The Complex Relationship Between Traumatic Brain Injuries, Childhood Externalizing Problems, and Violent Crime: Insights from Epidemiology and Diffusion MRI

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Abstract

Several studies have aimed to determine whether traumatic brain injuries (TBIs) are associated with aggressive behaviour and violent crimes. Studies of patient samples reported that individuals who sustained a TBI subsequently displayed aggressive behaviour. Studies of samples of incarcerated offenders have found a higher prevalence of TBIs among violent offenders than in the general population. Studies using prospectively collected health and criminal offending data have shown that the risk of criminal offending is higher among individuals who have sustained TBIs than the non-injured. However, these studies also demonstrated that accounting for predictors of aggressive behaviour or violent crime weakens the association between TBIs and violent crime. Decades of research using longitudinal, prospectively collected data, has shown that childhood externalizing problems are among the strongest predictors of future violent crime. This thesis aims to further understanding of the associations between childhood externalizing problems, TBIs, and violent crime. Three questions are addressed: 1) Does the association of TBIs and violent crime persist when childhood externalizing problems are taken into consideration? 2) Are childhood externalizing problems associated with an increased risk of subsequent TBIs? 3) Are TBIs associated with different alterations of white matter structure in children presenting externalizing problems as compared to typically developing children? The studies presented in this thesis suggest that: 1) Controlling for externalizing problems displayed in childhood accounts for the relationship between TBIs and violent crime; 2) Externalizing problems at age 10 are associated with increased risk of TBIs in adolescence and adulthood; and 3) Children with externalizing problems show sex-specific differences in white matter structure compared to typically developing children, and these alterations differed depending on whether or not children had sustained TBIs. In addressing these questions, the projects presented in this thesis challenge the popular view that TBIs lead to aggressive behaviour and

violent crime, identify a population of children at elevated risk to sustain TBIs through subsequent decades of life, and show that the altered neural development of these children is further altered by TBIs.

Résumé

Plusieurs études ont essayé de déterminer si les traumatismes craniocérébraux (TCCs) sont associés aux comportements agressifs et aux crimes violents. Des études auprès d'échantillons de patients ont reporté que les individus ayant souffert un TCCs ont par la suite démontré des comportements agressifs. Des études auprès d'échantillons de criminels emprisonnés ont trouvé une prévalence plus élevée de TCCs en comparaison avec la population générale. Des études utilisant des dossiers de santé et criminels, acquis prospectivement, ont démontré que le risque de criminalité est plus élevé chez ceux et celles qui ont subi un TCC comparé avec ceux et celles sans blessures. Par contre, ces études ont aussi démontré que tenir compte des prédicteurs de comportements agressifs ou de la criminalité violente affaiblit l'association entre les TCCs et la criminalité violente. Plusieurs études utilisant des données longitudinales et prospectives ont démontré que les troubles d'externalisation à l'enfance sont parmi les plus forts prédicteurs de future criminalité. Cette thèse vise à approfondir notre compréhension des associations entre les troubles d'externalisation à l'enfance, les TCCs, et la criminalité violente. Trois questions sont explorées : 1) Est-ce que l'association entre les TCCs et la criminalité violente persiste quand les troubles d'externalisation à l'enfance sont pris en considération ? 2) Est-ce que les troubles d'externalisation à l'enfance sont associés à un risque élevé de TCC ? 3) Est- ce que les TCCs sont associés à des altérations différentes de la structure de la matière blanche chez des enfants présentant des troubles d'externalisation comparés à des enfants en voie de développement typique ? Les études présentées dans cette thèse suggérèrent que : 1) Les troubles d'externalisation à l'enfance expliquent l'association entre les TCCs et la criminalité violente ; 2) Les troubles d'externalisation à l'âge de 10 ans sont associés à une augmentation du risque de TCC à l'adolescence et à l'âge adulte ; 3) Les enfants avec des troubles d'externalisation présentent des altérations de la structure de la matière blanche qui sont

différentes que chez ceux en voie de développement typique, et ces altérations dépendent du sexe de l'enfant et de TCCs précédents. En répondant aux questions de recherche, les projets présentés dans cette thèse défient l'idée traditionnelle que les TCCs peuvent causer le comportement agressif et la criminalité violente, identifient une population d'enfants à risque élevé de subir des TCCs durant l'adolescence et l'âge adulte, et démontrent que le développement neural altéré chez ces enfants est davantage altéré par les TCCs.

“If I have seen further it is by standing on the shoulders of giants”

- Sir Isaac Newton

Acknowledgements

I don't know if I have seen further, but what I have seen is entirely because I stood on the shoulders of giants. I owe everything to people who have, by contributions big and small, helped mould me into who I am today. To them, I must give thanks.

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I must also thank my mentors. My co-supervisor, **Dr. Sheilagh Hodgins**, thank you for teaching me how to be exhaustive in my literature review and precise in my writing. You have always tried to teach me to slow down and think about my results, sometimes I have listened. To my other co-supervisor, **Dr. Alain Ptito**, thank you for taking a chance on me and providing me room to explore. To **Dr. Maxime Descoteaux**, who with absolutely no obligation (as you were not my supervisor), welcomed me into your lab, took large amounts of time off your busy schedule, taught me everything I know about diffusion MRI, and drastically expanded my academic universe. Thank you for your mentorship and friendship, you continue to serve as a role model for me.

I must also thank friends and lab mates, for making tough periods more endurable, and for providing advice and support whenever needed.

Contribution to Original Knowledge

All three studies presented in this thesis represent original scholarship and have distinct contributions to knowledge. Study 1 is the first to account for childhood externalizing problems when assessing the relationship between traumatic brain injuries and violent crime. Study 2 is the first to assess whether childhood externalizing problems are associated increased risk of traumatic brain injuries in adolescence and adulthood. Study 3 is the first to assess whether traumatic brain injuries are associated with different alterations of white matter structure in children presenting externalizing problems as compared to typical children.

Contribution of Authors

The contributions of each author are listed narratively for each manuscript.

Study 1

The first manuscript presented in this thesis uses data from two prospective longitudinal datasets. For both, the principal investigator was Dr. Richard E. Tremblay. He was responsible for leading the studies. The current director of the unit responsible for storing and administering this dataset is Dr. Frank Vitaro. Their contributions to this manuscript were in the acquisition of the childhood measures and in providing revisions for this paper. Dr. Peter Larm, a post-doctoral fellow working with Dr. Sheilagh Hodgins, was responsible for compiling the measures of teacher ratings used in the paper. Dr. Hodgins obtained the official health and criminal records.

The original idea for this manuscript originated from discussions between myself, Dr. Hodgins, and Dr. Alain Ptito. At the start of my PhD, Dr. Hodgins, a world expert in conduct disorder and violent criminality, was already interested in assessing the relationship between these outcomes and traumatic brain injury (TBI). That is what brought together Dr. Hodgins and Dr. Ptito as my co-supervisors. With this idea in mind, I spent several months reading, getting acquainted with the dataset and the analytical software, organizing and compiling other variables we used, and learning about statistics. I was greatly assisted in this endeavour by Dr. Marie-Pier Robitaille, a post-doctoral fellow working with Dr. Hodgins. I performed all data preparation and statistical analyses, and along with Dr. Robitaille and Dr. Hodgins, participated in the interpretation of the results. I was responsible for drafting the original manuscript, and Dr. Hodgins was responsible for providing the most in-depth revisions. All listed co-authors provided feedback and revisions on the manuscript.

Study 2

The second manuscript used the same data as the first, and hence most of the author contributions are the same. The idea for this manuscript was a logical consequence of the first, and it was conceived around the same time as the idea for the first article. As with the first study, I performed all data preparation and statistical analyses, and along with Dr. Robitaille and Dr. Hodgins, participated in the interpretation of the results. I was responsible for drafting the original manuscript, and Dr. Hodgins was responsible for providing the most in-depth revisions. All listed co-authors provided feedback and revisions on the manuscript.

Study 3

The third manuscript used data from the Adolescent Brain Cognitive Development (ABCD) Study, and is the result of several years of collaboration. Although my laboratory at McGill specialized in functional MRI, I became increasingly interested in another modality, diffusion MRI. At the beginning of the second year of my PhD, seeking more in depth training in diffusion MRI, I reached out to Dr. Maxime Descoteaux, a world expert in this technique. I spent a year travelling back and forth to his lab at the University of Sherbrooke, learning about diffusion MRI modelling and processing and tractography, including both conventional and novel techniques. This collaboration was vital for my development, and resulted in two additional manuscripts that are not part of this thesis. But to be able to carry out these studies, including the third project of my thesis, required a lot of self-directed learning. I devoted all course-work of my PhD to statistics classes, and also pursued several extracurricular workshops to improve my computer programming skills, learning Matlab, R, Bash, and Python. These skills were critical to perform this last project.

The idea for this third project was the confluence of a few factors. First, the skills I had gained opened up a series of research questions which allowed us to probe further into the relationship between externalizing problems and TBIs. The collaboration I had established with Dr. Descoteaux and his lab allowed us to ask these research questions in

novel ways, and with increased computational efficiency. That coincided perfectly with the first full release of the baseline ABCD Study dataset, which, given its large sample size, offered a rare opportunity to study these research questions in previously underrepresented subgroups.

Along with Dr. Ptito, I was responsible for applying and obtaining access the ABCD dataset, downloading and processing the data. Dr. Hodgins and I designed the study and selected the measures/variables to use. We decided to use group definitions that had been used in a previous study of gray matter from another group. Dr. Samuel Hawes who had published a paper on the psychometric properties of the measure of callous-unemotional traits in this database assisted us in the implementation of these definitions. When the COVID-19 pandemic started, given the confinement and the need to work from home, my capacity to process the terabytes-worth of data drastically slowed down. As a result, I had to seek help from one of Dr. Descoteaux's students, Guillaume Theaud. Guillaume is the lead developer of Tractoflow, the processing algorithm I used for this study. Guillaume assisted in completing the data processing and post-processing. As before, I performed all statistical analyses and along with Dr. Hodgins, participated in the interpretation of the results. I was responsible for drafting the original manuscript, and Dr. Hodgins was responsible for providing the most in depth revisions. All listed co-authors provided feedback and revisions on the manuscript.

“The things that really change the world, according to Chaos theory, are the tiny things. A butterfly flaps its wings in the Amazonian jungle, and subsequently a storm ravages half of Europe.”

— Neil Gaiman, Good Omens: The Nice and Accurate Prophecies of Agnes Nutter, Witch[1]

Chapter 1. General Introduction

On September 13th 1848, while working on the construction of the Rutland and Burlington Rail Road near Cavendish, Vermont, Phineas P. Gage, a 25-year-old foreman of a railway construction crew, was involved in an accident that, unbeknownst to him, would become foundational to the field of modern neurology. While he was tamping down gunpowder into a hole deep within a rock, the friction between the metal rod he was using and the rock created a spark that ignited the gunpowder, propelling the rod upwards at bullet-like speed, traversing Gage's head in the process and landing 25-30 yards behind him.[2]

Gage not only survived the incident, but was reported to have remained conscious, and was even seen writing in his work book a few minutes later. The initial newspaper report printed in the Boston Post read: "The most singular circumstance connected with this melancholy affair is, that he was at two o'clock this afternoon, and in full possession of his reason, and free from pain".[2]

Over the ensuing days, his health deteriorated, but after this acute period, which included a month-long, life-threatening infection,[3] Gage recovered. His treating physician, Dr. John Martyn Harlow, later reported on his recovery, noting that Gage had survived with intellectual and vital capacities largely intact, but, according to his family and peers, with marked changes in personality, claiming that he was "no longer Gage".[4,5]

Over time, Gage's story became foundational to neurological and neuroscientific folklore. This unfortunate case study continues to be heralded to this day as the earliest example of how brain structure can underpin personality. This idea has been supported by subsequent lesion studies in non-human primates.[6] However, a possibly unintended corollary of this idea also permeated neuroscience: brain injuries can cause individuals to become hostile.[7] Although Gage's incident was a singular event, this presumed link between brain

injuries and personality changes, including increased aggressive behaviour, initiated an extensive and ever-growing field of research investigating the relationship between traumatic brain injuries (TBIs) and aggressive behaviour, including violent crime.

TBIs are the leading cause of death and disability in children and young adults, affecting an estimated 600 per 100,000 individuals wordwide.[8,9] Early evidence supporting a link between TBIs and aggressive behaviour came from studies that evaluated TBI patients 6 and 12 months post-injury and found that up to 31% of individuals displayed aggressive behaviour after their injury.[10-12] Related to this early research, a growing number of studies started focusing on links between TBIs and violent criminality from retrospective studies of incarcerated violent offenders.[13] Later, larger scale population prospective studies reported that TBIs preceded violent criminality.[14] On the basis of this work, it has been concluded that TBIs are an independent risk factor for violent criminality.[15] However, in all prior studies, the apparent link between TBIs and violent crime is weakened by the inclusion of known predictors of violent crime. Decades of research has shown that most violent crimes are committed by men who displayed lifelong externalizing problems*.[16-19] However, no prior studies linking TBIs and violent crime have accounted for these behaviours. Elucidating the complex relationship between childhood externalizing problems, TBIs, and violent criminality is the overarching objective of this thesis. Herein, we have explored three research questions: 1) Does the association of TBIs and violent crime persist when childhood externalizing problems are taken into consideration? 2) Are childhood externalizing problems associated with an increased risk of subsequent TBIs? 3) Are TBIs associated with different alterations of white matter structure in children presenting externalizing problems as compared to typically developing children? In addressing these questions, the projects presented in this thesis also fill several gaps in the existing literature, such as the influence of

* See section 2.4. for a definition of externalizing problems.

sex, age, attention-deficit/hyperactivity disorder, and callous-unemotional traits, and presents several methodological improvements over prior studies, such as the use of prospective longitudinal data, novel image processing techniques and statistical approaches. The results have important implications for the prevention of TBIs across the life-span.

“There are things known and there are things unknown, and in between are the doors of perception”

– Aldous Huxley

Chapter 2. General Background

2.1. Traumatic Brain Injury

Traumatic brain injury (TBI) is a broad term used to refer to disruptions in the normal structure and function of the brain as a result of an external mechanical insult. According to the World Health Organization (WHO), it is the leading cause of death and disability in children and young adults worldwide, and impacts, on average, up to 600 per 100 000 individuals every year.[8] Across the lifespan, the incidence rate of TBI has a trimodal distribution, whereby the highest rates are observed in children younger than age 5 (1592/100 000), adolescents/young adults aged 15 to 24 (1081/100 000), and adults older than 75 (2232/100 000). The incidence of TBI is worsening: TBI rates are increasing in high income countries among the elderly due to falls, and in low income countries due to road traffic accidents.[20] In children and adolescents, TBI rates have risen as much as 60% between 2007 and 2014.[21] Further, in this age category, there is a dearth of research on the impacts of TBIs on brain structure and function.[22] TBI outcomes are known to be worse in females,[23,24] yet, fewer neuroimaging studies of TBI patients have been conducted among women than among men.

Different definitions are used to classify TBIs according to severity. One well-known approach is the WHO Neurotrauma Task Force definition, which divides TBIs according to the duration of loss of consciousness, confusion, post-traumatic amnesia, and Glasgow Coma Scale.[25] On the severe end of the spectrum, TBIs can lead to death and coma. However, even mild forms can have serious, long-lasting consequences, such as physical, cognitive, and/or emotional problems.[26] Starting from case studies of single patients[27] and progressing to studies using large biobanks of post-mortem brains,[28] it has been shown that accumulation of damage from TBIs, even mild ones, is associated with a fatal neurodegenerative disease called chronic traumatic encephalopathy. Further, sustaining a TBI increases the risk of

sustaining further TBIs.[29] Despite millions of dollars in investments and decades of research, there has been little to no progress in mild TBI pharmacotherapy. Over 30 pharmaceutical clinical trials to treat mild TBI symptoms have failed, and Health Canada and the United States' Food and Drug Administration have yet to approve a single therapy to improve mild TBI recovery.[30] In the absence of effective therapeutic approaches, prevention of TBIs remains crucial to reduce overall associated morbidity and mortality. Developing effective prevention strategies requires a better understanding of the risk factors of TBIs.

2.2. TBI neuropathology

Knowledge about the neuropathology of TBIs originates from rat and mouse models, as well as human post-mortem microscopic and gross anatomical studies. TBIs across the severity spectrum are associated with metabolic and microstructural neuropathological cascades which can, when accumulated past a certain threshold, be detected via metabolic, functional, and structural neuroimaging.[31]

Minutes to hours post injury, transient metabolic disruptions take place.[32] Initially, abrupt, indiscriminate neuronal depolarization due to leakage from damaged neuronal membranes (primary axotomy) takes place. Binding of glutamate to N-methyl-D-aspartate (NMDA) receptors leads to further neuronal depolarization, characterized by efflux of potassium and influx of calcium. To restore the resting ionic balance, sodium-potassium pumps work at increased capacity, increasing the need for adenosine triphosphate (ATP) and hence glucose metabolism. In parallel, cerebral blood flow is diminished, worsening the mismatch between glucose supply and demand. After the accelerated glucose metabolism, the brain goes into a period of metabolic depression. Due to axonal leakage and neuronal depolarization, calcium is persistently increased, which can impair mitochondrial oxidative metabolism and exacerbate the energy insufficiency. The increased presence of calcium can also activate pathways leading to cell death. To overcome this energy deficit, lactate

production by glycolysis increases, and lactate metabolism decreases. The resulting lactate accumulation can lead to neuronal dysfunction due to acidosis, membrane damage, altered blood-brain-barrier permeability, and cerebral oedema.[32]

Accumulation of calcium can activate a variety of molecular cascades that can result in disruptions to the axonal cytoskeleton. Given the continued axonal transport along intact segments, organelles accumulate at the site of cytoskeletal disruption, leading to focal axonal swellings, secondary axotomy, the formation of axonal bulbs, and ultimately diffuse axonal injury. Calcium accumulation can also trigger cell death via activation of apoptotic genes and other mechanisms.[32]

Neurons have connections to supporting cells, called glial cells, via gap junctions that allow the free exchange of ions. Accumulation of calcium in neurons can lead to a concomitant increase in calcium levels in astrocytes and oligodendrocytes. Accumulations in the latter can lead to metabolic abnormalities within myelin sheaths, and the breakdown of proteins required to stabilize myelin structure, leading to myelin delamination. Given that myelin restricts the passage of ions through the axonal membrane, demyelination can further exacerbate ionic imbalances, including calcium homeostasis, leading to additional secondary axotomy.[33]

Thus, the neuropathology of TBIs is complex, occurring over different time scales and involving several different structures, and multi-faceted, with different molecular cascades occurring in parallel or in series.

2.3. Aggressive behaviour and violent crime

Aggressive behaviour refers to any action undertaken by an individual with the intent to cause physical and/or psychological injury to another individual or group. Only a small proportion of incidents of aggressive behaviour towards others leads to convictions for violent crime. However, violent crimes pose a heavy burden on society: a 2009 report from

the Justice Department of Canada estimated the total costs associated with victimization from assault, criminal harassment, homicide, robbery, and sexual assault and other sexual offences in Canada to be approximately $12.7 billion.[34] Although the link between TBIs and violent crime is unclear, given the heavy burden of violent crime and the high prevalence and incidence of TBIs, elucidating this potential link is of utmost importance.

2.4. Defining aggressive behaviour and other terminology

Aggressive behaviour has been classically divided in two types: reactive, and proactive. Reactive aggression is described as "hot", emotional, or defensive, and is displayed in response to threats. Proactive aggression is instead described as "cold", calculated, unemotional, usually goal-directed.[35] The neural basis of each type is described further below. Most prior literature linking TBIs to aggression has not explicitly explored this distinction.

The term "externalizing problems" refers to inattention-hyperactivity, rule breaking behaviour, oppositional/defiant behaviour, aggression, and impulsivity.[36] Conduct disorder (CD) is a paediatric psychiatric disorder characterized by high levels of aggression, delinquency, violations of rules, and lying,[37] and conduct problems refers to the behavioural phenotype (not the diagnosis) characterized by the symptoms of CD, making the terms nearly synonymous. Oppositional-defiant disorder (ODD) is another psychiatric disorder characterized by persistently angry/irritable mood, argumentative and defiant behaviour, and vindictiveness,[38] and oppositional-defiant problems refer to the behavioural phenotype characterized by the symptoms of ODD. Disruptive behaviour disorders (DBDs) refer to a behavioural phenotype characterized by persistent rule breaking and aggressive behaviour, thus encompassing CD/conduct problems and ODD/oppositional defiant problems. The adult diagnosis of Antisocial Personality Disorder (ASPD) requires a diagnosis of CD prior to age 15 and presents with the same symptoms, whereas antisocial behaviour refers to a

behavioural phenotype characterized by the symptoms of ASPD. Hence, individuals displaying CD/conduct problems, ODD/oppositional defiant problems, DBDs, or ASPD/antisocial behaviour display, by definition, externalizing problems.

According to the WHO criteria, a mild TBI (mTBI) is defined as an injury with loss of consciousness for less than 30 minutes, post-traumatic amnesia for less than 24 hours, and a Glasgow Coma Scale between 13 and 15 (out of 15). Most cases of mTBI fully recover, but a proportion can go on to develop persistent symptoms.[31,39] Any injury that has longer durations of loss of consciousness or post-traumatic amnesia, or lower Glasgow Coma Scale than mild TBI are considered to be moderate or severe TBIs. Mild TBI can be further subdivided based on the presence of intracranial injuries detected by computerized tomography.[40] A term that is often used when referring brain trauma is concussion. The use of this term has been inconsistent across the literature, and it is often used interchangeably with mTBI. For the purpose of this thesis and the work presented herein, concussion and mTBI will be used interchangeably, although it is important recognize that there is disagreement within the field about this decision. In the previous consensus statement on sports-related concussion (SRC), which took place in Berlin, SRC were defined in the following way:

- *SRC may be caused either by a direct blow to the head, face, neck or elsewhere on the body with an impulsive force transmitted to the head.*
- *SRC typically results in the rapid onset of short-lived impairment of neurological function that resolves spontaneously. However, in some cases, signs and symptoms evolve over a number of minutes to hours.*
- *SRC may result in neuropathological changes, but the acute clinical signs and symptoms largely reflect a functional disturbance rather than a structural injury and, as such, no abnormality is seen on standard structural neuroimaging studies.*
- *SRC results in a range of clinical signs and symptoms that may or may not involve loss of consciousness. Resolution of the clinical and cognitive features typically follows a sequential course. However, in some cases symptoms may be prolonged.*

  McCrory, et al. [41]

This idea reflects the efforts of the sports-injury community to define concussions as milder forms of brain trauma than mTBI. Although this idea is gaining traction, it still has not gained widespread acceptance within the field.[42]

2.5. Methodology

To appraise the relevant literature, it is necessary to understand the methodology employed. Study methodology can be broken down into sampling, procedures, measures, and statistics. Sampling refers to the strategies employed to recruit participants and acquire data. How and from where participants are recruited to a study will influence the results obtained. The literature studying the relationship between TBIs and violent crimes is broadly divided into three sampling strategies. One, a large number of prior studies were performed on patient samples.[43-47] Given that not all TBIs would lead patients to seek medical attention, patient studies are biased towards more serious, symptomatic, and debilitating cases. Two, another important segment of the prior studies were performed on individuals incarcerated for a violent crime.[48-51] These samples display high levels of antecedents of violent crimes, unlike patient sample studies, but are likely biased towards milder cases of TBI, given the long-term functional sequelae of moderate/severe TBIs.[52,53] Three, a smaller number of studies employ population/datasets.[14,54] This strategy has the advantage of using more representative samples and hence yields more generalizable results, but has the challenge of requiring large sample sizes. The procedures of a study refer to the technical aspects of how the data were collected. The measures of a study refer to what can be observed about study participants and what is used to compare them. The measures employed by the studies reviewed in this thesis vary substantially. The strengths and weaknesses of each measure depend on a number of factors. One, measures can be collected at different times with relation to the moment they have taken place. Most studies of patient samples collected pre-injury data retrospectively, that is, after it

had taken place. Studies of incarcerated individuals also collected data about the TBIs retrospectively. Instead, the population studies that will be reviewed collected data about TBIs prospectively, that is, as they occurred and were recorded in health files. Two, measures can be subjective or objective. Patient and incarcerated sample studies used subjective data in the form of surveys and structured interviews. Alternatively, some studies used data from raters (e.g.: parents, school teachers), to ascertain the participant's behaviour prior to injury. The reliability of these measures depends on the rater's relationship to the participant and the domains where they observe the participant. The population studies reviewed herein used national databases on citizens that typically include socio-demographic information, family history information, social service, health and criminal records. These studies identified individuals with TBIs and compared them to all others without TBIs on all the information available in the registers. These studies defined an anchor point in time – for example time at first TBI – and then defined data as future (after TBI) or past (before TBI). These studies present several advantages. Objective measures are likely to be more reliable,[55] and the use of prospectively-collected data allowed them to understand the temporal relationship between TBIs and violent crimes. However, the use of official health and criminal records likely underestimates the relationship between TBIs and violent crime since they only capture TBIs that necessitated health services and violent criminality that led to arrests/convictions. In the diffusion MRI literature on externalizing problems, the limitations of the measures used are critical. Most of those studies used the diffusion tensor model. The limitations of the measures obtained from this technique are reviewed below (section 2.15). Finally, the statistics used in a study will play an important role in the effects obtained. Most diffusion MRI studies on externalizing problems and on TBIs employ simple group comparisons. At the group level, the effects observed in comparisons of TBI patients with healthy controls will likely only reveal shared features, averaging out more idiosyncratic patterns of white

matter structure. The implications of employing traditional statistical approaches in TBI research are discussed later in this thesis (section 8.5).

2.6. Aggressive behaviour and criminal offending in TBI patients

The hypothesis that brain injury leads to aggression arguably originates from Phineas Gage's story, the disinhibition observed in frontal lobotomy and lobectomy patients, and the results of brain surgery for aggressive behaviour.[56] Experimentally, this idea was investigated in studies of war veterans. For instance, the Vietnam Head Injury study followed non-injured veterans and 279 veterans who had suffered penetrating brain injuries for 10 to 14 years after injury. According to family members, the head-injured veterans were more "aggressive/violent" than non-head-injured veterans. Those with focal ventromedial frontal lobe lesions, in particular, had a significantly higher frequency of "aggressive and violent behaviour" than non-injured veterans or than those who sustained lesions elsewhere in the brain. Physical violence was reported for 14% of the veterans with a lesion restricted to the frontal lobes and approximately 4% of the non-injured veterans. This frontal lobe-only injury group were similar to the non-injured veterans as to age, education level, pre-injury military test, post-injury IQ test, and depression symptoms.[43]

Early evidence linking aggression and TBIs came from studies on clinical samples. A study of patients who had sustained a TBI reported that from 11 to 96% engaged in aggressive behaviour and criminality following injury.[47] A review of such early studies found that many reported that TBI patients presented characteristics such as irritability, impulsivity, and lack of foresight thought to promote criminality.[57] More recently, two studies using small samples of TBI patients reported an increase in aggressive behaviour, compared to parent assessments at one month post-injury, in the two years following injury.[44,45] Another study using the same methodology did not find increases in aggressive behaviour after injury.[58] Another study compared individuals who sustained a TBI to those who sustained an

orthopaedic injury before age 18. During the subsequent 12 years, having sustained a mild TBI was associated with a four-fold increase in the risk of a criminal conviction and having sustained a severe TBI with a nine-fold increase.[46] While these studies demonstrated that varying proportions of patients with TBIs engage in aggressive behaviour and criminality after their injuries, most used subjective, self-report data with unknown validity and reliability, and none of these studies considered important confounding and pre-morbid factors.

2.7. TBIs among incarcerated criminal offenders

Another line of research that supports the link between TBIs and criminality comes from studies of incarcerated populations. Meta-analyses of studies from several countries have shown that the prevalence of TBIs is higher among adult and juvenile criminal offenders than in age and sex matched general population samples.[48,49,54] Many studies reported that offenders had sustained more than one TBI, and a study of a small sample of offenders reported that individuals who sustained more than one TBI had acquired more convictions than those with one or no TBIs.[51] Systematic reviews reported the prevalence rates of TBIs among male adult offenders to be typically above 50% and among male juvenile delinquents to range from 18% to 67%. A potential reason behind the variability in prevalence estimates is believed to be the use of self-report measures to identify previous TBIs.[55] The most frequent cause of TBIs in these studies was found to be physical assault. Among offenders, those who reported having experienced a TBI, compared to those who did not, reported depression, psychological distress, past victimisation, bullying others, fighting, alcohol and drug misuse.[59] While this evidence shows that the prevalence of TBIs is elevated among offenders as compared to non-offenders and adds to results of studies of TBI patients showing that some individuals who sustain TBIs subsequently engage in aggressive behaviour and/or criminal offending, these studies also relied on retrospective, self-report

data, and hence cannot reveal whether the aggressive behaviour and/or criminality preceded or followed a TBI.

2.8. Prospective, longitudinal studies of birth and population cohorts

To improve on studies using small patient samples or retrospectively collected data from incarcerated violent offenders, more recent studies investigated general population cohorts, using health records to identify TBIs and criminal records to document convictions for violent crimes. In a study of a Finnish birth cohort, from age 16 to 32, there was a higher prevalence of criminal convictions among those with prior TBIs. Among participants who had sustained a TBI by age 12, the first conviction occurred earlier.[60] A study of a New Zealand birth cohort classified participants based on age at first TBI (birth to age 5, age 6 to 15, and age 16 to 21). The authors found that irrespective of age at first TBI or whether hospitalisation was required, TBIs were associated with subsequent violent offending. The relationship between TBIs and subsequent offending was stronger for patients whose TBIs required hospitalization compared to those treated as outpatients.[61]

The strongest evidence linking TBIs to violent criminality came from a study of Swedish individuals born between 1958 and 1994, all of whom were at least 15 years old during the follow-up period from 1973 to 2009. Participants who were convicted before sustaining their first TBI were excluded. For each individual who had sustained a TBI (excluding concussions) (n=22,914), 10 participants without TBIs and matched for birth year and gender were selected from the general population (n=229,118) to serve as a comparison group. After sustaining their first TBI, 8.8% of patients had been convicted for a violent crime, compared to 3% of the comparison group. After adjusting for age, gender, and socio-demographic confounders, patients remained at a significantly increased risk (Odds Ratio (OR) 3.3, 95% Confidence Interval (CI) 3.1–3.5). When adjusting for substance use disorders, this risk was still significantly higher, but attenuated (OR 2.3, 95% CI 2.2-2.5).

