R-project.org/).

POMP (percentage of maximum possible) scores are a method to normalise data onto a 0-100 scale. As true POMP cannot be calculated for reaction time measures with no absolute maximum or minimum, it was calculated relative to the maximum and minimum performance of the sample population in subsequent analyses. Metacognitive insight is derived, where self-reflected performance is higher or lower than actual accuracy. Discrepancy scores were calculated for each task by subtracting subjects' CJ from normalised POMP scores. Scores close to 0 indicate good calibration of judging performance while values closer to +100 indicate overconfidence, and similarly, values closer to -100 indicate

underconfidence in performance. Metacognitive insight was compared across groups for each cognitive task using a 2-factor ANOVA, accounting for the subject as a random effect.

7.4 Results

7.4.1 Task performance

To investigate overall performance across tasks between groups a linear mixed effects model was performed, indicating poorer performance in patients across a range of cognitive domains. A significant interaction between cognitive tasks and group on performance was seen $F(1,1141) = 3.69$, $p < 0.001$; Post-hoc pairwise estimates with Tukey correction show that patients performed worse on all cognitive tasks compared to controls apart from emotional discrimination and emotional control. MC $t(1141) = 4.67$, $p < 0.001$; SRT $t(1141) = 5.32$, $p < 0.001$; CRT $t(1141) = 8.16$, $p < 0.001$; TD $t(1141) = 3.32$, $p < 0.001$; PAL $t(1141) = 5.13$, $p < 0.001$; Trails $t(1141) = 5.33$, $p < 0.001$; EMD $t(1141) = 0.41$, $p = 0.67$; EMC $t(1141) = 1.6$, $p = 0.1$.

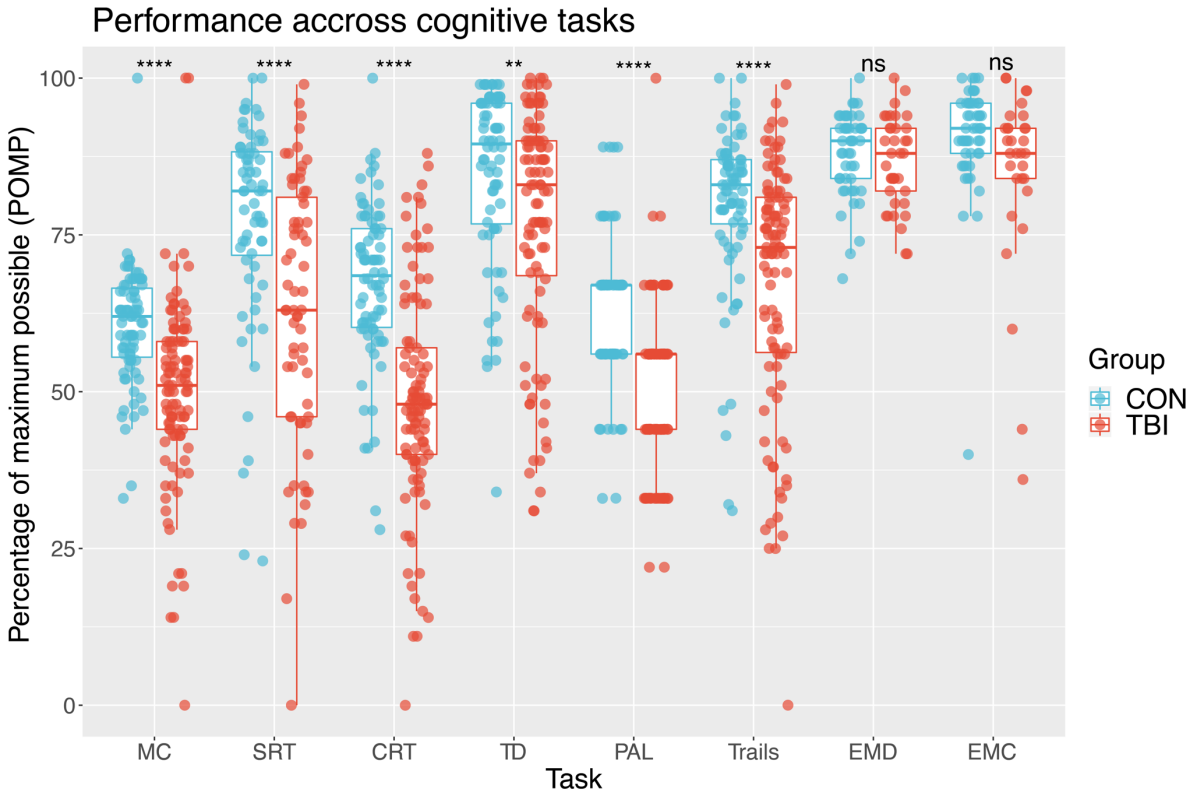


Figure 46: Normalised performance scores across cognitive tasks

MC = motor control; SRT = simple reaction time; CRT = choice reaction time; TD = target detection; PAL = paired associates learning; trails = trail making B-A; EMD = emotional discrimination; EMC = emotional control

7.4.2 Retrospective confidence judgment

Following completion of tasks, participants were asked to judge their performance. A linear mixed effects model was run investigating the relationship of task and group to retrospective confidence judgment with subject as a random effect (Figure 47). An interaction between group and cognitive domain fell below the predetermined significance level $F(1, 1014) = 2.05$, $p = 0.056$; A main effect of cognitive domain was seen $F(1,1014) = 25.05$, $p < 0.001$. Post-hoc pairwise estimates of tasks indicate the only cognitive domain with a significant group difference was for working memory (PAL), with patients indicating lower confidence compared to controls $t(1014) = 2.5$, $p = 0.01$.

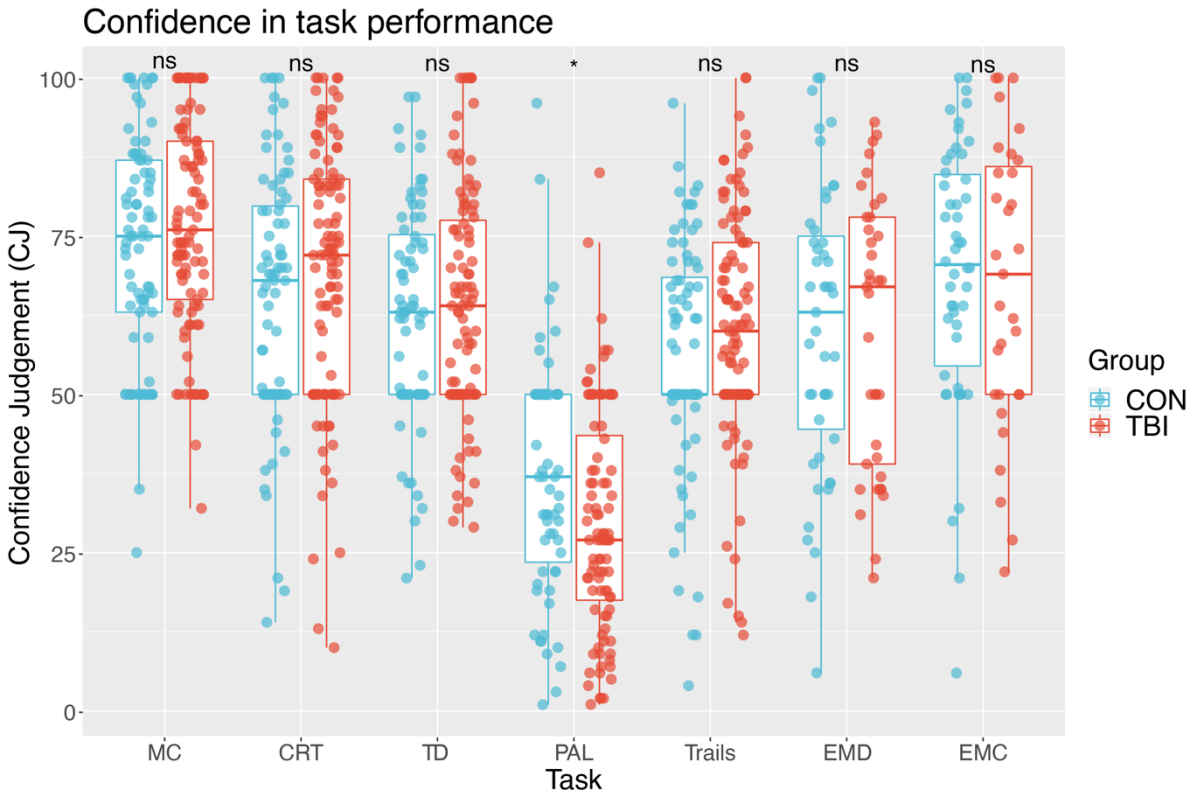


Figure 47: Rating of confidence of task performance

MC = motor control; SRT = simple reaction time; CRT = choice reaction time; TD = target detection; PAL = paired associates learning; trails = trail making B-A; EMD = emotional discrimination; EMC = emotional control

7.4.3 Metacognitive insight

Analysis of discrepancy measures (retrospective confidence judgment – performance) indicated there was a significant difference in pooled metacognitive insight between controls (mean = -8.41(26.85)) and patients (mean = 2.65(30.39)), $t(1086) = -6.37$, $p < 0.001$. A two-factor ANOVA was run to examine the relationship between group and cognitive domains with metacognitive insight (Figure 48). There was a significant interaction, where cognitive domain moderates group effects of metacognitive insight $F(7, 1073) = 3.63$, $p < 0.001$; post-hoc comparisons of patients and controls across cognitive domains were conducted using ordinary least squares, accounting for means across factors. Results were adjusted for multiple comparisons with Tukey correction. Both controls and patients had a positive bias on motor control, believing they did better than their actual performance, with patients

showing significantly higher bias compared to controls $t(1073) = -4.21$, $p < 0.001$. Patients overestimate their performance more compared to controls for SRT: $t(1073) = -4.44$, $p < 0.001$; and CRT $t(1073) = -6.79$, $p < 0.001$; A negative bias was seen in target detection, PAL, trails, emotional discrimination and emotional control, with patients showing a higher confidence bias in target detection $t(1073) = -2.61$, $p < 0.001$; and trails $t(1073) = -3.63$, $p < 0.001$ compared to controls. No significant difference were seen between groups for PAL $t(1073) = -1.3$, $p = 0.18$; and emotional discrimination $t(1073) = -0.21$, $p = 0.83$ or emotional control $t(1073) = 0.76$, $p = 0.44$

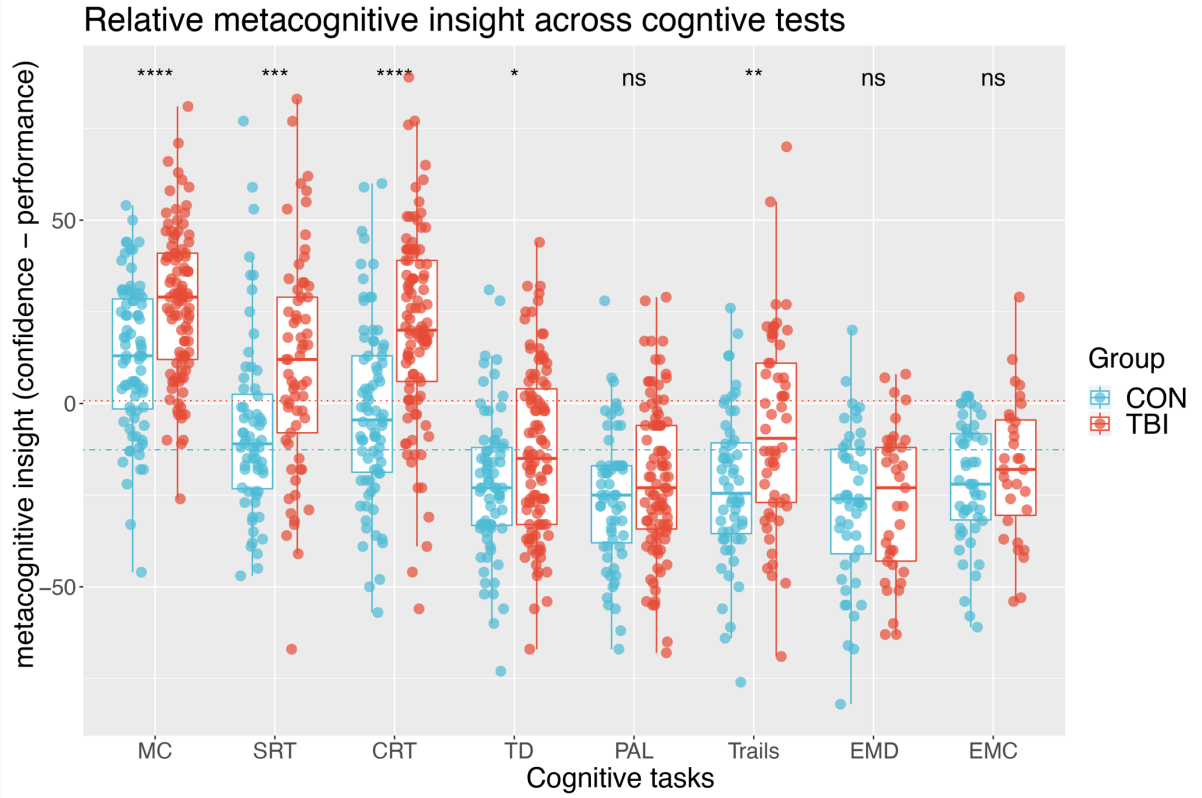


Figure 48: Metacognitive insight across cognitive tasks

Discrepancy was calculated by the difference between confidence judgment and task performance. Values closer to 100, indicate overestimation of performance, while values closer to -100 indicate underestimation. MC = motor control; SRT = simple reaction time; CRT = choice reaction time; TD = target detection; PAL = paired associates learning; trails = trail making B-A; EMD = emotional discrimination; EMC = emotional control. Dotted lines represent group pooled metacognitive insight.

7.4.4 Metacognitive accuracy

Metacognitive accuracy was looked at through the correlation between performance and confidence judgment in a given task.

Processing speed

There was no significant interaction between group, cognitive performance and retrospective confidence judgements for any of the processing speed tasks. Motor control $F(1,176) = 2.01$, $p = 0.16$; Simple reaction time $F(1,125) = 0.02$, $p = 0.88$; Choice reaction time $F(1,175) = 0.96$, $p = 0.32$. Similarly no main effects of performance was seen Motor control $F(1,176) = 0.38$, $p = 0.53$; Simple reaction time $F(1,125) = 0.41$, $p = 0.52$; Choice reaction time $F(1,175) = 0.51$, $p = 0.47$ or group effects Motor control $F(1,176) = 3.39$, $p = 0.06$; Simple reaction time $F(1,125) = 0.006$, $p = 0.98$; Choice reaction time $F(1,175) = 1.42$, $p = 0.23$

Attention

A generalised linear model was conducted comparing the main effects of group and target detection performance and the interaction between group and performance on confidence on target detection performance. No significant interaction between group and confidence judgement was seen $F(1,167) = 0.41$, $p = 0.51$ nor main effect of group $F(1,167) = 0.72$, $p = 0.39$, a main effect of performance was seen $F(1,167) = 4.66$, $p = 0.03$. Post-hoc analysis of each group's simple slope showed the main effect of performance was seen in both controls and patients. The slope coefficient for controls was 0.44, 95% CI [0.38, 0.85] and for patients was 0.28, 95% CI [0.02, 0.055].

Working memory

A generalised linear model was conducted comparing the main effects of group and working memory performance and the interaction between group and performance on confidence on working memory performance. No significant interaction between group and confidence

judgement was seen $F(1,151) = 3.89$, $p = 0.05$ nor group $F(1, 151) = 2.75$, $p = 0.1$, a significant main effect was seen for performance $F(1, 151) = 11.84$, $p < 0.001$

post-hoc analysis of each group's simple slope showed the main effect of performance was seen in controls but not patients. The slope coefficient for controls was 6.8, 95% CI [2.9, 10.7] and for patients was 1.37, 95% CI [-1.2, 4.9]; as the simple slope in patients crosses zero, no significant effect of performance and CJ is seen.

Executive

A generalised linear model was conducted comparing the main effects of group and switch cost performance and the interaction between group and performance on confidence on switch cost performance. No significant interaction between group and confidence judgement was seen $F(1,174) = 0.09$, $p = 0.76$; Significant main effects were seen for group $F(1, 174) = 7.12$, $p < 0.01$ and performance $F(1, 174) = 10.45$, $p < 0.01$.

Emotional processing

A generalised linear model was conducted comparing the main effects of group and performance with retrospective confidence judgements and the interaction between them. No significant interaction was seen between performance and retrospective confidence judgement between groups for emotional discrimination $F(1,80) = 0.13$, $p = 0.71$ or emotional control $F(1, 77) = 3.07$, $p = 0.08$ or main effects of group for emotional discrimination $F(1, 80) = 0.06$, $p = 0.79$ and emotional control $F(1, 77) = 1.11$, $p = 0.3$. A main effect of performance was seen for both emotional discrimination $F(1, 80) = 11.39$, $p < 0.01$ and emotional control $F(1, 77) = 39.12$, $p < 0.001$

7.4.5 Prospective judgement of memory and attention functioning

Further to metacognitive accuracy, investigating the relationship between task performance and retrospective confidence judgements, the link between task performance and reports of memory and attention functioning taken prospectively were investigated.

Working memory

A type III ANOVA was used to investigate the relationship of working memory performance and group on prospective judgements of memory. There was a significant interaction for performance modulated by group on memory judgement $F(1, 147) = 4.62$, $p = 0.03$; the model shows an overall significant effect for performance $F(1,147) = 7.98$, $p = 0.005$; no main effect of group was seen $F(1, 147) = 13.55$, $p = 0.07$; post-hoc analysis of each group's simple slope showed the main effect of performance was seen in controls but not patients. The slope coefficient for controls was 6.83, 95% CI [2.91, 10.76] and for patients was 1.37, 95% CI [-1.77, 4.51]; as the simple slope in patients crosses zero, no significant effect of performance and CJ is seen (Figure 49).

Attention

A type III ANOVA was conducted to investigate the relationship of attentional performance and group to prospective judgements of attention. There was no significant interaction for performance modulated by group on prospective judgement of attention $F(1, 160) = 0.63$, $p = 0.42$; the model shows an overall significant effect for performance $F(1,160) = 6.91$, $p = 0.009$.

