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Konigs, M.

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CHAPTER 1

GENERAL INTRODUCTION

BACKGROUND

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Traumatic Brain Injury (TBI) follows the transfer of kinetic energy between an external object and the head (Kristman et al., 2014). Varying definitions of TBI exist, ranging from any trauma to the head other than superficial injury (Hodgkinson, Pollit, Sharpin, & Lecky, 2014) to head trauma causing confusion, disorientation, loss of consciousness, and/or other neurological abnormalities such as focal signs, seizure and intracranial pathology (Kristman et al., 2014). The worldwide prevalence of TBI is estimated at 54-60 million individuals each year (Feigin et al., 2013). Epidemiological data from the Centers of Disease Control and Prevention (CDC, 2016) indicates that the highest incidence of emergency department visits for TBI is observed in babies and toddlers, followed by adolescents and primary school children. Primary causes of TBI in these young individuals are falls and motor vehicle accidents. With regard to gender, males have a ~30% higher risk of sustaining TBI as compared to females (CDC, 2016). TBI is also more likely to occur in socially disadvantaged environments (Kraus & McArthur, 1996) and in individuals with pre-existing psychiatric conditions (Gerring et al., 1998). The direct costs for medical treatment after TBI, and the indirect costs associated with chronic disability, place an enormous economic burden on society worth €33 billion each year in Europe alone (Olesen, Gustavsson, Svensson, Wittchen, & Jönsson, 2012). Taken together, these findings underline that TBI is a major public health problem. Especially children represent a high-risk group, for who TBI is the leading cause of death and acquired disability (World Health Organization, 2006).

In terms of outcome, children with TBI are at risk of chronic neurological injury (Roberts, Mathias, & Rose, 2014), neurocognitive impairment (Babikian & Asarnow, 2009), behavior problems (Li & Liu, 2013), poor social skills (Rosema, Crowe, & Anderson, 2012) and reduced academic achievement (Vu, Babikian, & Asarnow, 2011). These aspects of functioning are robust predictors of adaptive functioning and quality of life, including, for example, professional success and even delinquency later in life (Anderson, Brown, Newitt, & Hoile, 2011; Broidy et al., 2003). This highlights the potential impact of TBI and the importance of accurate prognostic models to predict the outcome of TBI. One robust predictor of TBI outcome is injury severity. Conventional classification systems of TBI severity use the level of consciousness assessed by the Glasgow Coma Scale (GCS) score, loss of consciousness (LOC) duration, and/or duration of post-traumatic amnesia (PTA, a transient period of confusion and disorientation) to discriminate between mild TBI (GCS score = 15-13, loss of consciousness [LOC] duration \leq 30 minutes, post-traumatic amnesia [PTA] duration \leq 1 hour), moderate TBI (GCS score = 12-9, LOC duration = 30-60 minutes, PTA duration 1 – 24 hours) and severe TBI (GCS score \leq 8, LOC duration \geq 60 minutes, PTA

duration ≥ 24 hours; Anderson, Northam, Hendy, & Wrennall, 2001). Although TBI severity has consistent predictive value for aspects of neurocognitive functioning (Babikian & Asarnow, 2009), behavioral functioning (Li & Liu, 2013), academic performance (Vu et al., 2011) and quality of life (Di Battista, Soo, Catroppa, & Anderson, 2012), recent research has made increasingly clear that outcome prediction is hampered by the complexity of pediatric TBI. The available evidence indicates that neurological, neurocognitive and behavioral dysfunction interact with premorbid functioning, child development and family environment to influence outcome in children with TBI (Catroppa, Anderson, Beauchamp, & Yeates, 2016). Therefore, a better understanding of the mechanisms that underlie dysfunction after pediatric TBI may importantly contribute to the precision and reliability of prognostic models, and may additionally provide targets for treatment approaches.