The risk of violent crime also differed by age at first TBI: 6.7% of those who had sustained a TBI before age 16 and 9.4% who had sustained a TBI after age 16 had acquired subsequent convictions for violent crimes. The risk also varied by lesion characteristics, with a higher risk of violent crime among those who sustained focal lesions compared to those with cerebral oedema or haemorrhage. Finally, data on unaffected siblings was available for a subset of the participants who had sustained a TBI. This sibling comparison group was used as a way to account for environmental conditions associated with criminality. Compared to this unaffected sibling group, the risk of subsequent convictions for violent crime appeared to be attenuated but remained nonetheless statistically significant (OR 2.0, 95% CI 1.8-2.3).[14] A study of an Australian population cohort also used health files to identify TBIs and criminal records. Males and females who had sustained a TBI had a higher risk of any conviction (males: Hazard Ratio (HR) 1.58, 95% CI 1.46-1.72; females: HR 1.52, 95% CI 1.28-1.81), and of a conviction for a violent crime (HR 1.65, 95% CI 1.42- 1.92) in males and in females (HR 1.73, 95% CI 1.21-2.47). These HRs were adjusted for substance use disorder treatment, mental illness, poverty, and age. When using sibling controls, the effects remained significant in males but not in females.[54]

2.9. Causality or a missing link?

The extant literature showed that a proportion of TBI patients engage in aggressive behaviour after sustaining their injury, that persons with convictions for a violent crime were more likely to report having sustained TBIs in the past, and that individuals who sustain TBIs were more likely than persons who did not to commit crimes later on. In contrast to the patient and offender studies, prospective longitudinal investigations of birth and population cohorts estimated the magnitude of the increased risk for criminality that was associated with sustaining a TBI. Because of the large sample sizes and design, these investigations suggested that TBIs sustained in childhood or early to mid-adolescence were similarly

associated with subsequent criminality, and that severity of injury may modify the association with criminality. On the basis of all this evidence, a recent review concluded that TBIs are an independent risk factor for subsequent criminal offending.[15]

However, what both the Swedish and Australian population cohort studies showed was that statistically controlling for substance use disorders and other pre-injury factors reduced the association between TBIs and convictions for violent crimes. Hence, the possibility that factors present before the injury were associated with both experiencing a TBI and committing a violent crime cannot be discounted based on prior evidence.

2.10. The importance of pre-injury factors

Studies focusing on pre-injury characteristics started to shed light on what factors distinguish patients who sustain TBIs and display aggressive behaviour/criminality from TBI patients who do not. A study of US veterans showed that TBIs were not associated with subsequent offending when analyses accounted for self-reports of prior arrests and pre-injury factors known to be associated with criminality such as having witnessed parents fighting, substance misuse, Post-Traumatic Stress Disorder, and irritability.[62] A study using data from the US Traumatic Brain Injury Model System National Database measured self and family reported criminality and TBIs, and found post-TBI arrests to be associated with gender, age, marital status, educational attainment, pre-TBI felonies, pre-TBI drug and alcohol abuse, and whether or not the TBIs had violent causes. The location of the lesion (frontal, temporal, parietal, or occipital lobe), identified from computed tomography scans, did not predict post-TBI criminal arrests. Instead, higher numbers of post-TBI arrests were predicted by loss of consciousness (≥24 hours) and retention of motor function.[63] Findings from these two studies, combined with the lack of pre-injury patient information in most prior studies, led to the possibility that TBI patients who display aggressive or criminal behaviour may have already

displayed such behaviours prior to injury, and hence, post-injury criminality may be a continuation of pre-injury behaviour.

2.11. Developmental origins of violent criminality

To understand why criminals may be more likely than others to sustain TBIs, it is necessary to understand how offenders differ from non-violent individuals. Prospective longitudinal studies from around the world, spanning several decades, have shown that the most reliable predictor of future criminality is a pattern of externalizing problems, including aggression, impulsivity and risk taking, that emerges in early childhood and remains stable across the life-span.[16-19] As children, future criminal offenders are often diagnosed with CD and of ODD, two neurodevelopmental disorders with documented differences in brain structure and function evident from childhood onwards.[64] Conduct problems have high heritability among a sub-type presenting callousness, and moderate heritability in the majority who are not callous.[65,66] One prospective longitudinal study of a birth cohort followed until their mid-forties has shown that by age 3, those who displayed conduct problems, as compared to typically developing children, showed neurological soft signs (motility, passive movements, reflexes, facial musculature, strabismus, nystagmus, foot posture, and gait), lower scores on the Bailey Motor Test, lower IQ and reading scores, uncontrolled temperament, and poor memory. From age 7 to 15, both females and males with early-onset stable conduct problems differed from healthy peers as to low IQ, poor reading capacity, and attention-deficit/hyperactivity disorder (ADHD) (33% males, 17% females). More of them also came from families with low socio-economic status, parental maltreatment, inconsistent parenting, family conflict, poor maternal mental health, low maternal IQ, and parental criminal history.[67] In contrast, longitudinal studies have also identified a small proportion of offenders whose conduct problems onset in adolescence who do not show neurological or cognitive deficits in early childhood and engage with less

frequency and severity in aggressive behaviour and criminality across the life-span.[68] Prospective longitudinal studies of Quebecois men have shown that physical aggression emerges during the first year of life, peaks in frequency and severity between the ages of 3 and 4, and then decreases in most children but remains stable in a small group. This small minority of persistently-aggressive children go on to become criminal offenders in adolescence and adulthood. In contrast, in these studies of large birth and population cohorts, there is no evidence of aggressive behaviour emerging later than toddlerhood.[69]

Despite robust evidence linking childhood externalizing problems with later violent criminality, no prior studies have examined whether TBIs influence this association. Do the childhood characteristics of those who will become offenders increase the risk of TBIs or, alternatively, do TBIs increase the risk of subsequent conduct problems which later progress into violent criminality?

2.12. Are TBIs sustained in early childhood associated with increased risk of subsequent conduct problems?

In line with the idea that TBIs can cause personality changes, studies have explored whether, instead of leading to observable aggression/criminality, TBIs could lead to conduct problems, which could later progress into aggression/violent criminality. A prospective study of a New Zealand birth cohort reported that ADHD was diagnosed in 10.5% of those who had received outpatient care for a TBI and 21.1% of those who received inpatient care for a TBI before age 5, compared to 6% of the 839 adolescents who had not sustained a TBI before age 5. Rates of CD or ODD also differed, with 8.6% of the adolescents without prior TBIs, 7% of the outpatient TBI group, and 36.8% of the inpatient TBI group having received the diagnosis.[70] However, the study could not determine which diagnosis came first – ADHD, CD/ODD, or TBI - because patients were not assessed prior to the TBI. Similarly, a study of 508 psychiatric inpatient adolescents from Northern Finland reported that 9.3% of those

diagnosed with CD had sustained a TBI, but, due to its retrospective design, failed to determine whether the TBI occurred before or after the onset of the CD.[71] A study of 694 paediatric psychiatric inpatients from the US reported that 8.1% had sustained a TBI, 50.3% had not, but no differences in diagnoses were found to be related to TBI status.[72] In a study of a large population cohort in the UK, parents and adolescents reported symptoms of mTBI before age 16 and alcohol and substance misuse and delinquency at age 17. Those who had sustained a mTBI prior to age 16 were at increased risk for alcohol misuse and for delinquency relative non-injured controls. However, adolescents who had sustained an orthopaedic injury were also at increased risk to engage in delinquency, and compared to this orthopaedic-injury group, children with mTBIs were not at increased risk for delinquency. Relative to the non-injured group, but not the orthopaedic-injury adolescents, those who had sustained TBIs before age 11 were at increased risk for conduct problems at age 17,[73] suggesting that when accounting for "accident proneness",[74] individuals who sustain TBIs are not at increased risk for delinquency and conduct problems. The remaining possibility is therefore that the childhood characteristics of those who will become offenders increase the risk of TBIs.

2.13. Neural substrates of aggression and violent criminality

Most knowledge on the neural substrates of aggression and violent criminality originates from studies on individuals with CD or ASPD, and focuses on reactive aggression.[75] Studies comparing individuals with CD/ASPD have identified differences in brain metabolism, function, and structure. Serotonergic projections from the dorsal raphe and prefrontal cortical regions such as the anterior cingulate (ACC) and orbitofrontal (OFC) cortices send inhibitory signals to a circuit of subcortical regions comprised of the amygdala, hypothalamus, and periacqueductal gray. This circuit is believed to govern aggressive responses to perceived threats.[76-78] When a threat is detected, serotonin is transiently reduced,

thereby decreasing inhibition to the circuit involved in the aggression response.[78] In individuals with CD/ASPD, basal serotonin activity in the brain is lower, thereby increasing the likelihood that a perceived threat will be responded to with aggression.[76,77] In aggressive rodents, primates, and humans, including men with ASPD, reduced levels of 5-hydroxindoleacetic acid, serotonin's primary metabolite, have been found in cerebrospinal fluid.[79,80] Dopaminergic dysregulation has also been associated with externalizing behaviours such as impulsivity and aggression.[79,81]

Gray matter alterations have also been reported in the context of this neural threat circuit. A study found that, compared to healthy men, a sample of men with a history of CD displayed higher gray matter volume in several areas, including the uncus and superior temporal cortex, extending into the right amygdala and hypothalamus, the temporoparietal junction, the inferior and superior parietal regions, the posterior cingulate, and the pre- and post-central gyri, after controlling for substance misuse.[82] Other studies have reported lower amygdala volumes in those with CD.[83,84]

Two fMRI studies showed that CD was associated with amygdala hyper-reactivity to fearful faces and not CU, ADHD, anxiety, depression, or alcohol use.[85,86] In another study, children with conduct problems without CU traits exhibited increased amygdala reactivity to fearful eyes, which was positively correlated with slower reaction time to those stimuli. These differences are believed to reflect difficulties in implicit emotion regulation.[87] Another fMRI study found that, in response to neutral faces, those with CD, compared to healthy controls, displayed amygdala and OFC hyper-reactivity, whereas in response to angry faces, displayed OFC hypo-reactivity.[88] These results underscore how CD, without CU, is associated with high levels of aggression as a result of excessive emotional reactivity in response to threat-evoking stimuli.

The OFC and amygdala are connected by a white matter tract called the Uncinate Fasciculus (UF). Early studies of white matter structure in CD focused therefore on this tract. Two studies reported that children with CD, compared to healthy controls, displayed higher fractional anisotropy (FA) – a measure that describes the directionality of water diffusion in a voxel – in the left[89,90] and right[89] UF. Longitudinal studies have shown that FA increases in all major tracts of the brain across childhood and adolescence.[91,92] Accordingly, studies reporting higher FA have interpreted their results as indicating abnormally accelerated white matter development in children with CD. However, a recent review of 22 diffusion MRI (dMRI) studies of antisocial behavior across development has suggested that the story is far more complicated. While the studies implicated several white matter tracts, in adults, the effects measured by conventional dMRI approaches were consistent. In studies of youth presenting antisocial behaviour however, results differed both with respect to the white matter structures implicated and the direction of effects.

Several challenges have been previously identified when studying the neurobiological bases of persistent aggression, as is displayed in children with lifelong externalizing problems.[93] One, the terms externalizing problems/DBDs/CD/ASPD identify populations that are heterogeneous with respect to CU traits and ADHD. These sub-groups show distinct neural abnormalities. Children with CU traits display aggression that is more proactive in nature.[75] Compared to non-offenders, offenders with psychopathy, which is characterized by callousness, showed alterations in white matter structure in the left dorsal cingulum, which was correlated with emotional detachment.[94] Children presenting CD and CU traits exhibit white matter alterations in the inferior fronto-occipital fasciculus and the inferior longitudinal fasciculus as compared to children presenting CD alone.[95,96] Compared to boys with CD alone, boys with comorbid CD and ADHD displayed alterations in the corticospinal tract.[97] Two, although risk factors and etiologies underlying CD males and females are largely

similar,[98] boys and girls with CD differ in important ways: boys display more physical aggression while girls display more relational aggression,[69,99] girls display less CU than boys[100] but more often display comorbid anxiety disorder,[101] and as they grow up, less girls compared to boys are diagnosed with antisocial personality disorder.[102,103] Some studies also suggest that the neurobiological mechanisms underpinning DBDs differ between males and females.[103-105] A study using the Generation R dataset, a large birth cohort from The Netherlands, reported that CU traits were associated with differences in the UF, cingulum, and the corpus callosum that were only present in girls [104]. Another study found that female and male youths with CD showed opposite changes in left hemisphere in internal capsule, fornix, posterior thalamic radiations, and the UF.[106] Fewer neuroimaging studies of externalizing problems exist in females. Three, white matter is known to undergo rapid development.[91,107] Different white matter tracts have been shown to follow specific trajectories of change in measures of white matter structure according to longitudinal studies. Although the exact biological basis for these changes is not yet understood, the influence of pubertal development on white matter structure has only recently started to be studied. Prior studies have posited alterations in maturation rates to interpret findings, but have not accounted for pubertal development. Studies accounting for relevant comorbidities, sex differences, and pubertal development are needed. Four, children with externalizing problems begin to use substances early, exerting effects on white matter structure.[108] To disentangle the impact of substance use from externalizing problems, it is necessary to use samples of children prior to the start of substance use. Five, children with externalizing problems are more likely than other children to be maltreated.[109,110] Six, many parents of children with externalizing problems present antisocial behaviour and non-optimal parenting that could involve inconsistent and/or inadequate surveillance of young children.[111,112]

2.14. Diffusion MRI: Principles and traditional methods

Diffusion is a physical process that is sensitive to the surrounding microenvironment. In larger, unobstructed environments, particles diffuse randomly in all directions (isotropic diffusion). In more restrictive, ordered microenvironments, particles diffuse more in the direction defined by the surrounding structures. In diffusion MRI (dMRI), the MRI signal is sensitized to the diffusion process of water molecules by using magnetic field gradients.[113] When water molecules can move freely, the signal loss relative to a scan without field gradients is larger. In the brain's white matter, composed primarily of axons and supporting structures, the displacement of water will be larger along the direction of the axon than perpendicular to it, leading to a higher signal loss. Diffusion MRI leverages these differences in signal loss as a function of the surrounding microenvironment to probe the structure of biological tissues.[113]

Once the image is acquired, it is processed and the signal is modelled. The most popular approach is to model water diffusion using a tensor. This approach, called diffusion tensor imaging (DTI), models the diffusion signal as a 3-dimensional Gaussian, described by three eigenvectors and their corresponding eigenvalues.[113-115] These parameters can then be used to build measures that describe water diffusion. These measures include Fractional Anisotropy (FA, defined as the normalized variance of eigenvalues, measures how elongated the tensor is), axial diffusivity (AD, defined as the largest eigenvalue), radial diffusivity (RD, defined as the average of the 2nd and 3rd eigenvalues), and mean diffusivity (MD, defined as the average of all 3 eigenvalues).[113]

The exact relationship between white matter microstructure and tensor-derived measures is not entirely understood and continues to be a topic of investigation to date.[116] However, simulation studies, as well as experiments in animal models of diverse neuropathologies, including TBI, have shed light onto a few of the microstructural

underpinnings of tensor-based metrics. For instance, in animal models, AD and FA were shown to be related to axonal density[117] and FA and RD to myelin loss.[118]

2.15. TBI and dMRI: The need for new techniques

TBIs can have functional, metabolic, as well as structural impacts on the brain.[31] Given their known impact on the brain's white matter, DTI has been extensively used to study white matter neuropathologies in individuals who sustained a TBI.[119,120] A 2013 review of over 100 DTI studies of TBI found that an overwhelming majority reported decreased FA in the corpus callosum of injured participants, demonstrating the high sensitivity of this measure for white matter damage.[119] However, FA, and DTI in general, have a fundamental limitation. The tensor model assumes that all diffusion in a voxel can be adequately described by a single Gaussian, and hence, implicitly assumes that every voxel contains a single homogeneous orientation of water diffusion, which often implies a single predominant fiber orientation.[121,122] In contrast, recent work suggests that over 90% of voxels in the white matter contain fibers that are heterogeneously oriented.[121] Any form of microstructural heterogeneity, whether it is from fiber configuration (e.g.: crossing, kissing, fanning, or converging fibers), myelination, or pathology (loss of axons, edema, microglial infiltration), will not be adequately discerned by a tensor. As a result, whereas FA can readily detect white matter damage in the context of TBI,[119] it cannot be used to discern between different forms of white matter neuropathology, highlighting its poor specificity.[123,124] A more recent review of DTI studies of TBI focused on injuries in the sub-acute period of recovery, when multiple different pathologies (each with differing, sometimes contradictory impacts on the dMRI signal) overlap and found that the trend of FA change was inconsistent, with an equal number of studies showing lower FA in participants with TBI compared to healthy controls as studies showing higher FA in patient groups.[123] Hence, more sophisticated dMRI approaches are needed.

The field of dMRI has undergone somewhat of a revolution in recent years with the development of new modelling techniques that aim to bypass the assumptions of the tensor model to account for microstructural heterogeneity.[125-128] One notable example is called constrained spherical deconvolution (CSD). This technique assumes that the measured diffusion signal can be estimated from a convolution between a true distribution of axonal fibers and a fiber response function (FRF). This FRF describes how the diffusion signal behaves in voxels containing homogeneous fibers, and can be estimated by fitting a tensor in voxels that are known to contain homogeneous fibers, such as deep within the corpus callosum. By performing the opposite computation, that is, deconvolving the FRF from the measured diffusion signal, CSD estimates the underlying fiber orientations, giving rise to a fiber orientation distribution function (fODF). Compared to the tensor and other alternatives, the fODF can discern multiple fiber orientations, even at small angles of crossing.[125,126] In addition, by representing a probability distribution function of fibers along different directions, instead of water diffusion, the fODF gives rise to a measure called Apparent Fiber Density (AFD), defined as the amplitude of the fODF. On simulation studies, this measure was shown to be specific to axonal density.[129] Further, because the fODFs have an amplitude for every direction, AFD can be computed for a specific orientation defined by a fiber, giving rise to a sub-voxel scale called the fiber element, or fixel.[129] Raffelt, et al. [129] studied patients with Amyotrophic Lateral Sclerosis (ALS), a disease that selectively affects motor neurons travelling through the corticospinal tract. They found paradoxically higher FA in patients compared to controls in voxels contained within regions where the corticospinal tract crosses with the corpus callosum. In contrast, AFD along fixels oriented along the corticospinal tract was lower in ALS patients, more accurately reflecting their axonal loss.

With these novel modelling techniques and other recent developments in dMRI processing, tractography, and tractometry, studies are renewing their search for reliable

biomarkers of TBI. A recent study from our group applied CSD on a sample of concussed youth in the sub-acute stage of recovery. We found patterns suggestive of diverse neuropathologies in the concussed group, with one thalamo-prefrontal tract displaying a pattern of change in diffusion measures suggestive of myelin structure alterations, and a cingulo-prefrontal tract displaying a pattern of change in diffusion measures suggestive of axonal density loss.[124] Another recent study used neurite orientation dispersion and density imaging (NODDI), another novel modelling approach, to investigate white matter microstructure early after injury and later in recovery in a sample of concussed adults. They found early increases in free water, suggestive of edema, and later decreases in neurite density, suggestive of axonal loss[130] and myelin density decrease.[131] These studies demonstrate how novel dMRI techniques have the potential to disambiguate between different concurrent white matter neuropathologies.

2.16. The problem

To summarize, follow-up studies of persons who have sustained TBIs report that they are at increased risk for aggressive behaviour and violent crime (see section 2.6). Studies of offenders report that many have sustained TBIs (see section 2.7). Studies of population cohorts using health and criminal records have shown that TBIs are associated with an increased risk of violent criminality (see section 2.8). Thus, substantial evidence supports an association between TBIs and violent crime. However, it is not known whether pre-injury characteristics determine outcomes following a TBI. Methodologically robust studies, using large sample sizes and longitudinal data have demonstrated an association between TBIs and criminality that is attenuated when controlling for pre-injury factors (see section 2.8). A few studies suggest that post-TBI crime may be a continuation of certain pre-TBI tendencies towards crime (see section 2.10). Robust evidence spanning decades has shown that one of the strongest predictors of violent criminality is childhood externalizing problems (see

section 2.11), but no prior studies have determined whether TBIs influence the association between externalizing problems and criminality. Diffusion MRI studies exploring the neurobiological underpinnings of externalizing problems have used conventional techniques, which are now known to be limited, and have not properly accounted for several factors known to impact white matter structure (see section 2.13). More importantly, none of these prior studies have accounted for TBIs. Altogether, the extant literature suggests that TBIs, childhood externalizing problems, and violent crimes are linked, but the exact nature of this link remains unclear. This thesis attempted to shed light on the association between externalizing problems, TBIs, and violent criminality. Three questions were addressed: 1) Does the association of TBIs and violent crime persist when childhood externalizing problems are taken into consideration? 2) Are childhood externalizing problems associated with an increased risk of subsequent TBIs? 3) Are TBIs associated with different alterations of white matter structure in children presenting externalizing problems as compared to typically developing children?

“One of the first things taught in introductory statistics textbooks is that correlation is not causation. It is also one of the first things forgotten.”

– Thomas Sowell, The Vision of the Anointed: Self-Congratulation as a Basis for Social Policy[132]

Chapter 3. Does the association of TBIs and violent crime persist when childhood externalizing problems are taken into consideration?

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Are traumatic brain injuries associated with criminality after taking account of childhood family social status and disruptive behaviors?

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Key words: Traumatic brain injury, criminality, family social status, childhood disruptive behaviors.

Abstract

We aimed to elucidate the links between traumatic brain injuries (TBIs) and criminal convictions in a sample, enriched with offenders, of 724 Canadian males followed to age 24. Prospectively collected data were analysed to determine whether prior TBIs predicted subsequent criminal convictions after taking account of family social status (FSS) and childhood disruptive behaviors. At age 24, diagnoses of TBIs were extracted from health records and convictions from official criminal records. In childhood, teachers rated disruptive behaviors and parents reported FSS. Proportionately more offenders than non-offenders sustained a TBI from age 18 to 24, but not before. Offenders who had sustained a TBI before and after their first conviction were similar in numbers, were raised in families of low social status, and presented high levels of disruptive behaviors from age 6 to 12. When FSS and childhood disruptive behaviors were included in multivariate regression models, sustaining a prior TBI was not associated with an increased risk of juvenile convictions for any type of crime or for violent crimes, or for convictions for any crime or violent crime from age 18 to 24, or for a first crime or a first violent crime from age 18 to 24. Thus, among males, we found no evidence that prior TBIs were associated with an increased risk of subsequent criminal convictions from age 13 to age 24 when taking account of FSS and childhood disruptive behaviors. These latter factors may, however, be associated with an increased prevalence of TBIs among adult offenders.

Are traumatic brain injuries associated with criminality after taking account of childhood family social status and disruptive behaviors?

3.1. Introduction

In the US, medical records indicate that more than 1.3 million persons sustain a TBI each year.[133] Meta-analyses[134-137] and successive studies[13,14,54,138-143] report that the prevalence of TBIs is higher among juvenile and adult criminal offenders than in age and sex matched general population samples. Evidence is lacking about the age at which injuries were sustained. Some studies[13,14,54,140,141,143] have determined that TBIs preceded arrest or conviction. For example, in a large population sample of Swedes, a TBI (excluding concussion) recorded in health records was associated with a three-fold increase in the risk of a subsequent conviction for a violent crime.[14] In a similar study of a large Australian cohort, among males, having sustained a TBI was associated with an increase of 1.58 (95% CI 1.46-1.72) in the risk of a subsequent conviction for any type of crime and with a 1.65 (95% CI 1.42-1.92) times increase in the risk of a subsequent conviction for a violent crime.[54]

The association between TBIs and criminality, however, may be confounded by antecedents and correlates of criminality. For instance, the Swedish study did not adjust analyses for prior offending, the strongest predictor of offending. It found that comparisons with siblings who show similar risks for offending reduced the strength of associations of TBIs with subsequent offending.[14] In the Australian study, compared to non-adjusted models, the risk of subsequent offending in males who sustained TBIs was lower after adjusting for drug and alcohol abuse, mental illness, Aboriginality, socioeconomic disadvantage, and year of birth.[54] A US study using data from the Traumatic Brain Injury Model System National Database concluded that having sustained a TBI may not have been associated with an increased risk of arrest among men presenting known antecedents of criminality.[144] Similarly, a study of US veterans showed that TBIs were not associated with subsequent offending

when analyses were adjusted for predictors of offending such as having witnessed parents fighting, previous arrests, substance misuse, irritability, and Post Traumatic Stress Disorder.[145]

A recent UK study[138] that used parent- and self-reports found that the association of TBIs with offending was robust to adjustment for mother's age, education, alcohol and nicotine use, social class, gender, life events, and parenting style, but detected no difference in risks of offending of participants who sustained TBIs and those who sustained orthopedic injuries. A prospective study of a New Zealand birth cohort used official health and criminal records and reported that after adjusting for gender, family SES, and parent-rated behavior problems up to age 5, TBIs sustained at different ages and of differing severity were associated with an increased risk of arrest for any type of crime, property crimes, and violent crimes.[140] Age at TBI and severity of TBI may further modify the association of TBIs with criminality.[138,140]

Taken together, the extant literature suggests that the association between TBIs and offending is weakened after taking account of known predictors of criminality. Robust evidence shows that childhood behavior problems predict criminal offending[146-150] and that most violent crimes are committed by men with a history of childhood behavior problems.[16,18,151,152] Thus, although an association between TBIs and crimes has been established, it is presently not known whether this association would persist after taking account of childhood predictors of criminality and the age at which the TBI is sustained.

The present study examined a sample of 724 males from Québec, Canada, followed to age 24. The aims were: (1) to document the prevalence of TBIs among offenders and non-offenders in childhood, adolescence, and early adulthood; (2) to determine whether TBIs preceded or followed criminal conviction; (3) to compare childhood characteristics of offenders who sustained TBIs before or after conviction with non-offenders with no TBI; and

(4) to determine whether experiencing a TBI at different developmental stages predicted offending after taking account of known childhood predictors of offending. Data were collected prospectively from age 6 to 24 allowing us to determine temporal associations of childhood behaviors and TBIs with criminal convictions. Well known predictors of criminality included social status of the participants' family when they were aged 6 years, and teacher ratings of disruptive behaviors when participants were aged 6, 10, and 12 years. Information on TBIs was extracted from health files. Information on juvenile and adult criminal convictions for any type of crime and for violent crimes was extracted from official records.

3.2. Method

Participants

Participants were males drawn from two cohorts recruited when they entered elementary school[153,154] and followed to age 24. From this sample of 2,631 males, 371 who were charged with a criminal offence from age 18 to 24 and a random sample of 371 without a criminal charge from age 18 to 24 were selected. Complete data for the present study were available for 724 of these 742 men.

Measures

Traumatic Brain Injuries. In Québec, there is one universal health system and each inhabitant has one digitalized health file from birth to death. The Régie de l'Assurance Maladie provided digital health records for each participant, which contained International Classification of Disease 9th Revision (ICD-9) codes and dates for every diagnosis. TBIs were defined as ICD-9 codes: 800.0-800.9 fractures of vault of skull; 801.0-801.9 fractures of base of skull; 802.0-802.9 fracture of face bones; 803.0-803.9 other and unqualified skull fractures; 850.0-850.9 concussion; 851.0-851.9 cerebral laceration and contusion; 852.0-852.9 subarachnoid, subdural, and extradural hemorrhage, following injury; 853.0-853.9 other and unspecified intracranial hemorrhage following injury; 854.0-854.9 intracranial

injury of other and unspecified nature; 959.0 head injury unspecified. Previous studies defined TBIs by using these same ICD-9 codes [13,54,143]. Since a diagnosis is noted in the file each time a physician sees a patient, all TBI diagnoses recorded within 30 days of each other were counted as one TBI.

Criminal Convictions. Criminal records were available from age 12 to 24. Criminal convictions were coded as any crime in the criminal code or violent crime (homicide, assault, sexual offences, offences with arms, burglary, harassment, and other crimes that physically hurt people) according to the Correctional Services of Canada classification.[155]

Childhood Behaviors. When participants were age 6, 10, and 12, their classroom teachers rated conduct problems, hurtful and uncaring behaviors, and inattention hyperactivity using the Social Behavior Questionnaire [154]. Items for each rating are described in Supplementary Material.

Family social status (FSS). This variable included parents' highest level of education, prestige of parental employment, age of the mother and father at participant's birth, and whether or not the participant lived with both biological parents. Elevated scores indicated lower FSS.[156]

Ethics approval

Initially, parents provided consent for participants' teachers to rate their child's behavior and also consented to their own participation in the study. Once participants were 18 years old, they provided consent. The Commission d'Accès à l'Information de Québec approved the use of data from health files and criminal files. The study was approved by ethics committees at the Université de Montréal, Centre Hospitalier Universitaire Sainte-Justine, and the Institut Philippe-Pinel de Montréal.

Statistical analyses

Categorical variables were compared using chi square tests and continuous variables using Mann-Whitney U tests or analysis of variance depending on distributions of values. To determine whether TBIs predicted criminal convictions when accounting for childhood behaviors and FSS, logistic regression models were computed to predict at least one conviction for any type of crime and for a violent crime, from age 12 to 17 and from age 18 to 24. Among participants who had no juvenile convictions, similar logistic regression models were computed to predict being convicted for the first time from age 18 to 24 years. In all models predicting at least one conviction for a violent crime, participants with a non-violent conviction during the same period were excluded from analyses. Since we found no association between the number of TBIs and the likelihood of conviction presence/absence of TBI was entered into regression analyses as a predictor. For each dependent variable, three initial models (age 6, 10, 12) tested associations of childhood behaviors and previous TBIs with convictions. The significant predictors from these initial models were included in final models along with FSS. In models predicting adult convictions for any crime and for a violent crime, TBIs prior to age 18 and having a juvenile conviction were added as predictors. Significant results of models are presented as odds ratios: each increase of 1 in a score for a childhood behavior increases the risk of conviction by one odds ratio; odds ratios for FSS indicate the risk for a participant with the lowest score as compared with one with the highest score.

3.3. Results

By age 24, 142 participants (19.6%) had sustained at least one TBI: 114 (15.7%) sustained a single TBI, 22 (3%) sustained two, and six (0.83%) sustained three or more TBIs. Sixty-one participants sustained at least one TBI up to age 12 (24 up to age 6), 37 sustained at

least one TBI from age 13 to 17, and 56 from age 18 to 24. By age 24, 355 (49.0%) participants had acquired at least one conviction for any type of crime and 132 (18.2%) for a violent crime.

TABLE 1. Comparisons of the Proportions of Nonoffenders and Offenders Who Sustained a Traumatic Brain Injury by Age Category[a]

Age (Years) Categories	Nonoffenders (N=369)		Offenders (N=355)		Violent Offenders (N=132)		Nonoffenders Versus Offenders (N=724)		Nonoffenders Versus Violent Offenders (N=501)	
	N	%	N	%	N	%	χ^2	p	χ^2	p
Up to age 24	64	17.3	78	22.0	34	25.8	2.458	0.117	**4.374**	**0.036**
Up to age 12	33	8.9	28	7.9	10	7.6	0.261	0.609	0.232	0.630
Ages 13–17	21	5.7	16	4.5	8	6.1	0.523	0.470	0.024	0.876
Ages 18–24	17	4.6	39	11.0	18	13.0	**10.316**	**0.001**	**12.198**	**<0.001**

[a] Statistical significance is indicated in bold.