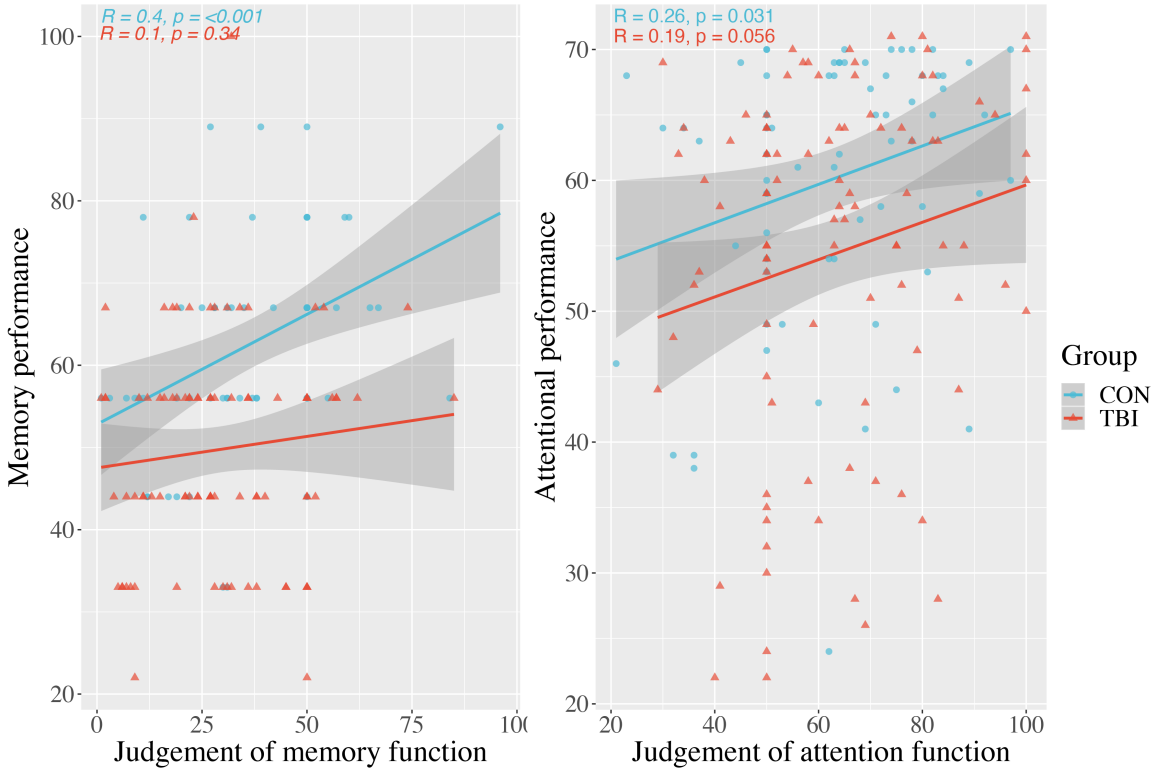


Figure 49: Relationship of general ratings of memory and attention with task performance

7.4.6 Relationship to reported measures of wellbeing

A linear regression was used to investigate the relationship of mood and group to relative metacognitive insight. No significant group by mood interaction was seen $F(1, 199) = 0.009$, $p = 0.92$; However main effects of mood $F(1, 199) = 12.35$, $p < 0.001$ and group $F(1, 199) = 39.71$, $p < 0.001$ were seen, indicating participants that rate having a lower mood tend to underestimate their performance to a greater degree, than those rating a higher mood in both patients and controls, while patients tend to overestimate their performance compared to controls overall (Figure 50). A similar model was run for anxiety and metacognitive insight. No significant group by anxiety interaction was seen $F(1, 199) = 1.72$, $p = 0.19$; However main effects of anxiety $F(1, 199) = 15.09$, $p < 0.001$ and group $F(1, 199) = 39.01$, $p < 0.001$ were seen, indicating patients that rate having a higher anxiety tend to underestimate their performance to a greater degree, than those rating a lower anxiety.

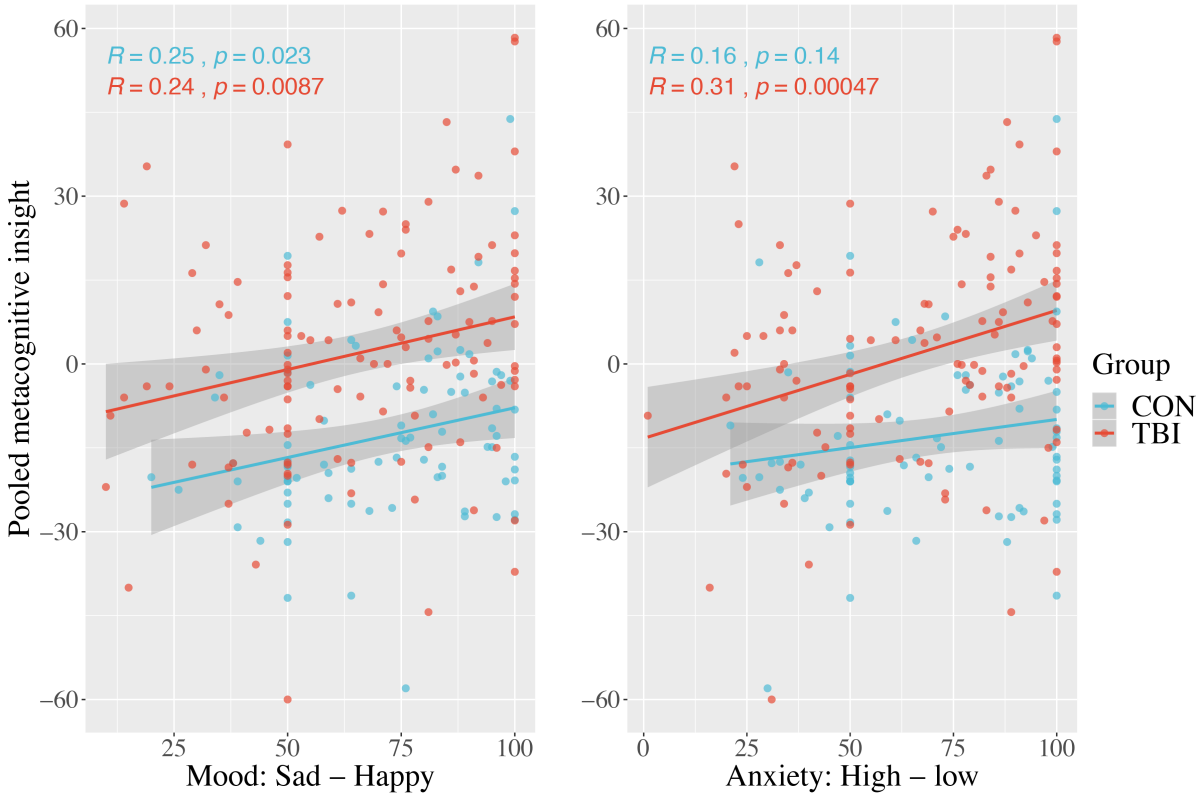


Figure 50: Pooled metacognitive insight and measures of mood and anxiety

7.5 Discussion

Here I present work on metacognitive confidence judgements of performance across a range of cognitive tasks, as well as prospective memory and attention reports. This easily-added measure at the end of cognitive assessments has little additional time cost but provides an informative semi-quantitative assessment of metacognition that can provide further context to raw cognitive scores.

Controls had good judgement of general memory ability when contrasted with performance on a working memory paradigm, whereas TBI patients did not. Similarly controls judgement of general attention was correlated with a subsequent attentional processing task, this effect was not seen in TBI patients. TBI patients showed significant impairment on all cognitive tasks compared to healthy controls apart from emotional discrimination. Overall retrospective

confidence judgements did not vary significantly between groups apart from working memory, which was appropriately lower in patients compared to controls. Metacognitive insight, the discrepancy measure between confidence and performance across the range of cognitive tasks patients showed overall higher positive bias compared to controls, over-estimating their performance except in the domains of memory and emotional processing. Accuracy between confidence judgements and performance were poor in both groups for processing speed. A significant relationship was seen in working memory performance and confidence judgment for controls but not patients. Both groups showed a relationship of performance and confidence judgement for attention, executive function and emotional processing. This variation of metacognitive insight accuracy across tasks indicates metacognition may be dissociable across cognitive domains. The relationship of metacognitive insight pooled across all tasks and self-reported levels of mood indicated a positive correlation between insight and mood in both groups. This may reflect a bias when evaluating performance whereby one tends to underestimate performance with lower mood, and overestimate with higher ratings of mood.

This measure of self-reflection has evident relevance for clinical populations. Generalising poor metacognition to broader aspects of behaviour, patients lacking a sense of their limitations may be at increased risk of harm through the manifestation of inappropriate behaviours. Coupled with other common TBI-related behavioural problems such as impulsivity, a profile of likely gambling behaviour or general contentiousness may emerge, compounding social, emotional and financial issues, or worse, leading to an elevated risk of physical altercations or assault (Regard et al., 2003; Turner et al., 2019; Williams et al., 2018). With increasing sample sizes, normative scores could be generated. This could contribute to clinical assessments of impaired insight whereby patients falling below a cut-off

score (e.g. <1SD) on performance misattributes high confidence to their performance. The current sample did not enable further investigations with reasonable sample sizes of patients who performed poorly (<1SD) but with high levels of confidence, or patients with good performance (>1 SD) with low levels of confidence. This subgrouping could be valuable in future work investigating significant discrepancies between metacognition and performance. An alternative to this frequentist approach is to use machine learning classifiers to investigate if the data can be split meaningfully into subgroups such as identifying high performers with low confidence or low performers with high confidence.

Metacognitive bias is highlighted as an important facet to consider (S. M. Fleming & Lau, 2014). While it cannot be experimentally disassociated from metacognitive sensitivity with global metacognitive measures it is worth considering from the current results across many cognitive tasks how this may vary. In particular task design may influence confidence in performance. In the current work there was a much lower confidence of memory, this may be due to the design of the working memory task which finishes after 3 incorrect trials. Despite having potentially reaching a high level this design may influence perception of performance.

Limitations of remote cognitive assessments need to be considered. For instance, while participants are requested to set time aside to complete the tasks in a distraction-free environment, this cannot be enforced, and expected noise will arise from variations in the setting. Similarly, another consequence of this lack of supervision lies in the inevitability of incomplete data. Third, as in the design of any cognitive battery, an effect of task sequence is unavoidable. In this case, the emotional paradigms were the last in the set of tasks to be completed over multiple sessions. As a result, due to attrition, the number of observations is substantially lower compared to that available for reaction time tasks in the first session.

While this could be addressed by running randomised, or pseudo-randomised ordering of tasks, a consistent standardised order was chosen for task delivery. Additionally, there may be non-random effects present in patients who completed all tasks vs those who only completed a subset; a conceivable source of bias relates to low motivation or injury severity. This being said, further analyses can easily be conducted to address these current concerns as the sample size increases.

The current work identifies areas of behavioural interest from remote assessments which could be the target of more detailed lab based and neuroimaging experiments. An additional online metacognition task would have added benefits alongside these confidence judgements. This could take the form of a trial-by-trial perceptual judgement, in which signal detection theory, or a paradigm such as the stop change task, could be adapted and applied. Previous work has utilised signal detection theory with modified cognitive paradigms, including retrospective confidence judgements following each trial (S. M. Fleming et al., 2010; S. M. Fleming & Dolan, 2012; Hauser et al., 2017). For my current work, this approach proved infeasible, as it would interfere with the paradigm structure of the cognitive tasks. Metacognitive sensitivity, or bias for trial by trial accuracy, is not measured here as in (Rouault et al., 2018). Instead, a single confidence judgement is given following completion of a task. Limitations of "single-shot" metacognition assessments have been described previously (S. M. Fleming & Lau, 2014). Most notably, the inability to distinguish between concepts such as metacognitive sensitivity and bias. However, the presented method in this work provides useful evaluation across multiple cognitive domains, with no time cost or need to modify existing cognitive paradigms. Its utility is most notably seen in (Kruger & Dunning, 1999). With this in mind, a specific paradigm to measure metacognition as part of a

testing battery would have added value to the current approach, fractionating components of metacognition.

This global metacognitive insight score would be most beneficial when considered alongside other standard questionnaires and detailed clinical information, such as the GOSE, PTA and other measures of functional outcome—or perhaps a customised digital testing paradigm. Initial results here highlight a link between metacognitive insight and mood, which could be investigated further. Such metacognitive measures may provide better insights into patient outcomes beyond what is conventionally assessed with cognitive tests. Further investigation of the neural correlates and relationship to functional outcomes is also required.

7.6 Conclusion

Short assessments of confidence judgements following task completion across cognitive assessments can provide a global measure of metacognition. This extra dimension in which to view raw cognitive results may be beneficial to our understanding of behavioural and functional outcomes. The results here support the argument of metacognition being domain specific as well as the dissociation between prospective and retrospective judgements. In addition to supporting this theoretical perspective, there are practical clinical implications. TBI patients' poor prospective judgment of memory compared to controls suggests this is an ill-posed question clinically, without measures of insight. Objective assessment of working memory with a retrospective confidence judgment would be a more appropriate measure. The present results suggest that measures of metacognition have additive value alongside cognitive measures in a population of TBI. Further work needs to be completed investigating the neural correlates and relationship of metacognition to functional outcomes.

In a similar vein to the concluding remarks of (Kruger & Dunning, 1999), I would like to express a few thoughts upon the closing of this last experimental chapter. With regards to the analysis and communication of this thesis, I feel I have performed with competence; however, the concern of imprecise logic or methodology due to gaps in my own knowledge is inescapable. While imperfections may be inevitable, I am confident in saying that every effort has been made to maintain robust analysis and draw appropriate interpretations throughout this body of work.

Chapter 8 | Discussion

In this chapter, I will summarise and interpret the main findings of the thesis. I will discuss how they contribute to our understanding of TBI and suggest possible future directions of research in this field.

8.1 Summary of findings

The aim of this thesis was primarily two-fold: to explore social cognitive impairments following TBI, and to develop potential ways to assess them. To this purpose, a combination of novel cognitive assessments and structural and diffusion MRI was used.

More specifically, the objectives of the thesis were:

- To re-evaluate "frontal" behaviours with respect to frontal lobe lesions
- To assess various metrics of white matter damage following TBI in relation to behavioural performance
- To test social decision making and motivation following TBI
- To test emotional processing following TBI and evaluate potential assessments of social cognition
- To examine metacognitive function across a range of cognitive domains following TBI

8.1.1 Chapter 3 | Revisiting "frontal" behaviour

In chapter 3, I investigated the relative contribution of focal lesions and white matter damage to executive function. Evidence from voxel-based lesion-symptom mapping (VLSM) indicated involvement of the right inferior frontal gyrus in symptoms of dysexecutive function, inhibition, and apathy. Further investigations revealed that in TBI patients classified as moderate-severe using the Mayo classification system, those without focal lesions showed the same level of behavioural symptoms as those in the lesion group. On the other hand, however, similar reductions in white matter FA are seen for lesion and non-lesion TBI patients, with no effect size difference across a range of white matter tracts. Together, these results indicate that although a direct link between behaviour and white matter structure was not seen, the observation that behavioural impairment is similar across both groups may be partially explained by the presence of widespread white matter disruption in non-lesion patients. This calls into question the validity of interpreting VLSM results alone in the context of behavioural research and supports the use of other neuroimaging methods such as diffusion to look at white matter structure. This builds on previous work, suggesting that behavioural impairment may be better accounted for by network disruption (Ham et al., 2014).

8.1.2 Chapter 4 | White matter assessment

Chapter 4 focuses on the comparison of standard metrics of white matter damage, including volume and FA, to newer metrics such as NDI and ODI. Assessment of white matter volume shows the largest effect size change in chronic TBI patients compared to controls. Measures of diffusion also indicated widespread disruption with moderate to large effect sizes. Advanced metrics based on data acquired with a multi-shell sequence show spatially overlapping but distinct patterns of disruption in NDI and ODI. While less sensitive to overall

change compared to volume, advanced diffusion metrics such as NDI and ODI may be more specific in relation to cognitive performance.

8.1.3 Chapter 5 | Social decision making

This third experimental chapter extends my focus on functional deficits in TBI. Here, I investigated the performance of TBI patients in social decision-making tasks. Surprisingly enough, results presented here were counter to my original hypotheses that TBI patients would have higher levels of apathy, which would then be associated with higher levels of reward discounting. While patients indeed exhibit higher levels of apathy, associated with both reduced DaT and widespread white matter disruption, this did not correlate with reward discounting. There was however a significant difference between patients and controls on this paradigm. Patients did not differentiate between self and other conditions as well as failing to discount reward by increasing effort levels.

8.1.4 Chapter 6 | Emotional processing

In chapter 6, I looked at emotional processing across three separate digital mediums; the web, face to face on a tablet and remotely via smartphone. In the large scale, remote, web-based assessment to evaluated social cognition in healthy controls. This provided information on demographic information likely to influence responses, allowing for the calculation of normative data. I Further investigated emotional processing in TBI patients and controls with a novel emotional discrimination included in the previous web-based study by face to face assessment and remotely by smartphone. Evidence supports some disruption of emotional recognition in TBI, associated with increased levels of depression symptoms and smaller social network size. These new social cognitive tasks could be useful additions when assessing cohorts of TBI patients.

8.1.5 Chapter 7 | Metacognition

In this last experimental chapter, metacognition was investigated using a combination of prospective and retrospective judgments of cognition across a range of cognitive domains. TBI patients indicated no relationship with general estimations of memory or attention and subsequent cognitive tasks, while controls did. In general TBI patients overestimated their performance compared to controls. The greatest discrepancy between the subject groups is seen for measures of processing speed. An association was seen between metacognitive insight and measures of anxiety and mood.

8.2 Interpretation

TBI patients may experience a range of social cognitive impairments, each with potentially detrimental effects on everyday life. Although emphasis has traditionally been placed on the role of focal lesions in the study of behavioural impairments following TBI, it has become increasingly evident that this approach alone is insufficient. While their presence may indicate injury severity and be helpful in approximating certain types of impairments that may be seen, the implementation of alternative quantitative neuroimaging measures may provide more comprehensive insights when predicting overall functional outcome. Analysis in chapter 3 investigating TBI patients with and without focal lesions highlights the severity of cognitive impairments that may be present even in the absence of focal lesions. Further results from diffusion imaging suggest that widespread white matter damage, potentially relating from DAI, which plays a large role in the pathophysiology of TBI and needs to be considered along with other measures when evaluating patients and predicting their recovery. Altogether, this series of results call attention to the importance of exploring investigative methods beyond those in the current literature when constructing a broader picture of cognitive functioning after TBI. Adapting graph theory and network approaches for TBI

research would be appropriate here. Investigating bother disruption to nodes through lesion analysis and effects on edges (connections) of white matter pathways disrupted through DAI.

Advancing imaging techniques and analysis may help improve our understanding of the underlying biophysical relationships between brain and behaviour. Results from this thesis show that behavioural impairments may be linked to the disruption of complex systems through focal lesions, white matter damage, atrophy, or dopaminergic disruption. In addition I present the NODDI model in a cohort of moderate-severe TBI. A comparison with other diffusion metrics and white matter volume indicates a high degree of shared variance. All of these metrics measure some form of disruption to white matter structure compared to healthy controls, with volume having the largest effect sizes in chronic TBI patients. However, these novel metrics may provide more specific insights into varying pathological processes that have occurred (Jespersen et al., 2012). Differentiating the type of structural alterations in more detail may lead to better prediction of processes such as atrophy, or functional outcomes.

TBI patients exhibit aberrant decision making when it comes to reward discounting in social conditions. In day-to-day life, our decisions are consistently being made within the context of our social environment. It is therefore unsurprising that our interactions with others, or our perceived gains or losses may have significant impacts on the choices we make (Sanfey, 2007). Increased reward discounting occurs when effort is perceived to outweigh the reward available. In general, controls consistently put in more effort for themselves than for others (Lockwood et al., 2017): an observation that holds true in my own results as well. However, TBI patients I investigated did not differentiate between self and others when making choices for financial reward. This cannot be explained by the original hypothesis that expected

reduced effort would be associated with self-reported apathy, a common symptom following TBI. It is thus possible that patients were more highly motivated by reward than controls in general, regardless of self-directed gain. Further work is warranted to investigate the roles of reward processing, self-other distinction, and their respective influences on decision making in a social context. A better understanding of perturbed behavioural systems would help inform rehabilitation management.

Another aspect of this work explores reductions in overall well-being and emotional processing in TBI patients. This is a critical issue to address as it can have long term implications in terms of recovery, the strain on interpersonal relationships and economic cost, not only to individuals but also to rehabilitation systems. The widely accepted somatic marker hypothesis sets out to explain how decision making may be influenced by emotion and how this process may be regulated by the orbitofrontal cortex, as demonstrated with thirteen ventral-medial lesion patients (Bechara et al., 2000). This hypothesis is pertinent to several themes of this work, not only from an emotional processing perspective but also because altered emotional processing may tie in with mechanisms of social decision making, causing biases in choices made. Orbitofrontal lesions may affect social behaviour through the disruption of self-conscious emotions. Compared to more basic emotions such as fear or anger, self-conscious emotions require a degree of self-reflection, and include examples such as guilt or embarrassment Beer et al., (2003).

