Traumatic brain injury (TBI) is a major public health concern. Worldwide, an estimated 54-60 million individuals sustain TBI each year (Feigin et al., 2013), placing a yearly economic burden worth €33 billion in Europe alone. TBI is also the primary cause of death and acquired disability in children and adolescents (World Health Organization, 2006).

The existing literature indicates that patients with more severe forms of TBI are at risk of widespread neuroanatomical damage (Blennow, Hardy, & Zetterberg, 2012), neurocognitive impairment (Ruttan, Martin, Liu, Colella, & Green, 2008), psychopathology (Schachar, Park, & Dennis, 2015) and reduced academic or vocational performance (Vu, Babikian, & Asarnow, 2011; Yasuda, Wehman, Targett, Cifu, & West, 2001). The severity of TBI is a robust predictor of functional outcome, but the conventional classification of cases into mild, moderate and severe TBI does not sufficiently account for the complexity of TBI to construct an accurate and reliable prognosis (Maas, Lingsma, & Roozenbeek, 2015). Recent evidence made increasingly clear that neurological, neurocognitive and behavioral dysfunction interact with premorbid functioning and environmental factors to influence the outcome of TBI (as reviewed in Catroppa, Anderson, Beauchamp, & Yeates, 2016). With regard to children, the primary consequences of TBI may additionally interfere with post-injury development (Anderson, Spencer-Smith, & Wood, 2011).

This thesis aims to quantify and predict the general neurocognitive outcome of children and adults with TBI (part I), and elucidate the neurocognitive and neuropathological mechanisms that may underpin dysfunction after pediatric TBI (part II & III, respectively). The current section summarizes the main findings of this thesis. A table summary is additionally provided in appendix 1. Subsequently, the findings are discussed in the broad context of existing literature and their implications for clinical practice. Limitations and strengths of the adopted methodological approaches are also discussed. To conclude this thesis, a research agenda is presented that may guide future research into pediatric TBI.
PART I - THE LITERATURE SECTION

SUMMARY OF MAIN FINDINGS

The first part of this thesis describes the results of literature research, aimed at determining and predicting the outcome of mild to severe TBI in children and adults with regard to general neurocognitive functioning. General neurocognitive functioning was operationalized as intelligence, a widely used construct in the field of neuropsychology. Intelligence 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, psychopathology, vocational functioning and quality of life after pediatric and adult TBI (Donders & Warschausky, 2007; Thaler et al., 2010; Yasuda et al., 2001).

In chapter 2, meta-analytic techniques were used to quantify intelligence impairment after TBI, and predict the magnitude of impairment using post-traumatic amnesia (PTA) duration. The meta-analysis includes 21 studies, representing a sample of 854 patients with mild to severe TBI. The results reveal no evidence for a detrimental impact of mild TBI on intelligence. In contrast, patients with severe TBI have large-sized impairment in full-scale IQ (FSIQ; Cohen's $d = -1.07$) in the subacute phase of recovery and medium to large-sized impairment ($d = -0.78$) in the chronic phase of recovery. Patients with severe TBI have greater impairment in performance IQ (PIQ) as compared to verbal IQ (VIQ) during the subacute phase of recovery, while these aspects of IQ are equally impaired in the chronic phase. The results further show that, despite the marked heterogeneity across studies in terms of the methodology that was used to assess PTA duration, PTA duration is a strong predictor of FSIQ, PIQ and VIQ in both the subacute phase of recovery (correlations ranging between -.76 and -.52) and the chronic phase (correlations ranging between -.80 and -.61).

Chapter 3 used meta-analytic techniques to compare the impact of TBI on intelligence between children and adults. In addition, this study compares the predictive values of three major measures of injury severity: the Glasgow Coma Scale (GCS) score, loss of consciousness (LOC) duration and PTA duration. The meta-analysis includes 81 studies encompassing 3,890 patients with mild to severe TBI. The results show that patients with mild TBI have no meaningful intelligence impairment in the subacute phase of recovery, while small-sized impairment in FSIQ is observed in the chronic phase ($d = -0.37$). Patients with moderate TBI have medium-sized FSIQ impairment in the subacute phase of recovery ($d = -0.61$) while small-sized FSIQ impairment is found in the chronic phase ($d = -0.19$). Patients with severe TBI show large-sized FSIQ impairment in both the subacute phase
(d = -1.09) and the chronic phase of recovery (d = -0.80). With regard to the role of age at injury, no differences between children and adults are observed in the subacute phase of recovery, while children with severe TBI have larger FSIQ impairment in the chronic phase of recovery as compared to adults. Lastly, GCS score, LOC duration and PTA duration all show strong predictive value for the magnitude of intelligence impairment in patients with TBI (correlations ranged between -.81 and -.36), but do not outperform one another in terms of the predictive value for intelligence impairment.