Are criminal offenders more likely to sustain a TBI than non-offenders?

As presented in Table 1, similar proportions of offenders (22.0%) and non-offenders (17.3%) sustained a TBI by age 24. While the proportions of offenders and non-offenders who sustained TBIs up to age 12 and from 13 to 17 years were similar, from 18 to 24 years, significantly more of the offenders (11.0%) than non-offenders (4.6%) sustained a TBI. Similar proportions of violent offenders and non-offenders sustained TBIs up to age 12 and from age 13 to 17, while significantly more violent offenders (13.6%) than non-offenders (4.6%) sustained a TBI at age 18 or older.

TABLE 2. Comparisons of Median Numbers of Traumatic Brain Injuries Sustained by Nonoffenders, Offenders, and Violent Offenders in Childhood, Adolescence, and Adulthood[a]

Age Categories	Nonoffenders (N=369)		Offenders (N=355)		Nonoffenders Versus Offenders (N=724)		Violent Offenders (N=132)		Nonoffenders Versus Violent Offenders (N=501)	
	Mean	Median	Mean	Median	U	p	Mean	Median	U	p
Up to age 24	0.24	0	0.26	0	62784.50	0.162	0.31	0	**22406.50**	**0.048**
Up to age 12	0.13	0	0.08	0	64724.00	0.568	0.09	0	24011.00	0.621
Ages 13–17	0.06	0	0.05	0	64716.50	0.467	0.07	0	24261.50	0.873
Ages 18–24	0.05	0	0.12	0	**61323.50**	**0.001**	0.15	0	**22156.00**	**<0.001**

[a] Statistical significance is indicated in bold.

Table 2 presents comparisons of the median number of TBIs for offenders and violent offenders as compared to non-offenders. No differences were detected in childhood or

adolescence, but offenders and violent offenders sustained significantly more TBIs from age 18 to 24 than non-offenders.

TABLE 3. Chi-Square Analyses of Individuals With Any Juvenile Conviction or a Juvenile Conviction for a Violent Offense by Number of Traumatic Brain Injuries (TBIs) That Occurred by Age 12

	Any Juvenile Conviction					Juvenile Conviction for Violence				
TBIs by Age 12	Total N	N	%	χ^2	p	Total N	N	%	χ^2	p
0 versus 1				1.35	0.246				0.54	0.464
0	663	165	25			663	74	11		
1	51	9	18			51	4	8		
0 versus 2				0.05	1.000				2.09	0.183
0	663	165	25			663	74	11		
2	7	2	29			7	2	29		
0 versus 3				0.99	1.000				0.38	1.000
0	663	165	25			663	74	11		
3	3	0	0			3	0	0		
1 versus 2				0.48	0.607				2.85	0.149
1	51	9	18			51	4	8		
2	7	2	29			7	2	29		
1 versus 3				0.64	1.000				0.25	1.000
1	51	9	18			51	4	8		
3	3	0	0			3	0	0		
2 versus 3				1.07	1.000				1.07	1.000
2	7	2	29			7	2	29		
3	3	0	0			3	0	0		

TABLE 4. Chi-Square Analyses of Individuals With Any Adult Conviction or an Adult Conviction for a Violent Offense by Number of Traumatic Brain Injuries (TBIs) That Occurred by Age 18

	Any Adult Conviction					Adult Conviction for Violence				
TBIs by Age 12	Total N	N	%	χ^2	p	Total N	N	%	χ^2	p
0 versus 1				0.28	0.598				0.003	0.956
0	634	278	44			634	83	13		
1	70	33	47			70	9	13		
0 versus 2				0.05	0.827				0.30	0.584
0	634	278	44			634	83	13		
2	17	7	41			17	3	18		
0 versus 3				2.33	0.261				0.45	1.000
0	634	278	44			634	83	13		
3	3	0	0			3	0	0		
1 versus 2				0.20	0.788				0.26	0.696
1	70	33	47			70	9	13		
2	17	7	41			17	3	18		
1 versus 3				2.58	0.247				0.44	1.000
1	70	33	47			70	9	13		
3	3	0	0			3	0	0		
2 versus 3				1.90	0.521				0.62	1.000
2	17	7	41			17	3	18		
3	3	0	0			3	0	0		

TABLE 5. Chi-Square Analyses of Individuals With a First Conviction of Any Type in Adulthood or a First Conviction for a Violent Offense by Number of Traumatic Brain Injuries (TBIs) That Occurred by Age 18

TBIs by Age 12	First Conviction of Any Type in Adulthood	First Conviction for a Violent Offense in Adulthood

	Total N	N	%	χ^2	p	Total N	N	%	χ^2	p
0 versus 1				0.01	0.907				1.01	0.314
0	634	159	25			634	48	8		
1	70	18	26			70	3	4		
0 versus 2				1.58	0.266				0.07	1.000
0	634	159	25			634	48	8		
2	17	2	12			17	1	6		
0 versus 3				1.00	0.577				0.25	1.000
0	634	159	25			634	48	8		
3	3	0	0			3	0	0		
1 versus 2				1.50	0.338				0.08	1.000
1	70	18	26			70	3	4		
2	17	2	12			17	1	6		
1 versus 3				1.02	0.570				0.13	1.000
1	70	18	26			70	3	4		
3	3	0	0			3	0	0		
2 versus 3				0.39	1.000				0.19	1.000
2	17	2	12			17	1	6		
3	3	0	0			3	0	0		

As shown in Tables 3, 4, and 5, participants with a conviction from age 12 to 17, a conviction for a violent crime from age 12 to 17, a conviction from age 18 to 24, a conviction for a violent crime from age 18 to 24, a first conviction from age 18 to 24 for any crime, and a first conviction for a violent crime from age 18 to 24, did not sustain more TBIs than non-offenders.

Do TBIs precede or follow first criminal conviction?

Among the 78 offenders with TBIs, 46 (59.0%) sustained their first TBI before their first conviction, and 32 (41.0%) after their first conviction ($\chi^2(1, N = 78) = 2.513, p = 0.113$). Of the 34 violent offenders with TBIs, 19 (55.9%) sustained their first TBI before their first conviction for a violent offence, and 15 (44.1%) after ($\chi^2(1, N = 34) = 0.471, p = 0.493$). The mean length of time from first TBI to first crime was 95.4 months ($SD = 71.28$) (range 1.2 to 225.36 months). Among the offenders who sustained a TBI prior to first crime, the average number of TBIs was 1.13 (SD = 0.34).

TABLE 6. Comparisons of Scores for Childhood Disruptive Behaviors Among Nonoffenders With No Traumatic Brain Injury (TBI) and Offenders Who Sustained a TBI Before Their First Conviction and With Offenders With a First TBI After the First Conviction[a]

Variable	Nonoffenders Without a TBI		Offenders With a TBI Before Their First Conviction		Offenders With a Conviction Before a TBI		Nonoffenders Without a TBI Versus Offenders With a TBI Before a Conviction			Nonoffenders Without a TBI Versus Offenders With a Conviction Before a TBI		
	Mean	SD	Mean	SD	Mean	SD	F	df	p	F	df	p
Age 6												
Familial social status	0.33	0.24	0.50	0.29	0.51	0.25	**18.04**	**1,353**	**<0.001**	**15.57**	**1,340**	**<0.001**
Hurtful behavior	1.51	1.85	2.93	2.42	2.34	2.30	**21.95**	**1,358**	**<0.001**	5.65	1,344	0.018
Uncaring behavior	4.97	2.04	5.87	1.93	5.67	1.86	**7.98**	**1,359**	**0.005**	3.28	1,343	0.071
Conduct problems	2.45	2.88	4.22	3.56	4.44	4.00	**14.18**	**1,360**	**<0.001**	**12.78**	**1,346**	**<0.001**
Inattention and hyperactivity	3.60	3.25	4.87	3.10	4.91	3.00	**6.20**	**1,358**	**0.013**	4.76	1,344	0.03
Age 10												
Hurtful behavior	1.44	1.88	3.44	2.38	3.04	2.53	**35.91**	**1,314**	**<0.001**	**17.07**	**1,303**	**<0.001**
Uncaring behavior	5.30	2.02	5.59	2.01	6.43	1.45	0.70	1,311	0.405	**8.33**	**1,302**	**0.004**
Conduct problems	1.93	2.70	4.26	3.51	4.43	3.48	**23.55**	**1,317**	**<0.001**	**20.65**	**1,306**	**<0.001**
Inattention and hyperactivity	3.99	3.40	6.10	3.11	6.96	3.43	**13.48**	**1,317**	**<0.001**	**19.44**	**1,306**	**<0.001**
Age 12												
Hurtful behavior	1.23	1.65	2.76	2.27	2.89	2.54	**23.57**	**1,283**	**<0.001**	**22.65**	**1,277**	**<0.001**
Uncaring behavior	5.79	1.82	5.97	1.67	6.00	1.85	0.311	1,286	0.578	0.33	1,279	0.564
Conduct problems	1.55	2.12	3.63	2.51	3.96	3.70	**28.42**	**1,286**	**<0.001**	**27.48**	**1,279**	**<0.001**
Inattention and hyperactivity	3.65	3.48	4.71	3.25	6.04	3.73	2.91	1,285	0.089	**11.65**	**1,278**	**<0.001**

[a] Bonferonni formula correction of p values equal to 0.05 within each year are 0.01 (indicated in bold).

Do offenders who sustained a TBI before a first conviction differ from non-offenders as to childhood predictors of crime?

As presented in Table 6, offenders who sustained a TBI before being convicted of a crime were raised in families of lower social status and obtained higher scores at age 6 for CP, hurtful and uncaring behaviors, and IH, at age 10 for CP, hurtful behavior, and IH, and at age 12 for hurtful behavior and CP than the non-offenders with no TBI.

Do offenders who were convicted of a crime before sustaining their first TBI differ from non-offenders as to childhood predictors of crime?

Also presented in Table 6 are results showing that the 32 men who were convicted of a criminal offence before sustaining a TBI were raised in families with lower social status than the non-offenders with no TBIs and they obtained higher scores at age 6 for CP, at age 10 for CP, hurtful and uncaring behaviors, and IH, and at age 12 for hurtful behavior, CP, and inattention.

TABLE 7. Final Logistic Regression Models Predicting Any Juvenile Conviction and a Juvenile Conviction for a Violent Offense[a]

	Any Type of Crime (N=503)						Violent Crime (N=437)					
Teacher Ratings	B	SE	Wald	p	Exp(B)	95% CI	B	SE	Wald	p	Exp(B)	95% CI
Age 10												
Hurtful behavior	0.169	0.053	10.060	0.002	1.185	1.07 1.32						
Inattention and hyperactivity	0.097	0.038	6.550	0.010	1.102	1.02 1.19	0.149	0.054	7.475	0.006	1.160	1.04 1.29
Age 12												
Uncaring behavior	0.250	0.073	11.689	0.001	1.284	1.11 1.48	0.418	0.121	11.901	0.001	1.519	1.20 1.93
Hurtful behavior							0.305	0.074	16.794	<0.001	1.357	1.17 1.57
Family social status	1.809	0.438	17.075	<0.001	6.102	2.59 14.39	3.104	0.712	19.003	<0.001	22.291	5.52 90.01

[a] The Cox and Snell R^2 for any type of crime and violent crime was 0.140 and 0.178, respectively; The Nagelkerke R^2 for any type of crime and violent crime was 0.213 and 0.346, respectively.

Does a TBI predict criminal convictions when taking account of well-known childhood predictors of criminal offending?

Juvenile convictions. Results of initial models revealed that having sustained a TBI prior to age 6, 10, or 12 was not associated with a juvenile conviction for any type of crime. The final model, presented in Table 7, included presence/absence of a TBI up to age 12, behavior scores that were significant in the initial models, and FSS. The risk of a juvenile conviction for any type of crime was increased 1.19 times (95%CI 1.07-1.32) by age 10 hurtful behavior, 1.1 times (95%CI 1.02-1.19) by age 10 IH, 1.3 times (95%CI 1.11-1.48) by age 12 uncaring behavior, and 6.1 times (2.59-14.39) by FSS.

A similar series of regression models were computed to predict a juvenile conviction for violence. In the age 6, 10, and 12 models, having sustained a prior TBI was not associated

with a juvenile conviction for violence. In the final model presence/absence of a TBI up to age 12, the childhood behavior scores that were significant in the initial models, and FSS were entered as predictors. The results, presented in Table 7, show that the risk of a violent conviction was increased 1.16 times (95% CI 1.04-1.29) by age 10 IH, 1.52 times (95% CI 1.20-1.93) by age 12 uncaring behavior, 1.36 times (95% CI 1.17-1.57) by age 12 hurtful behavior, and 22.29 (95% CI 5.52-90.01) times by FSS.

TABLE 8. Final Logistic Regression Models Predicting a Conviction for Any Crime and for a Violent Crime From Age 18 to Age 24[a]

	Any Type of Crime (N=564)						Violent Crime (N=350)					
Teacher Ratings	**B**	**SE**	**Wald**	**p**	**Exp(B)**	**95% CI**	**B**	**SE**	**Wald**	**p**	**Exp(B)**	**95% CI**
Age 6 hurtful behavior	0.201	0.048	17.281	<0.001	1.223	1.11 1.35						
Age 10 inattention and hyperactivity							0.179	0.063	8.102	0.004	1.196	1.06 1.35
Age 12 hurtful behavior	0.242	0.051	22.897	<0.001	1.274	1.15 1.41	0.329	0.092	12.814	<0.001	1.389	1.16 1.66
Family social status	1.974	0.377	27.464	<0.001	7.203	3.44 15.07	2.794	0.751	13.844	<0.001	16.343	3.75 71.19
Juvenile conviction	1.449	0.248	34.178	<0.001	4.260	2.62 6.93	2.536	0.396	41.061	<0.001	12.630	5.82 27.43

[a] The Cox and Snell R^2 for any type of crime and violent crime was 0.260 and 0.344, respectively; The Nagelkerke R^2 for any type of crime and violent crime was 0.348 and 0.561, respectively.

Convictions from age 18 to 24. Initial models detected no associations of TBIs prior to age 6, 10, or 12 with convictions from age 18 to 24 for any type of crime. The final model included as predictors: having sustained a TBI prior to age 18, scores for childhood behaviors that were significant in the initial models, FSS, and a juvenile conviction. Results are presented in Table 8. The risk of a conviction in adulthood for any type of crime was increased 1.22 times (95% CI 1.11-1.35) by age 6 hurtful behavior, 1.27 times (95% CI 1.15-1.41) by age 12 hurtful behavior, 7.20 times (95% CI 3.44-15.07) by FSS, and 4.26 times (95% CI 2.62-6.93) by a juvenile conviction.

A similar series of analyses were computed to determine the association of having sustained a TBI prior to age 18 and a conviction for violence from age 18 to 24, after taking account of FSS and childhood behavior scores. Again, the initial models of predictors at age

6, 10, and 12 indicated no association of prior TBIs with an adult conviction for violence. In the final model, presented in Table 8, predicting a conviction for a violent crime in adulthood, a TBI prior to age 18, FSS, the behavior scores that were significant in the initial models, and presence/absence of a juvenile conviction were entered as predictors. The risk of a violent conviction in adulthood was increased 1.20 times (95% CI=1.06–1.35) by age 10 IH, 1.40 times (95% CI=1.16–1.66) by age 12 hurtful behavior, 16.34 times (95% CI=3.75–71.19) by FSS, and 12.63 times (95% CI=5.82–27.43) by a juvenile conviction.

TABLE 9. Final Logistic Regression Models Predicting a First Criminal Conviction and a First Violent Conviction From Age 18 to Age 24[a]

	Any Type of Crime (N=463)						Violent Crime (N=295)					
Teacher Ratings	B	SE	Wald	p	Exp(B)	95% CI	B	SE	Wald	p	Exp(B)	95% CI
Age 6												
Hurtful behavior	1.151	0.055	7.544	0.006	1.163	1.04 1.30						
Uncaring behavior	0.116	0.055	4.430	0.035	1.123	1.01 1.25						
Age 10												
Hurtful behavior	0.148	0.052	8.233	0.004	1.160	1.05 1.28						
Inattention and hyperactivity							0.187	0.065	8.246	0.004	1.206	1.06 1.37
Age 12 hurtful behavior							0.355	0.101	12.260	<0.001	1.426	1.17 1.74
Family social status	1.715	0.413	17.250	<0.001	5.557	2.47 12.49	2.526	0.834	9.174	0.002	12.506	2.44 64.13

[a] Cox and Snell R^2 for any type of crime and violent crime was 0.124 and 0.155, respectively; Nagelkerke R^2 for any type of crime and violent crime was 0.174 and 0.303, respectively.

Convictions for a first crime from age 18 to 24. Similar series of models were computed to determine whether having sustained a prior TBI was associated with a first conviction for any type of crime from age 18 to 24 or a first conviction for violence from age 18 to 24. Only participants without a juvenile conviction were included in these models. Initial models showed that having sustained a TBI prior to age 6, 10, or 12 was not associated with an increased risk of a first conviction for any type of crime or for a violent crime in adulthood. The final models included presence/absence of a TBI prior to age 18, childhood behavior scores that were significant in the initial models and FSS. As shown in Table 9, prior TBIs

were not associated with an increased risk of a first conviction for any type of crime or for a violent crime from age 18 to 24, while childhood behavior problems and FSS were associated with increased risks.

3.4. Discussion

In a sample of 724 males, proportionately more of those who had acquired a criminal conviction by age 24 than those who had not, sustained a TBI from age 18 to 24, but not at younger ages. While previous studies reported a higher prevalence of TBIs among offenders than non-offenders,[134-137] in the present study the higher prevalence of TBIs among offenders emerged only at age 18 or later. We further extended knowledge by showing that similar proportions of offenders had sustained a first TBI before and after their first conviction for any type of crime or for a violent crime. Offenders who sustained at least one TBI prior to conviction and those who were convicted before sustaining a TBI were similar in childhood, having been raised in families of low social status and presenting high levels of disruptive behaviors. Taken together, these results suggest that it was men who had been raised by single parents who were young, poorly educated with low prestige jobs, and who had displayed conduct problems, behaviors that hurt other children, inattention and hyperactivity through elementary school that were at increased risk to sustain a TBI in adulthood.

Most offenders have a history of childhood disruptive behaviors.[16,18,146-152] As children presenting disruptive behaviors transition to adolescence, they begin misusing substances[157] and persistently engage in reckless behaviors that become more dangerous as they age. The same childhood behaviors that predict crime have been reported to predict accidents[158,159] and death in early adulthood.[16] Thus, engagement in risky behaviors such as driving motor vehicles at high speed, particularly while intoxicated, may account for the increased number of TBIs sustained by the offenders in early adulthood. The results of our study add to previous findings showing that adolescents and adults involved in the criminal

justice system constitute a population-at-risk for TBIs. Interventions aimed at preventing, assessing, and treating TBIs among adult offenders are needed, especially since repeated TBIs among individuals with a history of aggressive behavior have been reported to lead to increased aggressive behavior.[160] Our results additionally suggest that reducing disruptive behaviors in childhood so as to limit subsequent substance misuse and reckless behavior could potentially prevent TBIs.

We used prospectively collected data and found no evidence that sustaining a TBI prior to age 18 increased the risk of offending after taking account of well-known childhood predictors of criminality. TBIs were not associated with juvenile convictions for any type of crime or for a violent crime, for convictions for any type of crime or a violent crime from age 18 to 24, or for any type of first crime or a first violent crime from age 18 to 24 when FSS and disruptive childhood behaviors were included in the prediction models. In the initial logistic regression models, sustaining a TBI prior to age 6, prior to age 10, and prior to age 12 were entered as predictors, and in the models predicting convictions in adulthood TBIs sustained from age 13 to 17 were additionally entered. These results add further evidence[145] and support to the hypotheses[144,160] that TBIs do not predict criminal convictions after taking account of characteristics of the family of origin and previous aggressive behavior and criminality. These results require replication in cohorts with different demographics order to assess generalizability.

One previous study[140] reported that TBIs sustained by age 5 were associated with offending up to age 25 after taking account of family socio-economic status and participants' behaviors up to age five. We had too few participants who had sustained a TBI prior to school entry to examine associations with criminality. However, TBIs sustained prior to age 13, did not predict juvenile convictions. Rather, juvenile convictions for any type of crime were predicted by FSS, age 10 hurtful behavior and IH, and age 12 uncaring behavior, and

juvenile convictions for a violent crime were predicted by FSS, age 10 IH, and age 12 uncaring and hurtful behavior. One previous study[161] compared arrests to age 33 of males and females who had and who had not sustained a TBI by age 7. The two groups were matched on poverty of the family of origin, maternal age, parental education level, maternal marital status, and race/ethnicity and gender. Consistent with our results, TBIs were not associated with an increased risk of arrest.

Sustaining a TBI prior to age 18 did not increase the risk of a conviction for any crime or for a violent crime from age 18 to 24 regardless of whether or not participants had previous convictions. Rather, low FSS defined as parents' age at the birth of their first child, income and education, and whether or not they raised the participant, and childhood disruptive behaviors were consistently associated with increased risks of criminal convictions at all ages. A recent review [137] asked whether TBIs were a cause of violent crime and reported that TBIs were a risk factor for "earlier, more violent, offending". However, the review failed to distinguish studies that estimated the link between TBIs and offending after taking account of childhood behaviors that have been robustly associated with offending. Importantly, in our study, scores for hurtful behavior at age 6 were associated with an increased the risk of conviction for any type of crime, for a violent crime, and for a first conviction of any crime from age 18 to 24. Age 6 uncaring behavior predicted a first conviction for any type of crime from age 18 to 24. Similarly, the age 10 and 12 scores for disruptive behaviors were associated with increases in the risk of convictions. These results are consistent with those from many studies showing that low FSS and childhood disruptive behaviors predict subsequent criminal offending.[16,18,146-152,156]

Our measure of violent criminal convictions would not have captured all incidents of aggressive behavior. Two prior studies of children and adolescents observed high rates of aggressive behavior within six months[12] and two years[162] following a TBI. By contrast, a

recent study of 103 individuals who had sustained a first TBI that included loss of consciousness, a Glasgow Coma Score of 15 or less, evidence of contusion or hemorrhage, and who required inpatient treatment reported that none of the participants engaged in physically aggressive behavior in the first three months after the TBI, two did in the next three months, and one did in the following six months.[163] Several studies have reported that aggressive behavior following a TBI was not predicted by the TBI but rather by factors present prior to the TBI, including aggressive behavior, arrest, substance misuse, lower level of education, mood disturbance, suicidality, and Post Traumatic Stress Disorder.[145,164-166]

Limitations and strengths

Physicians were required to record a diagnosis each time they saw a patient. Our coding TBIs diagnosed within a period of 30 days as one TBI may have led to an underestimation of the number of TBIs. This may be the reason why we found no association between the numbers of TBIs and convictions. However, presence/absence of TBI at a specific age period was entered into regression models as a predictor of convictions. Further, it may be that diagnosing TBIs has changed over the decades during which the study took place. No information was available about the site and severity of injury, nor about neuropsychological symptoms and behaviors subsequent to the injury. It is possible that TBIs of a specific severity, in brain areas linked to antisocial and aggressive behavior,[75] may lead to changes in cognition, emotion processing, and impulsivity that do increase the risk of criminality. Lastly, our analyses only considered criminal convictions up to age 24. Given that it is possible for individuals to commit a first offence after age 24, additional studies with longer follow-up periods are necessary. Strengths of the study include the use of health records to identify TBIs and official criminal records to document adolescent and adult convictions for a sample of 724 men. Additionally, information was available on social status of participants' families in childhood, and ratings of participants' behavior at age 6, 10, and

12 by different classroom teachers. Studying a sample enriched with offenders ensured sufficient statistical power to robustly identify links, or absence of links, between TBIs and criminal convictions.

3.5. Conclusions

Using data collected prospectively to age 24 on 724 males, health file diagnoses of TBIs and official records of criminal convictions from age 13 to 24, there was no evidence that sustaining a TBI increased the subsequent risk of a conviction when regression models included family social status and scores for childhood disruptive behaviors. However, these childhood characteristics may explain, at least in part, the finding that offenders were more likely than non-offenders to sustain TBIs from age 18 to 24.

“Things are not always what they seem; the first appearance deceives many”

– Phaedrus

Chapter 4. Childhood conduct problems and accidents

Results from our first study on a prospective longitudinal sample of Quebecois men suggested that the link between TBIs and violent crimes did not persist when accounting for externalizing problems presented in childhood. In other words, the results suggested that it was the externalizing problems, not the TBIs, that were linked to criminality. Violent criminality observed after TBIs may thus be better explained as a continuation of a lifelong trajectory, which onsets in childhood as externalizing problems.

In 1995, in a special issue of *Criminal Behaviour and Mental Health*, a prior study using the same dataset we used found that children who displayed high levels of inattention-hyperactivity were at higher risk of sustaining motor vehicle accidents in adolescence compared to their healthy peers.[167] More recent studies have observed consistent results. Impulsivity was found to be associated with reckless driving and driving under the influence,[168] childhood ADHD comorbid with CD predicted unsafe driving and injuries to age 38,[169] and accidents and head injuries (not TBI diagnoses) to age 41.[170] Childhood externalizing problems predicted accidents in adolescence[171] and unintentional injuries to age 32.[68] Motor vehicle accidents account for 17% of all TBIs.[172] Hence, the next question we addressed was: are childhood externalizing problems associated with an increased risk of subsequent TBIs?

“Logic: The art of thinking and reasoning in strict accordance with the limitations and incapacities of the human misunderstanding”

– Ambrose Bierce

Chapter 5. Are childhood externalizing problems associated with an increased risk of subsequent TBIs?

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A prospective study of childhood predictors of traumatic brain injuries sustained in adolescence and adulthood

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Abstract

Objective: Traumatic brain injuries (TBIs) are sustained by approximately 17% of males in the general population, many whom subsequently present mental disorders, cognitive, and physical problems. Little is known about predictors of TBIs and how to prevent them. The present study aimed to determine whether inattention-hyperactivity and/or all externalizing problems presented by boys at age 10 predict subsequent TBIs to age 34 after taking account of previous TBIs and family social status (FSS).

Method: 742 Canadian males were followed, prospectively, from age 6 to 34. Diagnoses of TBIs were extracted from health files, parents reported socio-demographic and family characteristics at participants' age 6, and teachers rated participants' behaviors at age 10. Separate logistic regression models predicted TBIs sustained from age 11 to 17, and from age 18 to 34. For each age period, two models were computed, one included previous TBIs, inattention-hyperactivity, FSS, and interaction terms, the second included previous TBIs, externalizing problems, FSS, and interaction terms.

Results: In models that included inattention-hyperactivity: TBIs sustained from age 11 to 17 were predicted by age 10 inattention-hyperactivity (OR=1.46, 1.05-2.05) and by TBIs prior to age 11 (OR=3.50, 1.48-8.24); TBIs sustained from age 18 to 34 were predicted by age 10 inattention-hyperactivity (OR=1.31, 1.01-170). In models that included all externalizing problems: TBIs from age 11 to 17 were predicted by prior TBIs (OR=3.66, 1.51-8.39); TBIs sustained from age 18 to 34 were predicted by age 10 externalizing problems (OR=1.45, 1.12-1.86). Neither FSS nor interaction terms predicted TBIs in any of the models.

Conclusions: Among males, using evidence-based treatments to reduce inattention-hyperactivity and externalizing problems among boys could, potentially, decrease the risk of TBIs to age 34. Further, boys who sustain TBIs in childhood require monitoring to prevent recurrence in adolescence.

Keywords: Traumatic Brain Injuries, Childhood inattention-hyperactivity, Childhood externalizing Problems, Traumatic Brain Injury recurrence

5.1. Introduction

A meta-analysis of studies conducted in developed countries reported that Traumatic Brain Injuries (TBIs) affect approximately 12% of the general population, males (16.7%) more than females (8.5%).[173] TBIs are the leading cause of death and disability in children and young adults[174] and can alter brain development.[175] TBIs are associated with cognitive, physical, and psychological sequelae[176-181] that can have debilitating, often life-long consequences.[182] As many as 77% of individuals who sustain a head injury develop depression,[183] and 53% present major depression.[184] Sustaining a TBI increases the risk of death by suicide two-fold.[185] TBIs are also associated with increased risks of post-traumatic stress disorder,[186] anxiety disorders, schizophrenia, and bipolar disorder.[181] Sequelae depend, in part, on severity[15] and location of injury. Given the consequences of TBIs for those afflicted, their families, and the health system, knowledge of antecedents of TBIs is needed to inform prevention strategies. Studies have shown that male sex,[187] a previous TBI,[179,187,188] low socio-economic status,[189-192] adverse life events,[193] aggressive behavior,[194] and substance misuse[194] are associated with an increased risk of TBIs.

We hypothesized that teacher ratings of childhood inattentive-hyperactive behaviors and all externalizing problems (inattentive-hyperactive, uncaring, and hurtful behaviors, and conduct problems) would predict subsequent TBIs. Two lines of evidence support our hypothesis. First, motor vehicle accidents are among the leading causes of TBIs, even among children.[8,189,195] Prospectively collected data show that childhood inattention-hyperactivity predicted motor vehicle accidents in adolescence,[159] and that childhood Attention Deficit Hyperactivity Disorder (ADHD) comorbid with Conduct Disorder predicted unsafe driving and injuries to age 38[169] and accidents and head injuries to age 41.[170] Childhood externalizing problems predicted accidents in adolescence[171] and non-intentional injuries to age 32.[68] Second, the prevalence of TBIs is higher among male criminal offenders than among non-

offenders.[134-137] Robust evidence derived from investigations that prospectively followed birth or population cohorts in several countries showed that most offenders presented externalizing problems in childhood,[16,68,169,196-200] and that most violent crimes are committed by men with a history of externalizing problems.[16,18,151,152] Thus, we reasoned that the elevated prevalence of TBIs among offenders may result from childhood externalizing problems that in turn increase the risk of motor vehicle accidents and TBIs.

To test our hypothesis, we studied a sample of Canadian males. Prospectively collected data were used to determine whether age 10 inattention-hyperactivity alone, or in combination with other externalizing problems, predict subsequent diagnoses of TBIs noted in health files to age 34. We expected that childhood inattention-hyperactivity and externalizing behaviors would be more strongly associated with TBIs in adolescence than in adulthood given the temporal proximity of predictor and outcome and the high prevalence of motor-vehicle accidents in adolescence.[201] We therefore computed separate prediction models for the two age periods. As past studies have shown that sustaining one TBI increases the risk of sustaining a second TBI,[29,187,188,202] prior TBIs were entered into prediction models. Previous studies also suggest that family adversity and parent characteristics were associated with an increased risk of TBIs,[189-193] and therefore family social status (FSS) was included as a predictor. Interactions of predictors were entered into models. We expected that the risk of sustaining a TBI would be increased by a prior TBI accompanied by high levels of inattention-hyperactivity and/or externalizing problems among boys of families with low FSS, and among boys having experienced a prior TBI and low FSS.