NEUROPATHOLOGY

The neuropathology of TBI involves primary and secondary injury mechanisms (Catroppa et al., 2016). Primary injuries are caused by the direct impact of energetic forces on the brain, and involve both focal injuries caused by linear forces (e.g. cerebral contusion and laceration) and diffuse injury caused by rotational forces (e.g. diffuse axonal injury). These primary injuries give rise to a cascade of secondary injury mechanisms. One secondary injury mechanism is cerebral edema, which refers to the accumulation of fluid in the brain that leads to an increase in intracranial pressure. The subsequent impact of high intracranial pressure on cerebral perfusion may eventually cause hypoxia, which can exacerbate the initial impact of TBI on the brain. Another important secondary injury mechanism involves neurotoxic chemical cascades, such as excessive release of excitatory neurotransmitters. This deregulation in the release of excitatory neurotransmitters (e.g. glutamate) is known to cause excessive calcium influx in neurons, in turn leading to cell death due to necrosis or apoptosis (Muir, 2006). At the macroscopic level, the neuropathology of TBI may show distinct variability in terms of the presence and location of focal injuries (Bigler, Abildskov, & Petrie, 2013), which is likely to contribute to inter-individual differences in the outcome of TBI. However, innovative magnetic resonance imaging (MRI) techniques have revealed that the widespread detrimental impact of TBI on brain connectivity may represent a more fundamental aspect of the neuropathology (Sharp, Scott, & Leech, 2014), even in the absence of intracranial pathology on conventional neuroimaging modalities (Mac Donald et al., 2011).

The rise of innovative MRI techniques in clinical neuroscience, such as diffusion tensor imaging (DTI), has shown that children with moderate to severe TBI exhibit widespread

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abnormalities in white matter, which persist into the chronic phase of recovery (Roberts et al., 2014). Also after mild TBI, persisting effects have been found on major white matter tracts in adults (Aoki & Inokuchi, 2016). White matter tracts harbor the connections between (groups of) neurons and are essential for the relay of sensory information and the integration of specialized neural processes that give rise to brain functions (Park & Friston, 2013). Consequently, white matter abnormalities may play an important role in the consequences of pediatric TBI for functional outcome. Especially since TBI may additionally interfere with post-injury neurological development: longitudinal studies have shown that major white matter tracts (e.g. the corpus callosum) follow an aberrant developmental trajectory in the years after more severe TBI (Ewing-Cobbs et al., 2008; Wu, Wilde, Bigler, & Li, 2010). Taken together, the neuropathology of TBI is characterized by a broad range of injury mechanisms that likely contribute to inter-individual differences in the outcome of pediatric TBI. The delayed impact on post-injury neurological development further complicates the neuropathology of more severe forms of TBI.

NEUROCOGNITIVE FUNCTIONING

With regard to neurocognitive functioning, systematic reviews of the literature found no evidence for persisting neurocognitive deficits in children with mild TBI (Carroll et al., 2004, 2014). However, there is some evidence indicating that subgroups of children with more severe forms of mild TBI (e.g. clinical evidence for intracranial pathology) may be at risk of persisting postconcussional symptoms and neurocognitive deficits. Children with moderate to severe TBI typically have distinct deficits in general neurocognitive functioning (e.g. intelligence), which may be more specifically characterized by impairments in domains of attention, working memory, learning and long-term memory, as well as executive functioning (Babikian & Asarnow, 2009). Impairments in these neurocognitive functions are likely to secondarily affect academic performance (Kinsella et al., 1995; Raghubar, Barnes, Prasad, Johnson, & Ewing-Cobbs, 2013) and behavioral functioning (Levin & Hanten, 2005), highlighting the importance of sensitive screening methods to detect neurocognitive impairment in children with TBI.

Neurocognitive functions have been found differentially sensitive to the impact of TBI. Studies into the effect of pediatric TBI on intelligence have shown that fluid aspects of intelligence (e.g. psychomotor speed, attention and visuospatial function), are more vulnerable to pediatric TBI as compared to verbal IQ, or other crystallized aspects of intelligence (e.g. verbal comprehension; Babikian & Asarnow, 2009). Fluid aspects of intelligence are thought to be crucial for skill acquisition (Anderson, Catroppa, Morse, Haritou, & Rosenfeld, 2000), and impairments in these functions may therefore slow down

post-injury development of new skills. This idea, referred to as the *growing into deficit* hypothesis, is supported by a study among children with severe TBI, indicating that the younger the age at injury, the higher the risk of persisting impairments in intelligence (Anderson, Catroppa, Morse, Haritou, & Rosenfeld, 2005). This finding indicates that the effects of TBI on neurocognitive functioning may not only have a direct impact on child functioning, but that severe forms of TBI may also have a delayed impact on child development, resulting in increasing difficulties in the years post-injury.