The BBC web-based study on 'collective intelligence' has provided useful data from redeveloped gold-standard measures including the MITE, EQ, and Big-5, and has allowed for the collection of normative data on new social measures on a large scale. The novel emotional discrimination task reported here, along with other new social measures follow

similar age and gender curves to existing measures. In line with previous research, women tend to outperform men across measures of social and emotional processing. While not reported here, other batteries of cognitive performance were also conducted on the same platform. Gender differences were not seen in other domains, such as processing speed or memory.

As demonstrated here, TBI patients may not always be aware of their deficits. This is a particular concern when ascertaining profiles of behavioural dysfunction or relying on self-reports to assess symptomatology, as patients' responses may be distorted due to lack of insight into one's own behaviour. For this reason, having a close family member or friend to provide informant-rated measures is a more accurate way to assess' behavioural disturbances (Henry et al., 2016). Additional objective measures of metacognition may also be used to investigate patients' abilities to monitor their behaviour. The stop-change task or metacognitive assessment of visual processing may be useful additions to measures of cognitive functioning.

8.3 Future directions

The nature of TBI is heterogeneous in mechanism, impairment and outcome. The work described in this thesis elucidates several important aspects of social cognition following TBI. Further investigations could expand upon and clarify the current work, for instance by incorporating the novel social assessments presented in the final experimental chapter in further studies, perhaps in a longitudinal context.

The absence of focal lesions is clearly not evidence of healthy brain structure, and should not be treated as such. More sophisticated approaches need to be incorporated into clinical

investigations, especially in suspected milder cases. Work on lesion-symptom mapping could be extended to include features of functional and structural disconnection. The concept of diaschisis describes the disconnection of distal regions in the brain from the site of focal damage (Carrera & Tononi, 2014). Limited empirical work has been done to investigate this, but it is an exciting direction of research to take, particularly in TBI patients. It would be interesting to look at patterns of atrophy, to determine if there are spatial patterns associated with regions already damaged. One group has been set up to look at the human 'disconnectome', exploring the effects of lesions on connectivity (de Schotten et al., 2020; Foulon et al., 2018). With advancing acquisition methods, improving analysis techniques, and more massive datasets, the field of neuroimaging is in a prime position to extend investigations of the theory of diaschisis.

Here I have shown that white matter tracts are most likely to be disconnected due to focal lesions in the frontal lobe, the most common site of focal injury following TBI. This finding could be expanded upon using graph theory measures of structural connectivity, which evaluates the structural connection of different anatomical nodes, weighting disconnection on an individual basis due to the presence of focal lesions. A feature of TBI that distinguishes its pathology from other forms of damage such as stroke is that of DAI. Due to the unique biomechanical characteristics of injury, damage to white matter tracts may occur in the absence of focal lesions. Methods of assessment of white matter structure are explored in chapter 4. The availability of multi-shell diffusion-weighted imaging has led to the development of novel models for analysis. Here, I discussed the NODDI model in relation to DTI and white matter volume. Future analysis could investigate spherical deconvolution (SDC), which allows the derivation of a voxelwise metric of apparent fibre density (Christiaens et al., 2015; Raffelt et al., 2012). SDC allows the production of more

sophisticated probabilistic tractography, overcoming previously problematic technical limitations in samples with gross anatomical abnormalities, such as in TBI patients where lesions are common. The SDC-modelled diffusion data may then be combined with high-resolution structural images to assist with defining boundaries of different tissue types (grey matter, white matter, cerebrospinal fluid, pathology, etc.) (Jeurissen et al., 2014). A combination of these approaches may prove promising for addressing questions relating to diaschisis. Structural networks of particular consideration following TBI include fronto-striatal which have been highlighted in healthy controls to be vital for normal motivated behaviour (Le Heron et al., 2018). A Neurology review of social cognition indicated across a range of disorders disruption to frontal anatomical regions may disrupt circuits important for healthy social behaviour (Henry et al., 2016). The DMN is a key functional network which has a high overlap in regions in required for mentalising and social understanding of others. The DNM is frequently disrupted following TBI (Sharp et al., 2014). How this related to structural alteration of networks from damaged nodes is an interesting avenue of further exploration.

Lesions and DAI are compounding factors of injury which need to be evaluated together in a more holistic approach rather than being treated separately or treating lesions as a nuisance variable. Further work could also expand on the use of multi-modal approaches on resting-state data, alongside structural measures. As an example, functional ICA can be run on an independent set of controls, using lesion masks from patients as seed regions, to identify functional networks likely to be affected in the patient. Again, this could be expanded into graph theory metrics.

Previous work that has been expanded upon in the current thesis has also supported the use of multi-modal imaging. Perturbations to the dopaminergic system should be considered in the presence of particular symptoms such as fatigue and apathy. This has previously been associated with reduced DaT levels and has been treated successfully with dopaminergic medication (Jenkins et al., 2019). Further research should include multi-modal investigations of frontal networks and other behavioural components of social cognition. These could include areas functionally and structurally connected to the MPFC and amygdala, both essential for emotional processing. Previous work has shown similar networks consisting of the PFC and striatum to be important for executive functioning (De Simoni et al., 2018).

Work on social processing following TBI could be further explored in a number of ways. There are a number of factors which may influence decision making and appropriate social behaviour and need to be considered together. These include apathy, sensitivity to reward, disinhibition and metacognition. This is by no means an exhaustive list. As TBI is a heterogeneous disorder, patients may experience difficulties with one or more of these components of social functioning. A future study on social processing after TBI would benefit from incorporating collaborative reports from caregivers or close family members, measuring reward sensitivity, and developing objective paradigms of metacognition.

Further developments on behavioural measures used in this thesis could include the use of naturalistic expressions rather than acted representations of emotions, or dynamic rather than static facial paradigms. One particular advantage in clinical studies would be the inclusion of the social context task in conjunction with emotional recognition paradigms. This added dimension explores the understanding of others' feelings given a situation, rather than based

on the perception of expressions alone. In their current forms, these measures are also easily adaptable for fMRI paradigms, which could be used to expand upon our understanding of the neural bases of social and emotional processing following TBI.

Metacognition is a key component of cognitive functioning, required for optimal social behaviour. There are many avenues of measurements and aspects to look at with metacognition. CJ are a useful measure to collect following cognitive tasks with little additional time cost. Metacognitive research could be expanded to include a specifically designed paradigm to measure across-trial confidence, a measure of online error-monitoring such as the stop-change task, and collaborative reports from patients and caregivers about their daily functioning. This holistic approach could deliver insights into the relationships and differences between the different components of metacognition. This should be done with respect to a wider set of neuropsychological assessments and functional outcome measures. Feasibility of assessment in clinical contexts needs to be considered. While some limitations are undoubtedly present, CJ may provide additional informative insight along with standard cognitive measures.

Treatment for cognitive impairment following TBI would likely benefit from an individualised, targeted approach. Given the heterogeneity of the condition, the identification of underlying issues and the subgrouping of patients by their present deficits would be essential for this shift towards personalised medicine. The behavioural results I have presented indicate that there are subsets of patients with reduced awareness of their deficits, higher levels of depression symptoms, or reduced social support. These three groups alone may all require different management approaches to maximise their respective outcomes. Neuroimaging findings are also important for patient management. Radiological reporting of

the presence of lesions may be of limited value alone. Additional measures such as SPECT to investigate dopaminergic disruption, or minimum intensity projection reconstruction from susceptibility-weighted imaging (SWI) to detect microbleeds, or semi-quantitative forms of diffusion and volumetric imaging are undoubtedly beneficial. Neuroimaging measures can retrospectively change the classification of severity (Malec et al., 2007), or inform potential drug treatments (Jenkins et al., 2019).

Key outcome measures in the evaluation of TBI patients should relate to interpersonal relationships, loneliness, employment, mental health, and quality of life. This could be looked at from the perspective of the patient, but could also be just as valuable from close family members or caregivers. Close family members or caregivers can provide valuable collaborative reports, which also provide insights into metacognition. Scales such as the Beck Depression Inventory (BDI), are robust assessments of well-being which can be conducted in person or digitally, facilitating longitudinal evaluation. Assessments of perceived social support and social network size may be important outcomes, particularly for patients scoring highly in executive dysfunction or depression. Similarly, assessments of the quality of life should be considered key outcome measures. Several assessments are available, including the QOLIBRI (Quality of life after brain injury); the EQ5D, a measure of health outcome across five domains; and the Mayo-Portland inventory (MPAI), which covers a variety of physical and affective symptoms as well as lifestyle factors such as alcohol/drug use and employment.

8.4 Concluding remarks

Neurological deficits following a traumatic brain injury can vary substantially. The dispersed networks of regions involved in social cognition make this domain of behaviour particularly susceptible to injury (Kennedy & Adolphs, 2012), conferring considerable impacts on interpersonal relationships and on caregiver or family burdens (Tam et al., 2015). Examining social deficits within a TBI population in the context of clinical neuroscience is important, as targeted interventions and the expected improvement of behavioural disturbances are beneficial not only for patients but also for the well-being and quality of life indices of their carers and loved ones. Social cognitive dysfunction should be considered an essential component when planning rehabilitation pathways following TBI. Beyond traditional neurological and psychological examinations, the identification of deficits in this domain can have substantial impacts on recovery outcomes. Current clinical investigations of TBI often fail to assess impairments of social cognition, much less the relationships of these integral measures to long-term outcomes. An evident solution to this issue lies in the implementation of technological assessments of social cognition. These can be delivered via tablet, smartphone and the web, and are quick and effective screening measures of impairments and well-being. In addition, the maintenance of supportive relationships throughout the long recovery process for TBI-related neurocognitive or physical issues may prove fundamental to the overall improvement of injury outcomes.

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References

Abu-Akel, A., & Shamay-Tsoory, S. (2011). Neuroanatomical and neurochemical bases of theory of mind. *Neuropsychologia*, *49*(11), 2971–2984. https://doi.org/10.1016/j.neuropsychologia.2011.07.012

Adolphs, R. (2003). Cognitive neuroscience of human social behaviour. *Nature Reviews Neuroscience*, *4*(3), 165–178. https://doi.org/10.1038/nrn1056

Alexander, A. L., Eun Lee, J., Lazar, M., & Field, A. (2007). Diffusion Tensor Imaging of the Brain Andrew. *Neurotherapeutics*, *27*(4), 590–609. https://doi.org/10.1016/j.humov.2008.02.015.Changes

Allen, M., Glen, J. C., Müllensiefen, D., Schwarzkopf, D. S., Fardo, F., Frank, D., Callaghan, M. F., & Rees, G. (2017). Metacognitive ability correlates with hippocampal and prefrontal microstructure. *NeuroImage*, *149*, 415–423. https://doi.org/10.1016/j.neuroimage.2017.02.008

Andelic, N., Howe, E. I., Hellstrøm, T., Sanchez, M. F., Lu, J., Løvstad, M., & Røe, C. (2018). Disability and quality of life 20 years after traumatic brain injury. *Brain and Behavior*, *8*(7), e01018. https://doi.org/10.1002/brb3.1018

Anderson, C. V., Bigler, E. D., & Blatter, D. D. (1995). Frontal lobe lesions, diffuse damage, and neuropsychological functioning in traumatic brain-injured patients. *Journal of Clinical and Experimental Neuropsychology*, *17*(6), 900–908. https://doi.org/10.1080/01688639508402438

Ang, Y.-S., Lockwood, P., Apps, M. A. J., Muhammed, K., & Husain, M. (2017). Distinct Subtypes of Apathy Revealed by the Apathy Motivation Index. *PLOS ONE*, *12*(1), e0169938. https://doi.org/10.1371/journal.pone.0169938

Apps, M. A. J., Lesage, E., & Ramnani, N. (2015). Vicarious Reinforcement Learning Signals When Instructing Others. *Journal of Neuroscience*, *35*(7), 2904–2913. https://doi.org/10.1523/JNEUROSCI.3669-14.2015

Apps, M. A. J., & Ramnani, N. (2014). The Anterior Cingulate Gyrus Signals the Net Value of Others' Rewards. *Journal of Neuroscience*, *34*(18), 6190–6200. https://doi.org/10.1523/JNEUROSCI.2701-13.2014

Ashburner, J. (2007). A fast diffeomorphic image registration algorithm. *NeuroImage*, *38*(1), 95–113. https://doi.org/10.1016/j.neuroimage.2007.07.007

Avants, B. B., Tustison, N. J., Song, G., Cook, P. A., Klein, A., & Gee, J. C. (2011). A reproducible evaluation of ANTs similarity metric performance in brain image registration. *NeuroImage*, *54*(3), 2033–2044. https://doi.org/10.1016/j.neuroimage.2010.09.025

Baldo, J. V., Shimamura, A. P., Delis, D. C., Kramer, J., & Kaplan, E. (2001). Verbal and design fluency in patients with frontal lobe lesions. *Journal of the International Neuropsychological Society*, *7*(5), 586–596. https://doi.org/10.1017/S1355617701755063

Balestroni, G., & Bertolotti, G. (2012). [EuroQol-5D (EQ-5D): An instrument for measuring quality of life]. *Monaldi Archives for Chest Disease = Archivio Monaldi Per Le Malattie Del Torace*, *78*(3), 155–159. https://doi.org/10.4081/monaldi.2012.121

Baron-Cohen, S., O'Riordan, M., Stone, V., Jones, R., & Plaisted, K. (1999). Recognition of faux pas by normally developing children and children with Asperger syndrome or high-functioning autism. *Journal of Autism and Developmental Disorders*, *29*(5), 407–418. https://doi.org/10.1023/A:1023035012436

Baron-Cohen, S., & Wheelwright, S. (2004). The Empathy Quotient: An Investigation of Adults with Asperger Syndrome or High Functioning Autism, and Normal Sex

Differences. *Journal of Autism and Developmental Disorders*, *34*(2), 163–175. https://doi.org/10.1023/B:JADD.0000022607.19833.00

Baron-Cohen, S., Wheelwright, S., Hill, J., Raste, Y., & Plumb, I. (2001). The "Reading the Mind in the Eyes" Test Revised Version: A Study with Normal Adults, and Adults with Asperger Syndrome or High-functioning Autism. *The Journal of Child Psychology and Psychiatry and Allied Disciplines*, *42*(2), 241–251. Cambridge Core. https://doi.org/10.1017/S0021963001006643

Barrett, L. F., Adolphs, R., Marsella, S., Martinez, A. M., & Pollak, S. D. (2019). Emotional Expressions Reconsidered: Challenges to Inferring Emotion From Human Facial Movements: *Psychological Science in the Public Interest*. https://doi.org/10.1177/1529100619832930

Basser, P J, & Pierpaoli, C. (1998). A simplified method to measure the diffusion tensor from seven MR images. *Magn Reson Med*, *39*(6), 928–934. https://doi.org/10.1002/mrm.1910390610

Basser, Peter J., & Pierpaoli, C. (1996). Microstructural and physiological features of tissues elucidated by quantitative-diffusion-tensor MRI. *Journal of Magnetic Resonance*, *213*(2), 560–570. https://doi.org/10.1016/j.jmr.2011.09.022

Bates, E., Wilson, S. M., Saygin, A. P., Dick, F., Sereno, M. I., Knight, R. T., & Dronkers, N. F. (2003). Voxel-based lesion–symptom mapping. *Nature Neuroscience*, *6*(5), 448–450. https://doi.org/10.1038/nn1050

Beck, A. T., Steer, R. A., & Brown, G. (2011). *Beck Depression Inventory–II* [Data set]. American Psychological Association. https://doi.org/10.1037/t00742-000

Beer, J. S., John, O. P., Scabini, D., & Knight, R. T. (2006). Orbitofrontal cortex and social behavior: Integrating self-monitoring and emotion-cognition interactions. *Journal of Cognitive Neuroscience*, *18*(6), 871–879. https://doi.org/10.1162/jocn.2006.18.6.871

Beer, J. S., & Ochsner, K. N. (2006). Social cognition: A multi level analysis. *Brain Research*, *1079*(1), 98–105. https://doi.org/10.1016/j.brainres.2006.01.002

Behrens, T. E. J., Woolrich, M. W., Jenkinson, M., Johansen-Berg, H., Nunes, R. G., Clare, S., Matthews, P. M., Brady, J. M., & Smith, S. M. (2003). Characterization and Propagation of Uncertainty in Diffusion-Weighted MR Imaging. *Magnetic Resonance in Medicine*, *50*(5), 1077–1088. https://doi.org/10.1002/mrm.10609

Bernhardt, B. C., & Singer, T. (2012). The Neural Basis of Empathy. *Annual Review of Neuroscience*, *35*(1), 1–23. https://doi.org/10.1146/annurev-neuro-062111-150536

Białaszek, W., Marcowski, P., & Ostaszewski, P. (2017). Physical and cognitive effort discounting across different reward magnitudes: Tests of discounting models. *PLoS ONE*, *12*(7). https://doi.org/10.1371/journal.pone.0182353

Bibby, H., & McDonald, S. (2005). Theory of mind after traumatic brain injury. *Neuropsychologia*, *43*(1), 99–114. https://doi.org/10.1016/j.neuropsychologia.2004.04.027

Bickart, K. C., Dickerson, B. C., & Barrett, L. F. (2014). The amygdala as a hub in brain networks that support social life. *Neuropsychologia*, *63*, 235–248. https://doi.org/10.1016/j.neuropsychologia.2014.08.013

Bigler, E. D. (2001). The lesion(s) in traumatic brain injury: Implications for clinical neuropsychology. *Archives of Clinical Neuropsychology*, *16*(2), 95–131. https://doi.org/10.1016/S0887-6177(00)00095-0

Bivona, U., Ciurli, P., Barba, C., Onder, G., Azicnuda, E., Silvestro, D., Mangano, R., Rigon, J., & Formisano, R. (2008). Executive function and metacognitive self-awareness after Severe Traumatic Brain Injury. *Journal of the International Neuropsychological Society*, *14*(5), 862–868. https://doi.org/10.1017/S1355617708081125

Bland, A. R., Roiser, J. P., Mehta, M. A., Schei, T., Boland, H., Campbell-Meiklejohn, D. K., Emsley, R. A., Munafo, M. R., Penton-Voak, I. S., Seara-Cardoso, A., Viding, E., Voon, V., Sahakian, B. J., Robbins, T. W., & Elliott, R. (2016). EMOTICOM: A Neuropsychological Test Battery to Evaluate Emotion, Motivation, Impulsivity, and Social Cognition. *Frontiers in Behavioral Neuroscience*, *10*. https://doi.org/10.3389/fnbeh.2016.00025

Blennow, K., Brody, D. L., Kochanek, P. M., Levin, H., McKee, A., Ribbers, G. M., Yaffe, K., & Zetterberg, H. (2016). Traumatic brain injuries. *Nature Reviews Disease Primers*, *2*(1), 16084. https://doi.org/10.1038/nrdp.2016.84

Bonnelle, V., Ham, T. E., Leech, R., Kinnunen, K. M., Mehta, M. A., Greenwood, R. J., & Sharp, D. J. (2012). Salience network integrity predicts default mode network function after traumatic brain injury. *Proceedings of the National Academy of Sciences*, *109*(12), 4690–4695. https://doi.org/10.1073/pnas.1113455109

Botvinick, M. M., Cohen, J. D., & Carter, C. S. (2004). Conflict monitoring and anterior cingulate cortex: An update. *Trends in Cognitive Sciences*, 539–546.

Brothers, L. (1990). The neural basis of primate social communication. *Motivation and Emotion*, *14*(2), 81–91. https://doi.org/10.1007/BF00991637

Bullmore, E., & Sporns, O. (2009). Complex brain networks: Graph theoretical analysis of structural and functional systems. *Nature Reviews Neuroscience*, *10*(3), 186–198. https://doi.org/10.1038/nrn2575

Bush, G., Frazier, J. a, Rauch, S. L., Seidman, L. J., Whalen, P. J., Jenike, M. a, Rosen, B. R., & Biederman, J. (1999). Anterior cingulate cortex dysfunction in attention-deficit/hyperactivity disorder revealed by fMRI and the Counting Stroop. *Biological Psychiatry*, *45*(12), 1542–1552.