5.2. Materials and Methods

Sample

Participants were males from two prospective, longitudinal investigations[153,154] recruited in Quebec when they entered school at age 6 and followed to age 34. One cohort

was representative of age 6 children in Quebec,[153] the other was recruited in a deprived urban area.[154] From among these 2,631 males, we drew a sample that included all who had been charged with a criminal offence by age 24 (n=372) and a random sample of a similar number of those with no criminal record (n=371) (see Figure S1 in Supplementary Material). Studying a sample enriched with offenders ensured sufficient cases with inattention-hyperactivity and externalizing problems to provide the necessary statistical power to robustly test whether these behaviors predicted subsequent TBIs. Of the 743 men, health files were available for 724. Of these 724 participants, 96 were missing ratings of age 10 for inattention-hyperactivity. Those with missing and complete inattention-hyperactivity data included similar proportions who sustained a TBI prior to age 11, from age 11 to 17, and from age 18 to 34. Of the 724 men with health file data, 109 were missing age 10 ratings of externalizing problems. Similar proportions of those with and without missing ratings had sustained TBIs prior to age 11, from age 11 to 17, and from age 18 to 34. Hence, the final sample of participants with complete data was 628 for models that included inattention-hyperactivity and 615 for models that included externalizing behaviors.

Measures

Traumatic Brain Injuries. The Régie de l'Assurance Maladie du Québec provided data from the health records of 724 participants. TBIs were defined by the International Classification of Disease 9th Revision codes: 800.0-800.9 fractures of vault of skull; 801.0-801.9 fractures of base of skull; 802.0-802.9 fracture of face bones; 803.0-803.9 other and unqualified skull fractures; 850.0-850.9 concussion; 851.0-851.9 cerebral laceration and contusion; 852.0-852.9 subarachnoid, subdural, and extradural hemorrhage, following injury; 853.0-853.9 other and unspecified intracranial hemorrhage following injury; 854.0-854.9 intracranial injury of other and unspecified nature; 959.0 head injury unspecified. Previous

studies have defined TBIs by using these same ICD-9 codes.[13,54,143] Diagnoses repeated within 30 days were counted as one TBI.

Childhood Behaviors. When participants were age 10 their classroom teachers rated behaviors (absent=0, sometimes present=1, frequently present=2) using the Social Behavior Questionnaire.[154] Inattention-hyperactivity included the sum of scores from six items: restless, doesn't keep still, runs about or jumps up and down; squirmy, fidgety; poor concentration or short attention span; inattentive; gives up easily; stares into space. Externalizing problems were indexed by the sum of ratings for inattention-hyperactivity and conduct problems (destroys own or others' belongings; fights with other children; kicks, bites, or hits other children; doesn't share material; irritable, quick to fly off the handle; disobedient; truant from school; has stolen things on one or more occasions), Hurtful Behaviors (tells lies; bullies other children; blames others; inconsiderate of others) and Uncaring Behaviors (items were reverse coded: takes the opportunity to praise the work of less able children; shows sympathy to someone who has made a mistake; offers to help other children who are having difficulty with a task in the classroom; and comforts a youngster who is crying or upset). Ratings for each behavior were transformed to standardized Z scores.

Family social status (FSS). At participant's age 6, mothers reported socio-demographic information. This information was used to create a composite variable that included family status (whether or not participants lived with both biological parents), biological parents' ages at participant's birth, education, and job prestige.[203] This measure was previously validated.[156] The higher the score, the lower FSS.

Statistical analyses

Table S1 in Supplementary Material presents the variables used in the study. Logistic regression models were computed to determine whether age 10 inattention-hyperactivity predicted TBIs in adolescence (age 11 to 17) and in adulthood (age 18 to 34). Model 1

included two predictors, age 10 inattention-hyperactivity and a previous TBI. Model 2 added a third predictor, FSS. Consistent with much evidence,[169,170,204,205] scores for age 10 inattention-hyperactivity were significantly correlated with scores for age 10 conduct problems (r = 0.591, $p<0.001$), hurtful behaviors ($r = 0.553$, $p<0.001$), and uncaring behaviors ($r = 0.236$, $p<0.001$). A second set of regression models was computed to determine whether the sum of scores for age 10 inattention-hyperactivity, conduct problems, hurtful and uncaring behaviors would predict TBIs when taking account of previous TBIs and FSS. Lastly, regression analyses tested all two-way interactions and one three-way interaction (inattention-hyperactivity x previous TBI x FSS and externalizing behaviors x previous TBI x FSS). Results are reported as odds-ratios with 95% confidence intervals.

On the basis of simulation studies, Peduzzi et al.[206] determined that for the estimations of a logistic regression to be accurate, the number of Events Per Variable (EPV), defined by p/k (where p is the number of positive cases in a model and k is the number of predictors) must be at least 10. The minimum number of positive cases needed to obtain accurate estimations (p_{min}) can be defined as k*10. For models including inattention-hyperactivity: To predict TBIs from age 11 to 17, the number of positive cases (40) was insufficient for models including interaction terms, and sufficient for models including direct effects ($p_{min}=30$); To predict TBIs from age 18 to 34, the number of positive cases (72) was sufficient for models with and without interaction terms. For models including externalizing problems: To predict TBIs from age 11 to 17, the number of positive cases (39) was insufficient for models including interaction terms but sufficient for models including only direct effects; To predict TBIs from age 18 to 34, the number of positive cases (70) was sufficient for models with and without interaction terms.

Ethics Approval

Initially, parents provided consent for participants' teachers to rate their child's behavior and also consented to their own participation in the study. Once participants were 18 years old, they provided consent. The Commission d'Accès à l'Information de Québec approved the use of data from health files. The study was approved by ethics committees at the Université de Montréal, Centre Hospitalier Universitaire Sainte-Justine, and the Institut Philippe-Pinel de Montréal.

5.3. Results

From the 628 males with complete data for inattention-hyperactivity, 152 (24.2%) had sustained at least one TBI, 47 (7.5%) had sustained a TBI prior to age 11, 42 (6.7%) from age 11 to 17, and 78 (12.4%) from age 18 to 34. The average age at first TBI was 17.00 years (SD=8.27; range 1.8 to 34.4). The mean number of TBIs was 0.32 (SD=0.68, range 0 to 6) and the median was 0. The majority (117) of participants who sustained TBIs sustained only one. From the 615 males with complete data for externalizing problems, 149 (24.2%) had sustained at least one TBI, 46 (7.5%) had sustained a TBI prior to age 11, 41 (6.7%) from age 11 to 17, and 76 (12.4%) from age 18 to 34. The average age at first TBI was 17.06 years (SD=8.33; range 1.78 to 34.43). The mean number of TBIs was 0.32 (SD=0.67, range 0 to 6) and the median was 0. The majority (115) of participants who sustained TBIs sustained only one.

Does inattention-hyperactivity at age 10 predict subsequent TBIs?

Figure 1. Percentages of participants who experienced a Traumatic Brain Injury as a function of previous Traumatic Brain Injuries and age 10 inattention-hyperactivity or externalizing problems

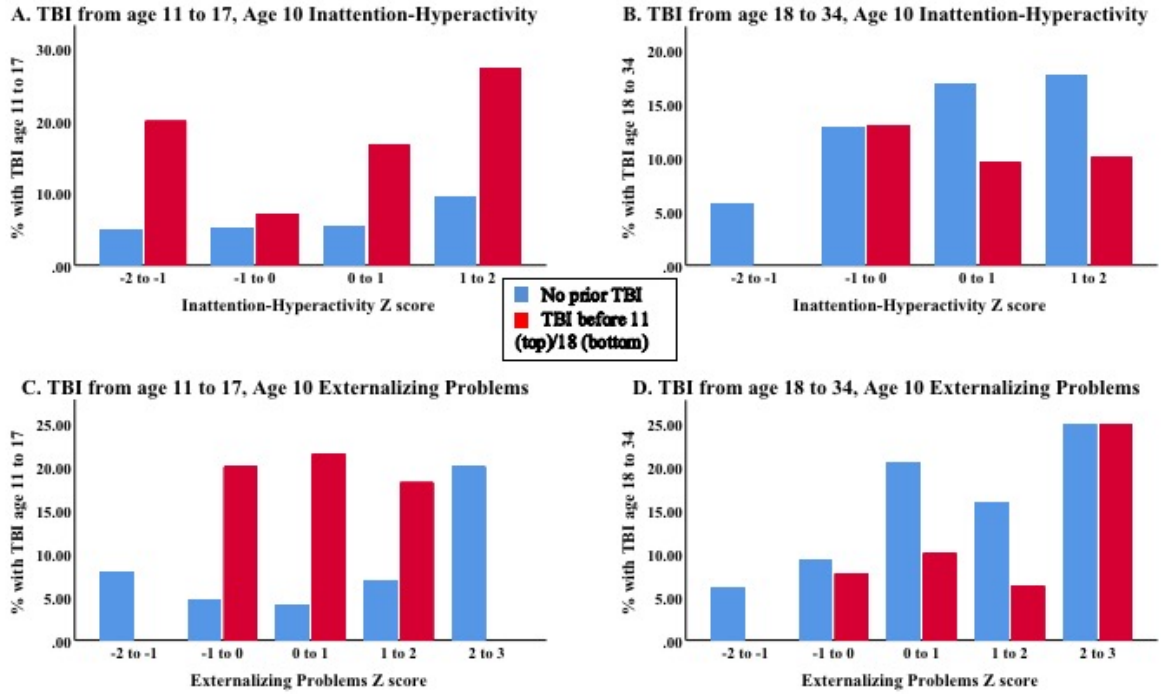

Table 1. Results of logistic regression models predicting traumatic brain injuries from age 11 to 17 and 18 to 34 years by age 10 inattention-hyperactivity and family social status

	Predictors of Traumatic Brain Injuries from age 11 to 17									
	Model 1 (n=628)					Model 2 (n=596)				
	B	*SE*	*Wald*	*p*	*Exp(B)* 95% CI	*B*	*SE*	*Wald*	*p*	*Exp(B)* 95% CI
Age 10 inattention-hyperactivity	0.341	0.162	4.410	0.036	1.406 1.02-1.93	0.382	0.170	5.056	0.025	1.456 1.05-2.05
Traumatic Brain Injury before age 11	1.177	0.429	7.513	0.006	3.245 1.40-7.53	1.250	0.438	8.138	0.004	3.490 1.48-8.24

Family social status						-0.256	0.172	2.213	0.137	0.774 0.55-1.09
Predictors of Traumatic Brain Injuries from age 18 to 34										
	Model 1 (n=628)					Model 2 (n=596)				
	B	*SE*	*Wald*	*p*	*Exp(B)* *95% CI*	*B*	*SE*	*Wald*	*p*	*Exp(B)* *95% CI*
Age 10 inattention-hyperactivity	0.383	0.123	9.703	0.002	1.467 1.15-1.87	0.271	0.131	4.264	0.039	1.311 1.01-1.70
Traumatic Brain Injury before age 18	-0.548	0.419	1.711	0.191	0.578 0.25-1.31	-0.644	0.448	2.073	0.150	0.525 0.22-1.26
Family social status						0.173	0.131	1.757	0.185	1.189 0.92-1.54

Results are presented in Table 1. The first model indicated that sustaining a TBI from age 11 to 17 was predicted by age 10 inattention-hyperactivity and previous TBIs. Model 2, where FSS was added as a predictor, showed that the risk of sustaining a TBI in adolescence was increased 1.46 (1.05-2.05) times by each increase of one in the standardized score for inattention-hyperactivity and 3.49 times (1.48-8.24) by a previous TBI. None of the interaction terms were significant.

As also shown in Table 1, TBIs sustained from age 18 to 34 were predicted by age 10 inattention-hyperactivity and previous TBIs. In model 2, sustaining a TBI in adulthood was not predicted by TBIs prior to age 18 nor by FSS. Rather, each increase of one in the

standardized score for age 10 inattention-hyperactivity was associated with a 1.31 (1.01-1.70) increase in the risk of TBIs in adulthood. None of the interaction terms were significant.

Figure 1 illustrates the percentages of participants who sustained TBIs from age 11 to 17 and from age 18 to 34 as a function of prior TBIs and inattention-hyperactivity.

Post-hoc analyses

Most boys presenting Attention Deficit Hyperactivity Disorder also present other externalizing problems.[207,208] Therefore, we conducted exploratory analyses to determine whether inattention-hyperactivity accompanied by low ratings for other externalizing problems was associated with an increased risk of sustaining a TBI. For both inattention-hyperactivity and externalizing (without inattention-hyperactivity) we defined low scores as a z score of -1.5 to 0, and high scores as 0 to 1.5. Participants were classified by low and high scores for inattention-hyperactivity and other externalizing problems. Proportionately more of the boys with high inattention-hyperactivity and low other externalizing (15.5%) as compared to boys with low scores for both measures (7.1%) sustained TBIs from age 18 to 34 (X^2(N=336)=5.22, p = .022). The proportions who sustained TBIs from age 11 to 17 were similar.

Table 2. Results of logistic regression models predicting traumatic brain injuries from age 11 to 17 and 18 to 34 years by age 10 externalizing problems and family social status

	Predictors of Traumatic Brain Injuries from age 11 to 17									
	Model 1 (n=615)					Model 2 (n=583)				
	B	*SE*	*Wald*	*p*	*Exp(B)* 95% CI	*B*	*SE*	*Wald*	*p*	*Exp(B)* 95% CI
Age 10 externalizing problems	0.208	0.158	1.720	0.190	1.231 0.90-1.68	0.267	0.167	2.545	0.111	1.306 0.94-1.81

TBI before age 11	1.200	0.430	7.791	0.005	3.319 1.43-7.71	1.271	0.437	8.452	0.004	3.564 1.51-8.39
Family social status						-0.218	0.177	1.525	0.217	0.804 0.57-1.14
Predictors of Traumatic Brain Injuries from age 18 to 34										
	Model 1 (n=615)					Model 2 (n=583)				
	B	*SE*	*Wald*	*p*	*Exp(B)* *95% CI*	*B*	*SE*	*Wald*	*p*	*Exp(B)* *95% CI*
Age 10 externalizing problems	0.436	0.119	13.324	<0.001	1.546 1.22-1.95	0.370	0.129	8.234	0.004	1.447 1.12-1.86
TBI before age 18	-0.712	0.449	2.519	0.113	0.491 0.20-1.18	-0.840	0.486	2.993	0.084	0.432 0.17-1.12
Family social status						0.058	0.137	0.177	0.674	1.059 0.81-1.39

Do externalizing problems at age 10 predict subsequent TBIs?

A total score for inattention-hyperactivity, conduct problems, hurtful and uncaring behaviors was calculated for each participant. As presented in Table 2, the risk of sustaining a TBI in adolescence was increased approximately 3.5 times in each model by a previous TBI, but not by the age 10 externalizing score or FSS. By contrast, sustaining a TBI from age 18 to 34 was predicted by age 10 scores for externalizing problems, and not by previous TBIs or FSS. In model 2, each increase of one in the age 10 standardized externalizing problems score was associated with a 1.45 (1.12-1.86) increase in the risk of TBIs in adulthood. No interaction terms were significant. In the bottom panel of Figure 1, the percentages of

participants who sustained TBIs from age 11 to 17 and from age 18 to 34 are presented as a function of prior TBIs and externalizing scores.

Ensuring generalizability

The present sample was enriched with criminal offenders as these men are very likely to have presented externalizing problems in childhood.[16,68,169,196-200] In order to increase confidence in the generalizability of results, analyses were re-run among only the non-offenders. Despite the smaller sample size, results were similar to those reported for the whole sample (see Supplementary Material).

5.4. Discussion

Prospectively collected data indicated that among males, teacher ratings of inattention-hyperactivity at age 10 predicted TBIs from age 11 to 17 and from age 18 to 34. Teacher ratings of age 10 externalizing behaviors did not predict TBIs sustained from age 11 to 17 but did predict TBIs sustained from age 18 to 34. Additionally, TBIs sustained prior to age 11 predicted TBIs from age 11 to 17, but TBIs sustained prior to age 18 did not predict TBIs from 18 to 34. FSS did not predict TBIs at any age. Thus, as illustrated in Figure 1, TBIs sustained in adolescence were associated with previous TBIs and high levels of inattention-hyperactivity, while TBIs sustained from age 18 to 34 were associated with inattention-hyperactivity and with a total score for age 10 externalizing problems. These findings are consistent with previous studies showing that childhood inattention-hyperactivity and externalizing problems were associated with increased risks of motor vehicle accidents,[68,159,169-171] a primary cause of TBIs,[8,189,195] from adolescence through the third decade of life. The findings from the present study are also consistent with reports that male offenders, most of whom have a history of childhood externalizing problems, are at elevated risk to sustain TBIs.[134-137]

Our finding that childhood TBIs were associated with an increased risk of TBIs in adolescence, although TBIs prior to age 18 did not increase risk of TBIs in adulthood, is consistent with results from a Swedish study[202] showing that recurrence was more likely after a childhood TBI than after an adolescent TBI. While previous studies have shown that sustaining a TBI increases the risk of future TBIs,[29,209-214] the risk of recurrence varies not only by age at first TBI and length of follow-up,[202,213-215] but also by sample characteristics (community,[138,161,194,202,213] prisoners,[142] sex, ethnicity[215]), self-report or medical diagnosis,[213,216] cause of injury,[187] severity of first TBI,[202,217] engagement in sports,[188,194] alcohol intoxication,[214] and seizure disorder.[215,217]

In our study, FSS of the family of origin was not associated with TBIs, consistent with results from a New Zealand birth cohort showing that neither SES nor family living standard was associated with child/adolescent TBIs,[193] and those from the British Columbia Trauma Registry showing that, of several measures of SES, only the percentage of people aged 15 and older in the neighborhood without a high school diploma was related to TBIs.[189] In a large UK cohort, low SES of the family was associated with the child/adolescent not experiencing a TBI.[138]

Results of the present study extend previous findings[159,169,170] by showing that childhood inattention-hyperactivity and externalizing problems were associated specifically with an increased risk of TBIs to age 34. Inattention-hyperactivity at age 10 predicted TBIs up to age 34, but as would be expected inattention-hyperactivity was strongly correlated with other externalizing problems. Recent studies show that externalizing problems precede inattention problems, and that the correlation between inattention and externalizing problems continues to increase to age 20.[218] In the present study, it was the total score for these childhood problems that predicted TBIs in adulthood, but not in adolescence. Robust evidence shows that the earlier the onset of externalizing problems the greater the likelihood

of antisocial and aggressive behaviors through adolescence and adulthood.[219] Thus, it is reasonable to speculate that the boys with the highest ratings of externalizing problems at age 10 would have displayed similar problems in adolescence and adulthood. In addition, most would have begun misusing substances early in adolescence and developed substance use disorders in adulthood.[75] Such boys engage in risky behaviors at all ages, but as they age risky behaviors become more dangerous. By age 18, they drive motor vehicles, often when intoxicated, and they fight with peers who use weapons, thereby increasing the risk of incidents that may lead to TBIs. This scenario may explain why age 10 externalizing problems did not predict TBIs sustained in adolescence but did predict TBIs sustained from age 18 to 34. TBIs sustained in adolescence are reported to result, principally, from accidents occurring when playing organized sports.[194,220] Boys with externalizing problems are less likely than healthy boys to participate in organized sports as they have difficulty following rules.[221,222] This may be an additional reason why childhood externalizing problems are not associated with an increased risk of TBIs in adolescence, but only from age 18 through 34 when the likelihood of accidents resulting from risk behaviors dramatically escalates. While statistically significant, childhood inattention-hyperactivity and externalizing problems are associated with a moderate increase risk of TBIs, indicating a need for future investigations that prospectively measure the multiple factors that increase and that decrease the risk of TBIs.

The results of the present study, if replicated, suggest that the interventions that effectively reduce childhood inattention-hyperactivity[223] and externalizing problems[224] could, potentially, reduce the risk of subsequent TBIs and their physical and psychological sequelae. This hypothesis requires testing. The present results add to previous evidence showing that children who sustain TBIs are at elevated risk to sustain similar injuries in adolescence and

thus require monitoring. Further, knowledge of behavioral, environmental, and family factors promoting TBIs and factors promoting recurrence of TBIs is also needed.

Limitations and strengths

The sample was relatively small. According to the Peduzzi et al[206] criteria, the number of participants who sustained TBIs in adolescence was insufficient for prediction models that included interaction terms, but the number who sustained TBIs from age 18 to 34 was sufficient for prediction models that included interaction terms. The number of TBIs may have been underestimated by using ICD codes to identify TBIs, as a Canadian study reported that one-in-six patients with concussion signs and symptoms were misdiagnosed in emergency departments.[225] Additionally, TBIs may have been underestimated by counting diagnoses given within a 30-day period as one TBI. This was done because physicians were required to record a diagnosis each time they saw a patient. Another limitation may be that diagnosing TBIs has changed over the decades during which data were collected, mid-1980s to 2013. Further, previous studies suggested that TBIs may lead to externalizing problems. One study found that TBIs requiring hospitalization sustained before age 5 predicted inattention-hyperactivity and externalizing behaviors in adolescence.[70] Two other studies reported an increase in aggressive behavior following child/adolescent TBIs,[12,162] others did not.[163] However, we found no significant difference in inattention-hyperactivity and externalizing scores between boys who had, and who had not, sustained TBIs before age 10. Finally, only males were studied. While inattention-hyperactivity[226] and externalizing problems[227,228] are at least twice as prevalent among boys and girls, stability into adulthood is similar.[68] Studies are needed to determine whether these childhood problems are linked to TBIs in females. Strengths of the study include the use of health records to identify TBIs, information on socio-demographic characteristics of participants' parents, composition and

socio-economic status of the family of origin at age 6, and teacher ratings of inattention-hyperactivity and externalizing problems at age 10.

5.5. Conclusion

Boys who sustain TBIs constitute a population-at-risk for further TBIs in adolescence. High levels of inattention and hyperactivity observed by teachers at age 10 were a precursor of TBIs to age 34. Boys who sustained a TBI in childhood and who displayed inattention and hyperactivity have an especially high risk for subsequent TBIs. Additionally, boys who presented high levels of externalizing problems at age 10, were at risk to sustain a TBI from age 18 to 34, probably as a result of increasingly reckless behavior. Future studies are needed to determine whether evidence-based treatments to reduce childhood inattention-hyperactivity and externalizing problems lower the risk of future TBIs.

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Declaration of conflicting interests

The authors have no conflicting interests to declare.

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“[…] when you have eliminated the impossible, whatever remains, *however improbable*, must be the truth"

– Sherlock Holmes, *The Sign of the Four*[229]

Chapter 6. White matter structure in children with externalizing problems

Results from our second study on this prospective longitudinal sample of Quebecois men demonstrated that childhood externalizing problems in general, and inattention-hyperactivity in particular, preceded TBIs and increased the risk of TBIs in adolescence and adulthood even when taking account of prior TBIs and family social status. Interestingly, a subsequent study from a group in Sweden using population data from the U.S. found that individuals with ADHD diagnoses were at higher risks of sustaining TBIs in the months they were off medications, as compared to months on medication, independently supporting our results.[230] Higher risk of TBI among children, adolescents, and adults with ADHD diagnoses was also found in another study of 72,181 individuals from Taiwan, which also reported lower risk of TBI associated with long-term use of ADHD medication.[231] Another recent study found that adverse childhood events – for example witnessing violence at home, financial precariousness – were associated with higher risk of TBIs, but this association was attenuated when accounting for ADHD and conduct problems.[232]

Why would externalizing problems be associated with increased risk of subsequent TBIs? As they grow up, children presenting inattention-hyperactivity or externalizing problems are at increased risk to continue to engage in aggressive behaviour towards others, to be convicted of violent crimes, to be injured in motor vehicle accidents, to misuse substances, and to take part in different types of reckless behaviours, all of which could lead to TBIs.

Externalizing problems are associated with abnormalities in brain structure and function, including white matter structure, although this literature is unclear given that few studies have accounted for common comorbidities such as CU traits and ADHD, as well as the influence of sex and pubertal development.[89,90,96,103-106,233-238] Study 2 suggested that

children displaying externalizing problems are at increased risk for TBIs, but no prior studies have accounted for TBIs when studying the white matter abnormalities of children with externalizing problems. Further, TBIs are also associated with alterations in brain structure and function, and are known to heavily impact white matter structure.[31,119,123] Despite children and young adults presenting some of the highest incidence rates of TBIs, neuroimaging research on this group is scarce.[22] Hence, we were interested in assessing whether TBIs are associated with different alterations of white matter structure in children presenting externalizing problems compared to typically developing children.

“Once a new technology rolls over you, if you're not part of the steamroller, you're part of the road.”

– Stewart Brand

Chapter 7. Are TBIs associated with different alterations of white matter structure in children presenting externalizing problems as compared to typically developing children?

Manuscript under review

White matter microstructure, traumatic brain injury, and disruptive behavior disorders in girls and boys

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Abstract

Girls and boys presenting disruptive behavior disorders (DBDs) display differences in white matter microstructure (WMM) relative to typically developing (TD) sex-matched peers. Boys with DBDs are at increased risk for traumatic brain injuries (TBIs). This study aimed to disentangle associations of WMM with DBDs and TBIs. The sample included 673 children with DBDs and 836 TD children, aged 9-10, from the Adolescent Brain Cognitive Development Study. Thirteen white matter bundles previously associated with DBDs were the focus of study. Analyses were undertaken separately by sex, adjusting for callous-unemotional traits (CU), attention-deficit hyperactivity disorder (ADHD), age, pubertal stage, IQ, ethnicity, and family income. Among children without TBIs, those with DBDs showed sex-specific differences in WMM of several tracts relative to TD. Most differences were associated with ADHD, CU, or both. Greater proportions of girls and boys with DBDs than sex-matched TD children had sustained TBIs. Among DBD girls and boys only, those who had sustained TBIs compared to those not injured, displayed WMM alterations that were robust to adjustment for all covariates. Children with DBDs are more likely than TD children to sustain TBIs that add to alterations of WMM. WMM alterations associated with DBDs, with and without TBIs, are sex-specific.

7.1. Introduction

Childhood disruptive behavior disorders (DBDs), characterized by persistent rule breaking and aggressive behavior, constitute the primary risk factor for adult antisocial behavior and criminality.[239] DBDs are estimated to affect 3% to 12% of children, more boys than girls.[240] The population presenting DBDs is heterogenous with respect to callous-unemotional traits presented by approximately 40% of girls and boys, [240] and Attention Deficit Hyperactivity Disorder (ADHD) presented by 24% of the boys and 36% of the girls.[241] CU is associated with more severe conduct problems, aggressive behaviour, and outcomes.[242]

DBDs are disorders of atypical development of gray and white matter.[243] A recent review concluded that alterations of white matter microstructure (WMM) were associated with antisocial behavior, noting however that results in children were inconclusive as to the implicated tracts and the direction of effects.[237] The few studies of the association of DBDs and WMM focused almost exclusively on teenage boys, and did not account for several factors known to affect WMM such as maltreatment[109] and substance misuse[244] that are more common among children with DBDs than those who are typically developing (TD). Further, almost all studies employed the diffusion tensor model, which, in the presence of underlying fiber heterogeneity, cannot disentangle the contributions of different neuropathologies to WMM.

Among children with DBDs, the most frequently reported alterations of WMM are found in the uncinate fasciculus (UF)[104,237] and the corpus callosum (CC),[106,245] consistent with findings among adults with Antisocial Personality Disorder who by definition presented DBDs in childhood.[246] The combination of DBDs and CU has been associated with differences in the UF[104,245] and the CC[106] among girls with conduct disorder.[235] When controlling for CU, the same bundles (tracts) have been found to be associated with DBDs.[106]

A study of a large birth cohort from The Netherlands reported that CU, not accounting for DBDs, was associated with differences in global mean diffusivity driven by the UF, cingulum and CC in girls not boys.[104]

Importantly, previous studies of children with DBDs did not take account of traumatic brain injuries (TBIs). Yet, boys with DBDs are at increased risk of accidents[158] and of TBIs[247] as compared to their peers. In a sample of 628 males, age 10 teacher ratings of inattention-hyperactivity predicted TBIs up to age 34, and ratings of a composite score for externalizing problems predicted TBIs from age 18 to 34, after accounting for previous TBIs and family social status.[247] Decades of research have shown that TBIs impact WMM in children.[119,123] Could TBIs play a role in altering WMM of children with DBDs thereby adding to, or compounding, the existing atypical neurodevelopment?

There are few studies of WMM in children who have sustained TBIs[123] and none to our knowledge that accounted for DBDs. In small samples of children/adolescents who had sustained TBIs, alterations have been observed in WMM maturation rates[248] including in the CC.[249] Few studies have investigated sex differences in WMM alterations following a concussion. One study of 244 children and adolescents who had sustained mild-to-severe TBIs and 263 matched non-injured peers reported that girls, not boys, exhibited lower fractional anisotropy in the UF.[250]

The present study

We used data collected on 11,875 children aged 9 to 10 years old from the Adolescent Brain Cognitive Development (ABCD) Study. We aimed to determine, for the first time, whether children with DBDs who had not experienced a TBI display differences in WMM relative to non-injured TD children. Next, we examined children who had sustained TBIs, and determined whether those with DBDs, relative to TD children, showed alterations in WMM. Finally, we determined whether TBIs were associated with the same differences in

WMM among children with DBDs and among TD children. We expected that given the distinctive neural development characterising DBD children, TBIs would be associated with alterations to structures distinct from those in the TD children.

Girls, as compared to boys, are less likely to present DBDs, obtain lower scores for CU,[242] display faster white matter development of,[251] mature more quickly, and have a higher risk of TBIs and of serious negative outcomes.[23] Among children with DBDs, much less is known about girls than boys, including differences in WMM as compared to healthy peers. Therefore, we examined boys and girls separately, hoping to maximize knowledge gained from this rare large sample of girls presenting DBDs. Within each sex, we controlled for pubertal stage and age.

Since previous studies suggested that among children with DBDs CU was associated with differences in WMM, perhaps in a sex-specific manner, analyses controlled for CU. Because comorbid inattention-hyperactivity has been found to be associated with distinct alterations of WMM, analyses also controlled for Attention Deficit Hyperactivity Disorder (ADHD).

In addressing these questions, the present study employed novel modelling and tractography techniques that are robust to the biases of diffusion tensor imaging (DTI) and novel statistical approaches (described in Supplementary Material) that leverage the information contained within diffusion measures to more exhaustively probe WMM.