BEHAVIORAL FUNCTIONING

Children with mild to severe TBI have a threefold risk of presenting behavior problems within three months post-injury, relative to children with orthopedic injuries (Max et al., 2012). Over time, as much as 50% of children with TBI are at risk of behavior problems (Li & Liu, 2013). These behavior problems may encompass symptoms of depression and anxiety (i.e. internalizing behavior), and/or aggression and symptoms of conduct disorder (i.e. externalizing behavior). Symptoms of inattention or hyperactivity are also frequently observed in children with TBI, and the development of secondary attention-deficit hyperactivity disorder after TBI has been associated with poorer neurocognitive functioning, adaptive functioning and personality change (Max et al., 2004). Importantly, behavior problems after pediatric TBI are associated with impoverished academic development (Yeates & Taylor, 2006), adverse social outcome (Rosema et al., 2012) and delinquency later in life (Timonen et al., 2002). These findings highlight the potential impact of behavior problems for the future of children with TBI.

There is also evidence for a delayed impact of TBI on the development of behavioral and adaptive functioning, since behavior problems of children with TBI may aggravate during the years post-injury (Li & Liu, 2013). A recent longitudinal study even showed that complicated mild to severe TBI triples the risk of developing a novel psychiatric disorder (Max, Wilde, Bigler, Thompson, et al., 2012). The development of novel psychiatric disorders after pediatric TBI has been associated with impaired white matter integrity in frontostriatal circuits, which are also critically involved in higher-order neurocognitive functions that guide, monitor and regulate social behavior (i.e. executive functions; Levin & Hanten, 2005; Max, Wilde, Bigler, Thompson, et al., 2012). These findings suggest that neurological and neurocognitive mechanisms may contribute to the aberrant development of behavioral functioning following pediatric TBI. Taken together, these findings highlight the importance of early identification and treatment of behavior problems after TBI. A better understanding of the mechanisms that contribute to the development of behavior problems may aid in the early identification of children at-risk, and may facilitate the deployment of early preventative interventions.

PREMORBID FUNCTIONING AND ENVIRONMENTAL INFLUENCE

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Premorbid functioning and environmental factors have also been found to influence outcome of pediatric TBI (Catroppa et al., 2016). For example, children with pre-injury psychiatric symptoms have an increased risk of daily life disability (Bonfield, Lam, Lin, & Greene, 2013). Likewise, the presence of pre-injury learning difficulties has been associated with a higher chance of post-injury behavior problems (Ponsford et al., 1999). Not only child characteristics, but also aspects of the child's environment may influence the outcome of TBI. In line with this idea, lower socio-economic status has been found predictive of poor outcome (Anderson, Morse, Catroppa, Haritou, & Rosenfeld, 2004). Furthermore, family functioning and parental mental health have also been identified as predictors of post-injury functioning (Anderson, Catroppa, Haritou, Morse, & Rosenfeld, 2005; Ryan et al., 2016). Taken together, these findings suggest that the potential of children and their environment (e.g. family, school) to handle the challenging consequences of TBI, may crucially influence outcome. Rehabilitation services can play a pivotal role in adapting and supporting the child's environment in order to cushion the impact of TBI (Catroppa et al., 2016), but effective rehabilitation treatment also requires a thorough understanding of the mechanisms that underpin dysfunction.

AIMS OF THIS THESIS

The three aims of this thesis are: (1) to determine and predict general neurocognitive outcome of mild to severe TBI in children and adults; and to increase our understanding of the (2) neurocognitive mechanisms and (3) neuropathological mechanisms that underpin dysfunction following pediatric TBI.