Calder, A. J., Young, A. W., Rowland, D., Perrett, D. I., Hodges, J. R., & EtcoŒ, N. L. (1996). Facial Emotion Recognition after Bilateral Amygdala Damage: DiŒerentially Severe Impairment of Fear. *Cognitive Neuropsychology*, *13*(5), 47.

Carrera, E., & Tononi, G. (2014). Diaschisis: Past, present, future. *Brain*, *137*(9), 2408–2422. https://doi.org/10.1093/brain/awu101

Carrington, S. J., & Bailey, A. J. (2009). Are there theory of mind regions in the brain? A review of the neuroimaging literature. *Human Brain Mapping*, *30*(8), 2313–2335. https://doi.org/10.1002/hbm.20671

Chiou, K. S., Carlson, R. A., Arnett, P. A., Cosentino, S. A., & Hillary, F. G. (2011). Metacognitive monitoring in moderate and severe traumatic brain injury. *Journal of the International Neuropsychological Society: JINS*, *17*(4), 720–731. https://doi.org/10.1017/S1355617711000658

Christiaens, D., Reisert, M., Dhollander, T., Sunaert, S., Suetens, P., & Maes, F. (2015). Global tractography of multi-shell diffusion-weighted imaging data using a multi-tissue model. *NeuroImage*, *123*, 89–101. https://doi.org/10.1016/j.neuroimage.2015.08.008

Chudasama, Y., Daniels, T. E., Gorrin, D. P., Rhodes, S. E. V., Rudebeck, P. H., & Murray, E. A. (2013). The Role of the Anterior Cingulate Cortex in Choices based on Reward Value and Reward Contingency. *Cerebral Cortex (New York, NY)*, *23*(12), 2884–2898. https://doi.org/10.1093/cercor/bhs266

Cicerone, K. D., & Tanenbaum, L. N. (1997). Disturbance of social cognition after traumatic orbitofrontal brain injury. *Archives of Clinical Neuropsychology: The Official Journal of the National Academy of Neuropsychologists*, *12*(2), 173–188.

Cohen, A. L., & Fox, M. D. (2020). Reply: The influence of sample size and arbitrary statistical thresholds in lesion-network mapping. *Brain*, *143*(5), e41–e41. https://doi.org/10.1093/brain/awaa095

Cohen, S. (1997). Social Ties and Susceptibility to the Common Cold. *JAMA: The Journal of the American Medical Association*, *277*(24), 1940. https://doi.org/10.1001/jama.1997.03540480040036

Cole, J H, Ritchie, S. J., Bastin, M. E., Valdés Hernández, M. C., Muñoz Maniega, S., Royle, N., Corley, J., Pattie, A., Harris, S. E., Zhang, Q., Wray, N. R., Redmond, P., Marioni, R. E., Starr, J. M., Cox, S. R., Wardlaw, J. M., Sharp, D. J., & Deary, I. J. (2018). Brain age predicts mortality. *Molecular Psychiatry*, *23*(5), 1385–1392. https://doi.org/10.1038/mp.2017.62

Cole, James H., Jolly, A., De Simoni, S., Bourke, N., Patel, M. C., Scott, G., & Sharp, D. J. (2018). Spatial patterns of progressive brain volume loss after moderate-severe traumatic brain injury. *Brain*, *141*(3), 822–836. https://doi.org/10.1093/brain/awx354

Cole, James H., Leech, R., Sharp, D. J., & for the Alzheimer's Disease Neuroimaging Initiative. (2015). Prediction of brain age suggests accelerated atrophy after traumatic brain injury: Brain Age Prediction after TBI. *Annals of Neurology*, *77*(4), 571–581. https://doi.org/10.1002/ana.24367

Corbetta, M., Patel, G., & Shulman, G. L. (2008). The Reorienting System of the Human Brain: From Environment to Theory of Mind. *Neuron*, *58*(3), 306–324. https://doi.org/10.1016/j.neuron.2008.04.017

Coupé, P., Manjón, J. V., Lanuza, E., & Catheline, G. (2019). Lifespan Changes of the Human Brain In Alzheimer's Disease. *Scientific Reports*, *9*(1), 3998. https://doi.org/10.1038/s41598-019-39809-8

Criminisi, A., Sharp, T., & Blake, A. (2008). GeoS: Geodesic Image Segmentation. In D. Forsyth, P. Torr, & A. Zisserman (Eds.), *Computer Vision – ECCV 2008* (pp. 99–112). Springer. https://doi.org/10.1007/978-3-540-88682-2_9

Daducci, A., Canales-rodríguez, E. J., Zhang, H., Dyrby, T. B., & Daniel, C. (2015). *Accelerated Microstructure Imaging via Convex Optimization (AMICO) from di ff usion MRI data*. *41*(0), 32–44.

Dajani, D. R., & Uddin, L. Q. (2015). Demystifying cognitive flexibility: Implications for clinical and developmental neuroscience. *Trends in Neurosciences*, *38*(9), 571–578. https://doi.org/10.1016/j.tins.2015.07.003

Dal Monte, O., Krueger, F., Solomon, J. M., Schintu, S., Knutson, K. M., Strenziok, M., Pardini, M., Leopold, A., Raymont, V., & Grafman, J. (2013). A voxel-based lesion study on facial emotion recognition after penetrating brain injury. *Social Cognitive and Affective Neuroscience*, *8*(6), 632–639. https://doi.org/10.1093/scan/nss041

Damasio, A. R., Everitt, B. J., Bishop, D., Roberts, A. C., Robbins, T. W., & Weiskrantz, L. (1996). The somatic marker hypothesis and the possible functions of the prefrontal cortex. *Philosophical Transactions of the Royal Society of London. Series B: Biological Sciences*, *351*(1346), 1413–1420. https://doi.org/10.1098/rstb.1996.0125

Darby, R. R., Horn, A., Cushman, F., & Fox, M. D. (2018). Lesion network localization of criminal behavior. *Proceedings of the National Academy of Sciences*, *115*(3), 601–606. https://doi.org/10.1073/pnas.1706587115

Davies, M. (2015). Should I accept gifts from patients? *BMJ*, *350*. https://doi.org/10.1136/bmj.h617

De Jaegher, H., Di Paolo, E., & Gallagher, S. (2010). Can social interaction constitute social cognition? *Trends in Cognitive Sciences*, *14*(10), 441–447. https://doi.org/10.1016/j.tics.2010.06.009

de Schotten, M. T., Foulon, C., & Nachev, P. (2020). *Brain disconnections link structural connectivity with function and behaviour* [Preprint]. Neuroscience. https://doi.org/10.1101/2020.02.27.967570

De Simoni, S., Jenkins, P. O., Bourke, N. J., Fleminger, J. J., Hellyer, P. J., Jolly, A. E., Patel, M. C., Cole, J. H., Leech, R., & Sharp, D. J. (2018). Altered caudate connectivity is associated with executive dysfunction after traumatic brain injury. *Brain*, *141*(1), 148–164. https://doi.org/10.1093/brain/awx309

de Sousa, A., McDonald, S., Rushby, J., Li, S., Dimoska, A., & James, C. (2011). Understanding deficits in empathy after traumatic brain injury: The role of affective responsivity. *Cortex; a Journal Devoted to the Study of the Nervous System and Behavior*, *47*(5), 526–535. https://doi.org/10.1016/j.cortex.2010.02.004

Delis, D. C., Kaplan, E., & Kramer, J. H. (2001). *Delis-Kaplan Executive Function System: D-KEFS.* Pearson.

Dennis, M., Simic, N., Bigler, E. D., Abildskov, T., Agostino, A., Taylor, H. G., Rubin, K., Vannatta, K., Gerhardt, C. A., Stancin, T., & Yeates, K. O. (2013). Cognitive, affective, and conative theory of mind (ToM) in children with traumatic brain injury. *Developmental Cognitive Neuroscience*, *5*, 25–39. https://doi.org/10.1016/j.dcn.2012.11.006

DeSimone, J. A. (2014). New Techniques for Evaluating Temporal Consistency: *Organizational Research Methods*. https://doi.org/10.1177/1094428114553061

Di Santo, L. (2019). The distinction between apathy and depression in neuroscience nursing practice. *British Journal of Neuroscience Nursing*, *15*(4), 164–168. https://doi.org/10.12968/bjnn.2019.15.4.164

Diaconescu, A. O., Mathys, C., Weber, L. A. E., Kasper, L., Mauer, J., & Stephan, K. E. (2017). Hierarchical prediction errors in midbrain and septum during social learning.

Social Cognitive and Affective Neuroscience, *12*(4), 618–634. https://doi.org/10.1093/scan/nsw171

Diamond, A. (2013). Executive Functions. *Annual Review of Psychology*, *64*, 135–168. https://doi.org/10.1146/annurev-psych-113011-143750

Dockree, P. M., O'Connell, R. G., & Robertson, I. H. (2015). Connecting clinical and experimental investigations of awareness in traumatic brain injury. *Handbook of Clinical Neurology*, *128*, 511–524. https://doi.org/10.1016/B978-0-444-63521-1.00032-7

Dockree, P. M., Tarleton, Y. M., Carton, S., & FitzGerald, M. C. C. (2015). Connecting Self-Awareness and Error-Awareness in Patients with Traumatic Brain Injury. *Journal of the International Neuropsychological Society : JINS*, *21*(7), 473–482. https://doi.org/10.1017/S1355617715000594

Dolan, R. J. (2002). Emotion, Cognition, and Behavior. *Science*, *298*(5596), 1191–1194. https://doi.org/10.1126/science.1076358

Donders, J., Tulsky, D. S., & Zhu, J. J. (2001). Criterion validity of new WAIS-III subtest scores after traumatic brain injury. *Journal of the International Neuropsychological Society*, *7*(7), 892–898. https://doi.org/10.1017/s1355617701246153

Draper, K., Ponsford, J., & Schönberger, M. (2007). Psychosocial and Emotional Outcomes 10 Years Following Traumatic Brain Injury. *The Journal of Head Trauma Rehabilitation*, *22*(5), 278. https://doi.org/10.1097/01.HTR.0000290972.63753.a7

Driscoll, D. M., Dal Monte, O., Solomon, J., Krueger, F., & Grafman, J. (2012). Empathic Deficits in Combat Veterans with Traumatic Brain Injury: A Voxel-Based Lesion-Symptom Mapping Study. *Cognitive and Behavioral Neurology*, *25*(4), 160. https://doi.org/10.1097/WNN.0b013e318280cf4e

Dronkers, N. F., Plaisant, O., Iba-Zizen, M. T., & Cabanis, E. A. (2007). Paul Broca's historic cases: High resolution MR imaging of the brains of Leborgne and Lelong. *Brain*, *130*(5), 1432–1441. https://doi.org/10.1093/brain/awm042

Elmose, M., & Happé, F. (2014). Being aware of own performance: How accurately do children with autism spectrum disorder judge own memory performance? *Autism Research: Official Journal of the International Society for Autism Research*, *7*(6), 712–719. https://doi.org/10.1002/aur.1421

Eriksen, B. A., & Eriksen, C. W. (1974). Effects of noise letters upon the identification of a target letter in a nonsearch task. *Perception & Psychophysics*, *16*(1), 143–149. https://doi.org/10.3758/BF03203267

Ferreira-Garcia, R., Fontenelle, L. F., Moll, J., & Oliveira-Souza, R. de. (2014). Pathological generosity: An atypical impulse control disorder after a left subcortical stroke. *Neurocase*, *20*(5), 496–500. https://doi.org/10.1080/13554794.2013.826681

Fitzgerald, L. M., Arvaneh, M., & Dockree, P. M. (2017). Domain-specific and domain-general processes underlying metacognitive judgments. *Consciousness and Cognition*, *49*, 264–277. https://doi.org/10.1016/j.concog.2017.01.011

FitzGerald, M. C. C., O'Keeffe, F., Carton, S., Coen, R. F., Kelly, S., & Dockree, P. (2019). Rehabilitation of emergent awareness of errors post traumatic brain injury: A pilot intervention. *Neuropsychological Rehabilitation*, *29*(6), 821–843. https://doi.org/10.1080/09602011.2017.1336102

Flavell, J. H. (1979). Metacognition and cognitive monitoring: A new area of cognitive-developmental inquiry. *American Psychologist*, *34*(10), 906–911. https://doi.org/10.1037/0003-066X.34.10.906

Fleming, J. M., Strong, J., & Ashton, R. (1996). Self-awareness of deficits in adults with traumatic brain injury: How best to measure? *Brain Injury*, *10*(1), 1–15. https://doi.org/10.1080/026990596124674

Fleming, S. M., & Dolan, R. J. (2012). The neural basis of metacognitive ability. *Philosophical Transactions of the Royal Society B: Biological Sciences*, *367*(1594), 1338–1349. https://doi.org/10.1098/rstb.2011.0417

Fleming, S. M., & Lau, H. C. (2014). How to measure metacognition. *Frontiers in Human Neuroscience*, *8*. https://doi.org/10.3389/fnhum.2014.00443

Fleming, S. M., Ryu, J., Golfinos, J. G., & Blackmon, K. E. (2014). Domain-specific impairment in metacognitive accuracy following anterior prefrontal lesions. *Brain*, *137*(10), 2811–2822. https://doi.org/10.1093/brain/awu221

Fleming, S. M., Weil, R. S., Nagy, Z., Dolan, R. J., & Rees, G. (2010). Relating Introspective Accuracy to Individual Differences in Brain Structure. *Science*, *329*(5998), 1541–1543. https://doi.org/10.1126/science.1191883

Forkel, S. J., & Catani, M. (2018). Lesion mapping in acute stroke aphasia and its implications for recovery. *Neuropsychologia*, *115*, 88–100. https://doi.org/10.1016/j.neuropsychologia.2018.03.036

Formisano, R., Longo, E., Azicnuda, E., Silvestro, D., D'Ippolito, M., Truelle, J.-L., von Steinbüchel, N., von Wild, K., Wilson, L., Rigon, J., Barba, C., Forcina, A., & Giustini, M. (2017). Quality of life in persons after traumatic brain injury as self-perceived and as perceived by the caregivers. *Neurological Sciences: Official Journal of the Italian Neurological Society and of the Italian Society of Clinical Neurophysiology*, *38*(2), 279–286. https://doi.org/10.1007/s10072-016-2755-y

Foulon, C., Cerliani, L., Kinkingnéhun, S., Levy, R., Rosso, C., Urbanski, M., Volle, E., & Thiebaut de Schotten, M. (2018). Advanced lesion symptom mapping analyses and

implementation as BCBtoolkit. *GigaScience*, *7*(3). https://doi.org/10.1093/gigascience/giy004

Frank, M. J., & O'Reilly, R. C. (2006). A mechanistic account of striatal dopamine function in human cognition: Psychopharmacological studies with cabergoline and haloperidol. *Behavioral Neuroscience*, *120*(3), 497–517. https://doi.org/10.1037/0735-7044.120.3.497

Friston, K. J., Tononi, G., Reeke, G. N., Sporns, O., & Edelman, G. M. (1994). Value-dependent selection in the brain: Simulation in a synthetic neural model. *Neuroscience*, *59*(2), 229–243. https://doi.org/10.1016/0306-4522(94)90592-4

Frith, C. D. (2008). Social cognition. *Philosophical Transactions of the Royal Society B: Biological Sciences*, *363*(1499), 2033–2039. https://doi.org/10.1098/rstb.2008.0005

Frith, C. D. (2012). The role of metacognition in human social interactions. *Philosophical Transactions of the Royal Society B: Biological Sciences*, *367*(1599), 2213–2223. https://doi.org/10.1098/rstb.2012.0123

Frith, C. D., & Frith, U. (1999). Interacting Minds—A Biological Basis. *Science*, *286*(5445), 1692–1695. https://doi.org/10.1126/science.286.5445.1692

Frith, C. D., & Frith, U. (2008). Implicit and Explicit Processes in Social Cognition. *Neuron*, *60*(3), 503–510. https://doi.org/10.1016/j.neuron.2008.10.032

Frith, U., & Frith, C. (2001). The Biological Basis of Social Interaction. *Current Directions in Psychological Science*, *10*(5).

Funes, C. M., Lavretsky, H., Ercoli, L., St. Cyr, N., & Siddarth, P. (2018). Apathy Mediates Cognitive Difficulties in Geriatric Depression. *The American Journal of Geriatric Psychiatry : Official Journal of the American Association for Geriatric Psychiatry*, *26*(1), 100–106. https://doi.org/10.1016/j.jagp.2017.06.012

Fusar-Poli, P., Placentino, A., Carletti, F., Landi, P., Allen, P., Surguladze, S., Benedetti, F., Abbamonte, M., Gasparotti, R., Barale, F., Perez, J., McGuire, P., & Politi, P. (2009). Functional atlas of emotional faces processing: A voxel-based meta-analysis of 105 functional magnetic resonance imaging studies. *Journal of Psychiatry & Neuroscience : JPN*, *34*(6), 418–432.

Gallagher, H. L., & Frith, C. D. (2003). Functional imaging of 'theory of mind'. *Trends in Cognitive Sciences*, *7*(2), 77–83. https://doi.org/10.1016/s1364-6613(02)00025-6

Genova, H. M., Rajagopalan, V., Chiaravalloti, N., Binder, A., Deluca, J., & Lengenfelder, J. (2015). Facial affect recognition linked to damage in specific white matter tracts in traumatic brain injury. *Social Neuroscience*, *10*(1), 27–34. https://doi.org/10.1080/17470919.2014.959618

Ghajar, J. (2000). Traumatic brain injury. *The Lancet*, *356*(9233), 923–929. https://doi.org/10.1016/S0140-6736(00)02689-1

Ghajari, M., Hellyer, P. J., & Sharp, D. J. (2017). Computational modelling of traumatic brain injury predicts the location of chronic traumatic encephalopathy pathology. *Brain*, *140*(2), 333–343. https://doi.org/10.1093/brain/aww317

Gleichgerrcht, E., Fridriksson, J., Rorden, C., & Bonilha, L. (2017). Connectome-based lesion-symptom mapping (CLSM): A novel approach to map neurological function. *NeuroImage: Clinical*, *16*, 461–467. https://doi.org/10.1016/j.nicl.2017.08.018

Gorgoraptis, N., Zaw-Linn, J., Feeney, C., Tenorio-Jimenez, C., Niemi, M., Malik, A., Ham, T., Goldstone, A. P., & Sharp, D. J. (2019). Cognitive impairment and health-related quality of life following traumatic brain injury. *NeuroRehabilitation*, *44*(3), 321–331. https://doi.org/10.3233/NRE-182618

Grace, J., Stout, J. C., & Malloy, P. F. (1999). Assessing frontal lobe behavioral syndromes with the frontal lobe personality scale. *Assessment*, *6*(3), 269–284. https://doi.org/10.1177/107319119900600307

Grace, Janet, & Malloy, P. (2001). *Frontal Systems Behavior Scale (FrSBe): Professional manual, Psychological Assessment Resources, Lutz, FL*. https://www.parinc.com/Products/Pkey/116

Grussu, F., Schneider, T., Tur, C., Yates, R. L., Tachrount, M., Ianuş, A., Yiannakas, M. C., Newcombe, J., Zhang, H., Alexander, D. C., DeLuca, G. C., & Gandini Wheeler-Kingshott, C. A. M. (2017). Neurite dispersion: A new marker of multiple sclerosis spinal cord pathology? *Annals of Clinical and Translational Neurology*, *4*(9), 663–679. https://doi.org/10.1002/acn3.445

Hacker, D. J., Dunlosky, J., & Graesser, A. C. (2009). *Handbook of Metacognition in Education*. Routledge.