7.2. Materials and Methods

Participants

Data were obtained from the ABCD study (https://abcdstudy.org/) 2.0 data release (https://data-archive.nimh.nih.gov/abcd) that recruited 11,875 healthy children, aged 9 to 10 years from across the United States (48% girls). The sample, procedures, and ethics approval have been described.[252]

Measures

Disruptive Behavior Disorders. As previously described,[253] children's behaviors were rated by one parent using self-administered computerized versions of the Child Behavior Checklist (CBCL) and the Schedule for Affective Disorders and Schizophrenia for school-age children (KSADS). A KSADS past or current diagnosis of conduct disorder and/or oppositional defiant disorder and/or CBCL scores on these scales of 66 or higher were coded as DBDs. Psychometric properties of this measure are good.[253]

CU Traits. We quantified CU traits using a measure derived and validated on ABCD Study participants and an independent sample of children that showed good psychometric properties, measurement invariance across sex, race, and age, and differences from conduct problems, oppositional defiant disorder, and ADHD, and meaningful associations with outcomes [254]. The measure of CU includes one item from the parent-rated CBCL, "lack of guilt after misbehaving" and 3 items from the parent rated Strengths and Difficulties Questionnaire, "is considerate of others' feelings"; "is helpful if someone is hurt or upset"; "offers to help others") (all 3 reverse-coded) rated on a three-point scale (0-1-2). Following (58, 59), we obtained two CU measures from these items, the sum of responses, and a maximum a posteriori (MAP) scale score that accounts for which items are endorsed by whom, providing person-specific factor scores for CU traits. We then dichotomized these scores defining the presence of high CU traits as a summed score of 4 or above and a CU traits *mean a posteriori* (MAP) score at or above the 90th percentile.

ADHD. ADHD was indexed using T-scores from the DSM-oriented Attention Problems scale from the CBCL.

Pubertal stage. Parents completed the Pubertal Development Scale and Menstrual Cycle Survey History questionnaire.[255] Responses were tallied by the ABCD Study team into three stages of pubertal development.

IQ. Children completed a computerized version of the National Institutes of Health Toolbox Cognitive function Battery [256] that assessed seven cognitive abilities. The ABCD Study team computed fully corrected T-Scores, comparing the score of the participant to those in the NIH Toolbox nationally representative normative sample, adjusted for age, gender, race/ethnicity, and parental educational attainment. We used this fully-corrected score as a measure of IQ. A fully corrected score derived from the child's score on the National Institutes of Health Toolbox Cognitive Function Battery was used to index IQ.

TBIs. Parents completed a modified version of the Ohio State University TBI Identification Method.[257] We defined a mild TBI as a head injury without loss of consciousness but with memory loss and/or a head injury with loss of consciousness for less than 30 minutes. In the present study, all TBIs met this definition of mild TBI. In the whole ABCD sample (n = 11,875), seven children had sustained TBIs of moderate or high severity. None of them met criteria for either the DBD or the TD group.

Sociodemographic measures. Parents completed the Parent Demographics Survey to report on their child's ethnicity, family income, their own education, and marital status.

Parent substance use. Parents completed the Family History Assessment to report on substance use.

Group Classification

Figure 1 presents the selection and exclusion criteria that led to a final sample of 751 girls and 749 boys. From the full baseline sample (n=11,875), within each sex, a DBD ("DBD raw") and a TD group were created. The DBD group was defined to include children with Child Behavior Checklist T-scores of 66 or higher on either the conduct problems or

oppositional defiant problems scales or a diagnosis of present or past Conduct Disorder or Oppositional Defiant Disorder on the KSADs. As previous studies have indicated that WMM differences may be associated with CU rather than directly with DBDs,[245] within this group we included participants with and without CU. We identified participants without CU, defined as CU sum scores of 0, and participants with high CU, defined as CU sum scores of four or more and CU MAP scores at or above the 90th percentile. These two sub-groups were combined to create a DBD group in which approximately half of the members had high CU and half no CU. The TD group was defined as individuals with no DBDs and no CU traits, and T scores of 50 on all Child Behavior Checklist scales. From the TD group, we excluded 16 participants who had missing diagnostic data, and seven who had other diagnoses.

Scans underwent pre-processing, processing, and post-processing, leading to the exclusion of 240 DBD participants and 248 TD participants due to missing or corrupted data files, poor image quality, and failures during image processing and post-processing. The final groups of DBD (boys n=557; girls n=352) and TD (boys n=451; girls n=628) participants were then divided according to presence or absence of at least one TBI.

Magnetic Resonance Imaging

We used multi-shell diffusion MRI (dMRI) and T1-weighted scans. Only scans rated "high quality" by the ABCD Study team were retained. Pre-processing verified that all had the necessary image requirements. We processed dMRI and T1-weighted scans using Tractoflow,[258] following steps outlined in Theaud et al.[258] Deviations from the default parameters were the use of white matter seeding and using 12 seeds-per-voxel for tractography.

We used *RBX-flow*[259] to extract 13 major white matter bundles previously found to differ in children with DBDs:[104,106,237,245] bilateral UF, inferior fronto-occipital fasciculus (IFOF), cingulum, inferior longitudinal fasciculus (ILF), corticospinal tract (CST), and three

portions of the CC, genu, body, and splenium (Figure S1). We then obtained six scalar measures averaged across bundles: fractional anisotropy, mean, radial, and axial diffusivity, number of fiber orientations,[260] and apparent fiber density along fixels.[129] We imputed missing data by randomly selecting data from other participants separately for each bundle and each diffusion measure.

In a final step, we applied principal component analysis on the concatenated set of standardized measures across participants and bundles (Figure S2), for the TD group without TBIs, separately for boys and girls. We then projected data from all other participants onto the selected components. In both sexes, we obtained three components: absolute diffusivity, axonal density, and number of fiber orientations that together accounted for 93-94% of the total variance in WMM measures (Figure 2). Further details are presented in Supplementary Material.

Statistical analyses

We performed all analyses separately by sex. We compared four groups (TD/TBI+, TD/TBI-, DBD/TBI+, DBD/TBI-) as to individual and family characteristics using two-sample t-tests for continuous variables and chi-squared tests for categorical variables with 2000 Monte Carlo simulations to calculate p-values. We conducted three sets of comparisons of WMM: (1) among children without a prior TBI, comparing DBD and TD groups; (2) among children with a prior TBI, comparing DBD and TD groups; (3) within DBD and TD groups, comparing children with and without a prior TBI. We used multivariate regression analyses to identify WMM differences, separately by bundle, after having regressed out scanner, non-adjusted and then adjusted separately for each covariate (CU MAP, ADHD, IQ, age, pubertal stage, ethnicity (0=non-Hispanic White, 1=other), and family income (0=above $50,000, 1=below $50,000). For bundles displaying significant group differences, we ran post-hoc analyses comparing each WMM component.

7.3. Results

Sample characteristics

Sample characteristics of boys and girls are summarized in Tables 1 and 2. Among the 749 boys, TBIs had been sustained by 7.75% of the DBD group and 2.59% of the TD group (χ^2= 9.859, p = 0.005). Among the 751 girls, TBIs had been sustained by 4.83% of DBD group and 2.07% of the TD group (χ^2 = 4.424, p = 0.048). Given that the TD group was defined not to include psychopathology, we reasoned that the excluded children who presented some psychopathology might have a higher risk of TBIs. To determine whether the elevations in risk of TBIs was specific to children presenting DBDs we compared them to all the other children in the ABCD sample. Among the boys who did not present DBDs (n=5,631) 4.14% had sustained a TBI as compared to 7.36% among the full (i.e.: before quality control, pre- and post-processing) boys DBD group (X^2 = 12.442, p = 0.002). Among the girls who did not present DBDs (5,329), 3.0% sustained a TBI as compared to 4.26% among the full girls DBD group (X^2 = 1.357, p = 0.206).

Children presenting DBDs, their parents and families, differed from TD children, parents and families, obtaining higher scores for conduct problems, oppositional defiant problems, CU, ADHD, and lower IQ, lower family income, fewer living with two parents, and more had a family member presenting substance misuse. Among the DBD boys, there was only one difference between those with and without TBIs; previously injured boys obtained higher ADHD scores. Among the TD boys, only family income distinguished those with and without TBIs. Among the DBD girls, those who had sustained a TBI differed from those who had not by having parents with a lower level of education, higher scores for conduct problems and for ADHD. Among TD girls, those with TBIs differed from those without by coming from families with higher income and by obtaining higher CU scores.

Among children without TBIs, are there WMM differences between those presenting DBDs and TD children?

As presented in Table 3, among boys who had not experienced TBIs, those with DBDs as compared to TD boys displayed a multivariate difference of WMM in the left CST, robust to adjustment for age, ethnicity, and family income, but not for CU, ADHD, IQ, or pubertal stage, and in the CC genu, robust to adjustment for IQ, age, pubertal stage, ethnicity, and family income, but not CU and ADHD. In post-hoc analyses, no differences were detected in the three components of WMM of the CST. In the CC genu, absolute diffusivity was lower and axonal density was higher in DBD boys compared to TD boys.

Among girls without TBIs, those presenting DBDs, as compared to TD girls, displayed a multivariate difference of WMM in the left IFOF, robust to adjustment for all covariates except CU, in the right IFOF, robust to adjustment for all covariates except CU and ADHD, in the right ILF, robust to adjustment only for age and family income, and in the body of the CC, robust to adjustment for CU, age, pubertal stage, and ethnicity. Post-hoc analyses revealed that DBD girls showed higher axonal density in the left and right IFOF, lower axonal density in the right ILF, and lower absolute diffusivity in the CC body.

Among children with TBIs, are there WMM differences between those presenting DBDs and TD children?

As presented in Table 4, among boys with TBIs, those with DBDs as compared to TD boys displayed a multivariate difference of WMM in the left CST, robust to adjustment for CU, IQ, pubertal stage, and ethnicity. In post-hoc analyses, no differences in the three components of WMM were detected.

Among girls with TBIs, those presenting DBDs, as compared to the TD, showed a multivariate difference in WMM in the right UF, robust to adjustment for all covariates except family income. In post hoc analyses, the UF of DBD girls showed higher axonal density.

Among TD boys and girls, do those who have sustained TBIs show WMM differences from those with no TBIs?

Among both TD boys and girls, there were no significant differences in WMM between those with and without TBIs in any of the 13 bundles studied.

Among boys and girls presenting DBDs, do those who have sustained TBIs differ from those with no TBIs?

As presented in Table 5, among boys presenting DBDs, those with prior TBIs compared to those without displayed a multivariate difference of WMM in the left CST, robust to adjustment for CU, ADHD, age, ethnicity, and family income, and in the right ILF, robust to adjustment for all covariates except ADHD and family income. Post-hoc analyses revealed that DBD boys who had sustained TBIs showed higher axonal density in the left CST and higher absolute diffusivity in the right ILF, compared to DBD boys without TBIs.

Among girls presenting DBDs, there was only one significant difference between those who had and who had not sustained TBIs that was observed in the genu of the CC, robust to adjustment for all covariates except family income. Post-hoc analyses revealed that DBD girls who had sustained TBIs showed higher absolute diffusivity in the CC genu compared to DBD girls without TBIs.

7.4. Discussion

The present study found that greater proportions of boys and girls with DBDs than TD boys and girls had sustained at least one TBI by age 10, consistent with previous findings.[247] Factors associated with increased risk of TBIs may differ in the two groups. Children with DBDs are more likely than TD children to have experienced harsh parenting and/or maltreatment[109] and to engage in risky behaviors, such as physical fighting. By contrast, TD children may be more likely to participate in organized sports involving heightened risk of TBIs. The prevalence of TBIs was higher among boys than girls with DBDs, and similar in TD boys and girls. There is a paucity of research on girls with DBDs, although existing studies identify few sex differences in developmental trajectories.[261] While CU traits are lower in girls with DBDs they have similar correlates.[262] However, some characteristics that could be associated with TBIs have been reported to be elevated in boys such as risky decision making,[263] impulsivity,[264] and risky behaviors leading to premature death.[17] Among children with DBDs, those without TBIs showed sex-specific alterations in WMM relative to sex-matched TD children. Within the DBD group, those who had sustained TBIs showed sex-specific differences in WMM relative to the non-injured. Disentangling alterations of WMM associated with TBIs from those associated with DBDs, CU, and ADHD provides information useful to the treatment of each comorbid condition and will further understanding of the etiology of these common childhood disorders that often have negative life-long consequences.

Children who had not sustained a TBI

In the present study, among children who had not sustained TBIs, alterations of WMM were observed among those with DBDs relative to those TD. All alterations were sex-specific and related to ADHD, CU or both. Among boys without TBIs, those with DBDs relative to the TD group showed differences in the left CST and the genu of the CC. Previous

studies that did not exclude participants who had sustained TBIs, identified differences in the CST and the CC genu among those with DBDs comorbid with ADHD relative to those with DBDs alone and higher fractional anisotropy and lower mean/radial diffusivity among boys with conduct disorder and CU, but not among those with conduct disorder alone [245]. Further, a systematic review and meta-analysis reported that children/adolescents with ADHD showed alterations in the CST believed to be related to motor disinhibition or dysregulation of dopamine in downstream pathways.[265]

Among girls who had not experienced TBIs, those presenting DBDs displayed differences in the left and right IFOF, the right ILF, and the body of the CC. Only the difference in the CC was robust to adjustment for CU. These results are consistent with previous studies of females with current or past conduct disorder, that reported alterations in the CC and lower fractional anisotropy and axial diffusivity in the anterior/superior corona radiata, ILF and IFOF.[266]

Both girls and boys presenting with DBDs without TBIs showed differences relative to TD children in the CC, which has long been associated with antisocial behavior among adult males.[267] Alterations of the CC are believed to underlie problems in emotional regulation, motor coordination, motor planning, executive functions, and impulsivity.[268] Corpus callosum axial diffusivity has been shown to mediate the association between CU and impulsive responses to emotional faces.[106] In the present study, among girls who had not sustained TBIs, those with DBDs displayed differences in the right ILF and bilateral IFOF that connect the posterior temporal and occipital lobes, including visual and auditory association areas, to the prefrontal cortex,[269] and the ILF to the amygdala.[270] Alterations of these tracts are believed to be related to impairments in emotion processing[271] and goal-oriented behavior.[272] Among children/adolescents with DBDs, these regions show alterations of gray matter and functioning. A recent study of the ABCD sample reported that children

with DBDs with and without CU, compared to TD children, displayed smaller amygdala volumes bilaterally.[253] A European multi-center study of 118 children presenting DBDs and 89 healthy children found proactive aggression was related to increased functional coupling between the amygdala and precuneus, reactive aggression to amygdala-left lateral cortex hyperconnectivity, and callousness to right prefrontal cortex-right precentral gyrus hyperconnectivity.[273]

Children who had sustained at least one TBI

Among boys with prior TBIs, those with DBDs showed only one difference relative to TD boys that was in the left CST, as was the case for boys without prior TBIs. This difference did not survive adjustment for ADHD. This finding is consistent with a prior report of differences in WMM in the CST among male TBI patients with ADHD compared to healthy children.[265] Among girls with prior TBIs, those presenting DBDs displayed only one difference relative to TD girls that was in the right UF, robust to adjustment for all covariates. The UF has been previously associated with DBDs,[104,106,237] as it connects neural regions involved in behavioral control, such as the orbitofrontal cortex, with areas involved in threat perception, such as the amygdala.[274]

Children presenting DBDs or TD with and without a history of TBIs

We observed striking differences when examining WMM of children with and without TBIs within the DBD and TD groups. Among TD children, no significant differences were detected in any WMM bundles between those with and without prior TBIs. Given the variability in the consequences of TBIs, group comparisons may only detect shared abnormalities,[275] such that alterations in WMM may only be detected within a group displaying a common underlying structural abnormality. For example, in the Philadelphia Neurodevelopmental Cohort, children who had sustained a TBI, relative to healthy children,

displayed differences in deep white matter, but when compared to children who were matched for levels of psychopathology, no differences were detected.[276]

Development of WMM

The use of our multidimensional approach to measure WMM provided information regarding the nature of the abnormalities not available from previous studies. Across most DBD/TD comparisons (except right ILF in DBD girls without TBIs), axonal density scores were higher among children presenting DBDs, suggesting accelerated development of WMM. This hypothesis is consistent with a recent study reporting increases in apparent fiber density across development among healthy children.[107] In these same comparisons, other bundles consistently displayed lower absolute diffusivity in the DBD group. If WMM development is accelerated among children with DBDs, lower absolute diffusivity may reflect other processes, such as the increased presence of neurofibrils, microglia, and myelin from oligodendrocytes,[277] perhaps to support the higher number of axons. Longitudinal studies of healthy children have shown concurrent decreases in axial and radial diffusivity across development.[91] The observation of these concurrent microstructural processes, occasionally present simultaneously in the same bundle (for example boys' CC genu, Table 3), reveals a particular strength of the measures of WMM used in the present study. The principal components analyses yielded three orthogonal (independent) components of WMM, a distinct advantage over the highly-correlated tensor-based measures. Unlike the findings from comparisons of DBD and TD groups, within the DBD group, absolute diffusivity scores were higher among children who had sustained TBIs relative to the non-injured. This finding may reflect injury-related loss of myelin and other supporting structures, although this conclusion requires histological validation. Among boys with DBDs, those with TBIs displayed higher axonal density scores than those without. This result is surprising, and runs counter to prior research.[124] However, this effect was lost when adjusting for pubertal stage

and IQ, suggesting possibly that differences in WMM maturation may be partly responsible, even if pubertal stage and IQ were similar in the two groups.

Ethnicity and family income

Ethnicity differed little in DBD and TD boys and girls, with and without TBIs. In comparisons of WMM, ethnicity modified the significance of only one result. Among girls who had not experienced TBIs, the difference between the DBD and TD groups in the right ILF did not survive adjustment for ethnicity. The TD boys and girls came from families reporting slightly higher income than the DBD children. Family income played no role in comparisons of DBD and TD children who did not sustain TBIs. By contrast, in comparisons of DBD children who had sustained TBIs to both TD children with TBIs and to DBD children without TBIs, several differences lost significance when models were adjusted for family income. Low family income may index a number of factors that directly or indirectly impact the child's neural development, such as harsh parenting, neglect, and monitoring of child behavior.

Clinical implications

Children at risk for TBIs include those presenting conduct problems and/or inattention-hyperactivity, some of whom engage in aggressive behavior, those who have experienced a prior TBI, and those experiencing maltreatment and/or neglect and/or age-inappropriate parental monitoring. Nurse visitation programs in the years following birth could be modified to include assessments of toddlers' impulsivity, risk taking, obedience, and aggressive behavior and parents' harsh and inappropriate punishment, neglect, and age-appropriate monitoring of the child's behavior. These same child and parent characteristics could be assessed by pre-school staff and elementary school teachers. Ideally, interventions could be provided to children and/or parents presenting characteristics that elevate the risk of

TBIs. Adding components to treatment programs for conduct problems and ADHD that focus on impulsivity and risk taking has the potential to prevent TBIs. Effectively eliminating maltreatment and neglect would also prevent TBIs. The effectiveness of treatments for childhood TBIs would be improved by taking account of the child's and the family's pre-injury characteristics and by implementing strategies to prevent further TBIs. Consistent with the current findings, previous research has found that after taking account of either inattention-hyperactivity or conduct problems, children who sustained a TBI by age 10, were three times more likely than children who had not sustained a TBI to experience at least one more TBI before age 18 years.[247]

Limitations and strengths

Limitations include the low number of children in the sample who had sustained TBIs. Even among those with DBDs, the prevalence was lower than that of 12% in the general population.[173] The number of TD participants who had sustained a TBI was particularly low. In the within sex comparisons of DBD and TD groups with a history of TBIs, this low number of TBI cases could have led to issues with homogeneity of variance due to unequal sample sizes. Further, in these comparisons, effect sizes, as measured by the Generalized η^2 statistic were found to be larger than in other analyses. This statistic is believed to overestimate the true effect size, and this bias decreases with increasing sample size.[278] Hence, it is possible that the differences in effect size observed in this set of analyses appeared larger as a consequence of their smaller sample size. TBIs were reported by parents, and information about the number of TBIs sustained by participants and ages when the injuries occurred was not available. The commitment of parents and children required by the ABCD Study is considerable, perhaps discouraging families whose children have sustained more severe head injuries from participating. Another limitation was the lack of information

on maltreatment that is more common among children with than without DBDs[109] and a cause of TBIs especially in young children.[279]

Strengths of the study include the relatively large sample, especially of females who presented DBDs. Another strength was the age of participants that probably precluded substance use. The study employed novel modelling, tractography, tractometry, and statistical approaches to measure WMM that are robust to the limitations of more conventional analyses and that extract more exhaustive information, thereby minimizing biases present in more conventional approaches. Utilizing tractography robust to partial volume effects and a highly reproducible automatic bundle clustering algorithm increases the accuracy of bundle reconstructions and hence the localization of the reported effects. The use of a modelling technique robust to crossing fibers and a data recombination approach to create more biologically-interpretable measures of WMM allowed us to make more fine-grained interpretations of the obtained effects.

7.5. Conclusion

Children with DBDs are at increased risk relative to healthy children to sustain TBIs. Those who have not sustained TBIs show sex-specific alterations of WMM relative to TD children, while those who have sustained such injuries show additional sex-specific alterations. Furthering understanding of the etiology and improving treatment of DBDs will require disentangling alterations of WMM that are specific to girls and boys, with and without CU, ADHD, and TBIs. Additionally, it is critical to determine the temporal associations of DBD onset and persistence with TBIs. Assessing pre-injury characteristics of children who have sustained TBIs could contribute to personalizing treatment.

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USING AN AUTOENCODER (Patent Application No.: 17/337,413). No other authors have any financial or other conflicts of interest.

Table 1. Comparisons of boys presenting Disruptive Behavior Disorders and their typically developing peers with and without traumatic brain injuries

	DBD (n=400)		TD (n=349)		Statistics			
	TBI (n=31)	No TBI (n=369)	TBI (n=9)	No TBI (n=340)	DBD/TBI- vs DBD/TBI+	TD/TBI- vs TD/TBI+	DBD/TBI- vs TD/TBI-	DBD/TBI+ vs TD/TBI+
					χ^2, p			
Pubertal Stage[1]								
1	20 (66.7%)	241 (66.6%)	6 (66.7%)	224 (68.9%)				
2	8 (26.7%)	96 (26.5%)	2 (22.2%)	79 (24.3%)	0.003, 1.000	0.262, 1.000	0.473, 0.778	0.231, 1.000
3+	2 (6.6%)	25 (6.9%)	1 (11.1%)	22 (6.8%)				
Race/Ethnicity								
Hispanic	5 (16.1%)	43 (11.7%)	3 (33.3%)	71 (20.9%)				
Non-Hispanic Black	3 (9.7%)	60 (16.3%)	0 (0%)	52 (15.3%)	1.293, 0.755	3.520, 0.311	11.893, **0.007**	3.097, 0.375
Non-Hispanic White	19 (61.3%)	222 (60.2%)	6 (66.7%)	175 (51.5%)				
Other/Multi-racial	4 (12.9%)	44 (11.9%)	0 (0%)	42 (12.3%)				
Combined Household Income[2]								
<$50,000	10 (36%)	102 (30.4%)	0 (0%)	75 (24.2%)				
$50,000-$100,000	9 (32%)	96 (28.6%)	0 (0%)	76 (24.5%)	0.866, 0.684	7.420, **0.026**	6.894, 0.**036**	11.496, **0.003**
≥$100,000	9 (32%)	138 (41.0%)	8 (100%)	159 (51.3%)				
Highest Parent Education								
Some college or less	4 (12.9%)	41 (11.1%)	2 (22.2%)	46 (13.5%)				
Associate degree	3 (9.7%)	57 (15.4%)	0 (0%)	49 (14.4%)	0.778, 0.755	1.819, 0.349	1.017, 0.592	1.275, 0.549
Bachelor's and above	24 (77.4%)	271 (73.5%)	7 (77.8%)	245 (72.1%)				
Parent Marital Status[3]								
Married/Living With Partner n (%)	19 (61%)	248 (68.5%)	8 (88.9%)	260 (77.8%)	0.683, 0.423	0.626, 0.679	7.680, 0.**009**	2.422, 0.237

Parent Substance Use[4] ≥1 parent with substance use n (%)	12 (40%)	104 (29.1%)	1 (11.1%)	28 (8.4%)	1.557, 0.223	0.086, 1	48.314, **<0.001**	2.600, 0.214
					t, df, p			
Conduct Problems	62.7 (8.58)	60.0 (8.87)	50 (0)	50 (0)	-1.705, 35.607, 0.097	-	21.657, 368, **<0.001**	8.270, 30, **<0.001**
Oppositional Defiant Problems	64.0 (9.39)	61.1 (8.16)	50 (0)	50 (0)	-1.701, 33.911, 0.098	-	26.076, 368, **<0.001**	8.318, 30, **<0.001**
NIH Total Cognition Fully-Corrected T-score	44.6 (10.1)	47.2 (11.3)	55.9 (13.0)	50.2 (11.9)	1.354, 35.673, 0.184	-1.307, 8.407, 0.226	-3.232, 623.55, **0.001**	-2.409, 11.086, **0.035**
CU MAP	1.02 (1.17)	0.887 (1.15)	-0.207 (0.07)	-0.214 (0.07)	-0.630, 35.054, 0.533	-0.283, 8.377, 0.784	18.303, 370.74, **<0.001**	5.811, 30.765, **<0.001**
ADHD Score	65.1 (9.23)	58.7 (8.22)	50 (0)	50 (0)	-3.734, 34.116, **<0.001**	-	20.352, 368, **<0.001**	9.109, 30, **<0.001**
Mean Age (sd)	9.95 (0.64)	9.94 (0.61)	10.35 (0.63)	9.95 (0.63)	-0.102, 34.691, 0.919	-1.899, 8.425, 0.092	-0.253, 698.34, 0.800	-1.685, 13.228, 0.115

[1]1 boy in the disruptive behavior disorder (DBD) group with traumatic brain injury (TBI), 7 boys in the DBD group without a TBI, and 15 boys in TD group without TBI had missing pubertal stage data. [2]3 boys presenting DBD with a TBI, 33 boys presenting DBD without a TBI, 1 TD boy with a TBI, and 30 TD boys without a TBI had missing combined household income data. [3]Parents of 7 DBD boys without a TBI and 6 TD boys without a TBI had missing marital status data. [4]Parents from 1 DBD boy with TBI, 12 DBD boys without TBI, and 5 TD boys without a TBI had missing data on substance use problems. DBD: disruptive behavior disorders; TBI: traumatic brain injury; CU: callous-unemotional traits; ADHD: attention deficit disorder; NIH: National Institutes of Health.

Table 2. Comparisons of girls presenting Disruptive Behavior Disorders and their typically developing peers with and without traumatic brain injuries

	DBD (n=269)		TD (n=482)		Statistics			
	TBI (n=13)	No TBI (n=256)	TBI (n=10)	No TBI (n=472)	DBD/TBI- vs DBD/TBI+	TD/TBI- vs TD/TBI+	DBD/TBI- vs TD/TBI-	DBD/TBI+ vs TD/TBI+
					χ^2, p			
Pubertal Stage[1]								
1	3 (25%)	72 (29.3%)	3 (30%)	154 (33.6%)				
2	1 (8.3%)	50 (20.3%)	1 (10%)	118 (25.8%)	1.500, 0.513	1.892, 0.401	6.417, **0.043**	0.105, 1.000
3+	8 (66.7%)	124 (50.4%)	6 (60%)	186 (40.6%)				
Race/Ethnicity[2]								
Hispanic	3 (23.1%)	36 (14.1%)	0 (0%)	95 (20.2%)				
Non-Hispanic Black	1 (7.7%)	30 (11.7%)	1 (10%)	67 (14.2%)	1.123, 0.788	3.386, 0.374	6.022, 0.104	2.654, 0.555
Non-Hispanic White	8 (61.5%)	157 (61.3%)	8 (80%)	254 (53.9%)				
Other/Multi-racial	1 (7.7%)	33 (12.9%)	1 (10%)	55 (11.7%)				
Combined Household Income[3]								
<$50,000	5 (45.4%)	73 (31.1%)	1 (10%)	93 (21.5%)				
$50,000-$100,000	3 (27.3%)	59 (25.1%)	0 (0%)	122 (28.2%)	1.374, 0.508	6.458, **0.026**	7.413, **0.029**	8.639, 0.010
≥$100,000	3 (27.3%)	103 (43.8%)	9 (90%)	217 (50.3%)				
Highest Parent Education								
Some college or less	0 (0%)	29 (11.3%)	0 (0%)	52 (11%)				
Associate degree	5 (38.5%)	35 (13.7%)	0 (0%)	60 (12.7%)	6.887, **0.036**	3.091, 0.227	0.167, 0.921	4.915, 0.053
Bachelor's and above	8 (61.5%)	192 (75%)	10 (100%)	360 (76.3%)				
Parent Marital Status[4]								
Married/Living With Partner[5] n (%)	8 (61.5%)	173 (67.6%)	9 (90%)	369 (78.8%)	0.205, 0.775	0.736, 0.496	11.165, **0.002**	2.375, 0.164

Parent Substance Use[5] ≥1 parent with substance use n (%)	6 (46.2%)	80 (32.1%)	1 (10%)	54 (11.8%)	1.102, 0.374	0.031, 1	43.245, **<0.001**	3.490, 0.088
					t, df, p			
Conduct Problems	64.1 (8.89)	58.2 (8.44)	50 (0)	50 (0)	-2.338, 13.121, **0.036**	-	15.509, 255, **<0.001**	5.708, 12, **<0.001**
Oppositional Defiant Problems	64.8 (8.58)	59.8 (7.52)	50 (0)	50 (0)	-2.096, 12.952, 0.056	-	20.780, 255, **<0.001**	6.238, 12, **<0.001**
NIH Total Cognition Fully-Corrected T-score	46.8 (12.2)	47.7 (11.4)	49.6 (8.43)	50.4 (10.9)	0.240, 13.212, 0.814	-0.293, 8.580, 0.776	-2.940, 449.34, **0.003**	-0.615, 19.997, 0.546
CU MAP	0.174 (1.04)	0.360 (1.19)	-0.485 (0.04)	-0.515 (0.07)	0.627, 13.648, 0.541	-2.317, 10.021, **0.043**	11.759, 255.85, **<0.001**	2.280, 12.048, **0.042**
ADHD Score	62.8 (8.21)	56.9 (7.46)	50 (0)	50 (0)	-2.549, 13.025, **0.024**	-	14.835, 255, **<0.001**	5.639, 12, **<0.001**
Mean Age (sd)	10.11 (0.64)	9.89 (0.63)	10.40 (0.62)	10.00 (0.60)	-1.206, 13.233, 0.249	-2.053, 9.359, 0.070	-2.177, 496.57, **0.030**	-1.106, 19.812, 0.282

[1]1 girl with disruptive behavior disorder (DBD) with a traumatic brain injury (TBI), 10 DBD girls without TBIs, and 14 TD without TBIs had missing pubertal stage data. [2]1 TD girl without a TBI had missing race/ethnicity data. [3]Parents of 2 DBD girls with a TBI, 21 DBD girls without a TBI, and 40 TD girls without a TBI had missing combined household income data. [4]Parents of 4 TD girls without TBIs had missing marital status data. [5]Parents from 7 DBD girls without a TBI and 15 TD girls without a TBI had missing data on substance use problems. DBD: disruptive behavior disorders; TBI: traumatic brain injury; CU: callous-unemotional traits; ADHD: attention deficit disorder.