**GENERAL DISCUSSION**

The results of part I of this thesis show that moderate to severe TBI causes medium to large-sized impairments in general neurocognitive functioning that persist into the chronic phase of recovery. The observed chronic impact of severe TBI on intelligence translates into an average 12-point decrease in FSIQ. These findings are in line with the existing literature that exposed the detrimental impact of TBI on a wide range of neurocognitive functions in both children (Babikian & Asarnow, 2009) and adults (Ruttan et al., 2008). Furthermore, the GCS score, LOC duration and PTA duration are strong predictors of intelligence outcome in patients with TBI, despite distinct heterogeneity that is observed in the definition and measurement of these injury severity indices across studies. Taken together, these findings warrant the systematic and robust measurement of injury severity in clinical practice.

Analyses assessing the impact of mild TBI on intelligence in chapter 2 and 3 reveal contradicting results. The study in chapter 2 reports no significant intelligence impairment in patients with mild TBI (ds > -0.36), while the study in chapter 3 reports small-sized impairment in FSIQ (d = -0.37) and VIQ (d = -0.30) during the chronic phase of recovery from mild TBI. The most likely explanation for these contradicting findings lies within the number of studies that was available for meta-analysis. In chapter 2, between two to four studies on mild TBI were available for the calculation of the reported effect sizes, while in chapter 3, between nine to sixteen studies were available. Consequently, the study in chapter 3 features superior robustness of the meta-analytic estimates and higher statistical power to detect intelligence impairment in patients with mild TBI. Taken together, these findings indicate that mild TBI may be associated with small-sized intelligence impairment during the chronic phase of recovery.

Comparisons of the GCS score, LOC duration and PTA duration reveal that these measures of injury severity do not outperform one another in terms of their predictive value for intelligence outcome. Although it would be tempting to conclude that the measures are therefore redundant, we argue that such a conclusion could be unjustified. The GCS score, LOC duration and PTA duration have been reported to account for only 8% to 45% in one
another’s variance (Knights et al., 1991; Sherer, Struchen, Yablon, Wang, & Nick, 2008), suggesting that these measures capture differential aspects of injury severity. In line with this reasoning, the GCS score and LOC duration measure the level and recovery of consciousness, a low level of neurocognitive functioning, whereas PTA duration measures the recovery of orientation and amnesia (Tittle & Burgess, 2011), which are higher-order neurocognitive functions that may be more closely related to intelligence and daily life functioning. Consequently, the GCS score, LOC duration and PTA-duration may provide complementary information for the prognosis of intelligence outcome in patients with TBI. This hypothesis awaits empirical testing in future research.

Findings from part I also show that fluid aspects of intelligence (i.e. PIQ, predominantly measuring psychomotor speed, visuospatial function and working memory) are more vulnerable to the impact of TBI as compared to crystalized aspects of intelligence (i.e. VIQ, predominantly measuring verbal knowledge and comprehension). The vulnerability of fluid intelligence relative to crystalized intelligence to the impact of TBI has been reported earlier in a meta-analysis on neurocognitive functioning after pediatric TBI (Babikian & Asarnow, 2009). Since fluid intelligence is crucial for the acquisition of new knowledge and skills (Primi, Ferrão, & Almeida, 2010), the relatively large impact of TBI on fluid intelligence may have important consequences for post-injury development in children. In line with this idea, chapter 2 reports on evidence indicating that children have poorer long-term intelligence outcome of severe TBI than adults. This difference between children and adults was not present in the acute phase of recovery, but emerged in the chronic phase, suggesting that the direct impact of TBI may protract the post-injury development of children with severe TBI. More specifically, these chronic differences in the magnitude of intelligence impairment between children and adults are present in FSIQ and VIQ, but not in PIQ. This pattern might suggest that initial PIQ impairment in children with severe TBI may slow down the post-injury development of verbal skills, representing a neurocognitive mechanism contributing to the ‘growing into deficit’ phenomenon (Anderson, Spencer-Smith, et al., 2011). Taken together, these findings underline the importance of research aimed at unraveling the neurocognitive mechanisms contributing to dysfunction in children with TBI.