Ham, T. E., Bonnelle, V., Hellyer, P., Jilka, S., Robertson, I. H., Leech, R., & Sharp, D. J. (2014). The neural basis of impaired self-awareness after traumatic brain injury. *Brain: A Journal of Neurology*, *137*(Pt 2), 586–597. https://doi.org/10.1093/brain/awt350

Hampshire, A., Sandrone, S., & Hellyer, P. J. (2019). A Large-Scale, Cross-Sectional Investigation Into the Efficacy of Brain Training. *Frontiers in Human Neuroscience*, *13*, 221. https://doi.org/10.3389/fnhum.2019.00221

Hampshire, A., Thompson, R., Duncan, J., & Owen, A. M. (2011). Lateral Prefrontal Cortex Subregions Make Dissociable Contributions during Fluid Reasoning. *Cerebral Cortex*, *21*(1), 1–10. https://doi.org/10.1093/cercor/bhq085

Hampton, A. N., Bossaerts, P., & O'Doherty, J. P. (2008). Neural correlates of mentalizing-related computations during strategic interactions in humans. *Proceedings of the*

National Academy of Sciences, *105*(18), 6741–6746. https://doi.org/10.1073/pnas.0711099105

Happé, F., Cook, J. L., & Bird, G. (2017). The Structure of Social Cognition: In(ter)dependence of Sociocognitive Processes. *Annual Review of Psychology*, *68*(1), 243–267. https://doi.org/10.1146/annurev-psych-010416-044046

Happé, F., & Frith, U. (2014). Annual Research Review: Towards a developmental neuroscience of atypical social cognition. *Journal of Child Psychology and Psychiatry*, *55*(6), 553–577. https://doi.org/10.1111/jcpp.12162

Harlow, J. M. (1993). Recovery from the passage of an iron bar through the head. *History of Psychiatry*, *4*(14), 274–281. https://doi.org/10.1177/0957154X9300401407

Hart, M. G., Ypma, R. J. F., Romero-Garcia, R., Price, S. J., & Suckling, J. (2016). Graph theory analysis of complex brain networks: New concepts in brain mapping applied to neurosurgery. *Journal of Neurosurgery*, *124*(6), 1665–1678. https://doi.org/10.3171/2015.4.JNS142683

Hart, T., Giovannetti, T., Montgomery, M. W., & Schwartz, M. F. (1998). Awareness of errors in naturalistic action after traumatic brain injury. *The Journal of Head Trauma Rehabilitation*, *13*(5), 16–28. https://doi.org/10.1097/00001199-199810000-00004

Hart, T., Whyte, J., Polansky, M., Kersey-Matusiak, G., & Fidler-Sheppard, R. (2005). Community Outcomes Following Traumatic Brain Injury: Impact of Race and Preinjury Status. *Journal of Head Trauma Rehabilitation*, *20*(2), 158–172.

Hauser, T. U., Allen, M., Purg, N., Moutoussis, M., Rees, G., & Dolan, R. J. (2017). Noradrenaline blockade specifically enhances metacognitive performance. *ELife*, *6*, e24901. https://doi.org/10.7554/eLife.24901

Henry, J. D., von Hippel, W., Molenberghs, P., Lee, T., & Sachdev, P. S. (2016). Clinical assessment of social cognitive function in neurological disorders. *Nature Reviews. Neurology*, *12*(1), 28–39. https://doi.org/10.1038/nrneurol.2015.229

Hillis, A. E. (2014). Inability to empathize: Brain lesions that disrupt sharing and understanding another's emotions. *Brain*, *137*(4), 981–997. https://doi.org/10.1093/brain/awt317

Hofmann, W., Schmeichel, B. J., & Baddeley, A. D. (2012). Executive functions and self-regulation. *Trends in Cognitive Sciences*, *16*(3), 174–180. https://doi.org/10.1016/j.tics.2012.01.006

Holland, C. A. C., Ebner, N. C., Lin, T., & Samanez-Larkin, G. R. (2019). Emotion identification across adulthood using the Dynamic FACES database of emotional expressions in younger, middle aged, and older adults. *Cognition and Emotion*, *33*(2), 245–257. https://doi.org/10.1080/02699931.2018.1445981

Horn, J. L. (1965). A RATIONALE AND TEST FOR THE NUMBER OF FACTORS IN FACTOR ANALYSIS. *Psychometrika*, *30*, 179–185. https://doi.org/10.1007/bf02289447

Horn, H. J. van der, Liemburg, E. J., Scheenen, M. E., Koning, M. E. de, Spikman, J. M., & Naalt, J. van der. (2017). Graph Analysis of Functional Brain Networks in Patients with Mild Traumatic Brain Injury. *PLOS ONE*, *12*(1), e0171031. https://doi.org/10.1371/journal.pone.0171031

Hoskinson, K. R., Bigler, E. D., Abildskov, T. J., Dennis, M., Taylor, H. G., Rubin, K., Gerhardt, C. A., Vannatta, K., Stancin, T., & Yeates, K. O. (2020). The mentalizing network and theory of mind mediate adjustment after childhood traumatic brain injury. *Social Cognitive and Affective Neuroscience*. https://doi.org/10.1093/scan/nsaa006

Iacobacci, C. (2017). Common and Different Features Between Depression and Apathy in Neurocognitive Disorders. *Clinical and Experimental Psychology*, *03*(03). https://doi.org/10.4172/2471-2701.1000163

Izuma, K., & Adolphs, R. (2013). Social manipulation of preference in the human brain. *Neuron*, *78*(3), 563–573. https://doi.org/10.1016/j.neuron.2013.03.023

James, S. L., Theadom, A., Ellenbogen, R. G., Bannick, M. S., Montjoy-Venning, W., Lucchesi, L. R., Abbasi, N., Abdulkader, R., Abraha, H. N., Adsuar, J. C., Afarideh, M., Agrawal, S., Ahmadi, A., Ahmed, M. B., Aichour, A. N., Aichour, I., Aichour, M. T. E., Akinyemi, R. O., Akseer, N., … Murray, C. J. L. (2019). Global, regional, and national burden of traumatic brain injury and spinal cord injury, 1990–2016: A systematic analysis for the Global Burden of Disease Study 2016. *The Lancet Neurology*, *18*(1), 56–87. https://doi.org/10.1016/S1474-4422(18)30415-0

Jenkins, P. O., De Simoni, S., Bourke, N. J., Fleminger, J., Scott, G., Towey, D. J., Svensson, W., Khan, S., Patel, M. C., Greenwood, R., Friedland, D., Hampshire, A., Cole, J. H., & Sharp, D. J. (2019). Stratifying drug treatment of cognitive impairments after traumatic brain injury using neuroimaging. *Brain*, *142*(8), 2367–2379. https://doi.org/10.1093/brain/awz149

Jenkins, P. O., De Simoni, S., Bourke, N. J., Fleminger, J., Scott, G., Towey, D. J., Svensson, W., Khan, S., Patel, M., Greenwood, R., Cole, J. H., & Sharp, D. J. (2018). Dopaminergic abnormalities following traumatic brain injury. *Brain*, *141*(3), 797–810. https://doi.org/10.1093/brain/awx357

Jenkinson, M., Beckmann, C. F., Behrens, T. E. J., Woolrich, M. W., & Smith, S. M. (2012). FSL. *NeuroImage*, *62*(2), 782–790. https://doi.org/10.1016/j.neuroimage.2011.09.015

Jespersen, S., Bjarkam, C., Nyengaard, J., Charkravarty, M., Hansen, B., Vosegaard, T., Ostergaard, L., Yablonskiy, D., Nielsen, N., & Vestergaard-Poulsen, P. (2010).

Neurite density from magnetic resonance diffusion measurements at ultrahigh field: Comparison with light microscopy and electron microscopy. *Neuroimage*, *23*(1), 1–7. https://doi.org/10.1038/jid.2014.371

Jespersen, S., Leigland, L., Cornea, A., & Kroenke, C. (2012). Determination of Axonal and Dendritic Orientation Distributions Within the developing Cerebral Cortex by Diffusion Tensor Imaging. *IEEE Trans Med Imaging*, *31*(Serres 1985), 759–785. https://doi.org/10.1146/annurev-cellbio-092910-154240.Sensory

Jeurissen, B., Tournier, J.-D., Dhollander, T., Connelly, A., & Sijbers, J. (2014). Multi-tissue constrained spherical deconvolution for improved analysis of multi-shell diffusion MRI data. *NeuroImage*, *103*, 411–426. https://doi.org/10.1016/j.neuroimage.2014.07.061

Johnson, V. E., Stewart, W., & Smith, D. H. (2013). Axonal pathology in traumatic brain injury. *Experimental Neurology*, *246*, 35–43. https://doi.org/10.1016/j.expneurol.2012.01.013

Jolly, A., Balaet, M., Azor, A., Friedland, D., Sandrone, S., Graham, N. S. N., Zimmerman, K., & Sharp, D. J. (2020). Detecting axonal injury in individual patients after traumatic brain injury. *Brain*.

Jonas, E., & Kording, K. P. (2017). Could a Neuroscientist Understand a Microprocessor? *PLOS Computational Biology*, *13*(1), e1005268. https://doi.org/10.1371/journal.pcbi.1005268

Jones, D. K., & Cercignani, M. (2010). Twenty-five pitfalls in the analysis of diffusion MRI data. *NMR in Biomedicine*, *23*(7), 803–820. https://doi.org/10.1002/nbm.1543

Jones, D. K., Knosche, T. R., & Turner, R. (2013). White matter integrity, fiber count, and other fallacies: The do's and don'ts of diffusion MRI. *NeuroImage*, *73*, 239–254. https://doi.org/10.1016/j.neuroimage.2012.06.081

Kelly, K. J., & Metcalfe, J. (2011). Metacognition of emotional face recognition. *Emotion*, *11*(4), 896–906. https://doi.org/10.1037/a0023746

Kelly, M., McDonald, S., & Kellett, D. (2014). Development of a novel task for investigating decision making in a social context following traumatic brain injury. *Journal of Clinical and Experimental Neuropsychology*, *36*(9), 897–913. https://doi.org/10.1080/13803395.2014.955784

Kennedy, D. P., & Adolphs, R. (2012). The social brain in psychiatric and neurological disorders. *Trends in Cognitive Sciences*, *16*(11), 559–572. https://doi.org/10.1016/j.tics.2012.09.006

Kimberg, D. Y., Coslett, H. B., & Schwartz, M. F. (2007). Power in Voxel-based lesion-symptom mapping. *Journal of Cognitive Neuroscience*, *19*(7), 1067–1080. https://doi.org/10.1162/jocn.2007.19.7.1067

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

Kirsch-Darrow, L., Marsiske, M., Okun, M. S., Bauer, R., & Bowers, D. (2011). Apathy and Depression: Separate Factors in Parkinson's Disease. *Journal of the International Neuropsychological Society*, *17*(6), 1058–1066. https://doi.org/10.1017/S1355617711001068

Kruger, J., & Dunning, D. (1999). Unskilled and unaware of it: How difficulties in recognizing one's own incompetence lead to inflated self-assessments. *Journal of Personality and Social Psychology*, *77*(6), 1121–1134. https://doi.org/10.1037//0022-3514.77.6.1121

Kuceyeski, A., Maruta, J., Niogi, S. N., Ghajar, J., & Raj, A. (2011). The generation and validation of white matter connectivity importance maps. *NeuroImage*, *58*(1), 109–121. https://doi.org/10.1016/j.neuroimage.2011.05.087

Kunz, A., Dirnagl, U., & Mergenthaler, P. (2010). Acute pathophysiological processes after ischaemic and traumatic brain injury. *Best Practice & Research. Clinical Anaesthesiology*, *24*(4), 495–509. https://doi.org/10.1016/j.bpa.2010.10.001

Le Heron, C., Plant, O., Manohar, S., Ang, Y.-S., Jackson, M., Lennox, G., Hu, M. T., & Husain, M. (2018). Distinct effects of apathy and dopamine on effort-based decision-making in Parkinson's disease. *Brain*, *141*(5), 1455–1469. https://doi.org/10.1093/brain/awy110

Levy, M. L., Cummings, J. L., Fairbanks, L. A., Masterman, D., Miller, B. L., Craig, A. H., Paulsen, J. S., & Litvan, I. (1998). Apathy Is Not Depression. *The Journal of Neuropsychiatry and Clinical Neurosciences*, *10*(3), 314–319. https://doi.org/10.1176/jnp.10.3.314

Li, C. R., Huang, C., Constable, R. T., & Sinha, R. (2006). Imaging Response Inhibition in a Stop-Signal Task: Neural Correlates Independent of Signal Monitoring and Post-Response Processing. *Journal of Neuroscience*, *26*(1), 186–192. https://doi.org/10.1523/JNEUROSCI.3741-05.2006

Li, L. M., Violante, I. R., Leech, R., Ross, E., Hampshire, A., Opitz, A., Rothwell, J. C., Carmichael, D. W., & Sharp, D. J. (2019). Brain state and polarity dependent modulation of brain networks by transcranial direct current stimulation. *Human Brain Mapping*, *40*(3), 904–915. https://doi.org/10.1002/hbm.24420

Li, L. M., Violante, I. R., Zimmerman, K., Leech, R., Hampshire, A., Patel, M., Opitz, A., McArthur, D., Jolly, A., Carmichael, D. W., & Sharp, D. J. (2019). Traumatic axonal

injury influences the cognitive effect of non-invasive brain stimulation. *Brain*, *142*(10), 3280–3293. https://doi.org/10.1093/brain/awz252

Li, W., Mai, X., & Liu, C. (2014). The default mode network and social understanding of others: What do brain connectivity studies tell us. *Frontiers in Human Neuroscience*, *8*. https://doi.org/10.3389/fnhum.2014.00074

Lockwood, P. L., Apps, M. A. J., Valton, V., Viding, E., & Roiser, J. P. (2016). Neurocomputational mechanisms of prosocial learning and links to empathy. *Proceedings of the National Academy of Sciences*, *113*(35), 9763–9768. https://doi.org/10.1073/pnas.1603198113

Lockwood, P. L., Hamonet, M., Zhang, S. H., Ratnavel, A., Salmony, F. U., Husain, M., & Apps, M. A. J. (2017). Prosocial apathy for helping others when effort is required. *Nature Human Behaviour*, *1*(7). https://doi.org/10.1038/s41562-017-0131

Lockwood, Patricia. L., Apps, M. A. J., Roiser, J. P., & Viding, E. (2015). Encoding of Vicarious Reward Prediction in Anterior Cingulate Cortex and Relationship with Trait Empathy. *The Journal of Neuroscience*, *35*(40), 13720–13727. https://doi.org/10.1523/JNEUROSCI.1703-15.2015

Ma, D. S., Correll, J., & Wittenbrink, B. (2015). The Chicago face database: A free stimulus set of faces and norming data. *Behavior Research Methods*, *47*(4), 1122–1135. https://doi.org/10.3758/s13428-014-0532-5

Maas, A. I. R., Menon, D. K., Adelson, P. D., Andelic, N., Bell, M. J., Belli, A., Bragge, P., Brazinova, A., Büki, A., Chesnut, R. M., Citerio, G., Coburn, M., Cooper, D. J., Crowder, A. T., Czeiter, E., Czosnyka, M., Diaz-Arrastia, R., Dreier, J. P., Duhaime, A.-C., … Zumbo, F. (2017). Traumatic brain injury: Integrated approaches to improve prevention, clinical care, and research. *The Lancet Neurology*, *16*(12), 987–1048. https://doi.org/10.1016/S1474-4422(17)30371-X

Mac Donald, C. L., Dikranian, K., Bayly, P., Holtzman, D., & Brody, D. (2007). Diffusion Tensor Imaging Reliably Detects Experimental Traumatic Axonal Injury and Indicates Approximate Time of Injury. *Journal of Neuroscience*, *27*(44), 11869–11876. https://doi.org/10.1523/JNEUROSCI.3647-07.2007

Majdan, M., Plancikova, D., Brazinova, A., Rusnak, M., Nieboer, D., Feigin, V., & Maas, A. (2016). Epidemiology of traumatic brain injuries in Europe: A cross-sectional analysis. *The Lancet Public Health*, *1*(2), e76–e83. https://doi.org/10.1016/S2468-2667(16)30017-2

Malec, J. F., Brown, A. W., Leibson, C. L., Flaada, J. T., Mandrekar, J. N., Diehl, N. N., & Perkins, P. K. (2007). The Mayo Classification System for Traumatic Brain Injury Severity. *Journal of Neurotrauma*, *24*(9), 1417–1424. https://doi.org/10.1089/neu.2006.0245

Malloy, P., Bihrle, A., Duffy, J., & Cimino, C. (1993). The orbitomedial frontal syndrome. *Archives of Clinical Neuropsychology: The Official Journal of the National Academy of Neuropsychologists*, *8*(3), 185–201.

Margulies, D. S., Kelly, A. M. C., Uddin, L. Q., Biswal, B. B., Castellanos, F. X., & Milham, M. P. (2007). Mapping the functional connectivity of anterior cingulate cortex. *NeuroImage*, *37*(2), 579–588. https://doi.org/10.1016/j.neuroimage.2007.05.019

May, M., Milders, M., Downey, B., Whyte, M., Higgins, V., Wojcik, Z., Amin, S., & O'Rourke, S. (2017). Social Behavior and Impairments in Social Cognition Following Traumatic Brain Injury. *Journal of the International Neuropsychological Society: JINS*, *23*(5), 400–411. https://doi.org/10.1017/S1355617717000182

Mazancieux, A., Fleming, S. M., Souchay, C., & Moulin, C. J. A. (2020). Is there a G factor for metacognition? Correlations in retrospective metacognitive sensitivity across

tasks. *Journal of Experimental Psychology. General*. https://doi.org/10.1037/xge0000746

McCabe, D. P., Roediger, H. L., McDaniel, M. A., Balota, D. A., & Hambrick, D. Z. (2010). The Relationship Between Working Memory Capacity and Executive Functioning: Evidence for a Common Executive Attention Construct. *Neuropsychology*, *24*(2), 222–243. https://doi.org/10.1037/a0017619

McDonald, S. (2013). Impairments in Social Cognition Following Severe Traumatic Brain Injury. *Journal of the International Neuropsychological Society*, *19*(3), 231–246. https://doi.org/10.1017/S1355617712001506

McMahon, P. J., Hricik, A., Yue, J. K., Puccio, A. M., Inoue, T., Lingsma, H. F., Beers, S. R., Gordon, W. A., Valadka, A. B., Manley, G. T., Okonkwo and the TRACK-TBI investiga, D. O., Casey, S. S., Cooper, S. R., Dams-O'Connor, K., Menon, D. K., Sorani, M. D., Yuh, E. L., Mukherjee, P., Schnyer, D. M., & Vassar, M. J. (2014). Symptomatology and Functional Outcome in Mild Traumatic Brain Injury: Results from the Prospective TRACK-TBI Study. *Journal of Neurotrauma*, *31*(1), 26–33. https://doi.org/10.1089/neu.2013.2984

Medina, J., Kimberg, D. Y., Chatterjee, A., & Coslett, H. B. (2010). Inappropriate usage of the Brunner-Munzel test in recent voxel-based lesion-symptom mapping studies. *Neuropsychologia*, *48*(1), 341–343. https://doi.org/10.1016/j.neuropsychologia.2009.09.016

Mehler, J. (2001). *Language, Brain, and Cognitive Development: Essays in Honor of Jacques Mehler*. MIT Press.