STUDY DESIGN

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According to the study aims, we: (1) performed meta-analyses of the available literature on general neurocognitive outcome of TBI in children and adults; (2) set up a cross-sectional observational study into the neurocognitive mechanisms that may underpin dysfunction in children with TBI; and (3) followed-up on a selected subsample of children with conventional and innovative MRI techniques. In our cross-sectional observational study, we compared a group of 113 children with TBI to a trauma control (TC) group of 53 children with traumatic injury not involving the head, to control for pre-injury risk factors for TBI and potential psychological effects of hospitalization (Max, Koele, & Smith Jr., 1998). Children were retrospectively recruited from a consecutive cohort of three university-affiliated level I trauma centers and several rehabilitation centers in the Netherlands. Inclusion criteria were: (1) age 6-13 years; (2) proficient in the Dutch language; (3) hospital admission with a clinical diagnosis of TBI for inclusion in the TBI group; (4) hospital admission for traumatic injuries below the clavicles for inclusion in the TC group (American College of Surgeons, 2004); and (5) more than two months post-injury. Exclusion criteria were: (1) previous TBI; (2) visual disorder interfering with neurocognitive testing; or (3) current condition affecting the central nervous system, other than TBI. Of all 375 children admitted between October 2009 - October 2013 that were eligible for inclusion (TBI: $n = 232$, TC: $n = 143$), a total of 166 children participated in the study (TBI: $n = 113$, TC: $n = 53$). Neurocognitive functioning was assessed using a battery of (computerized) tests for intelligence, attention, feedback learning and sensory integration. Behavioral functioning was assessed using parent and teacher questionnaires, whereas academic achievement was assessed using scores on tests of the Dutch pupil monitoring system for primary schools.

Informed by preliminary results of this study, a follow-up study was set up for a subsample of children with TBI, in order to investigate how the neuropathology of TBI may underlie neurocognitive and behavioral impairments following pediatric TBI. More specifically, from our original sample of children with TBI, we selected children that had a history of hospital admission with a clinical diagnosis of either: (a) mild TBI (GCS = 15 - 13, loss of consciousness [LOC] duration ≤ 30 minutes, post-traumatic amnesia [PTA] duration ≤ 1 hour) with at least one of the following risk factors for complicated TBI (mild^{RF+} TBI) according to the European Federation of Neurological Societies' guidelines on mild TBI: impaired consciousness (GCS = 13-14), focal neurological deficits, persistent vomiting (≥ 3 episodes), post-injury epileptic seizure, progressive headache and abnormal head CT-scan (Vos & Battistin, 2002); or (b) moderate/severe TBI (GCS = 12-3, LOC duration > 30 minutes, PTA duration > 1 hour; Teasdale & Jennett, 1976). Of all 123 children that were

eligible (TBI: $n = 67$; TC: $n = 56$), a total of 64 children participated in the follow-up study (TBI: $n = 37$, TC: $n = 27$). The participating samples did not differ from their respective cohorts in the original study in terms of age, gender and SES (TBI: $ps \geq .28$; TC: $ps \geq .07$), or GCS score (TBI: $p = .68$). In this follow-up study, neuroimaging was performed on a 3 Tesla MRI scanner with sequences for high-resolution structural imaging, DTI, resting-state and active-state functional MRI. In addition, neurocognitive functioning was assessed using a (computerized) battery of tests for intelligence, visual working memory precision and verbal learning.

OUTLINE OF THIS THESIS

The described study aims translate into three parts that compose the current thesis. Consequently, **part I** aims to determine and predict outcome of mild to severe TBI in children and adults with regard to general neurocognitive functioning. General neurocognitive outcome was operationalized as intelligence, since this construct represents a broad range of neurocognitive functions (Wechsler, 2005), has superior psychometric properties (Strauss, Sherman, & Spreen, 2006) and is a robust predictor of academic achievement, behavioral functioning, vocational functioning and quality of life after pediatric and adult TBI (Anderson et al., 2011; Bowman, 1996; Donders & Warschawsky, 2007; Donders, 1994; Thaler et al., 2010; Yasuda, Wehman, Targett, Cifu, & West, 2001). The first meta-analysis, described in **chapter 2**, investigates the impact of TBI on intelligence in children and adults. Furthermore, this study explores the predictive value of PTA duration, a well-known measure of TBI severity with high prognostic potential, for impairments in intelligence in patients with TBI. The meta-analysis described in **chapter 3** follows up on chapter 2, by aggregating the evidence from 81 studies to compare the impact of mild to severe TBI on intelligence between children and adults. Furthermore, this study compares three primary measures of TBI severity (GSC score, LOC duration and PTA duration) in terms of their predictive value for impairments in intelligence.