Table 3. Among children who have not experienced a traumatic brain injury, comparisons of white matter microstructure between boys and girls with Disruptive Behavior Disorders and typically developing boys and girls, with adjustment for callous-unemotional traits, Attention Deficit Hyperactivity Disorder, IQ, age, pubertal stage, ethnicity, and family income

Boys (n = 709)									
	Multivariate model *p* values								
Bundle	Non-adjusted	Adjusted for							Differences in components
	p values (η^2)	CU MAP	ADHD	IQ	Age	Pubertal Stage	Ethnicity	Family Income	
Left									
UF	0.3346								
IFOF	0.9611								
CG	0.9893								
ILF	0.8612								
CST	**0.0366** (0.01)	0.2511	0.1532	0.0813	**0.0354**	0.0764	**0.0211**	**0.0373**	None
Right									
UF	0.5173								
IFOF	0.9762								
CG	0.9219								
ILF	0.6080								
CST	0.2058								
CC									
Genu	**0.0077** (0.02)	0.3117	0.0880	**0.0293**	**0.0080**	**0.0097**	**0.0051**	**0.0074**	Absolute diffusivity: TD>DBD Axonal density: TD<DBD
Body	0.5306								
Splenium	0.9581								
Girls (n = 728)									
Left									
UF	0.0585								
IFOF	**0.0257** (0.01)	0.1329	**0.0277**	**0.0388**	**0.0271**	**0.0275**	**0.0284**	**0.0480**	Axonal density: TD<DBD
CG	0.6011								
ILF	0.7111								
CST	0.7171								
Right									
UF	0.1683								

IFOF	**0.0118** (0.02)	0.2511	0.2249	**0.0173**	**0.0115**	**0.0084**	**0.0160**	**0.0133**	Axonal density: TD<DBD
CG	0.3848								
ILF	**0.0428** (0.01)	0.1644	0.2937	0.1566	**0.0306**	0.0882	0.0572	**0.0101**	Axonal density: TD>DBD
CST	0.6183								
CC									
Genu	0.0560								
Body	**0.0214** (0.01)	**0.0156**	0.1504	0.0651	**0.0249**	**0.0304**	**0.0120**	0.0535	Absolute diffusivity: TD>DBD
Splenium	0.2957								

TD: typically developing; DBD: Disruptive Behavior Disorders; UF: Uncinate Fasciculus; IFOF: Inferior Fronto-Occipital Fasciculus; CG: Cingulum; ILF: Inferior Longitudinal Fasciculus; CST: Corticospinal Tract; CC: Corpus Callosum; CU MAP: Callous Unemotional *mean a posteriori* scores; ADHD: Attention Deficit/Hyperactivity Disorder. η^2: Generalized eta squared.

Table 4. Among children who have experienced a traumatic brain injury, comparisons of white matter microstructure between boys and girls with Disruptive Behavior Disorders and typically developing boys and girls, with adjustment for callous-unemotional traits, Attention Deficit Hyperactivity Disorder, IQ, age, pubertal stage, ethnicity, and family income

Boys (n = 40)									
		Multivariate model *p* values							
Bundle	Non-adjusted	Adjusted for							Differences in components
	p values (η^2)	CU MAP	ADHD	IQ	Age	Pubertal Stage	Ethnicity	Family Income	
Left									
UF	0.3374								
IFOF	0.1219								
CG	0.2818								
ILF	0.0910								
CST	**0.0263** (0.22)	**0.0185**	0.1104	**0.0313**	0.0568	**0.0397**	**0.0275**	0.0863	None
Right									
UF	0.7966								
IFOF	0.6124								
CG	0.5597								
ILF	0.7011								
CST	0.2385								
CC									
Genu	0.6557								
Body	0.3704								
Splenium	0.1050								
Girls (n = 23)									
Left									
UF	0.5464								
IFOF	0.4380								
CG	0.9113								
ILF	0.8297								
CST	0.4828								
Right									
UF	**0.0251** (0.38)	**0.0058**	**0.0111**	**0.0375**	**0.0375**	**0.0048**	**0.0352**	0.1657	Axonal density: TD<DBD
IFOF	0.0963								
CG	0.3728								
ILF	0.3205								
CST	0.5709								
CC									
Genu	0.3739								

Body	0.4913
Splenium	0.6331

TD: typically developing; DBD: Disruptive Behavior Disorders; UF: Uncinate Fasciculus; IFOF: Inferior Fronto-Occipital Fasciculus; CG: Cingulum; ILF: Inferior Longitudinal Fasciculus; CST: Corticospinal Tract; CC: Corpus Callosum; CU MAP: Callous Unemotional *mean a posteriori* scores; ADHD: Attention Deficit/Hyperactivity Disorder. η^2: Generalized eta squared.

Table 5. Among boys and girls presenting Disruptive Behavior Disorders, comparisons of white matter microstructure between those who had and had not sustained a traumatic brain injury, with adjustment for callous-unemotional traits, Attention Deficit Hyperactivity Disorder, IQ, age, and pubertal stage, ethnicity, and family income

Boys (n = 400)									
		Multivariate model *p* values							
Bundle	Non-adjusted	Adjusted for							Differences in components
	p values (η^2)	CU MAP	ADHD	IQ	Age	Pubertal Stage	Ethnicity	Family Income	
Left									
UF	0.4662								
IFOF	0.8035								
CG	0.7851								
ILF	0.2472								
CST	**0.0392** (0.02)	**0.0349**	**0.0236**	0.1085	**0.0390**	0.0813	**0.0394**	**0.0231**	Axonal density: TBI+>TBI-
Right									
UF	0.6261								
IFOF	0.5252								
CG	0.5661								
ILF	**0.0241** (0.02)	**0.0262**	0.0656	**0.0240**	**0.0230**	**0.0174**	**0.0244**	0.2794	Absolute diffusivity: TBI+>TBI-
CST	0.9050								
CC									
Genu	0.9735								
Body	0.3543								
Splenium	0.6314								
Girls (n = 269)									
Left									
UF	0.9623								
IFOF	0.6460								
CG	0.9446								
ILF	0.8010								
CST	0.5054								
Right									
UF	0.3650								
IFOF	0.4694								
CG	0.8951								
ILF	0.4452								
CST	0.6829								
CC									

Genu	**0.0369** (0.03)	**0.0358**	**0.0249**	**0.0483**	**0.0436**	**0.0052**	**0.0363**	0.2069	Absolute diffusivity: TBI+>TBI-
Body	0.3849								
Splenium	0.7792								

TD: typically developing; DBD: Disruptive Behavior Disorders; UF: Uncinate Fasciculus; IFOF: Inferior Fronto-Occipital Fasciculus; CG: Cingulum; ILF: Inferior Longitudinal Fasciculus; CST: Corticospinal Tract; CC: Corpus Callosum; CU MAP: Callous Unemotional *mean a posteriori* scores; ADHD: Attention Deficit/Hyperactivity Disorder. η^2: Generalized eta squared.

Figure 1. Flow chart of participant selection.

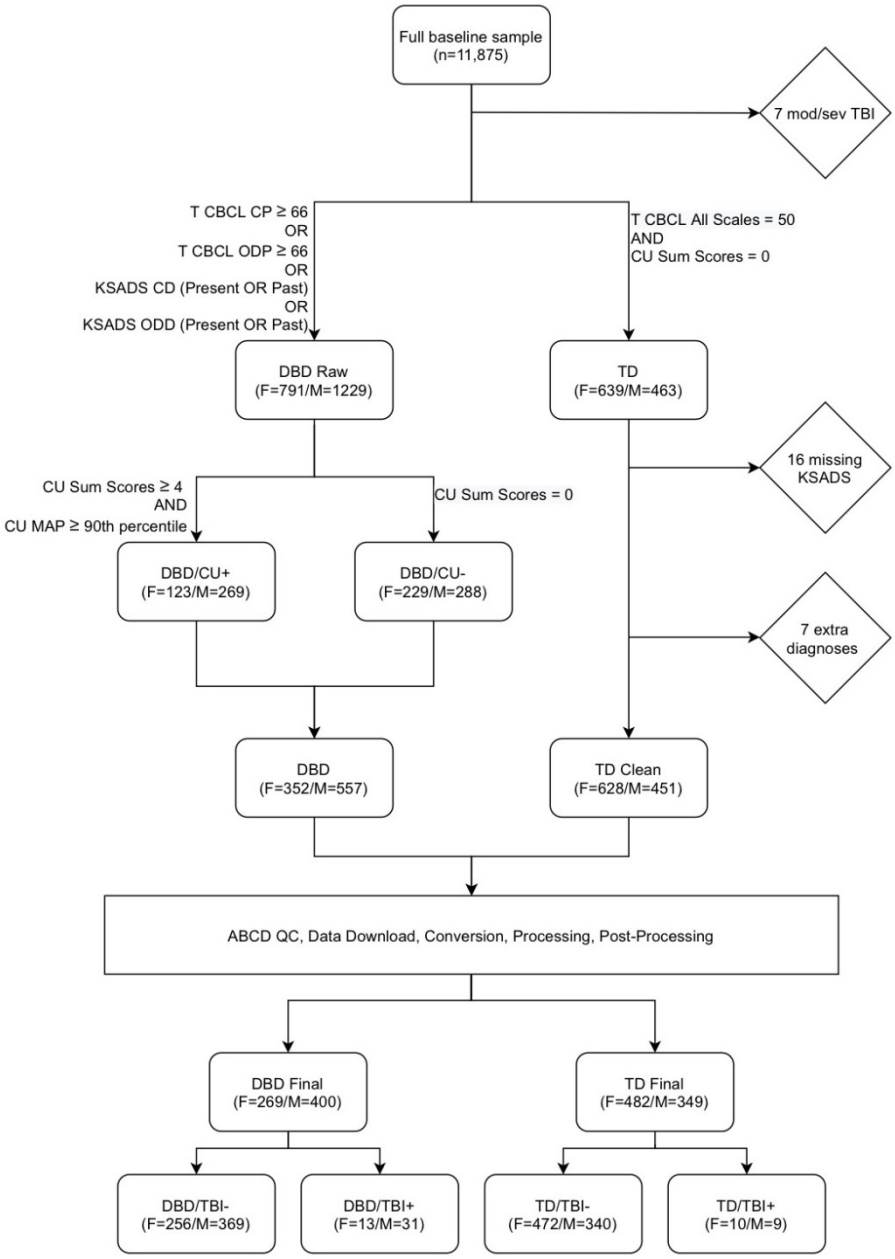

Figure 1. Flowchart describing participant selection. From the full baseline sample (n=11,875), a disruptive behavior disorders ("DBD raw") and a typically developing ("TD") group were created. The disruptive behavior disorder (DBD) group was defined as Child Behavior Checklist T-scores of 66 or higher on either the conduct problems or oppositional defiant problems scales or a diagnosis of present or past Conduct Disorder or Oppositional Defiant Disorder on the Schedule for Affective Disorders and Schizophrenia for school-age children (KSADS). The typically developing (TD) group was defined as individuals with no DBDs and no callous-

unemotional traits (CU), and T scores of 50 on all Child Behavior Checklist scales. From the TD group, we excluded 16 participants who had missing diagnostic data, and 7 who had other diagnoses. We identified participants without CU, defined as CU sum scores of 0, and participants with high CU, defined as CU sum scores of 4 or more and a *maximum a posteriori* (MAP) CU scale score scores at or above the 90th percentile. These two groups were combined to create a DBD group with approximately half of the members with high CU, and half with no CU. Scans underwent pre-processing, processing, and post-processing, leading to the exclusion of 240 DBD participants and 248 TD participants due to missing or corrupt data files, poor image quality, and failures during image processing and post-processing. The final groups of DBD and TD participants were then divided according to history of traumatic brain injury (TBI).

Figure 2. Illustration of results from principal components analysis.

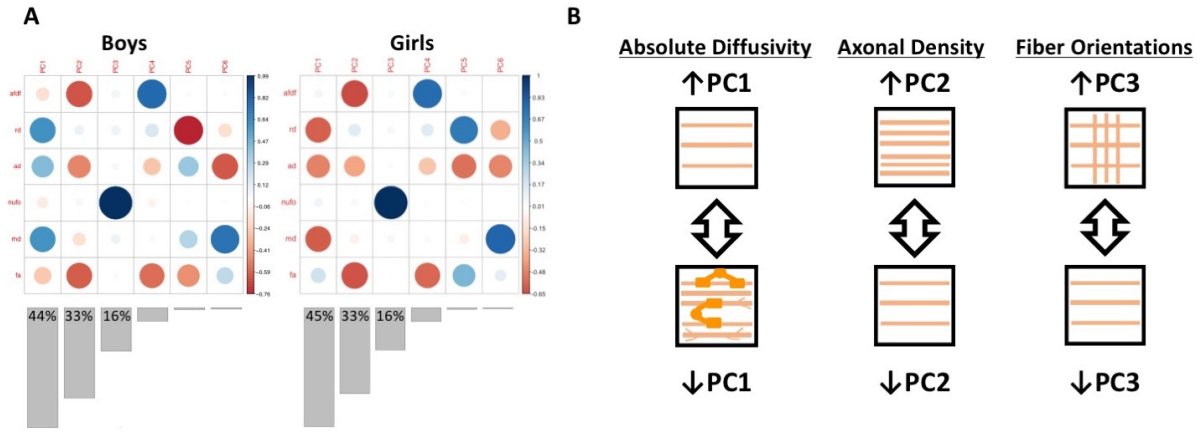

Figure 2. Illustration of the results from the Principal Components Analyses. Panel A. Plot illustrating the loadings of each diffusion measure onto each principal component (PC). Red colors represent negative loadings, blue colors represent positive loadings. The size of the circles also the magnitude of the loadings. Bar graphs underneath illustrate the variance explained by each PC, with the variance explained by the first three PCs indicated numerically on the graphs. Panel B. Schematic illustration of the interpretation of the first three PCs. PC1 appears to capture measures of absolute diffusivity. The loadings in girls were multiplied by -1 to ensure consistency with the boys' loadings. PC2 appears to capture measures related to axonal density. PC3 appears to capture selectively the number of fiber orientations. AFDf: Apparent Fiber Density along fixels; RD: Radial diffusivity; AD: Axial diffusivity; NuFO: Number of fiber orientations; MD: Mean diffusivity; FA: Fractional Anisotropy.

“Science never solves a problem without creating ten more”

– George Bernard Shaw

Chapter 8. Overall Discussion

8.1. The link between childhood externalizing problems, TBIs, and violent crime

The results of the three studies presented herein shed light on the relationship between childhood externalizing problems, TBIs, and violent crime. The first study demonstrated that controlling for childhood externalizing problems accounted, in part, for the relationship between TBIs and violent crime. This result contradicts the view held by some in the field that purports that TBIs can cause previously non-aggressive individuals to become aggressive, potentially criminal. However, this study, others that preceded[14,47,54,60,62,63,71] and others that followed it,[280,281] raised another question: if not causal, what is the relationship between TBIs and violent crime?

The second study of this thesis showed that inattention-hyperactivity and externalizing problems at age 10 predicted TBIs in adolescence and adulthood after controlling for prior TBIs and family social status to age 34. Thus, TBIs and violent crime may be linked because they are both associated with a common risk factor, childhood externalizing problems. However, this study did not address the temporal relationship of inattention-hyperactivity and externalizing problems with TBIs that were sustained before age 11.

TBIs are known to impact the brain's white matter. Inattention-hyperactivity and externalizing problems are associated with abnormal neural development, and specifically with alterations of white matter microstructure. Therefore, the third study in this thesis determined whether TBIs were associated with alterations of white matter microstructure that differ among children presenting externalizing problems as compared to those who are typically developing. We found sex-specific differences in white matter structure in children with disruptive behaviour

disorders*, compared to typically developing children, and these alterations differed depending on whether or not children had sustained prior TBIs. These relationships were associated with symptoms of ADHD, and callousness.

At the level of the brain, TBIs and externalizing problems have a complex relationship that our third study has only started to characterize. To fully understand the implications of the present findings, additional questions need to be explored. How could childhood externalizing problems increase the risk of TBIs? Could treatments for externalizing problems reduce the risk of TBIs? How exactly may TBIs and DBDs be compounded at the level of the brain? What other factors still need to be accounted for when studying the relationship between externalizing problems, TBIs, and violent crimes? What are the methodological considerations of the present work? And finally, what do these studies say about TBIs in general? Exploring these questions will outline potential future directions of research.

8.2. How could childhood externalizing problems increase the risk of TBIs?

Evidence suggests that childhood externalizing problems along with their associated environmental factors, may predispose children to sustain injuries in two ways: through maltreatment in early ages, and through engaging in risky behaviours. Conduct disorder, a diagnosis often received by children presenting lifelong externalizing problems, are moderately to highly heritable.[65,66] Unsurprisingly, children presenting conduct problems often have parents who themselves present antisocial behaviour and substance misuse. These parents provide chaotic family environments and are three-times more likely than other parents to physically maltreat their children.[111,112] Parent antisocial behaviour has been associated with injuries in their

* In Study 1 and 2, externalizing problems included inattention-hyperactivity, whereas in Study 3, DBDs included all externalizing problems except inattention-hyperactivity, which was measured as ADHD.

children. Boys whose mothers had presented aggressive behaviour in childhood were more likely than peers without aggressive mothers to suffer injuries requiring hospitalization.[282] Parental alcohol misuse and depression have also been linked to increased risk of TBIs in their children.[283] Abusive trauma is a major cause of serious head injury in infants and young children,[279] with an estimated mortality rate in clinical samples between 13% to 35%.[284] In children younger than age two, maltreatment is the most common cause of head injury.[284] Compared to healthy children, those presenting conduct problems are more often victims of maltreatment.[109,110] A prospective longitudinal study of a cohort of twins concluded that early-onset conduct problems were most likely to emerge when children with genetic predispositions suffered maltreatment.[109] Further, children who will go on to display lifelong conduct problems present as early as age three years "difficult temperaments", defined as emotional lability, restlessness, short attention span, negativism, willful, rough behavior.[285] Prolonged unsoothable infant crying has been found to be a trigger for maltreatment causing infant head injuries.[286] Children with the most severe lifelong conduct problems also present CU traits as early as early as age two that are preceded by specific behavioural and temperamental features observable as early as age 6 months.[287,288] These callous traits in toddlers have also been shown to provoke harsh parenting.[288]

Another factor linking externalizing problems to TBIs may be through risk-taking behaviour. Impulsivity was found to be associated with reckless driving and driving under the influence,[168] childhood ADHD comorbid with conduct disorder predicted unsafe driving and injuries to age 38,[169] and accidents and head injuries to age 41.[170] Childhood externalizing problems predicted accidents in adolescence[171] and unintentional injuries to age 32.[68] Motor vehicle accidents account for 17% of all TBIs.[172] In children with TBIs, ADHD has been

reported to be the most common pre-injury psychiatric condition.[289] Further, a recent study found that adverse childhood events – parent divorce, parent death, parent incarceration, domestic violence, neighborhood violence, family mental illness, family substance use, discrimination, financial hardship – was associated with higher risk of TBIs. This association was attenuated when accounting for ADHD and conduct problems, but only in children whose TBIs was not associated with sports.[232] Adverse childhood events are more common in children with ADHD[290,291] and conduct problems.[292] Risk-taking behaviour may also consist in finding oneself in rough environments where assaults may be more likely. In most retrospective studies of incarcerated individuals that found TBIs to be more common when compared to non-incarcerated controls, the most common cause of the injury was physical assault.[48,49]

Hence, children who display life-long patterns of externalizing problems constitute a particular group at risk for TBIs. These risks accumulate across the lifespan, starting with genetic factors present before their birth transmitted by parents presenting antisocial behaviour, growing up in chaotic family environments with harsh parenting and physical maltreatment, which may directly lead to TBIs, experiencing adverse childhood experiences, and developing into adolescents who engage in risky behaviours that put them at risk for motor vehicle accidents and physical assault.

8.3. Could treatments for externalizing problems reduce the risk of TBIs?

The results from Study 2 suggest that a composite measure of externalizing problems, as well as inattention-hyperactivity specifically, in childhood are associated with an increased risk of subsequent TBIs. Although the exact link between childhood externalizing problems and TBIs needs further study, it does raise the possibility that treatments for these externalizing problems could reduce the risk of future TBIs. Trials of parent-management programs demonstrate

effectiveness in reducing conduct problems,[293] including in children with conduct problems comorbid with callousness.[294,295] These programs are well-known and are considered best practice.[224] Research is needed to determine whether these parent-management training programs, known to reduce conduct problems, could prevent future TBIs in children.

ADHD is effectively treated with medication (typically methylphenidate) and cognitive-behavioural interventions.[223] A recent US study[230] reported that male and female children/adolescents with ADHD had decreased risk of motor vehicle accidents and TBI diagnoses during the months that they took medication compared to months spent off medication. Healthcare practitioners should inform their patients about their risks for TBIs and the importance of complying with ADHD medication.

8.4. How exactly may TBIs and DBDs be compounded at the level of the brain?

Study 3 suggested that DBDs were associated with white matter structure differences, compared to typically developing children, that differ depending on whether they have sustained prior TBIs, especially in girls. Put differently, TBIs and DBDs appear to be compounded at the level of the brain. To understand how this may potentially be the case, it is necessary to understand how particular brain structures may be susceptible to damage from TBIs.

One reason particular structures may be susceptible to damage from what could ostensibly be an infinite number of different potential mechanisms of injury is the biomechanical constraints imposed by the brain and surrounding structures.[296,297] For instance, the corpus callosum lies near the falx cerebri, a rigid outpouching of dura mater that has been shown in biomechanical models to reflect and redirect shearing waves transmitted through the brain during injury.[298,299] Previous studies have shown that biomechanical strain can concentrate in the corpus callosum.[296] However, other biomechanical modelling studies have shown that the strain

sustained by the corpus callosum is highly dependent on the direction of angular acceleration during an injury.[297] Hence, the unique position and orientation of different white matter tracts, as well as their surrounding milieu may lead them to be more susceptible to damage in the context of different injury mechanisms. Biomechanical factors are unlikely to explain the differences observed between the groups in Study 3 unless most individuals within a group had similar injury mechanisms. In the ABCD dataset, due to the way TBI data were acquired, individual injury mechanisms could not be associated with individual instances of TBIs.

Another way that white matter bundles may be differentially susceptible to damage from TBIs is through the metabolic demands of these different structures. Areas of the brain are interconnected, and information processing requires large amounts of metabolic energy.[300] It has been estimated on the basis of animal studies that neural metabolism is dominated by the sodium-potassium pump (Na+/K+ ATPase). Areas participating in more extensive information processing theoretically have higher energy demands. This finding has been demonstrated experimentally: regions of the brain considered to be hubs of information processing have been shown to have higher rates of cerebral blood flow, aerobic glycolysis, and oxidative glucose metabolism.[301-303] A meta-analysis of voxel-based morphometry studies showed that these "biologically-costly" regions of the brain are preferentially targeted by several neurological diseases, although TBI was not included among the studied conditions.[304] Likewise, more dense bundles are more energetically demanding, due to a higher number of axons requiring more Na+/K+ ATPases to maintain the resting electric potential, and due to the fact that myelin is energy consuming.[305] Hence, it stands to reason that more dense bundles may be more susceptible to the secondary damage that can result from TBIs.[32,33] In Study 3 we found higher axonal density in the genu of the corpus callosum in DBD boys without TBIs compared to TD

boys, and in the left and right IFOF in DBD girls without TBIs compared to TD girls. None of these bundles were implicated when comparing DBD girls and boys with TBIs against DBD children without TBIs. The one bundle that was consistently implicated in all comparisons was the left CST in boys. Although in comparisons of DBD boys without TBIs against TD boys, and DBD boys with TBIs against TD boys, no differences in the components of white matter were found, comparisons of DBD/TBI+ boys against DBD/TBI- boys revealed higher axonal density in this bundle.

Finally, both biomechanics and biological cost may together influence local white matter susceptibility to injury. A recent study used both finite element modelling and graph theory techniques to assess how both biomechanical and biological cost factors could predict concussion risk. The study reported that brain regions experiencing the highest deformations did not overlap with areas most important for network communication (i.e.: more biologically costly areas). However, both measures predicted with equivalent accuracy concussion incidence using leave-one-out cross validation methods.[306] Biomechanical constraints could explain primary damage (e.g.: primary axotomy), whereas metabolic demands could explain secondary damage (e.g.: secondary axotomy) (see section 2.2).

In Study 3, we found sex-specific differences in white matter structure alterations associated with DBDs and TBIs. Sex differences have been observed in rates of white matter maturation, which are associated with pubertal development. A recent study found that in females, and not males, increases in testosterone from early to mid-puberty were associated with increases in FA in the splenium and genu of the corpus callosum, bilateral cingulum, and bilateral CST.[307] A longitudinal study of 130 children aged 9-13 analyzed changes in AFD over time. A significant interaction between pubertal stage and age on change in AFD was detected:

for the left CST, IFOF, ILF, and UF, changes in pubertal stage score combined with older age resulted in larger increases in AFD.[107] In Study 3, among girls who had not sustained TBIs, a greater proportion of the DBD than the TD group had reached later stages of pubertal development while being younger in age, a finding that is consistent with prior literature.[308] The exact mechanism underlying sex differences in white matter maturation, especially in relation to sex hormones, is poorly understood.[309] Animal studies have shown that gonadal steroids stimulate neurogenesis and neurite outgrowth,[310] axonal myelination,[311] and growth of astrocyte processes in white matter.[312] As mentioned above, higher biological cost render white matter structures more susceptible to secondary damage from TBIs. Hormone-related differences in white matter structure development may additionally play a role in conferring sex-specific susceptibility to TBIs. How hormones factor into the relationship between DBDs and TBIs requires further research.

Hence, the processes by which white matter structure alterations resulting from TBIs can be compounded by DBDs remains unclear. Different factors leading to white matter susceptibility appear to only explain part of the results in Study 3. Future research needs to explore this question in more detail, using longitudinal studies to tease apart effects associated with DBDs present prior to the injury from those apparent afterwards.

8.5. What other factors still need to be accounted for?

The relationship between externalizing problems, TBIs, and violent crimes is complex. The evidence presented herein suggests that children who go on to display lifelong externalizing problems constitute a group at risk for both TBIs and violent crimes. This relationship involves factors present across the lifespan, including genes, pre-natal factors, family environment, parenting, schooling, and pubertal development. Although several efforts were taken to ensure

adequate control of most of these factors, important ones were not accounted for and require discussion. Two of those factors, maltreatment and risk taking, were discussed above (section 8.2).

A number of genes have been identified that increase the risk of conduct problems alone,[313] or in the presence of CU traits,[314-316] by interacting with environmental factors. A review of 27 studies found that parental maltreatment increased the risk of antisocial personality in males with the low-activity, relative to the high-activity, monoamine oxidase genotype. In females, this interaction between monoamine oxidase genotype and risk of antisocial behaviour was not found.[313] In another study, variations in the oxytocin receptor gene were associated with high levels of CU traits,[314] and with the odds of displaying high CU traits in individuals who had lived through stressful events. In addition, environmental factors can influence the functioning of genes through epigenetic processes.[317] These environmental factors have been shown to include parental stress prior to pregnancy, maternal stress and smoking during pregnancy, and adverse life events after birth.[318-320] Childhood maltreatment has been associated with epigenetic alterations in genes expressed in hippocampal neurons.[321] These studies suggest that genes play an important role in the risk of conduct problems and CU traits, and in the influence that environmental factors have on conduct problems and CU traits. What the role of genetic susceptibilities are in the relationship between externalizing problems and TBIs needs to be explored further. One recent study on a community sample from the Philadelphia Neurodevelopmental Cohort found that youths with TBI reported greater ADHD symptom severity compared to those without TBIs, and polygenic risk scores were positively associated with ADHD symptoms in youths without TBI but not in youths with TBI. Further, the relationship between ADHD symptoms and FA in the genu of the corpus callosum was negative

in youths with TBI and positive in youths without TBIs.[322] Longitudinal studies exploring a broader range of externalizing problems will be required to fully understand the role that genes play in this relationship.

One important characteristic of children presenting externalizing problems is impulsivity. Impulsivity is defined as "swift action without forethought or conscious judgment".[323] In a longitudinal study on a community sample of 595 males and females assessed at three time points, measures of impulsivity and sensation-seeking were predictive of later aggression and rule-breaking.[324] In a study on 132 inmates, 20% were found to have committed primarily impulsive aggressive acts and 23% primarily non-impulsive aggressive acts. These impulsive aggressive inmates had poorer verbal skills and showed alterations in differences in brain activity, measured by electroencephalography, compared to non-impulsive aggression inmates.[325] The presence of impulsive behaviour is also used to subcategorize children with ADHD. Children with the impulsive/hyperactive subtype, but not the inattentive subtype, was associated with a high rate of comorbidity with ODD and CD.[326] The relationship between CU traits and impulsivity is unclear. Future studies are needed to explore the specific role of impulsivity in sustaining TBIs. Children who display conduct problems comorbid with CU traits are known to obtain high scores for the interpersonal and impulsive dimensions of psychopathy,[327] suggesting that CU traits may be related to both impulsive and planned (i.e.: reactive and proactive) aggression. However, a longitudinal study on 334 boys found that a proactive aggression construct obtained from factor analysis at age 16 was characterized at age 7 by initiation of fights, strong-arm tactics, delinquency, poor school motivation, poor peer relationships, single-arent status, low family social class, poorly educated and unemployed fathers, substance-abusing parents, and hyperactivity, and at age 16 by psychopathic personality,

blunted affect, and serious violent offending. Instead, reactive aggression at age 16 was only characterized by impulsivity, hostility-aggression, social anxiety, lack of close friends, unusual perceptual experiences, odd speech, and ideas of reference.[328] Further, individuals who engage in proactive aggression regulate aggressive impulses to concentrate them into planned aggression.[329] A more recent study of 822 high school students from Spain found significant correlations between several different measures of impulsivity (gratification, automatism, attentional impulsivity, emotion-seeking, disinhibition, susceptibility to boredom) and physical and relational proactive and reactive aggression. Disinhibition was found to be the strongest predictor of physical and relational proactive and reactive aggression.[330] Hence, how impulsivity is related to aggression is still not fully understood. Given the relationship between impulsivity and risk-taking, and given that risk-taking may partly explain how inattention-hyperactivity is associated with increased risk of TBIs, future studies will need to explicitly account for measures of impulsivity when exploring the relationship between other externalizing problems and TBIs.