Mendez, M. F., & Shapira, J. S. (2011). Loss of emotional insight in behavioral variant frontotemporal dementia or "frontal anosodiaphoria". *Consciousness and Cognition*, *20*(4), 1690–1696. https://doi.org/10.1016/j.concog.2011.09.005

Menon, D. K., Schwab, K., Wright, D. W., & Maas, A. I. (2010). Position Statement: Definition of Traumatic Brain Injury. *Archives of Physical Medicine and Rehabilitation*, *91*(11), 1637–1640. https://doi.org/10.1016/j.apmr.2010.05.017

Menon, V., Adleman, N. E., White, C. D., Glover, G. H., & Reiss, A. L. (2001). Error-related brain activation during a Go/NoGo response inhibition task. *Human Brain Mapping*, *12*(3), 131–143. https://doi.org/10.1002/1097-0193(200103)12:3<131::AID-HBM1010>3.0.CO;2-C

Metcalfe, J., & Shimamura, A. P. (1994). *Metacognition: Knowing about knowing*.

Meyer, S., Kessner, S. S., Cheng, B., Bönstrup, M., Schulz, R., Hummel, F. C., De Bruyn, N., Peeters, A., Van Pesch, V., Duprez, T., Sunaert, S., Schrooten, M., Feys, H., Gerloff, C., Thomalla, G., Thijs, V., & Verheyden, G. (2016). Voxel-based lesion-symptom mapping of stroke lesions underlying somatosensory deficits. *NeuroImage. Clinical*, *10*, 257–266. https://doi.org/10.1016/j.nicl.2015.12.005

Milders, M. (2019). Relationship between social cognition and social behaviour following traumatic brain injury. *Brain Injury*, *33*(1), 62–68. https://doi.org/10.1080/02699052.2018.1531301

Muller, F., Simion, A., Reviriego, E., Galera, C., Mazaux, J.-M., Barat, M., & Joseph, P.-A. (2010). Exploring theory of mind after severe traumatic brain injury. *Cortex*, *46*(9), 1088–1099. https://doi.org/10.1016/j.cortex.2009.08.014

National Clinical Guideline Centre (UK). (2014). *Head Injury: Triage, Assessment, Investigation and Early Management of Head Injury in Children, Young People and Adults*. National Institute for Health and Care Excellence (UK). http://www.ncbi.nlm.nih.gov/books/NBK248061/

Neumann, D. (2017). Treatments for Emotional Issues After Traumatic Brain Injury: *Journal of Head Trauma Rehabilitation*, *32*(5), 283–285. https://doi.org/10.1097/HTR.0000000000000337

Neumann, D., Keiski, M. A., McDonald, B. C., & Wang, Y. (2014). Neuroimaging and facial affect processing: Implications for traumatic brain injury. *Brain Imaging and Behavior*, *8*(3), 460–473. https://doi.org/10.1007/s11682-013-9285-5

Ng, S. Y., & Lee, A. Y. W. (2019). Traumatic Brain Injuries: Pathophysiology and Potential Therapeutic Targets. *Frontiers in Cellular Neuroscience*, *13*. https://doi.org/10.3389/fncel.2019.00528

Nicolle, A., Klein-Flügge, M. C., Hunt, L. T., Vlaev, I., Dolan, R. J., & Behrens, T. E. J. (2012). An agent independent axis for executed and modeled choice in medial prefrontal cortex. *Neuron*, *75*(6), 1114–1121. https://doi.org/10.1016/j.neuron.2012.07.023

Oakley, B. F. M., Brewer, R., Bird, G., & Catmur, C. (2016). Theory of mind is not theory of emotion: A cautionary note on the Reading the Mind in the Eyes Test. *Journal of Abnormal Psychology*, *125*(6), 818. https://doi.org/10.1037/abn0000182

Ochsner, K. N., Silvers, J. A., & Buhle, J. T. (2012). Functional imaging studies of emotion regulation: A synthetic review and evolving model of the cognitive control of emotion. *Annals of the New York Academy of Sciences*, *1251*, E1-24. https://doi.org/10.1111/j.1749-6632.2012.06751.x

Oishi, K., Zilles, K., Amunts, K., Faria, A., Jiang, H., Li, X., Akhter, K., Hua, K., Woods, R., Toga, A. W., Pike, G. B., Rosa-Neto, P., Evans, A., Zhang, J., Huang, H., Miller, M. I., van Zijl, P. C. M., Mazziotta, J., & Mori, S. (2008). Human brain white matter atlas: Identification and assignment of common anatomical structures in superficial

white matter. *NeuroImage*, *43*(3), 447–457. https://doi.org/10.1016/j.neuroimage.2008.07.009

O'Keeffe, F., Dockree, P., Moloney, P., Carton, S., & Robertson, I. H. (2007). Awareness of deficits in traumatic brain injury: A multidimensional approach to assessing metacognitive knowledge and online-awareness. *Journal of the International Neuropsychological Society: JINS*, *13*(1), 38–49. https://doi.org/10.1017/S1355617707070075

Olesen, J., Gustavsson, A., Svensson, M., Wittchen, H.-U., & Jönsson, B. (2012). The economic cost of brain disorders in Europe. *European Journal of Neurology*, *19*(1), 155–162. https://doi.org/10.1111/j.1468-1331.2011.03590.x

Owen, A. M., Hampshire, A., Grahn, J. A., Stenton, R., Dajani, S., Burns, A. S., Howard, R. J., & Ballard, C. G. (2010). Putting brain training to the test. *Nature*, *465*(7299), 775–778. https://doi.org/10.1038/nature09042

Ownsworth, T., & Fleming, J. (2005). The Relative Importance of Metacognitive Skills, Emotional Status, and Executive Function in Psychosocial Adjustment Following Acquired Brain Injury. *The Journal of Head Trauma Rehabilitation*, *20*(4), 315–332.

Ozen, L. J., & Fernandes, M. A. (2012). Slowing Down after a Mild Traumatic Brain Injury: A Strategy to Improve Cognitive Task Performance? *Archives of Clinical Neuropsychology*, *27*(1), 85–100. https://doi.org/10.1093/arclin/acr087

Pagonabarraga, J., Kulisevsky, J., Strafella, A. P., & Krack, P. (2015). Apathy in Parkinson's disease: Clinical features, neural substrates, diagnosis, and treatment. *The Lancet. Neurology*, *14*(5), 518–531. https://doi.org/10.1016/S1474-4422(15)00019-8

Peirce, J., Gray, J. R., Simpson, S., MacAskill, M., Höchenberger, R., Sogo, H., Kastman, E., & Lindeløv, J. K. (2019). PsychoPy2: Experiments in behavior made easy. *Behavior Research Methods*, *51*(1), 195–203. https://doi.org/10.3758/s13428-018-01193-y

Peters, R. (2006). Ageing and the brain. *Postgraduate Medical Journal*, *82*(964), 84–88. https://doi.org/10.1136/pgmj.2005.036665

Plowman, E., Hentz, B., & Ellis, C. (2012). Post-stroke aphasia prognosis: A review of patient-related and stroke-related factors: Aphasia prognosis. *Journal of Evaluation in Clinical Practice*, *18*(3), 689–694. https://doi.org/10.1111/j.1365-2753.2011.01650.x

Prigatano, G. P. (2005). Disturbances of Self-awareness and Rehabilitation of Patients With Traumatic Brain Injury: A 20-Year Perspective. *The Journal of Head Trauma Rehabilitation*, *20*(1), 19–29. https://doi.org/10.1097/00001199-200501000-00004

R Core Team. (2018). *R: A language and environment for statistical computing.* R Foundation for Statistical Computing. https://www.R-project.org/

Rabinowitz, A. R., & Levin, H. S. (2014). Cognitive Sequelae of Traumatic Brain Injury. *Psychiatric Clinics of North America*, *37*(1), 1–11. https://doi.org/10.1016/j.psc.2013.11.004

Raffelt, D., Tournier, J.-D., Rose, S., Ridgway, G. R., Henderson, R., Crozier, S., Salvado, O., & Connelly, A. (2012). Apparent Fibre Density: A novel measure for the analysis of diffusion-weighted magnetic resonance images. *NeuroImage*, *59*(4), 3976–3994. https://doi.org/10.1016/j.neuroimage.2011.10.045

Regard, M., Knoch, D., Gütling, E., & Landis, T. (2003). Brain damage and addictive behavior: A neuropsychological and electroencephalogram investigation with pathologic gamblers. *Cognitive and Behavioral Neurology: Official Journal of the Society for Behavioral and Cognitive Neurology*, *16*(1), 47–53. https://doi.org/10.1097/00146965-200303000-00006

Reid-Arndt, S. A., Nehl, C., & Hinkebein, J. (2007). The Frontal Systems Behaviour Scale (FrSBe) as a predictor of community integration following a traumatic brain injury. *Brain Injury*, *21*(13–14), 1361–1369. https://doi.org/10.1080/02699050701785062

Reitan, R. M. (1958). Validity of the Trail Making Test as an Indicator of Organic Brain Damage. *Perceptual and Motor Skills*, *8*(3), 271–276. https://doi.org/10.2466/pms.1958.8.3.271

Richardson, C., McKay, A., & Ponsford, J. L. (2014). The trajectory of awareness across the first year after traumatic brain injury: The role of biopsychosocial factors. *Brain Injury*, *28*(13–14), 1711–1720. https://doi.org/10.3109/02699052.2014.954270

Robertson, K., & Schmitter-Edgecombe, M. (2015). Self-awareness and traumatic brain injury outcome. *Brain Injury*, *29*(0), 848–858. https://doi.org/10.3109/02699052.2015.1005135

Robinson, G. A., Cipolotti, L., Walker, D. G., Biggs, V., Bozzali, M., & Shallice, T. (2015). Verbal suppression and strategy use: A role for the right lateral prefrontal cortex? *Brain*, *138*(4), 1084–1096. https://doi.org/10.1093/brain/awv003

Roozenbeek, B., Maas, A. I. R., & Menon, D. K. (2013). Changing patterns in the epidemiology of traumatic brain injury. *Nature Reviews Neurology*, *9*(4), 231–236. https://doi.org/10.1038/nrneurol.2013.22

Rorden, C., Karnath, H.-O., & Bonilha, L. (2007). Improving lesion-symptom mapping. *Journal of Cognitive Neuroscience*, *19*(7), 1081–1088. https://doi.org/10.1162/jocn.2007.19.7.1081

Rouault, M., McWilliams, A., Allen, M. G., & Fleming, S. M. (2018). Human Metacognition Across Domains: Insights from Individual Differences and Neuroimaging. *Personality Neuroscience*, *1*. https://doi.org/10.1017/pen.2018.16

Rubiano, A. M., Carney, N., Chesnut, R., & Puyana, J. C. (2015). Global neurotrauma research challenges and opportunities. *Nature*, *527*(7578), S193–S197. https://doi.org/10.1038/nature16035

Sabatinelli, D., Fortune, E. E., Li, Q., Siddiqui, A., Krafft, C., Oliver, W. T., Beck, S., & Jeffries, J. (2011). Emotional perception: Meta-analyses of face and natural scene processing. *NeuroImage*, *54*(3), 2524–2533. https://doi.org/10.1016/j.neuroimage.2010.10.011

Sanfey, A. G. (2007). Social decision-making: Insights from game theory and neuroscience. *Science (New York, N.Y.)*, *318*(5850), 598–602. https://doi.org/10.1126/science.1142996

Sato, K., Kerever, A., Kamagata, K., Tsuruta, K., Irie, R., Tagawa, K., Okazawa, H., Arikawa-Hirasawa, E., Nitta, N., Aoki, I., & Aoki, S. (2017). Understanding microstructure of the brain by comparison of neurite orientation dispersion and density imaging (NODDI) with transparent mouse brain. *Acta Radiologica Open*, *6*(4), 205846011770381–205846011770381. https://doi.org/10.1177/2058460117703816

Saxe, R., & Kanwisher, N. (2003). People thinking about thinking people. The role of the temporo-parietal junction in 'theory of mind'. *NeuroImage*, *19*(4), 1835–1842. https://doi.org/10.1016/s1053-8119(03)00230-1

Saxe, Rebecca, & Powell, L. J. (2006). It's the Thought That Counts: Specific Brain Regions for One Component of Theory of Mind. *Psychological Science*, *17*(8), 692–699. https://doi.org/10.1111/j.1467-9280.2006.01768.x

Scahill, R. I., Frost, C., Jenkins, R., Whitwell, J. L., Rossor, M. N., & Fox, N. C. (2003). A Longitudinal Study of Brain Volume Changes in Normal Aging Using Serial Registered Magnetic Resonance Imaging. *Archives of Neurology*, *60*(7), 989. https://doi.org/10.1001/archneur.60.7.989

Schwartz, M. F., Kimberg, D. Y., Walker, G. M., Faseyitan, O., Brecher, A., Dell, G. S., & Coslett, H. B. (2009). Anterior temporal involvement in semantic word retrieval:

Voxel-based lesion-symptom mapping evidence from aphasia. *Brain*, *132*(12), 3411–3427. https://doi.org/10.1093/brain/awp284

Schweizer, S., Grahn, J., Hampshire, A., Mobbs, D., & Dalgleish, T. (2013). Training the Emotional Brain: Improving Affective Control through Emotional Working Memory Training. *Journal of Neuroscience*, *33*(12), 5301–5311. https://doi.org/10.1523/JNEUROSCI.2593-12.2013

Scoville, W. B., & Milner, B. (1957). LOSS OF RECENT MEMORY AFTER BILATERAL HIPPOCAMPAL LESIONS. *Journal of Neurology, Neurosurgery & Psychiatry*, *20*(1), 11–21. https://doi.org/10.1136/jnnp.20.1.11

Seifert, C. L., Schönbach, E. M., Magon, S., Gross, E., Zimmer, C., Förschler, A., Tölle, T. R., Mühlau, M., Sprenger, T., & Poppert, H. (2016). Headache in acute ischaemic stroke: A lesion mapping study. *Brain*, *139*(1), 217–226. https://doi.org/10.1093/brain/awv333

Sepehrband, F., Clark, K. A., Ullmann, J. F. P., Kurniawan, N. D., Leanage, G., Reutens, D. C., & Yang, Z. (2015). Brain tissue compartment density estimated using diffusion-weighted MRI yields tissue parameters consistent with histology. *Human Brain Mapping*, *36*(9), 3687–3702. https://doi.org/10.1002/hbm.22872

Shallice, T., & Burgess, P. (1996). The domain of supervisory processes and temporal organization of behaviour. *Philosophical Transactions of the Royal Society of London. Series B, Biological Sciences*, *351*(1346), 1405–1411; discussion 1411-1412. https://doi.org/10.1098/rstb.1996.0124

Shallice, T., & Burgess, P. W. (1991). Deficits in strategy application following frontal lobe damage in man. *Brain: A Journal of Neurology*, *114 (Pt 2)*, 727–741. https://doi.org/10.1093/brain/114.2.727

Shallice, Tim, Stuss, D. T., Picton, T. W., Alexander, M. P., & Gillingham, S. (2008a). Multiple effects of prefrontal lesions on task-switching. *Frontiers in Human Neuroscience*, *2*. https://doi.org/10.3389/neuro.09.002.2007

Shallice, Tim, Stuss, D. T., Picton, T. W., Alexander, M. P., & Gillingham, S. (2008b). Multiple Effects of Prefrontal Lesions on Task-Switching. *Frontiers in Human Neuroscience*, *1*. https://doi.org/10.3389/neuro.09.002.2007

Sharp, D. J., & Ham, T. E. (2011). Investigating white matter injury after mild traumatic brain injury. *Current Opinion in Neurology*, *24*(6). https://journals.lww.com/co-neurology/Fulltext/2011/12000/Investigating_white_matter_injury_after_mild.8.aspx

Sharp, D. J., & Jenkins, P. O. (2015). Concussion is confusing us all. *Practical Neurology*, *15*(3), 172–186. https://doi.org/10.1136/practneurol-2015-001087

Sharp, D. J., Scott, G., & Leech, R. (2014). Network dysfunction after traumatic brain injury. *Nature Reviews Neurology*, *10*(3), 156–166. https://doi.org/10.1038/nrneurol.2014.15

Sherer, M., Stouter, J., Hart, T., Nakase-Richardson, R., Olivier, J., Manning, E., & Yablon, S. A. (2006). Computed tomography findings and early cognitive outcome after traumatic brain injury. *Brain Injury*, *20*(10), 997–1005. https://doi.org/10.1080/02699050600677055

Siedlecka, M., Paulewicz, B., & Wierzchoń, M. (2016). But I Was So Sure! Metacognitive Judgments Are Less Accurate Given Prospectively than Retrospectively. *Frontiers in Psychology*, *7*. https://doi.org/10.3389/fpsyg.2016.00218

Skerry, A. E., & Saxe, R. (2015). Neural representations of emotion are organized around abstract event features. *Current Biology: CB*, *25*(15), 1945–1954. https://doi.org/10.1016/j.cub.2015.06.009

Smith, S. M., Jenkinson, M., Johansen-Berg, H., Rueckert, D., Nichols, T. E., Mackay, C. E., Watkins, K. E., Ciccarelli, O., Cader, M. Z., Matthews, P. M., & Behrens, T. E. J.

(2006). Tract-based spatial statistics: Voxelwise analysis of multi-subject diffusion data. *NeuroImage*, *31*(4), 1487–1505. https://doi.org/10.1016/j.neuroimage.2006.02.024

Smith, S. M., Jenkinson, M., Woolrich, M. W., Beckmann, C. F., Behrens, T. E. J., Johansen-Berg, H., Bannister, P. R., De Luca, M., Drobnjak, I., Flitney, D. E., Niazy, R. K., Saunders, J., Vickers, J., Zhang, Y., De Stefano, N., Brady, J. M., & Matthews, P. M. (2004). Advances in functional and structural MR image analysis and implementation as FSL. *NeuroImage*, *23 Suppl 1*, S208-219. https://doi.org/10.1016/j.neuroimage.2004.07.051

Sockeel, P., Dujardin, K., Devos, D., Denève, C., Destée, A., & Defebvre, L. (2006). The Lille apathy rating scale (LARS), a new instrument for detecting and quantifying apathy: Validation in Parkinson's disease. *Journal of Neurology, Neurosurgery, and Psychiatry*, *77*(5), 579–584. https://doi.org/10.1136/jnnp.2005.075929

Spikman, J. M., Timmerman, M. E., Milders, M. V., Veenstra, W. S., & van der Naalt, J. (2012). Social cognition impairments in relation to general cognitive deficits, injury severity, and prefrontal lesions in traumatic brain injury patients. *Journal of Neurotrauma*, *29*(1), 101–111. https://doi.org/10.1089/neu.2011.2084

Squire, L. R. (2009). The Legacy of Patient H.M. for Neuroscience. *Neuron*, *61*(1), 6–9. https://doi.org/10.1016/j.neuron.2008.12.023

Stevens, F. L., Hurley, R. A., Taber, K. H., Hurley, R. A., Hayman, L. A., & Taber, K. H. (2011). Anterior Cingulate Cortex: Unique Role in Cognition and Emotion. *The Journal of Neuropsychiatry and Clinical Neurosciences*, *23*(2), 121–125. https://doi.org/10.1176/jnp.23.2.jnp121

Stuss, D. T. (2011). Functions of the Frontal Lobes: Relation to Executive Functions. *Journal of the International Neuropsychological Society*, *17*(5), 759–765. https://doi.org/10.1017/S1355617711000695

Stuss, D. T., & Alexander, M. P. (2007). Is there a dysexecutive syndrome? *Philosophical Transactions of the Royal Society B: Biological Sciences*, *362*(1481), 901–915. https://doi.org/10.1098/rstb.2007.2096

Sul, S., Tobler, P. N., Hein, G., Leiberg, S., Jung, D., Fehr, E., & Kim, H. (2015). Spatial gradient in value representation along the medial prefrontal cortex reflects individual differences in prosociality. *Proceedings of the National Academy of Sciences*, *112*(25), 7851–7856. https://doi.org/10.1073/pnas.1423895112

Suzuki, S., Harasawa, N., Ueno, K., Gardner, J. L., Ichinohe, N., Haruno, M., Cheng, K., & Nakahara, H. (2012). Learning to Simulate Others' Decisions. *Neuron*, *74*(6), 1125–1137. https://doi.org/10.1016/j.neuron.2012.04.030