Part II of this thesis describes empirical studies that originate from the original observational study, serving the aim to unravel the neurocognitive mechanisms of dysfunction after pediatric TBI. **Chapter 4** presents the results of a study into the impact of pediatric TBI on attention, a fundamental aspect of neurocognitive functioning. Attention comprises a set of processes that gate the perception of sensory stimuli and select relevant information for processing by higher-order neurocognitive processes. Disturbances in attention processes are known to contribute to inattentive and/or hyperactive behavior, which are in turn frequently observed in children with TBI. This study uses sophisticated computerized testing in combination with ex-Gaussian modeling to track down the effects of TBI on differential attention processes. Furthermore, mediation analysis is used to explore how attention deficits may relate to behavioral attention problems as observed by parents and teachers. The relation between higher-order neurocognitive functions and internalizing behavior (e.g. symptoms of depression and anxiety) and externalizing behavior (e.g. symptoms of aggression and conduct disorder) is further assessed in **chapter 5**. This study investigates whether the ability to adapt behavior in response to feedback (i.e. feedback learning) may be involved in the behavior problems that are frequently observed in children with TBI. Since children continuously use feedback on current behavior to shape future behavior, deficits in feedback learning may cause

inefficient adaptation to the environment, in turn causing behavior problems. Feedback learning is complex due to inconsistency in feedback (e.g. differences between parents, teachers, etc.) and changing contexts (e.g. at home, at school, at the playground, etc.). Therefore, this study uses the Probabilistic Learning Test to study the impact of pediatric TBI on feedback learning, the influence of feedback inconsistency and generalization of learning to novel contexts. Additionally, the relations between feedback learning and ratings of internalizing and externalizing behavior problems are investigated.

Chapter 6 and **chapter 7** are directed to sensory integration in children with TBI. The brain has a high degree of local specialization, where specialized groups of neurons process differential aspects of sensory stimuli (e.g. identity vs. location of visual stimuli). Sensory integration refers to the coupling of these specialized processes, which is essential to construct an accurate neural representation of our environment. The integration of visual processes is the focus of chapter 6, describing the results of a study that used an experimental paradigm to measure the impact of pediatric TBI on visual integration. Although visual integration is essential for the reconstruction of visual aspects of our environment, stimuli from our environment are rarely unimodal objects. For example, classic neuropsychological research by McGurk and MacDonald (1976) has shown that speech processing is not only dependent on the perception of auditory information, but also involves the integration of this auditory information with visual information on lip movements. Chapter 7 describes a study into the impact of pediatric TBI on multi sensory integration. Chapter 6 and 7 use the diffusion model to track down the impact of TBI on isolated aspects of performance (e.g. strategy, efficiency of information processing and response execution). Mediation analysis is used to investigate whether deficits in sensory integration may contribute to impairments in intelligence after pediatric TBI.

Informed by the observations in the described studies, **chapter 8** focuses on children with mild TBI. This study investigates whether risk factors for intracranial pathology after mild TBI (i.e. complicated mild TBI) may be predictive of neurocognitive and behavioral impairment in children. Furthermore, the prognostic value of specific risk factors is assessed for this group of children with mild^{RF+} TBI.

Part III aims to elucidate how the neuropathology of pediatric TBI may underlie and/or predict neurocognitive and behavioral impairments. **Chapter 9** investigates the predictive value of conventional and innovative neuroimaging techniques (acute computed tomography, high-resolution structural MRI and DTI) for neurocognitive and behavioral impairments after mild^{RF+} TBI and moderate/severe TBI in children. This study uses tract-based spatial statistics to determine the impact of TBI on white matter integrity and uses voxel-wise regression methodology to assess regional associations between white matter

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integrity and neurocognitive and behavioral functioning. Mediation analysis is used to explore which neuroimaging parameters may underlie neurocognitive and behavioral impairment after pediatric TBI. **Chapter 10** further uses sophisticated techniques to investigate how the impact of pediatric TBI on white matter integrity may affect the structural connectivity of the brain. Probabilistic tractography is used to reconstruct the network of white matter pathways in the brain (i.e. the connectome). The probability of connections between brain areas, as well as the integrity of these connections, are subsequently used to capture differential aspects of the connectome, while the minimum spanning tree is used to specifically focus on the backbone of the structural network. Graph theory is applied to describe global network properties, determine the impact of TBI on the connectome, and explore the relation between network properties and neurocognitive and behavioral impairment following TBI.

To conclude this thesis, a general summary and discussion is presented in **chapter 11**. This chapter attempts to integrate findings of the studies presented in this thesis towards a clearer picture of the neurocognitive outcome of TBI in children and adults, and a better understanding of the neurocognitive and neuropathological mechanisms that underpin dysfunction in children with TBI. Last, a research agenda is presented to guide future research on TBI.

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