Substance abuse is a specific pattern of risk-taking behaviour. A study using the Christchurch Health and Development dataset, a longitudinal birth cohort, evaluated the association of TBI at ages 0-5, 6-15, and 16-21 years with drug and alcohol abuse and engagement in later criminality. Except for TBIs, all other measures relied on self-report. Participants with TBIs were divided into an inpatient and outpatient group. Adjusted for child and family factors, when compared to non-injured individuals, inpatients injured between ages 0 to 5 or 16 to 21 years were more likely to report symptoms of substance abuse. Although the inpatient group, across all ages of first TBI, had a higher risk of arrest, when models were adjusted for alcohol and drug dependence, TBIs was no longer associated with criminality in the 0 to 5 age group.[61] The authors of this study concluded that substance abuse may mediate the

relationship between early childhood TBIs and violent criminality. Similar to the literature on violent crime, the relationship between substance abuse and TBIs has been the subject of several studies which have found higher risk of substance abuse in individuals with TBIs. For instance, in a prospective longitudinal study of 4,645 soldiers deployed to Afghanistan that used self-report measures of TBI and past-month binge or heavy drinking at four different time points, soldiers who reported sustaining TBIs during their lifetime had higher risk of past-month binge drinking when tested three months post deployment.[331] Another study investigated a sample of individuals over the age of 20 randomly drawn from the Ohio Behavioral Risk Factor Surveillance System survey who self-reported a lifetime history of at least one TBI with loss of consciousness (n=2,935). Individuals whose first self-reported TBI with loss of consciousness occurred before age 20, compared to those who reported later-life TBIs, reported with greater likelihood binge drinking in the preceding month.[332] The results of these and similar studies, as well as some studies on animal models demonstrating higher alcohol and substance consumption after experimental injuries, has led some groups to conclude that TBIs can cause later substance abuse.[332-334]

Is it possible that TBIs lead to substance abuse which may increase the risk of subsequent criminality? Similar to the relationship between TBIs and violent crimes, this literature has several limitations in terms of methodology. The study on US soldiers mentioned above,[331] as well as the one on the Ohio sample,[332] could not establish the temporal relationship between TBIs and violent crimes. The Christchurch study mentioned above[61] did not account for pre-injury impulsivity and other predictors of substance abuse. As reviewed earlier in this thesis (see section 2.12), the evidence that TBIs may be associated with subsequent increases in conduct problems, which could be associated with other risk-taking behaviour, is poor. This literature

reflects the predominant trend in the field, present since the tale of Phineas Gage, of attempting to establish causal relationships between TBIs and personality changes. However, establishing causal relationships between TBIs and behavioural outcomes, some of which are only observed several years later, requires controlling for every single possible predictor of the behavioural outcome, and every single possible variable post-injury that is not biologically linked to the behaviour in question. Nonetheless, understanding the consequences of TBIs is vitally important. However, it is also important to remember that there are no effective pharmacotherapies for TBIs. Prevention remains the most important strategy to reduce TBI-associated morbidity and mortality.

While several studies have focused on the comorbidity of CD with other externalizing problems,[241,335] fewer have focused on the relationship between CD and internalizing problems. According to a meta-analysis, the co-occurrence between conduct problems and depression is between 8.5% and 45.5%,[336] although this number is higher in clinical samples,[337,338] including men with ASPD.[339] Longitudinal studies have shown that the co-occurrence between conduct problems and mood disorders is stable across the lifespan, and is associated with low academic achievement and social competence.[336,340,341] The relationship between conduct problems and anxiety remains poorly understood. Evidence is mixed: some studies show low levels of transition from CD to ASPD and better responses to treatment in the presence of comorbid anxiety disorders.[342-345] Other studies show instead elevated rates of delinquency in youths with CD and anxiety disorder,[339,346,347] and higher proportions of offenders with ASPD and anxiety disorders who had been convinced of serious crimes involving interpersonal violence.[339] It is believed that anxiety disorder may potentiate aggression in CD due to the heightened responsiveness to threat. A description of the relationship between threat perception and

aggressive behaviour can be found in the Background, section 2.13. One study found that a group of 23 women presenting CD and lifetime anxiety disorder and a group of 30 women presenting anxiety disorder alone, compared to a group of 17 with neither disorder, displayed lower FA in the UF. However, in the group with anxiety disorder only, FA of the UF was correlated with harm avoidance, whereas in the group with CD comorbid with anxiety disorder, FA of the UF was correlated with the interaction between poor anger control and anxiety symptoms.[234] These results support the idea that anxiety disorder comorbid with CD may be associated with an aggressive response to threatening stimuli. More research is needed to understand how anxiety disorder and other internalizing problems factor into the relationship between externalizing problems, TBIs, and violent crime.

Lastly, TBI outcomes are known to differ depending on injury severity.[348] The study presented in this thesis suggests that violent crimes are not outcomes of TBIs, and hence severity should not play a role in predicting post-TBI violent criminality. Instead, the present work suggests externalizing problems are predictors of both TBIs and violent crime. What still requires discussion is whether this relationship, between externalizing problems and TBIs, differs according to severity of the TBI. In other words, does the risk of TBIs associated with externalizing problems differ according to severity? Our Study 2 used official health records to find ICD-9 diagnoses of TBI. These injuries are arguably more serious in severity given that they required healthcare services, and given that up to one-third of mild TBIs, even with the increased education and awareness of today, still go undetected.[349] By contrast, Study 3 used data from the ABCD Study, which is likely to be biased towards milder TBIs for several reasons. One, only 7 participants in the ABCD study had sustained severe/moderate TBIs. Two, even in the DBD group, the prevalence of TBIs was lower than that of 12% previously reported in the general

population.[173] Three, a recent study investigated incidental MRI findings in children from the ABCD Study, and found none of the radiological abnormalities typically associated with complicated mTBIs,[350] such as contusions, small subarachnoid or intraparenchymal hemorrhages, subdural and epidural collections, edema, and skull fractures.[351] The ABCD study requires considerable effort on the part of parents and children thereby perhaps discouraging participation from families with children with worse outcomes after head injuries. Further, parents of children with DBDs are more likely than parents of TD children to present antisocial behavior and maltreat their children. Such parents would be unlikely to participate in the ABCD Study. Interestingly, despite this apparent bias towards milder, likely uncomplicated TBIs, the prevalence of TBIs was still higher in DBD boys and girls compared to typically developing children and even compared to all the other ABCD participants without DBDs. Together, these results suggest that externalizing problems are associated with TBIs across the spectrum of severity. However, repeating these analyses on samples especially designed to capture large numbers of TBIs across the severity spectrum would be required to confirm this idea.

8.6. Methodology Revisited

Critically appraising the literature requires understanding the advantages and disadvantages of each study's methodology. Although the methodology used in the relevant literature was discussed in the Background of this thesis (see section 2.5), it is necessary to discuss the advantages and disadvantages of the studies presented herein.

Studies 1 and 2 used a dataset with objective measures of TBIs and criminality, and teacher reports of disruptive behaviours observed in classroom settings. This dataset originated from two prospective longitudinal studies,[153,154] in which samples of six-year-old children were enriched with children who presented conduct problems or who lived in a deprived, inner city,

neighbourhood. Given that externalizing problems and criminality are more common among males, only this subset of the original sample was selected for these studies. Although this highly selected subsample allowed us to achieve greater statistical power by providing more individuals with persistent externalizing problems and criminality, this advantage came with the cost of lower generalizability. The longitudinal nature of our sample allowed us to understand the temporal relationship between externalizing problems, TBIs, and violent crime. However, in Study 2, we were unable to identify the temporal relationship between externalizing problems and TBIs prior to age 11. In other words, the results from Study 2 do not discount the possibility that TBIs prior to age 11 may have influenced the externalizing problems at age 10 that were associated with higher risks of TBIs from age 11 to 34. Further, the use of health files to document cases of brain injury may have underestimated the incidence of TBIs, since not all individuals who sustain TBIs seek medical care, and for the same reason may have been biased towards more severe cases of TBIs. Finally, studies 1 and 2 were observational cohort studies. The strength of such studies is in the capacity to control for a greater number of confounding factors than other types of studies. The models used in Studies 1 and 2 were multivariable regressions that controlled for all the predictors of criminality (Study 1) or TBIs (Study 2) that were available in the dataset. Nonetheless, many other confounders exist that were not controlled in our models (see section 8.5 for a discussion). Further, more sophisticated statistical models could have allowed us to probe further into the potential relationship between TBIs, externalizing problems, and violent crime. For instance, in Studies 1 and 2, although moderation effects were tested, mediation effects between TBIs and childhood externalizing problems were not. Despite having access to longitudinal data, we did not employ longitudinal models such as Cox proportional hazards models. This decision was deliberate, as Studies 1 and 2 were meant to

address a very specific literature that used equally simplistic models. However, future studies should consider employing more sophisticated models to probe more specific questions about TBIs, externalizing problems, and violent crime.

Study 3 used data from the ABCD Study. A particular strength of this dataset was the large sample size, which gave us the rare opportunity to study girls with DBDs, a typically understudied sample. The limitation of this dataset was the cross-sectional aspect, which prevented us from understanding the temporal relationships between DBDs and TBIs. Future waves of ABCD data collection will allow follow-up of those with and without DBDs. The ABCD Study sample was likely biased towards milder TBIs (see section 8.5). Despite this sampling issue with respect to TBI data, the finding of higher proportions of children with externalizing problems who sustained TBIs compared to typically developing children is consistent between Studies 2 and 3. Finally, as in Study 1 and 2, the choice in statistical models in Study 3 needs to be discussed. All models in Study 3 were performed within sex. These models revealed differences related to the presence of DBDs and TBIs that differed between boys and girls. In supplementary analyses, we explored the use of moderation analyses to further characterize sex differences (see Appendix: Supplementary material for Study 3). Certain group effects were consistent with the original results, and several sex differences in white matter microstructure were found when comparing boys and girls. However, no significant group-by-sex moderation effects were found. These models suggest that boys and girls, across groups defined by the presence of DBDs and TBIs, demonstrate differences in WMM, and that children with DBDs with and without TBIs also demonstrate WMM differences that are independent of sex. Within-sex models allowed us to demonstrate sex differences without statistically testing them, identifying future potential areas of research. Models that incorporate group-by-sex

interaction terms formally test sex differences, and control for the main effect of sex. These models are more complete than within-sex models, but also require higher statistical power. As the field advances further, refinements in statistical modelling will be necessary.

Part of the discrepancies observed in the dMRI literature on DBDs and TBIs may be related to differences in the diffusion measures used. Only two studies prior to ours used dMRI measures that are robust to the limitations of the diffusion tensor model.[352,353] These two studies did not use the same measures, but one of them found higher AFD in several white matter bundles, including the corpus callosum, that was correlated with aggression levels.[353] Further studies using the same methodology as ours are needed to assess whether this novel methodology will lead to more consistent effects. However, based on theory, our techniques allow us to make more reliable, fine-grained interpretations of the results. Studies reporting differences in tensor-based measures such as FA, MD, AD, and RD, cannot disentangle effects that may be due to different microstructural properties from the fact that these measures are so highly correlated they may be capturing the same underlying biological effect. Instead, Study 3 identified homogenous components of WMM that were orthogonal, and thus independent from each other, allowing us to posit different microstructural processes associated with each. Animal models have identified consistent relationships between histologically-defined axonal density and apparent fiber density.[116] Similar studies are needed to confirm the interpretations of the data recombination techniques used in Study 3.

Another important novelty in Study 3 was the use of advanced tractography and bundling techniques. The anatomically-constrained particle filtering tractography approach used in Study 3 is robust to partial volume effects and can therefore provide much more accurate bundle reconstructions.[354] However, recent work has shown that there are inherent problems with

tractography. At its core, tractography consists in growing streamlines iteratively using the local model contained at each voxel. Studies have shown that in voxels within some areas of the brain, the local model lacks sufficient information to inform on the correct trajectory of a streamline,[355,356] yielding more erroneous streamline pathways than correct ones. Now that tractography has become highly capable of reconstructing true positive streamlines, the challenge that it will face will be to reduce false positive ones.[357]

Across different conditions, such as Alzheimer's disease,[358] dyslexia,[359] multiple sclerosis,[360] and epilepsy,[361] novel dMRI techniques are gaining popularity. The measures used in Study 3 require validation in different samples, and using histological analyses. Further, dMRI alone does not hold all the answers. TBIs and externalizing problems are both associated with disruptions in brain structure, function, and metabolism. Incorporating other modalities, including up and coming MRI sequences that provide myelin-specific information,[362] will be critical to further understanding of the complex neurobiological interplay between DBDs and TBIs.

8.7. What do these studies say about TBIs in general?

TBIs have been studied using a variety of clinical and brain imaging techniques, such as task-based or resting state functional MRI, electroencephalography, positron emission tomography, magnetic resonance spectroscopy, dMRI, and neuropsychological tests. Other studies have employed several modalities simultaneously. Whatever the modality, the conventional approach to TBI neuroimaging research and clinical trials has historically consisted in using group-comparisons in the form of univariate linear models.[119,123] Other studies have used more sophisticated statistical techniques, including multivariate approaches to summarize brain structure, and machine learning models to classify patients from controls.[363-365] Whatever

the statistical approach, the vast majority of studies to date have been designed with the same goal in mind: compare concussed individuals and healthy controls.[30] This approach reflects the underlying belief, prevalent across most of the field, that "TBI" refers to a single disease with a unique "backbone" of injury. This basic assumption has driven the search for *a* biomarker, *a* therapy, or *a* cure for TBI for decades. Only recently has the tide begun to turn. Decades of failed clinical trials have forced the field to question pre-existing assumptions. In this introspection, the heterogeneity of TBIs has been identified as a key obstacle.[30,366] Patients who sustain TBIs are heterogeneous with respect to pre-injury factors, including genes, sociodemographic characteristics, comorbidities, injury-related factors, such as different neuropathologies and different locations affected, and clinical factors, such as the symptoms manifested, severity, and their recovery periods.[30] Only recently have studies begun to take into account this heterogeneity, although in different ways. The biggest initiatives in TBI research, such as the IMPACT,[367] InTBIR,[368] CENTER TBI,[369] and TRACK TBI[370] studies aim to standardize and pool vast amounts of multi-center data, collected across sociodemographic strata, to statistically correct for pre-injury factors known to impact brain structure. The objective of these landmark initiatives is to develop diagnostic and prognostic tools leveraging multimodal data and increasingly sophisticated machine-learning approaches. Importantly however, even these initiatives retain the original goal. These studies see heterogeneity as an obstacle to statistical power.

But what if, instead of being an obstacle, this heterogeneity contained the key to moving forward? The results from the work presented in this thesis support this idea. Studies 1 and 2 suggest that children with lifelong DBDs constitute a population at-risk for TBIs. The study on adverse childhood events mentioned earlier found that higher risk of TBIs was associated with

these adverse events. This association was attenuated when accounting for ADHD and conduct problems, but only in children whose TBIs was not associated with sports.[232] Children with lifelong externalizing problems have been shown to participate less frequently in organized sports.[221,222] Instead, these children have a higher risk of sustaining TBIs, more likely due to motor vehicle accidents and assaults. Further, as Study 3 suggests, the white matter abnormalities associated with TBIs appear to be different in children with DBDs compared to typically developing children. Together, these results underline the importance of considering comorbidities when studying TBIs, and demonstrate that TBIs sustained in children with lifelong externalizing problems may not necessarily be comparable to TBIs sustained by other individuals, for instance children without externalizing problems who participate in sports.

Further, Study 3 also demonstrated that when comparing typically developing children with TBIs against those without, no significant differences at the group level were apparent. These results are consistent with a study on the Philadelphia Neurodevelopmental Cohort that found that, when compared with a random group of controls, children with TBIs had differences in deep white matter structure, but when compared to a group that was matched for psychopathology, no differences in deep white matter structure were found.[276] These results suggest that at the group level, differences in white matter structure may be found only when the group shares a common feature, such as externalizing problems, that may confer a susceptibility to certain areas of the brain to sustain damage. Instead, among typically developing children, heterogeneity of alterations to white matter resulting from TBIs may prevent detection of differences at the group level. Given the association between TBIs and comorbidities such as ADHD and CD, prior studies may have confounded effects related to comorbidities with effects related to the TBI. Accounting for pre-injury factors, not by statistically controlling for them, but

by treating them as defining different subgroups of patients, may be a promising avenue forward. The same conclusion can be drawn from the comparisons within sex. Sex differences have been reported in TBI outcomes,[23,24] as well as studies employing a variety of different techniques, such as task-based[371] and resting-state[372] functional MRI, and electroencephalography.[373] Study 3 also adds to this literature by showing that sex differences were also apparent in white matter alterations observed among children with DBDs who had sustained TBIs. Further studies, using advanced neuroimaging technologies in clinical samples of patients with DBDs who sustained TBIs are needed to investigate whether this subgroup of children have different clinical outcomes than other brain injured children, for instance those injured in sports. Research on whether different treatments would be required in this group is also needed.

The search for *a* TBI biomarker is rooted in an assumption that has supporting evidence. For instance, as mentioned earlier, biomechanical modelling studies have suggested the corpus callosum is a structure where shearing strain can be maximal. Across hundreds of dMRI studies of TBI, the corpus callosum has been repeatedly reported as an area displaying differences between TBI patients and healthy controls.[119] This consistent finding has led some to suggest that the corpus callosum may be a potential "biomarker" of concussion.[119] A recent dMRI study developed a measure, based on z-scores, to quantify how many voxels were abnormal in concussed patients. They found that, when performing group comparisons, the corpus callosum showed differences at a group level, but when analyzing individual patterns, the consistency was much lower. This result confirms that traditional group comparisons average out heterogeneity, and the patterns that arise at the group level are less reflective of individual variability, which may be much more clinically important.[374] A small but slowly growing number of studies are looking to leverage TBI heterogeneity instead of statistically control it. Studies have started

employing clustering algorithms to describe subtypes of concussions, based on symptoms.[375,376] A study I performed, outside of this thesis, used instead a double-multivariate approach to find patterns across white matter structure and symptoms simultaneously. In this study, we found highly informative multi-tract multi-symptom relationships that predicted adverse psychiatric outcomes in unseen data. In contrast, univariate group comparisons only identified white matter connections that were most similar to those identified by the highest covariance-explaining multivariate feature, and much less similar to the connections identified by more idiosyncratic multivariate features. Further, the connections identified by these univariate group comparisons implicated more often the corpus callosum than the connections identified by more idiosyncratic multivariate features, suggesting once again that findings in the literature implicating the corpus callosum may arise from the choice in statistical approach rather than from the corpus callosum being a concussion "backbone". The expression of these multi-tract multi-symptom features did not show any patterns across sociodemographic strata defined by sex, total combined household income, and race/ethnicity.[275]

The optimal approach to advance TBI research remains unclear. Are there really subtypes of TBI? Should TBIs instead be studied using a dimensional approach, as the Research Domain Criteria approach does for psychopathology?[377] What is clear is that the field of TBI research needs to abandon the assumption that "TBI" is a single disease with a unique "backbone" of injury.

“The human brain has 100 billion neurons, each neuron connected to 10 thousand other neurons. Sitting on your shoulders is the most complicated object in the known universe”

– Michio Kaku

Chapter 9. Overall Conclusion

In conclusion, the work presented in this thesis challenges the traditional view that TBIs lead to aggressive behaviour and violent crime, identifies a population of children at elevated risk to sustain TBIs through subsequent decades of life, and suggests that the altered neural development of these children may be further altered by TBIs. These results have important clinical implications that will require further study. Randomized clinical trials will be needed to conclusively demonstrate whether the risk of TBIs can be reduced by interventions known to reduce conduct problems as well as ADHD medication. The work presented herein also has important implications for the field of TBI research. There seem to be different combinations of factors that predict TBIs, and different subgroups of individuals who sustain them. Public health approaches aiming to reduce the incidence of TBIs may benefit from further exploring the potential existence of these subgroups. Further, there is mounting evidence to which the studies performed in this thesis add suggesting that that the term "TBI", even when referring to injuries of the same severity, may not refer to a single condition with a single "backbone" of injury. It is too early to tell what the future holds for the field of TBI research, but using large datasets, leveraging novel imaging approaches and more sophisticated statistical techniques will likely open new and exciting avenues of investigation. However, as these approaches gain popularity, it is crucial that the field reconsider the pre-existing assumptions. The real paradigm shift will not come simply from more sophisticated methodology, it will come from a radical rethinking of what TBIs are.

One thing from this thesis is clear: it's possible that either Gage's story was widely exaggerated, or he was already engaging in the behaviours reported after injury long before the tamping iron passed through his brain. The human brain has always captivated the interest of the

general public and thinkers across centuries. It is not surprising, this approximately 1.3kg mass of jelly sitting within our cranium holds the key to our dreams, our emotions, who we love, who we are. In the earliest days of modern neurology, the story of how one previously charming young man suddenly became a drastically different person undoubtedly revolutionized the way people thought about the brain. This thesis presents instead a more boring alternative story. But I would argue, this story is much more important. Our understanding of the brain is barely at its infancy, and until we find a way to repair it, let us focus on finding ways to protect it.

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Appendix

Supplementary material for Study 1

Method

Childhood Behaviors

When participants were ages 6, 10, and 12, their classroom teachers rated behaviors (absent, sometimes, frequently) using the Social Behavior Questionnaire [154]. Cronbach alpha coefficients were calculated on the total cohort from which the sample was drawn.

Conduct problems (CP). Age 6: destroys own or others' belongings; fights with other children; kicks, bites, or hits other children; doesn't share material; irritable, quick to fly off the handle; disobedient. Age 10 and 12: these same items plus truant from school; has stolen things on one or more occasions. Cronbach alpha: 0.88 age 6, 0.81 age 10, 0.79 age 12.

Hurtful Behaviors. Tells lies; bullies other children; blames others; inconsiderate of others. Cronbach alpha: 0.83 age 6, 0.82 age 10, 0.81 age 12.

Uncaring Behaviors. Items were reverse coded: takes the opportunity to praise the work of less able children; shows sympathy to someone who has made a mistake; offers to help other children who are having difficulty with a task in the classroom; and comforts a youngster who is crying or upset. Cronbach alpha: 0.85 age 6, 0.82 age 10, and 0.81 age 12.

Inattention-hyperactivity (IH). Restless, runs about or jumps up and down, doesn't keep still; squirmy, fidgety child; poor concentration or short attention span; inattentive; gives up easily; stares into space. Cronbach alpha: 0.84 age 6, 0.85 age 10, 0.86 age 12.

Results

Table S1. Results of Chi-Squared comparisons between percentage of individuals with any juvenile conviction or a juvenile conviction for a violent offence, with different numbers of TBIs up to age 12

Number of TBIs up to age 12	Any juvenile conviction		Juvenile conviction for violence	
	n/N	%	n/N	%
0	165/663	24.9%	74/663	11.2%
1	9/51	17.6%	4/51	7.8%
χ^2, p	1.347, 0.246		0.536, 0.464	
Number of TBIs up to age 12	Any juvenile conviction		Juvenile conviction for violence	
	n/N	%	n/N	%
0	165/663	24.9%	74/663	11.2%
2	2/7	28.6%	2/7	28.6%
χ^2, p	FET=0.050, 1.000		FET=2.088, 0.183	
Number of TBIs up to age 12	Any juvenile conviction		Juvenile conviction for violence	
	n/N	%	n/N	%
0	165/663	24.9%	74/663	11.2%
3 or more	0/3	0%	0/3	0%
χ^2, p	FET=0.992, 1.000		FET=0.377, 1.000	
Number of TBIs up to age 12	Any juvenile conviction		Juvenile conviction for violence	
	n/N	%	n/N	%
1	9/51	17.6%	4/51	7.8%
2	2/7	28.6%	2/7	28.6%
χ^2, p	FET=0.479, 0.607		FET=2.851, 0.149	
Number of TBIs up to age 12	Any juvenile conviction		Juvenile conviction for violence	
	n/N	%	n/N	%
1	9/51	17.6%	4/51	7.8%
3 or more	0/3	0%	0/3	0%
χ^2, p	FET=0.635, 1.000		FET=0.254, 1.000	
Number of TBIs up to age 12	Any juvenile conviction		Juvenile conviction for violence	
	n/N	%	n/N	%
2	2/7	28.6%	2/7	28.6%
3 or more	0/3	0%	0/3	0%
χ^2, p	FET=1.071, 1.000		FET=1.071, 1.000	

FET= Fisher Exact Test

Table S2. Results of Chi-Squared comparisons between percentage of individuals with any juvenile conviction or a juvenile conviction for a violent offence, with different numbers of TBIs up to age 18

Number of TBIs up to age 18	Any juvenile conviction		Juvenile conviction for violence	
	n/N	%	n/N	%
0	278/634	43.8%	83/634	13.1%
1	33/70	47.1%	9/70	12.9%
χ^2, p	0.277, 0.598		0.003, 0.956	
Number of TBIs up to age 18	Any juvenile conviction		Juvenile conviction for violence	
	n/N	%	n/N	%
0	278/634	43.8%	83/634	13.1%
2	7/17	41.2%	3/17	17.6%
χ^2, p	0.048, 0.827		FET=0.300, 0.584	
Number of TBIs up to age 18	Any juvenile conviction		Juvenile conviction for violence	
	n/N	%	n/N	%
0	278/634	43.8%	83/634	13.1%
3 or more	0/3	0%	0/3	0%
χ^2, p	FET=2.334, 0.261		FET=0.452, 1.000	
Number of TBIs up to age 18	Any juvenile conviction		Juvenile conviction for violence	
	n/N	%	n/N	%
1	33/70	47.1%	9/70	12.9%
2	7/17	41.2%	3/17	17.6%
χ^2, p	0.196, 0.788		FET=0.264, 0.696	
Number of TBIs up to age 18	Any juvenile conviction		Juvenile conviction for violence	
	n/N	%	n/N	%
1	33/70	47.1%	9/70	12.9%
3 or more	0/3	0%	0/3	0%
χ^2, p	FET=2.581, 0.247		FET=0.440, 1.000	
Number of TBIs up to age 18	Any juvenile conviction		Juvenile conviction for violence	
	n/N	%	n/N	%
2	7/17	41.2%	3/17	17.6%
3 or more	0/3	0%	0/3	0%
χ^2, p	FET=1.900, 0.521		FET=0.623, 1.000	

FET= Fisher Exact Test

Table S3. Results of Chi-Squared comparisons between percentage of individuals with a first conviction of any type in adulthood and a first conviction for a violent offence in adulthood, with different numbers of TBIs up to age 18

Number of TBIs up to age 18	First conviction of any type in adulthood		First conviction for a violent offence	
	n/N	%	n/N	%
0	159/634	25.1%	48/634	7.6%
1	18/70	25.7%	3/70	4.3%
χ^2, p	0.014, 0.907		1.013, 0.314	
Number of TBIs up to age 18	First conviction of any type in adulthood		First conviction for a violent offence	
	n/N	%	n/N	%
0	159/634	25.1%	48/634	7.6%
2	2/17	11.8%	1/17	5.9%
χ^2, p	FET=1.577, 0.266		FET=0.068, 1.000	
Number of TBIs up to age 18	First conviction of any type in adulthood		First conviction for a violent offence	
	n/N	%	n/N	%
0	159/634	25.1%	48/634	7.6%
3 or more	0/3	0%	0/3	0%
χ^2, p	FET=1.003, 0.577		FET=0.246, 1.000	
Number of TBIs up to age 18	First conviction of any type in adulthood		First conviction for a violent offence	
	n/N	%	n/N	%
1	18/70	25.7%	3/70	4.3%
2	2/17	11.8%	1/17	5.9%
χ^2, p	FET=1.503, 0.338		FET=0.079, 1.000	
Number of TBIs up to age 18	First conviction of any type in adulthood		First conviction for a violent offence	
	n/N	%	n/N	%
1	18/70	25.7%	3/70	4.3%
3 or more	0/3	0%	0/3	0%
χ^2, p	FET=1.024, 0.570		FET=0.134, 1.000	
Number of TBIs up to age 18	First conviction of any type in adulthood		First conviction for a violent offence	
	n/N	%	n/N	%
2	2/17	11.8%	1/17	5.9%
3 or more	0/3	0%	0/3	0%
χ^2, p	FET=0.392, 1.000		FET=0.186, 1.000	

FET= Fisher Exact Test

Supplementary material for Study 2

Figure S1. Selection of participants for current study

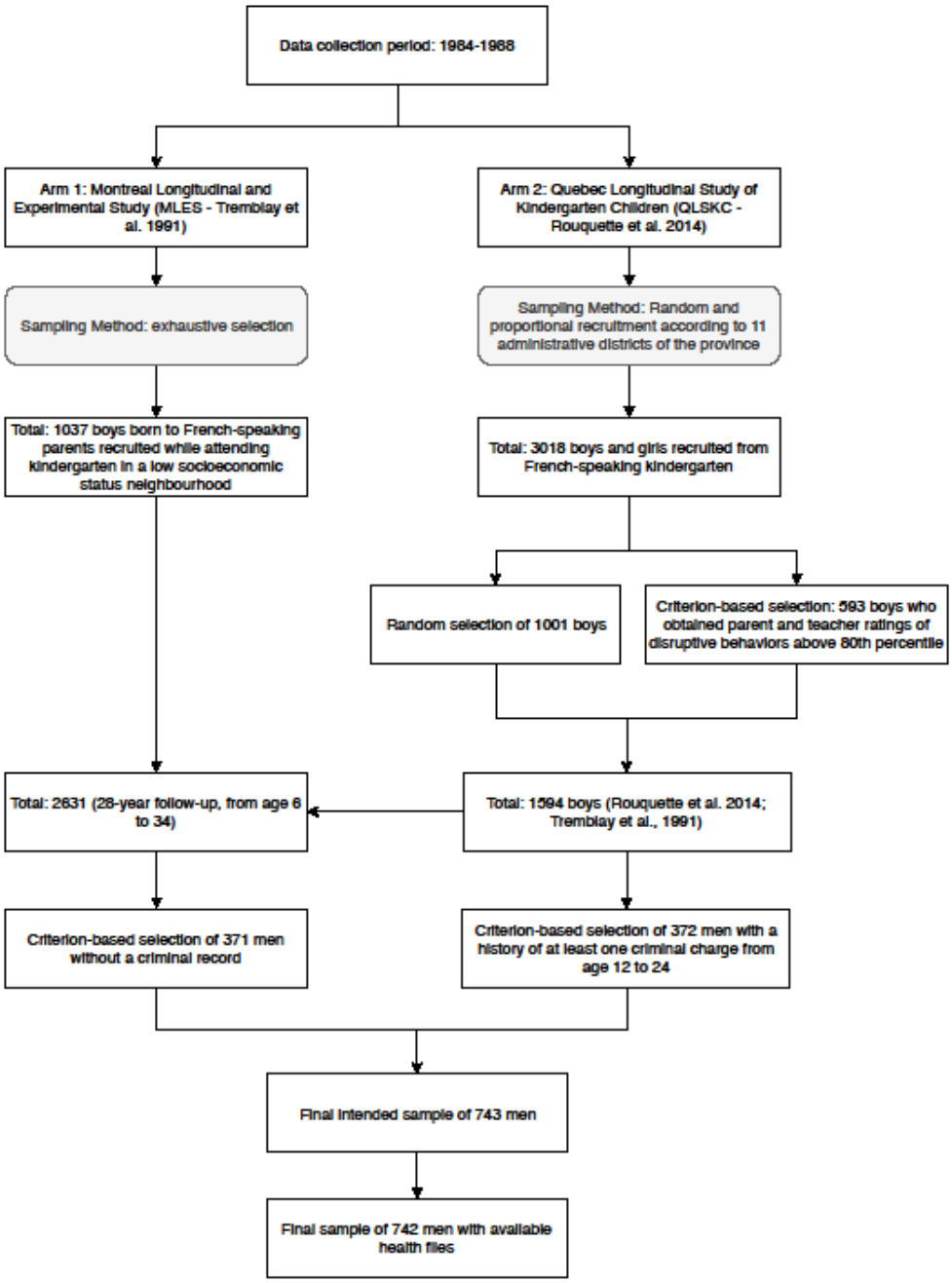

Table S1. Variables used in the study

	Complete Inattention-Hyperactivity and FSS (n=596)			Complete Externalizing Behaviors and FSS (n=583)		
	Range	Mean	SD	Range	Mean	SD
Inattention-Hyperactivity	0 – 10	4.19	3.02			
Externalizing Behaviors				0 – 38	15.07	8.27
Family Social Status	0 – 1	0.35	0.26	0 – 1	0.35	0.26
	Percentage[a] (n=144)			Percentage[a] (n=141)		
ICD-9 Diagnosis Category						
800.0 – 800.9 Fractures of vault of skull		2.78			2.84	
801.9 – 801.9 Fractures of base of skull		2.78			2.84	
802.0 – 802.9 Fracture of face bones		15.97			15.60	
803.0 – 803.9 Other and unqualified skull fractures		1.39			1.42	
850.0 – 850.9 Concussions		20.14			20.57	
851.0 – 851.9 Cerebral laceration and contusion		4.86			4.96	
852.0 – 852.9 Subarachnoid, subdural, and extradural hemorrhage, following injury		0.00			0.00	
853.0 – 853.9 Other and unspecified intracranial hemorrhage following injury		0.69			0.71	
854.0 – 854.9 Intracranial injury of other and unspecified nature		84.72			83.69	
959.0 Head injury unspecified		0.00			0.00	

a. Some participants had multiple diagnoses. Percentages may add up to more than 100.