Swick, D., Ashley, V., & Turken, U. (2011). Are the neural correlates of stopping and not going identical? Quantitative meta-analysis of two response inhibition tasks. *NeuroImage*, *56*(3), 1655–1665. https://doi.org/10.1016/j.neuroimage.2011.02.070

Tam, S., McKay, A., Sloan, S., & Ponsford, J. (2015). The experience of challenging behaviours following severe TBI: A family perspective. *Brain Injury*, *29*(7–8), 813–821. https://doi.org/10.3109/02699052.2015.1005134

Tariq, M., Schneider, T., Alexander, D. C., Gandini Wheeler-Kingshott, C. A., & Zhang, H. (2016). Bingham-NODDI: Mapping anisotropic orientation dispersion of neurites using diffusion MRI. *NeuroImage*, *133*, 207–223. https://doi.org/10.1016/j.neuroimage.2016.01.046

Tarnowski, P., Kołodziej, M., Majkowski, A., & Rak, R. J. (2017). Emotion recognition using facial expressions. *Procedia Computer Science*, *108*, 1175–1184. https://doi.org/10.1016/j.procs.2017.05.025

Teasdale, G., Maas, A., Lecky, F., Manley, G., Stocchetti, N., & Murray, G. (2014). The Glasgow Coma Scale at 40 years: Standing the test of time. *The Lancet Neurology*, *13*(8), 844–854. https://doi.org/10.1016/S1474-4422(14)70120-6

Thompson, R. A. (1994). Emotion Regulation: A Theme in Search of Definition. *Monographs of the Society for Research in Child Development*, *59*(2–3), 25–52. https://doi.org/10.1111/j.1540-5834.1994.tb01276.x

Thompson, R. J., Berenbaum, H., & Bredemeier, K. (2011). Cross-sectional and longitudinal relations between affective instability and depression. *Journal of Affective Disorders*, *130*(1), 53–59. https://doi.org/10.1016/j.jad.2010.09.021

Turner, N. E., McDonald, A. J., Ialomiteanu, A. R., Mann, R. E., McCready, J., Millstone, D., Hamilton, H., Elton-Marshall, T., Rehm, J., Kurdyak, P., Ilie, G., Wickens, C. M., Le, T. L., van der Maas, M., Faregh, N., Cook, S., Bondy, S., Sanchez, S., & Cusimano, M. D. (2019). Moderate to severe gambling problems and traumatic brain injury: A population-based study. *Psychiatry Research*, *272*, 692–697. https://doi.org/10.1016/j.psychres.2018.12.170

Vaccaro, A. G., & Fleming, S. M. (2018). Thinking about thinking: A coordinate-based meta-analysis of neuroimaging studies of metacognitive judgements. *Brain and Neuroscience Advances*, *2*. https://doi.org/10.1177/2398212818810591

Varjacic, A., Mantini, D., Demeyere, N., & Gillebert, C. R. (2018). Neural signatures of Trail Making Test performance: Evidence from lesion-mapping and neuroimaging studies. *Neuropsychologia*, *115*, 78–87. https://doi.org/10.1016/j.neuropsychologia.2018.03.031

Verbruggen, F., & Logan, G. D. (2008). Response inhibition in the stop-signal paradigm. *Trends in Cognitive Sciences*, *12*(11), 418–424. https://doi.org/10.1016/j.tics.2008.07.005

Viano, D. C., Casson, I. R., Pellman, E. J., Bir, C. A., Zhang, L., Sherman, D. C., & Boitano, M. A. (2005). Concussion in professional football: Comparison with boxing head impacts—Part 10. *Neurosurgery*, *57*(6), 1154–1172.

Vuilleumier, P., & Pourtois, G. (2007). Distributed and interactive brain mechanisms during emotion face perception: Evidence from functional neuroimaging. *Neuropsychologia*, *45*(1), 174–194. https://doi.org/10.1016/j.neuropsychologia.2006.06.003

Wardlaw, J. M., Easton, V. J., & Statham, P. (2002). Which CT features help predict outcome after head injury? *J Neurol Neurosurg Psychiatry*, *72*, 5.

Wechsler, D. A. (1945). A standardized Memory Scale for Clinical Use. *The Journal of Psychology*, *19*, 87–95.

Werner, C., & Engelhard, K. (2007). Pathophysiology of traumatic brain injury. *British Journal of Anaesthesia*, *99*(1), 4–9. https://doi.org/10.1093/bja/aem131

Whisman, M. A., Perez, J. E., & Ramel, W. (2000). Factor structure of the Beck Depression Inventory—Second Edition (BDI-ii) in a student sample. *Journal of Clinical Psychology*, *56*(4), 545–551. https://doi.org/10.1002/(SICI)1097-4679(200004)56:4<545::AID-JCLP7>3.0.CO;2-U

Williams, W. H., Chitsabesan, P., Fazel, S., McMillan, T., Hughes, N., Parsonage, M., & Tonks, J. (2018). Traumatic brain injury: A potential cause of violent crime? *The Lancet. Psychiatry*, *5*(10), 836–844. https://doi.org/10.1016/S2215-0366(18)30062-2

Winkler, A. M., Ridgway, G. R., Webster, M. A., Smith, S. M., & Nichols, T. E. (2014). Permutation inference for the general linear model. *NeuroImage*, *92*, 381–397. https://doi.org/10.1016/j.neuroimage.2014.01.060

Winston, J. S., Strange, B. A., O'Doherty, J., & Dolan, R. J. (2002). Automatic and intentional brain responses during evaluation of trustworthiness of faces. *Nature Neuroscience*, *5*(3), 277–283. https://doi.org/10.1038/nn816

Wittmann, M. K., Kolling, N., Faber, N. S., Scholl, J., Nelissen, N., & Rushworth, M. F. S. (2016). Self-Other Mergence in the Frontal Cortex during Cooperation and Competition. *Neuron*, *91*(2), 482–493. https://doi.org/10.1016/j.neuron.2016.06.022

Wood, D., Harms, P. D., Lowman, G. H., & DeSimone, J. A. (2017). Response Speed and Response Consistency as Mutually Validating Indicators of Data Quality in Online Samples. *Social Psychological and Personality Science*, *8*(4), 454–464. https://doi.org/10.1177/1948550617703168

Wood, R., & Williams, C. (2008). Inability to empathize following traumatic brain injury. *Journal of the International Neuropsychological Society: JINS*, *14*(2), 289–296. https://doi.org/10.1017/S1355617708080326

Worthington, A., & Wood, R. L. (2018). Apathy following traumatic brain injury: A review. *Neuropsychologia*, *118*, 40–47. https://doi.org/10.1016/j.neuropsychologia.2018.04.012

Wylie, G. R., Dobryakova, E., DeLuca, J., Chiaravalloti, N., Essad, K., & Genova, H. (2017). Cognitive fatigue in individuals with traumatic brain injury is associated with caudate activation. *Scientific Reports*, *7*(1), 8973. https://doi.org/10.1038/s41598-017-08846-6

Zadra, J. R., & Clore, G. L. (2011). Emotion and Perception: The Role of Affective Information. *Wiley Interdisciplinary Reviews. Cognitive Science*, *2*(6), 676–685. https://doi.org/10.1002/wcs.147

Zappalà, G., Thiebaut de Schotten, M., & Eslinger, P. J. (2012). Traumatic brain injury and the frontal lobes: What can we gain with diffusion tensor imaging? *Cortex*, *48*(2), 156–165. https://doi.org/10.1016/j.cortex.2011.06.020

Zhang, H., Schneider, T., Wheeler-Kingshott, C. A., & Alexander, D. C. (2012a). NODDI: Practical in vivo neurite orientation dispersion and density imaging of the human brain. *NeuroImage*, *61*(4), 1000–1016. https://doi.org/10.1016/j.neuroimage.2012.03.072

Zhang, H., Schneider, T., Wheeler-Kingshott, C. A., & Alexander, D. C. (2012b). NODDI: Practical in vivo neurite orientation dispersion and density imaging of the human brain. *NeuroImage*, *61*(4), 1000–1016. https://doi.org/10.1016/j.neuroimage.2012.03.072

Zhang, H., Yushkevich, P. A., Alexander, D. C., & Gee, J. C. (2006). Deformable registration of diffusion tensor MR images with explicit orientation optimization. *Medical Image Analysis*, *10*(5), 764–785. https://doi.org/10.1016/j.media.2006.06.004

Ziino, C., & Ponsford, J. (2006). Selective attention deficits and subjective fatigue following traumatic brain injury. *Neuropsychology*, *20*(3), 383–390. https://doi.org/10.1037/0894-4105.20.3.383

Zuur, A. F., Ieno, E. N., & Elphick, C. S. (2010). A protocol for data exploration to avoid common statistical problems. *Methods in Ecology and Evolution*, *1*(1), 3–14. https://doi.org/10.1111/j.2041-210X.2009.00001.x

Appendix 1: Supplementary analysis

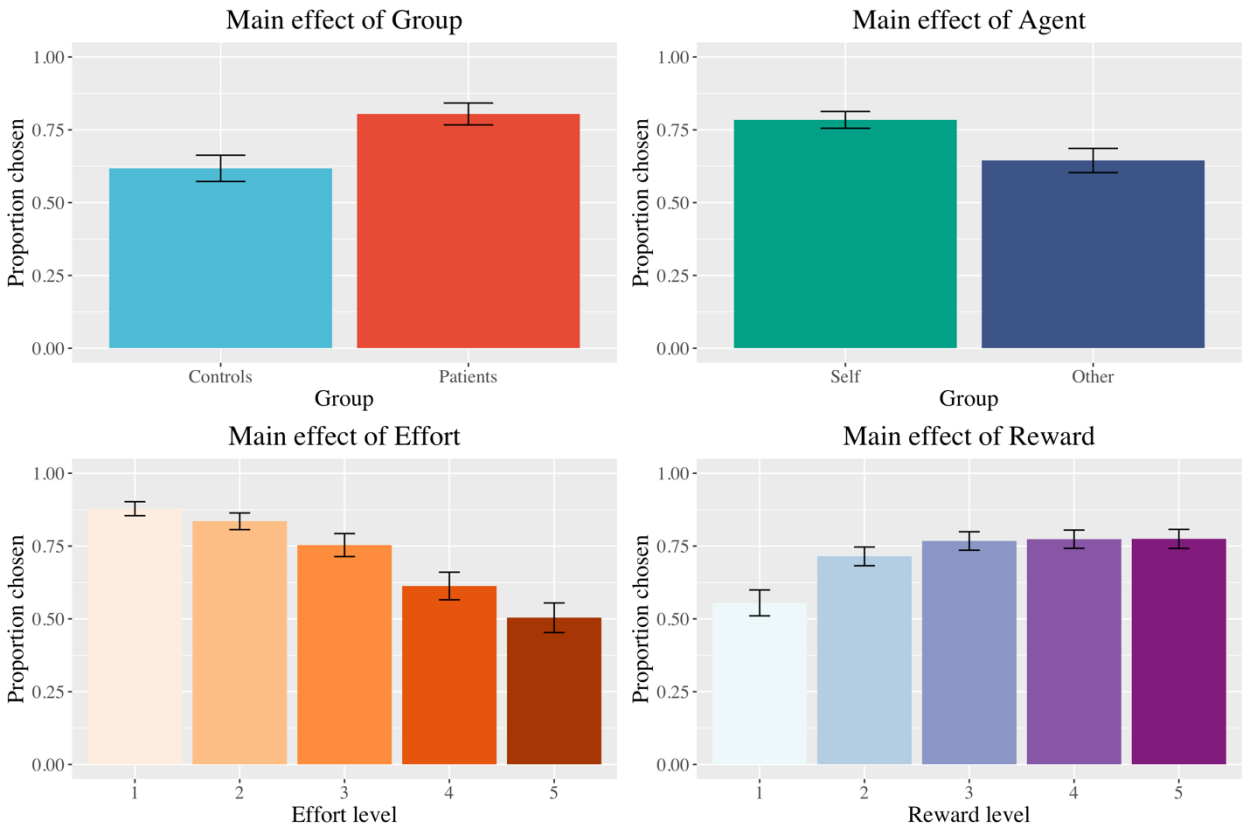
Table 4: Choice of effort by group (Chapter 5)

Post-hoc comparisons: testing the Group effect at each level of Effort

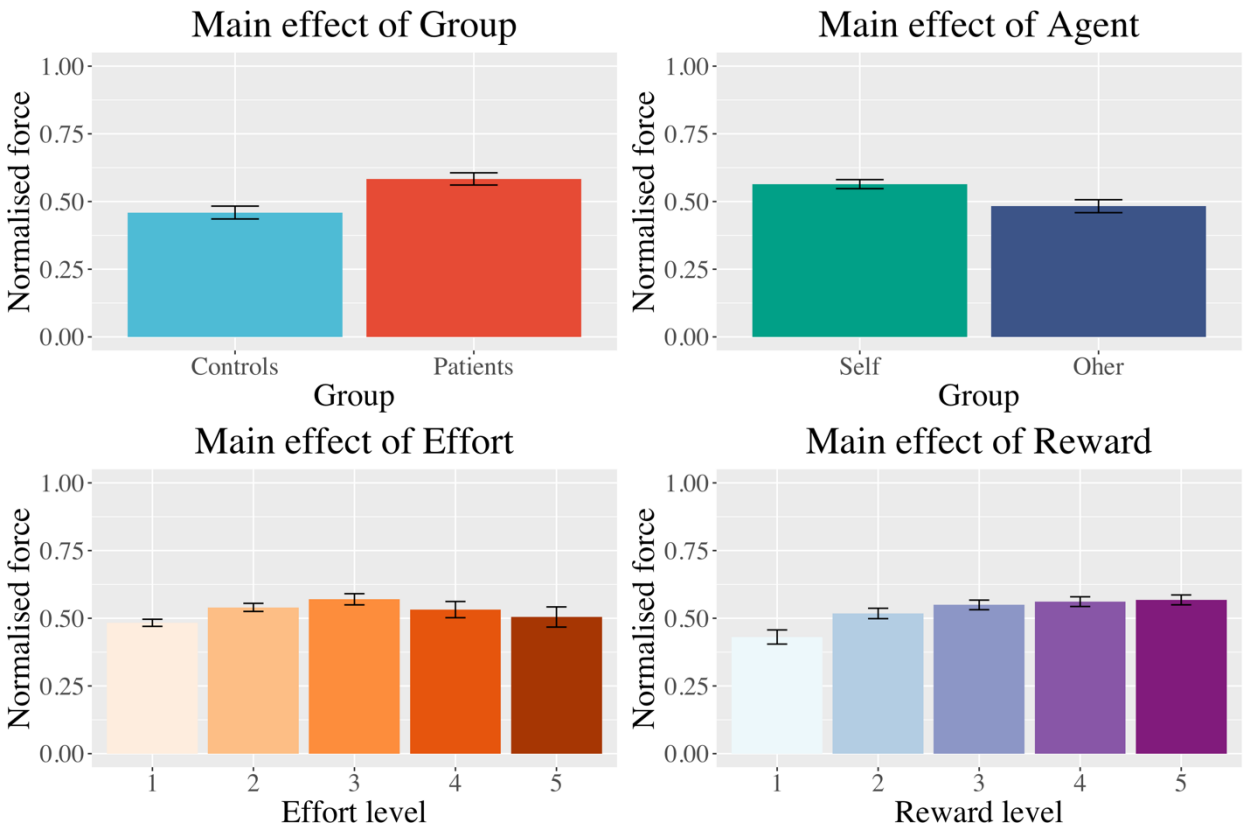
Effort	odds.ratio	SE	df	z.ratio	p.value
1	5.492	3.842	Inf	2.434	0.015
2	13.721	9.557	Inf	3.760	0.000
3	9.104	6.163	Inf	3.263	0.001
4	8.012	5.365	Inf	3.107	0.002
5	6.355	4.250	Inf	2.766	0.006

Note:
p-values uncorrected

Choice and force plots (Chapter 5)



Main effects of force



Physical & Mental Health Questionnaire (PMHQ)

I developed and implemented a novel short 12 item questionnaire, named the Physical and Mental Health Questionnaire (PMHQ). The PMHQ is based on standard clinical questions relating to physical difficulties and emotional well-being, along with judgements on memory and concentration. The first 5 questions on the measure are 4 point Likert scales relating to similar questions on the EQ5D corresponding to physical symptoms affecting quality of life (Balestroni & Bertolotti, 2012). The following questions consist of a slider indicating a score from 0-100, with negative responses being lower and positive being higher on the scale addressing mood, anxiety, memory, concentration.

Factor analysis

An exploratory factor analysis was conducted on the PMHQ to assess the factor structure from the constructed questions. This was run twice: The first run consisted of 85 control participants on a single time point, while the second included multiple timepoints for these 85 control participants, giving 320 observations in total. A parallel factor analysis was then conducted to determine the number of factors to select (J. L. Horn, 1965). This plots a minimal residual factor solution and the eigenvalues for a principal components scree plot, along with the same for random matrices of the same dimension as the original data. The factoring method used to minimise residual error was Ordinary Least Squares (OLS) with oblique rotation. A loading cut-off score of 0.3 was set. Where individual items load onto multiple factors, the factor with the highest loading is selected.

The following criteria for assessing the factor analysis were investigated:

1. Does the model have a simple structure?
2. Evaluating model results
    a. RMSR (The root mean square of residuals). This value should be close to 0.
    b. RMSEA (root mean square error of approximation). Should be below 0.06, where a smaller value indicates a better fit.
    c. TLI (The Tucker-Lewis Index), where an acceptable value is >0.9, and a good value is >0.95.

Test-retest reliability

Test-retest reliability is an essential feature in psychological testing. This is particularly true when applying digital cognitive assessments remotely, as assessments are not conducted under typical experimentally controlled conditions, which may lead to non-random sources of

noise. Rational and methods of statistical analysis for test-retest reliability have been discussed previously (DeSimone, 2014; D. Wood et al., 2017). Including the need to account for item-level temporal consistency. The inter-relatability of items across time can be captured by looking at factor structures using principal component analysis (PCA), which incorporates all of the variances in the data. Test-retest reliability was conducted for two timepoints on items in the PMHQ with 60 healthy controls. For each control participant, a correlation of scores between assessments was conducted as a measure of temporal consistency. This coefficient between the two timepoints is squared to give an estimate of variance in responses across the two timepoints; the remaining variance is considered error for factors not controlled for (exposure effects, variations in administration, altered perception of the measure, etc.).

Results

Factor analysis

For a single time point (n=85), 3 factors were derived from the parallel scree plot analysis. The minimal residuals from each task loaded onto the three-factor structure, which includes the following factor descriptions: F1 = Psychological well-being, F2 = Physical well-being, F3 = Cognitive state.

This breakdown nicely matches the intended domains to investigate. Assessment of a three-component factor analysis adequacy found the root mean square of the residuals (RMSR) to be 0.03, the Tucker Lewis Index of factoring reliability = 0.993, and an RMSEA index = 0.041, and the 90 % confidence intervals are 0-0.092.

A between-factor correlation was also seen with cognitive state (memory, concentration) and psychological well-being (sad, anxious, outlook, etc..).

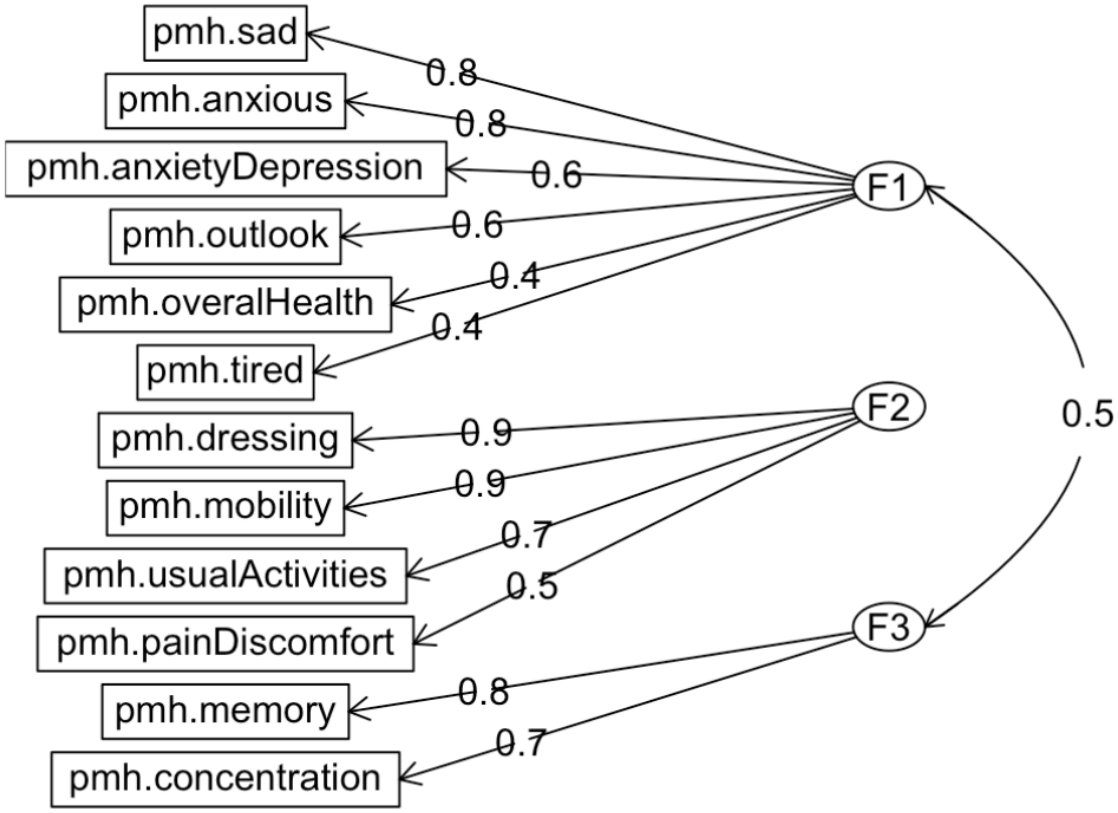


Figure 51: **PMHQ factor structure**

A three-factor solution with factor 1 (F1) labelled as psychological, Factor 2 (F2) labelled as physical, and the third factor (F3) as cognitive. A moderate relationship was found between psychological and cognitive factors.

Test-Retest Reliability

Test-retest reliability was conducted with controls that had data recorded at two timepoints (n = 60). The duration between timepoints was short approximately, 1-2 days providing dependability correlation. The mean between participant, across item reliability = 0.7, with a mean within participant, across item reliability = 0.96, with a standard deviation of 0.05, Correlation of scale scores over time = 0.85.

Table 5: **PMHQ test-retest reliability across two timepoints.**

Rii - correlation between timepoints, PC1 & PC2 are principal component scores for timepoint 1 & 2, mean 1 & 2 are the mean scores for the measure at timepoint 1 & 2.

	rii	PC1	PC2	mean1	mean2
mobility	0.49	0.08	0.06	3.87	3.97
usual activities	0.89	0.23	0.45	3.95	3.92
pain/discomfort	0.52	0.26	0.34	3.78	3.80
anxiety/depression	0.73	0.50	0.63	3.57	3.67
overall health	0.76	0.80	0.82	81.53	80.43
memory	0.60	0.37	0.69	73.70	69.63
concentration	0.64	0.70	0.74	70.83	69.20
tired	0.74	0.64	0.66	57.58	57.82
sad	0.82	0.83	0.88	74.82	73.98
anxious	0.73	0.76	0.89	71.92	73.43
outlook	0.78	0.51	0.69	73.85	75.28

PMHQ in TBI patients compared to controls

Linear mixed effect models were conducted to examine individual elements of the PMHQ in relation to Group and Time Point. Subjects were included as random effects. The analysis was constricted to the first five timepoints (following timepoints have diminishing observations $n < 25$ per time point). Both groups had a balanced number of observations of the outcome measures across all timepoints (control $n = 248$, patient $n = 264$).

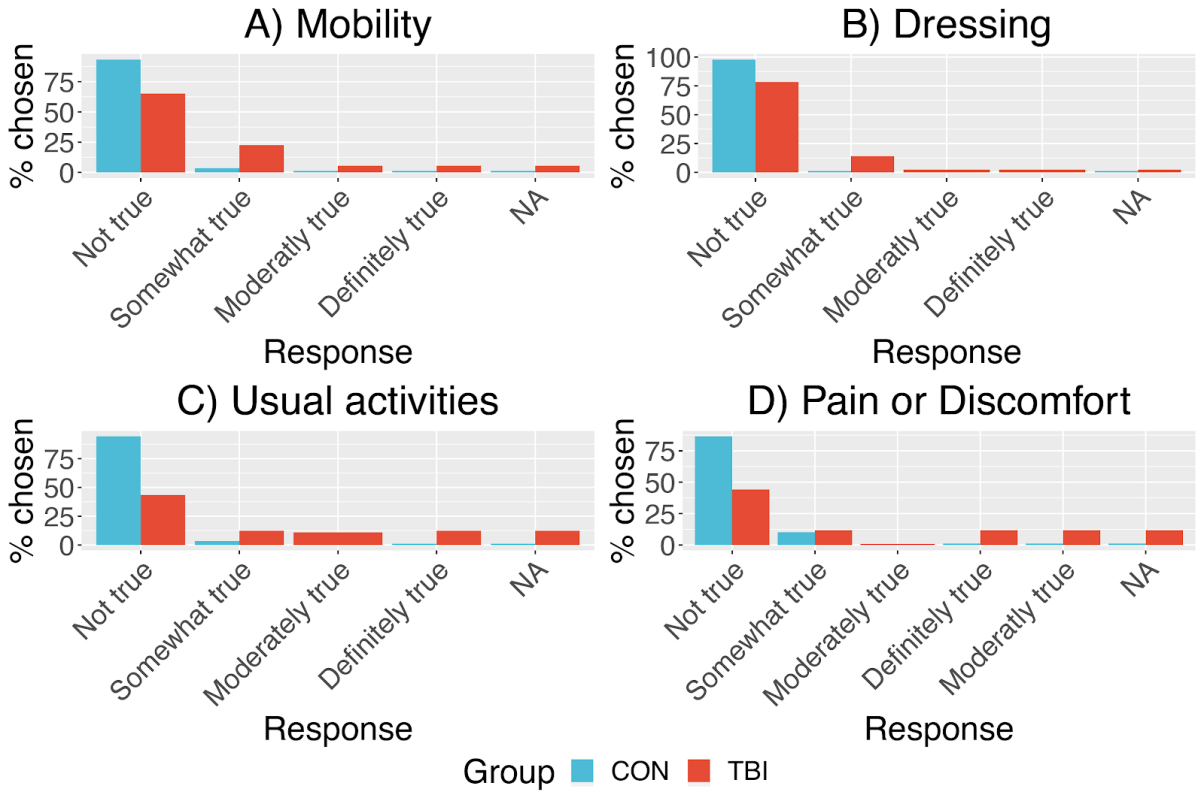


Figure 52: **Physical component of PMHQ**

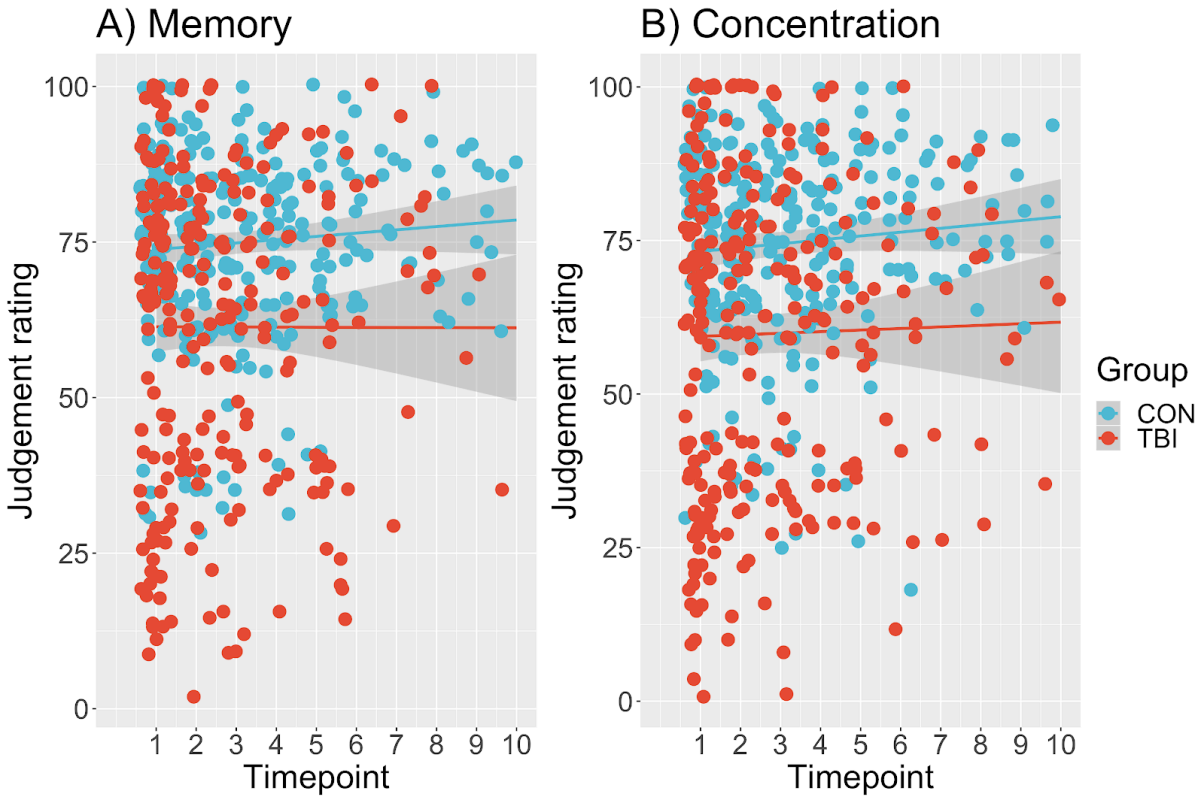


Figure 53: **Cognitive component of PMHQ**

TBI patients reported overall poorer memory (M = 61.58(25.05)) compared to control participants (M = 74.12(15.34)), X^2 (1, N = 512) = 19.85, p < 0.001, No effect was seen for timepoint X^2 (1, N = 512) = 3.02, p = 0.08.

TBI patients reported overall poorer concentration (M = 59.89(26.63)) compared to control participants (M = 73.79(15.78)), X^2 (1, N = 512) = 15.56, p < 0.001, No effect was seen for timepoint X^2 (1, N = 512) = 1.12, p = 0.28.

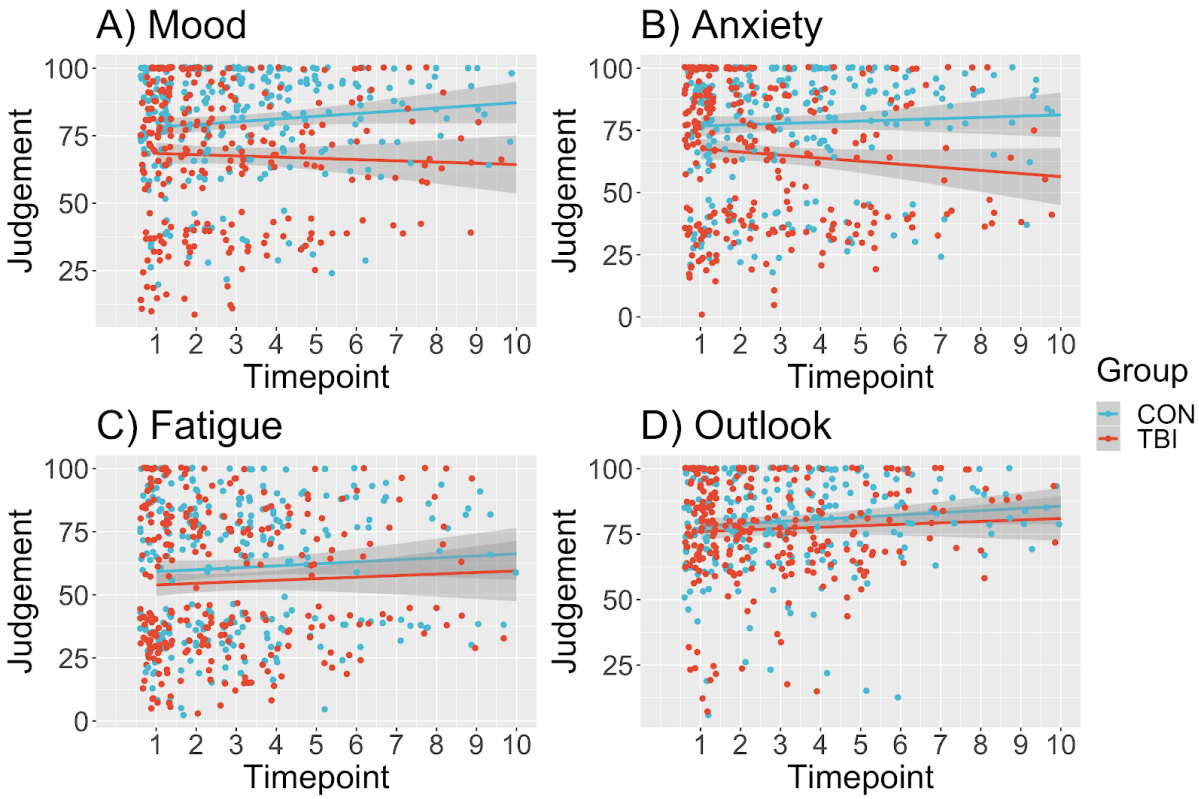


Figure 54: **Psychological component of PMHQ**

TBI patients reported overall lower mood (M = 67.78(26.04)) compared to control participants (M = 79.64(20.11)), X^2 (1, N = 512) = 10.64, p = 0.001, No effect was seen for timepoint X^2 (1, N = 512) = 0.86, p = 0.35.

TBI patients reported overall lower anxiety (M = 66.4(27.69)) compared to control participants (M = 77.67(23.89)), X^2 (1, N = 512) = 7.78, p = 0.005, No effect was seen for timepoint X^2 (1, N = 512) = 1.79, p = 0.18.

No significant difference in reported levels of fatigue were observed in TBI patients (M = 54.13(28.96)) compared to control participants (M = 59.91(26.93)), X^2 (1, N = 512) = 0.43, p = 0.50, No effect was seen for timepoint X^2 (1, N = 512) = 0.31, p =0.57.

No significant difference in reported levels of outlook were observed in TBI patients (M = 79.42(17.96)) compared to control participants (M = 76.25(19.86)), X^2 (1, N = 512) = 0.44, p = 0.50, No effect was seen for timepoint X^2 (1, N = 512) = 0.21, p = 0.64.

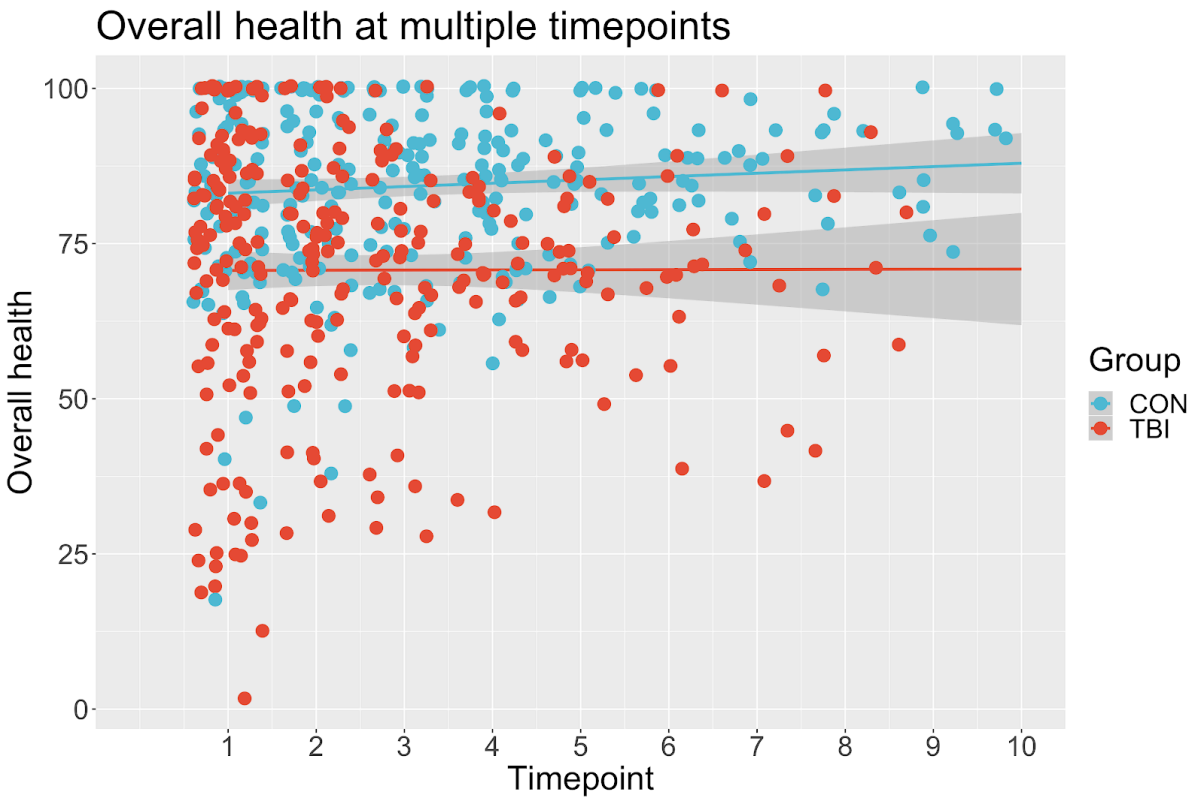


Figure 55: **Judgment of overall health from PMHQ**

TBI patients reported overall poorer health (M = 67.39(20.85)) compared to control participants (M = 79.95(17.28)), X^2 (1, N = 512) = 17.13, $p < 0.001$, No effect was seen for timepoint X^2 (1, N = 512) = 0.05, p = 0.81

Summary

An exploratory factor analysis classified the individual items from the PMHQ into components labelled as physical well-being, emotional well-being, cognitive state. These latent factor structures match closely with the intended health domains to be evaluated. While responses of each question on the measure are of direct interest, future work with this could further take these latent factors as summary scores from the tool and relate them to other aspects of cognitive or brain function. The PMHQ showed good test-retest reliability, with consistent responses between testing sessions. This analysis was conducted over the first two testing points.

The PMHQ was tested on a modest sample of controls, yielding results from which a sensible factor structure in line with my hypotheses was derived. This promising result indicates the potential for future work with this tool. For reliable assessments of construct validity, replication on independent samples is required, as done in (Ang et al., 2017). Going forward, a similar analysis on a larger cohort that includes existing measures of well-being such as the BDI, SF-36, etc., would demonstrate the utility of this quick measure that is easily remotely administered. A reproducibility test on a large sample of the general population for this measure would also allow for the generation of normative scoring results. Cut-off scores could be made for normal fluctuations of well-being and identify clinically important scores, facilitating its translation into an elegantly pragmatic clinical tool.

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Clinical assessment of social cognitive function in neurological disorders

Author: Julie D. Henry et al
Publication: Nature Reviews Neurology
Publisher: Springer Nature
Date: Dec 16, 2015

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Publication: Nature Human Behaviour
Publisher: Springer Nature
Date: Jun 30, 2017

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