Results

Ensuring generalizability

In order to increase confidence in the generalizability of results, analyses were re-run among only the non-offenders. Despite the small sample size, results were similar to those reported for the whole sample. In the final model (n=312), the risk of TBIs sustained from age 11 to 17 were increased 1.46 (1.05-2.05) times by age 10 inattention-hyperactivity, and 3.53 (1.15-10.86) times by previous TBIs. Neither FSS nor interaction terms were significant. In the final model (n=312) predicting TBIs sustained from age 18 to 34, neither inattention-hyperactivity, previous TBIs, FSS, nor the interaction terms were significant. In the final model (n=305), the risk of TBIs sustained from age 11 to 17 was increased 1.31 (1.01-2.34) times by age 10 externalizing problems, 3.65 (1.19-11.22) times by previous TBIs; neither FSS nor the interaction terms were significant. In the final model (n=305), the risk of TBIs sustained from age 18 to 34 was increased 1.67 (1.10-2.52) times by age 10 externalizing problems; neither previous TBIs, FSS, nor the interaction terms were significant**.**

Supplementary material for Study 3

METHODS AND MATERIALS

DWI scans

MRI scans were acquired across 21 sites, using 28 different scanners. Details about the acquisition protocols are outlined in Casey, et al. [378] Multi-shell dMRI scans had 96 diffusion-weighted directions, with 6 directions of b=500 s/mm^2, 15 of b=1000s/mm^2, 15 of b=2000s/mm^2, and 60 of b=3000s/mm^2. The b=2000s/mm^2 shell, which had directions that were collinear with the b=1000s/mm^2 shell was excluded from processing. In addition, scans had 6 or 7 b=0s/mm^2 images, depending on scanner type. A reverse b0 image was included for each participant to correct for EPI distortions.

Processing. During processing we selected white matter seeding given that this method yields fuller bundle reconstructions.[259,379] In comparison, white-gray matter interface seeding is known to yield thinner tracts, especially when reconstructing long bundles, given that the chances of a streamline encountering an obstacle causing premature termination increases as a function of the number of voxels it must traverse.

We selected 12 seeds-per-voxel, to obtain approximately 2 million streamlines across the brain. The objective achieving this number is to achieve adequate "saturation" of bundles, that is, capture their full spatial extent.[259,379] One way of calculating bundle saturation is by comparing the volume occupied by a bundle against the total number of streamlines in the full tractogram. Although there is no agreed-upon consensus for the optimal total number of streamlines, and different bundles may have different saturation points, preliminary evidence suggests that several of the major white matter bundles appear to reach a stable volume around 2 million streamlines.[259]

We used the b=0, 500, and 1000 shells to perform tensor fitting, and the b=0 and 3000 shells to perform Constrained Spherical Deconvolution (CSD).[125,126] We fixed the fiber-response functions for the entire sample by first calculating it on a subset of 71 randomly-selected typically developing children, using voxels with high (>0.70) fractional anisotropy (FA). The fiber response function was set to $17*10^{-4}$, $4*10^{-4}$, $4*10^{-4}$ (17, 4, 4 in Tractoflow using the *manual_frf* option). Lastly, we created tractograms using a probabilistic particle-filtering tractography algorithm.[354] This tractography technique consists in informing stopping criteria using partial volume estimation maps computed from the high resolution T1-weighted images that were transformed to DWI space during processing with Tractoflow. PFT can achieve tractography results that are less biased by length, shape, size, and position.[354] To increase the anatomical validity, this algorithm also imposes the anatomical constraint that streamlines obligatorily terminate in gray matter.

Post-processing. *RBX-flow* uses Nextflow,[380,381] a parallelizable programming language, to implement RBX, a multi-atlas multi-parameters version of Recobundles[382] with label fusion. Technical details about this pipeline can be found in.[259] Briefly, this technique consists in first simplifying a whole-brain tractogram using a small number of clusters, grouping together streamlines by shape and similarity. Bundle "models", manual segmentations performed by expert neuroanatomists, are then used to identify clusters that match the models with respect to a similarity measure based on shape and orientation. This approach is repeated several times, using multiple models, and multiple thresholds of similarity. Streamlines are given a score, determining, for every bundle, how often each streamline was assigned to each model. For instance, if we wish to extract 15 bundles and use 5 models for each, and test 10 different thresholds, every streamline will have a score of 50 (5 models x 10 thresholds) for each one of

our 15 bundles. Streamlines can then be assigned to the bundle for which they obtained the highest score. Prior work has shown that manual segmentations have inherent variability.[383] By using a clustering algorithm this approach can provide more consistent bundle segmentations, and by using a multi-atlas approach, it can minimize the variability introduced by manual segmentations.

Data Imputation. Partial volume effects, subtle imperfections in brain tissue classification, and other potential errors introduced during tractography can prevent automatic bundling algorithms from extracting bundles.[356] Out of 1500 participants with complete data, 386 had at least one bundle that could not be extracted. The lowest number of bundles a participant had was 6. Out of all 19500 bundles to extract (1500 participants x 13 bundles/participant), 765 (3.92%) were missing.

Multidimensional microstructural features. Measures from dMRI provide partly overlapping information about underlying microstructure. Used in combination, these measures can provide more information than in parallel.[124,275] To extract this shared information, we used principal component analysis (PCA) on the concatenated set of standardized measures across subjects and bundles. This approach generated new biologically-interpretable indices of white matter microstructure (WMM).[384] We applied this technique on the TD group, separately for boys and girls, to obtain measures representative of neurotypical WMM. In both sexes, we obtained 3 principal components (PCs) that together accounted for 93-94% of the total variance (Figure 2). Each corresponding PC was highly similar between the two sexes. The first reflected an index of absolute diffusivity. Changes to supporting structures such as neurofibrils and microglia, as well as myelin from oligodendrocytes, can lead to alterations in water diffusion that are proportional along the directions of the three eigenvectors, leading to higher axial, mean, and

radial diffusivity, without any changes in FA.[277] The second PC reflected an index of axonal density, and the third a measure of the number of fiber orientations in a voxel. We then projected data from all other participants onto these 3 PCs.

Figure S1. White matter bundles illustration.

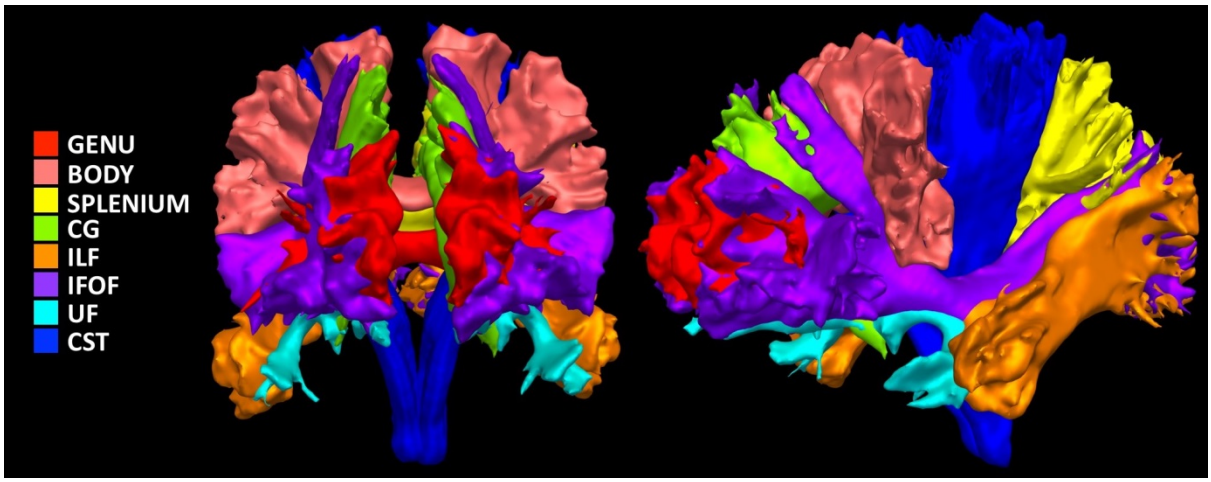

Figure S1. Illustration of the investigated white matter bundles. Genu: Genu of corpus callosum. Body: Body of corpus callosum. Splenium: Splenium of corpus callosum. CG: Cingulum. ILF: Inferior Longitudinal Fasciculus. IFOF: Inferior Fronto-Occipital Fasciculus. UF: Uncinate Fasciculus. CST: Corticospinal Tract.

Figure S2. Illustration of principal components analysis procedure.

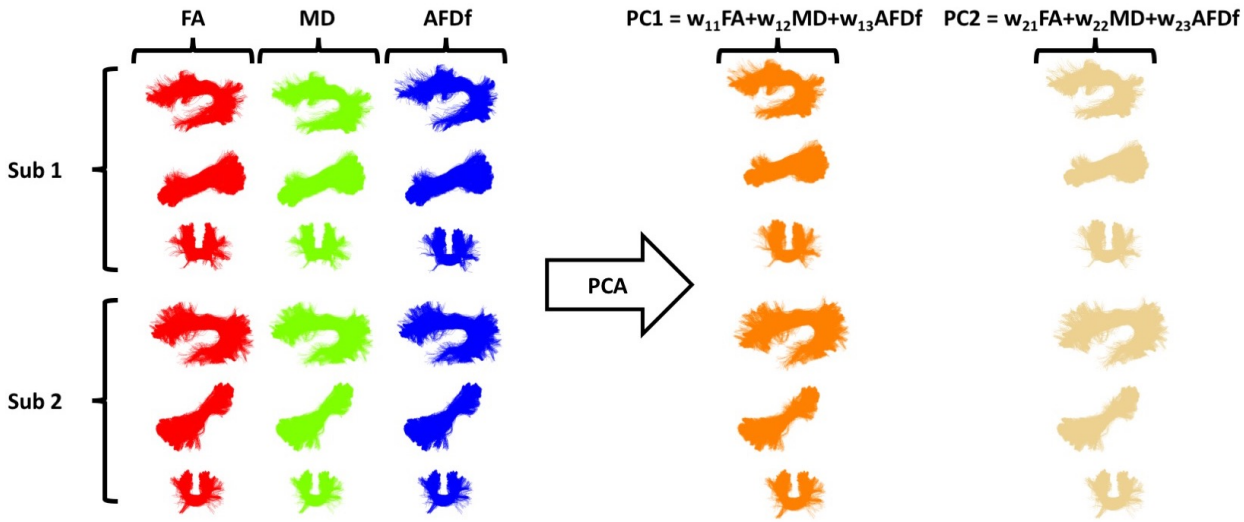

Figure S2. Schematic illustration of the PCA procedure. We performed PCA on the concatenated set of standardized diffusion measures across subjects ("sub") and bundles. This approach yielded principal components ("PC"), linear combinations of every diffusion measure. These linear combinations are represented by the equations on the top right, where every measure is multiplied by a weight ("w"). These weights (also called loadings) are selected so that PCs account for the most variance across measures. Every subject's bundle has a value (referred to as a "score") for every PC. FA: Fractional Anisotropy; MD: Mean diffusivity; AFDf: Apparent Fiber Density along fixels.

Additional analyses

In Study 3, using within-sex models, we found differences in WMM between children with and without disruptive behavior disorders and with and without a history of TBI. These effects were different in boys than in girls. To explore another method of testing for sex differences, we ran models incorporating all participants in the sample, and built models using group-by-sex interaction terms. To do so, we first reran the principal components analysis on typically developing boys and girls without TBIs together, and projected all other participants to the first three principal components spaces. Figure S3 illustrates the component loadings for each principal component obtained. The principal components obtained are nearly identical to those obtained in the original analyses, and hence their interpretation is the same (namely: absolute diffusivity, axonal density, and number of fiber orientations). We then reran multivariate regression models, conducting the same three sets of comparisons of WMM as before: (1) among children without a prior TBI, comparing DBD and TD groups; (2) among children with a prior TBI, comparing DBD and TD groups; (3) within DBD and TD groups, comparing children with and without a prior TBI. However, in each model we also included a main effect of sex, and a group-by-sex interaction term. We used multivariate regression analyses to identify WMM differences, separately by bundle, after having regressed out scanner, non-adjusted and then adjusted separately for each covariate (CU MAP, ADHD, IQ, age, pubertal stage, ethnicity (0=non-Hispanic White, 1=other), and family income (0=above $50,000, 1=below $50,000). For bundles displaying significant group differences, we ran post-hoc analyses comparing each WMM measure. When adjusting for confounders or reporting post-hoc analyses, only the p-values for variables that had significant main effects were reported.

Among children without TBIs, are there WMM differences between those presenting DBDs and TD children?

As presented in Table S1, among children who had not experienced TBIs, those with DBDs as compared to TD children displayed a multivariate difference of WMM in the left UF, robust to adjustment for age, pubertal stage, ethnicity, and family income, in the right ILF robust to adjustment for CU, age, ethnicity, and family income, and in the body of the CC, robust to adjustment for age, pubertal stage, ethnicity, and family income. In post-hoc analyses, TD children had higher absolute diffusivity and lower axonal density in the Genu of the CC only. No other differences were detected in the three components of WMM for the left UF and the right ILF.

All girls (TD and DBD) without TBIs, compared to all boys without TBIs displayed differences in the left and right IFOF, CG, ILF, CST, the right UF, and the Genu, Body, and Splenium of the CC. With the exception of the left IFOF that was robust to all covariates except pubertal stage, the effect in all other significant tracts was robust to adjustment for all covariates. In post hoc analyses, girls had lower absolute diffusivity than boys in the left and right IFOF, the right CG, right ILF, the Body and Splenium of the CC. In addition, girls had higher axonal density than boys in the right IFOF, lower axonal density in the Genu and Splenium of the CC. The left CG, ILF, CST, and right UF and CST showed no significant differences in any of the three measures of WMM in post-hoc analyses. No group-by-sex interaction terms were found to be significant.

Among children with TBIs, are there WMM differences between those presenting DBDs and TD children?

As presented in Table S2, among children who had experienced TBIs, those with DBDs as compared to TD children displayed a multivariate difference of WMM in the left IFOF, robust to adjustment for ethnicity and family income only, the left CST, robust for adjustment of all covariates except family income, and the right UF, robust to adjustment for CU, ADHD, pubertal stage, and ethnicity. In post-hoc analyses, children with TBIs had lower axonal density than children without in the left IFOF and in the right UF, but showed no differences in any of the three measures of WMM in the left CST. No differences were found between all girls (with and without TBIs) compared to all boys, and no significant group-by-sex interactions were found. No group-by-sex interaction terms were found to be significant.

Among TD children, do those who have sustained TBIs show WMM differences from those with no TBIs?

Among both TD boys and girls, there were no significant differences in WMM between those with and without TBIs in any of the 13 bundles studied. Differences between all TD girls compared to all TD boys were found in the left IFOF, ILF, CST, and right UF, IFOF, ILF, and CST. In post-hoc analyses, girls had higher number of fiber orientations than boys in the right UF, left CST, lower absolute diffusivity in the left and right IFOF, left and right ILF, and left and right CST. No group-by-sex interaction terms were found to be significant.

Among children presenting DBDs, do those who have sustained TBIs differ from those with no TBIs?

As presented in Table S3, among girls and boys presenting DBDs, those with prior TBIs compared to those without displayed a multivariate difference of WMM in the left CST, robust

to adjustment for all covariates except IQ, and in the right ILF, robust to adjustment for all covariates except IQ. Post-hoc analyses revealed that DBD children who had sustained TBIs showed higher axonal density in the left CST and higher absolute diffusivity in the right ILF, compared to DBD children without TBIs.

All DBD girls (with and without TBI) compared to all DBD boys showed significant multivariate differences in WMM in the right IFOF, right ILF, as well as the Genu, Body, and Splenium of the CC that were robust to adjustment for all covariates. Post-hoc analyses revealed that all DBD girls, compared to all DBD boys, displayed lower absolute diffusivity in the right IFOF, right ILF, and the Body and Splenium of the CC, higher axonal density in the right IFOF, lower axonal density in the Genu and Splenium of the CC, and a higher number of fiber orientations in the Genu of the CC. No group-by-sex interaction terms were found to be significant.

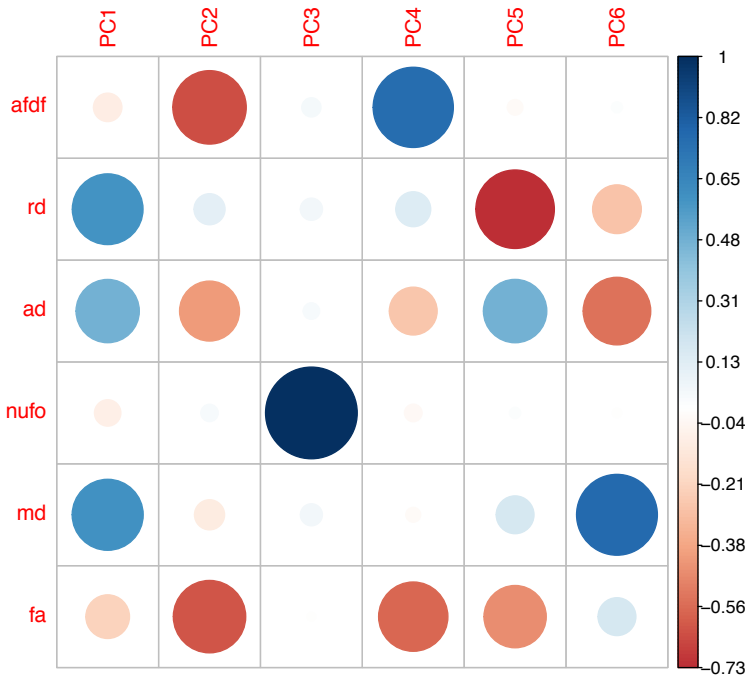

Figure S3. Illustration of the results from the Principal Components Analyses. Plot illustrating the loadings of each diffusion measure onto each principal component (PC). Red colors represent negative loadings, blue colors represent positive loadings. The size of the circles also the magnitude of the loadings. PC1 appears to capture measures of absolute diffusivity. PC2 appears to capture measures related to axonal density. PC3 appears to capture selectively the number of fiber orientations. AFDf: Apparent Fiber Density along fixels; RD: Radial diffusivity; AD: Axial diffusivity; NuFO: Number of fiber orientations; MD: Mean diffusivity; FA: Fractional Anisotropy.

Table S1. Among children who have not experienced a traumatic brain injury, comparisons of white matter microstructure between boys and girls with Disruptive Behavior Disorders and typically developing boys and girls, with adjustment for callous-unemotional traits, Attention Deficit Hyperactivity Disorder, IQ, age, pubertal stage, ethnicity, and family income

n = 1437											
Bundle	Non-adjusted *p* values (η^2)			Multivariate model *p* values Adjusted for							Differences in components
	Group	Sex	Group x Sex	CU MAP	ADHD	IQ	Age	Pubertal Stage	Ethnicity	Family Income	
Left											
UF	**0.0372**	0.0700	0.5705	0.0950	0.0847	0.0769	**0.0441**	**0.0397**	**0.0269**	**0.0459**	None
IFOF	0.3352	**<0.001**	0.1455	**<0.001**	**<0.001**	**<0.001**	**<0.001**	0.0609	**<0.001**	**0.0040**	Absolute diffusivity: F<M
CG	0.7714	**0.0165**	0.9010	**0.0106**	**0.0104**	**0.0065**	**0.0168**	**0.0049**	**0.0135**	**0.0410**	None
ILF	0.6102	**0.0128**	0.9186	**0.0041**	**0.0084**	**0.0225**	**0.0131**	**0.0250**	**0.0132**	**0.0341**	None
CST	0.0651	**0.0052**	0.2948	**0.0034**	**0.0038**	**0.0080**	**0.0051**	**0.0040**	**0.0043**	**0.0110**	None
Right											
UF	0.0846	**0.0013**	0.9622	**0.0015**	**0.0012**	**<0.001**	**<0.001**	**0.0014**	**0.0011**	**0.0060**	None
IFOF	0.2187	**<0.001**	0.0911	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	Absolute diffusivity: F<M Axonal density: F>M
CG	0.5635	**0.0116**	0.7997	**0.0113**	**0.0090**	**0.0122**	**0.0117**	**0.0068**	**0.0087**	**0.0248**	Absolute diffusivity: F<M
ILF	**0.0361**	**<0.001**	0.8338	Group: **0.0219**	Group: 0.1374	Group: 0.0746	Group: **0.0283**	Group: 0.0520	Group: **0.0479**	Group: **0.0223**	Group: None Sex:

					Sex: **<0.001**	Sex: **<0.001**	Sex: **0.0028**	Sex: **<0.001**	Sex: **0.0033**	Sex: **<0.001**	Sex: **0.0014**	Absolute diffusivity: F<M
CC	CST	0.2097	**<0.001**	0.5266	**0.0023**	**<0.001**	**0.0040**	**<0.001**	**0.0113**	**<0.001**	**<0.001**	None
	Genu	**<0.001**	**0.0086**	0.4535	Group: **0.0200**	Group: 0.1168	Group: **0.0039**	Group: **<0.001**	Group: **0.0011**	Group: **<0.001**	Group: **0.0014**	Group: Absolute diffusivity: TD>DBD
					Sex: **0.0174**	Sex: **0.0103**	Sex: **0.0082**	Sex: **0.0088**	Sex: **0.0050**	Sex: **0.0086**	Sex: **0.0249**	Axonal Density: TD<DBD
	Body	**0.0151**	**<0.001**	0.5998	Group: 0.0596	Group: 0.3956	Group: 0.0893	Group: **0.0150**	Group: **0.0320**	Group: **0.0041**	Group: **0.0292**	Sex: Axonal density: F<M Group: None
					Sex: **<0.001**	Sex: **<0.001**	Sex: **0.0055**	Sex: **<0.001**	Sex: **0.0017**	Sex: **<0.001**	Sex: **0.0024**	Sex: Absolute diffusivity: F<M
	Splenium	0.4868	**0.0083**	0.5745	**0.0117**	**0.0061**	**0.0154**	**0.0083**	**0.0079**	**0.0077**	**0.0066**	Absolute diffusivity: F<M Axonal density: F<M

TD: typically developing; DBD: Disruptive Behavior Disorders; UF: Uncinate Fasciculus; IFOF: Inferior Fronto-Occipital Fasciculus; CG: Cingulum; ILF: Inferior Longitudinal Fasciculus; CST: Corticospinal Tract; CC: Corpus Callosum; CU MAP: Callous Unemotional *mean a posteriori* scores; ADHD: Attention Deficit/Hyperactivity Disorder. Note: Only variables that had a significant non-adjusted effect are reported in adjusted models.

Table S2. Among children who have experienced a traumatic brain injury, comparisons of white matter microstructure between boys and girls with Disruptive Behavior Disorders and typically developing boys and girls, with adjustment for callous-unemotional traits, Attention Deficit Hyperactivity Disorder, IQ, age, pubertal stage, ethnicity, and family income

n = 63

Bundle	Non-adjusted *p* values (η^2)			Multivariate model *p* values Adjusted for							Differences in components
	Group	Sex	Group x Sex	CU MAP	ADHD	IQ	Age	Pubertal Stage	Ethnicity	Family Income	
Left											
UF	0.1534	0.6965	0.9154								
IFOF	**0.0373**	0.2146	0.9986	0.0535	0.0880	0.0863	0.0735	0.0530	**0.0376**	**0.0269**	Axonal density: TBI+ < TBI-
CG	0.3711	0.7537	0.8313								
ILF	0.2697	0.1872	0.3949								
CST	**0.0106**	0.2050	0.5827	**0.0107**	**0.0321**	**0.0069**	**0.0132**	**0.0127**	**0.0064**	0.0512	None
Right											
UF	**0.0417**	0.4960	0.0705	**0.0078**	**0.0317**	0.0796	0.0668	**0.0212**	**0.0389**	0.0802	Axonal density: TBI+ < TBI-
IFOF	0.1300	0.1982	0.7747								
CG	0.6708	0.4752	0.4486								
ILF	0.5310	0.1508	0.8051								
CST	0.1106	0.8037	0.8467								
CC											
Genu	0.2287	0.1346	0.8081								
Body	0.2126	0.5276	0.9883								
Splenium	0.0874	0.8899	0.6611								

TD: typically developing; DBD: Disruptive Behavior Disorders; UF: Uncinate Fasciculus; IFOF: Inferior Fronto-Occipital Fasciculus; CG: Cingulum; ILF: Inferior Longitudinal Fasciculus; CST: Corticospinal Tract; CC: Corpus Callosum; CU MAP: Callous Unemotional *mean a posteriori* scores; ADHD: Attention Deficit/Hyperactivity Disorder. Note: Only variables that had a significant non-adjusted effect are reported in adjusted models.

Table S3. Among boys and girls presenting Disruptive Behavior Disorders, comparisons of white matter microstructure between those who had and had not sustained a traumatic brain injury, with adjustment for callous-unemotional traits, Attention Deficit Hyperactivity Disorder, IQ, age, and pubertal stage, ethnicity, and family income

n = 669

Bundle	Non-adjusted *p* values (η^2)			Multivariate model *p* values Adjusted for							Differences in components
	Group	Sex	Group x Sex	CU MAP	ADHD	IQ	Age	Pubertal Stage	Ethnicity	Family Income	
Left											
UF	0.7033	0.1962	0.7665								
IFOF	0.7576	0.0659	0.6858								
CG	0.8489	0.0630	0.8704								
ILF	0.6229	0.3880	0.6282								
CST	**0.0413**	0.7227	0.3058	**0.0404**	**0.0214**	0.1346	**0.0415**	**0.0554**	**0.0416**	**0.0191**	Axonal density: TBI+ > TBI-
Right											
UF	0.9461	0.1585	0.2117								
IFOF	0.5975	**<0.001**	0.4476	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**0.0012**	**<0.001**	**<0.001**	Absolute diffusivity: F <M Axonal density: F > M
CG	0.6698	0.0641	0.6323								
ILF	**0.0283**	**<0.001**	0.3128	Group: **0.0286** Sex: **0.0012**	Group: **0.0387** Sex: **0.0013**	Group: 0.0331 Sex: **0.0087**	Group: **0.0242** Sex: **<0.001**	Group: **0.0139** Sex: **0.0423**	Group: **0.0285** Sex: **<0.001**	Group: **0.3924** Sex: **0.0019**	Group: Absolute diffusivity: TBI+ > TBI- Sex: Absolute diffusivity:

											F < M
	CST	0.7844	0.3928	0.8800							
CC											
	Genu	0.2927	**0.0300**	0.1386	**0.0362**	**0.0355**	**0.0208**	**0.0291**	**0.0065**	**0.0304**	**0.0398**	Sex: Axonal density: F < M Fiber orientations: F > M
	Body	0.1876	**0.0087**	0.6270	**0.0095**	**0.0079**	**<0.001**	**0.0076**	**0.0298**	**0.0080**	**0.0073**	Sex: Absolute diffusivity: F < M
	Splenium	0.5813	**0.0138**	0.8622	**0.0132**	**0.0090**	**0.0341**	**0.0137**	**0.0456**	**0.0137**	**0.0112**	Absolute diffusivity: F < M Axonal density: F < M

TBI+: individuals who have sustained a traumatic brain injury; TBI-: individuals who have not sustained a traumatic brain injury; DBD: Disruptive Behavior Disorders; UF: Uncinate Fasciculus; IFOF: Inferior Fronto-Occipital Fasciculus; CG: Cingulum; ILF: Inferior Longitudinal Fasciculus; CST: Corticospinal Tract; CC: Corpus Callosum; CU MAP: Callous Unemotional *mean a posteriori* scores; ADHD: Attention Deficit/Hyperactivity Disorder. Note: Only variables that had a significant non-adjusted effect are reported in adjusted models.

Glossary

TBI: traumatic brain injury

MRI: magnetic resonance imaging

dMRI: diffusion MRI

DWI: diffusion-weighted imaging

DBD: disruptive behaviour disorders

CP: conduct problems

CD: conduct disorder

ODP: oppositional defiant problems

ODD: oppositional defiant disorder

CSD: constrained spherical deconvolution

DTI: diffusion tensor imaging

FSS: family social status

CST: corticospinal tract

IFOF: inferior fronto-occipital fasciculus

ILF: inferior longitudinal fasciculus

CG: cingulum

CC: corpus callosum

UF: uncinate fasciculus

TD: typically developing

IH: inattention-hyperactivity

FET: Fishers' Exact Test

PCA: principal component analysis

PC: principal component

CU: callous-unemotional

ADHD: attention-deficit/hyperactivity disorder

WMM: white matter microstructure

CI: confidence interval

SES: socioeconomic status