IMPLICATIONS FOR CLINICAL PRACTICE

The results of part I have implications for clinical practice. The studies in part I are based on very large sample of patients with TBI to quantify intelligence impairments associated with mild, moderate and severe TBI, in the subacute phase of recovery as well as the chronic phase. Clinicians may use these robust quantifications of general neurocognitive outcome after TBI for coarse prognostication purposes, but should also respect the
distinct heterogeneity that is observed in general neurocognitive outcome of TBI. This heterogeneity reflects the importance of prognostic factors other than injury severity and recovery phase in the general neurocognitive outcome of TBI, which should also be taken into account (e.g. demographic and environmental factors; for a review see Catroppa et al., 2016). Heterogeneity is also observed in the definition of injury severity and adopted measurement methodology, especially with regard to PTA duration. These observations warrant prospective measurement of injury severity using standardized instruments, especially for the assessment of PTA duration.

Part I also exposes age at injury as a critical factor influencing general neurocognitive outcome after TBI. Children are shown to have poorer intelligence outcome after severe TBI in the chronic phase of recovery, as compared to adults. This finding is based on a large meta-analytic sample, providing convincing evidence for disturbed post-injury development of general neurocognitive outcome in children with severe TBI. Given that the brain is not fully maturated until around the age of 30 (Gogtay et al., 2004) and intelligence is thought to play a crucial role in behavioral functioning, academic performance, vocational placement and quality of life after TBI (Donders & Warschausky, 2007; Donders, 1994; Yasuda et al., 2001), the current meta-analytic evidence for disturbed development of intelligence calls for systematic long-term, if not life-long, clinical follow-up of children with severe TBI.

LIMITATIONS & STRENGTHS

Part I of this thesis has some specific limitations. First, the use of meta-analytic techniques to quantify the impact of TBI on intelligence across studies may be questioned by the distinct heterogeneity among patients with TBI. For example, the impact of TBI on intelligence may be influenced by differences between patients in terms of premorbid characteristics (e.g. socio-economic status, psychiatric symptoms or learning difficulties) and aspects of TBI severity other than those that were taken into account (e.g. the type, extent and severity of intracranial pathology). Second, distinct methodological variability is observed between studies in terms of the measurement of intelligence (i.e. version of the Wechsler Scale), the availability of a reference group (i.e. the normative mean vs. a control group vs. a trauma control group) and the measurement and definition of injury severity. Especially in terms of post-traumatic amnesia duration, great variability is present in the definition (e.g. time between injury and resolution of PTA vs. time between regaining consciousness and resolution of PTA) and measurement methodology (e.g. retrospective vs. prospective recording, subjective report vs. objective measurement, and even differences between instruments that are used for the prospective and objective measurement of PTA). Third and last, the cross-sectional approach that is used to track
the recovery of intelligence after TBI is, for obvious reasons, inferior to a longitudinal design, but studies with systematic longitudinal assessment of intelligence are too sparse to allow a robust analysis of recovery. Fortunately, comparisons of the meta-analytic TBI samples in terms of demographics and injury-severity reveal no evidence suggesting that systematic differences between groups in the subacute and chronic phases of recovery have confounded the reported analyses.

Part I also has several strengths. First, the use of meta-analytic techniques allows statistical aggregation of the available empirical evidence on the relation between injury severity and intelligence impairment in patients with TBI. The results in part I are based on a large meta-analytic sample representing up to 3,890 patients with mild, moderate or severe TBI from a total of 81 peer-reviewed articles (chapter 3). This large sample of patients with TBI produces robust quantifications of intelligence impairment in the subacute phase of recovery and the chronic phase, which can be used for coarse prognostication purposes in clinical practice. Second, the research described in part I is among the first to report meta-analytic evidence on the predictive value of three major measures of injury severity for intelligence outcome. The results indicate that these measures, which are widely used in clinical practice around the world for acute medical decision-making and early prognostication purposes, have strong predictive value for intelligence impairment after TBI. The relevance of these findings for clinical practice is highlighted by the strong predictive value of intelligence for psychopathology, academic functioning, vocational functioning and quality of life after pediatric and adult TBI (Anderson, Brown, Newitt, & Hoile, 2011; Bowman, 1996; Donders & Warschausky, 2007; Donders, 1994; Thaler et al., 2010; Yasuda et al., 2001). Third and last, the study in chapter 3 is the first to report on meta-analytic evidence for the ‘growing into deficit’ theory, indicating that severe TBI causes abnormal post-injury neurocognitive development in children.
PART II - THE NEUROCOGNITIVE SECTION

SUMMARY OF MAIN FINDINGS

The second part of this thesis aims to elucidate the neurocognitive mechanisms that underpin dysfunction after pediatric TBI. Chapter 4 to 7 present the results of a multicenter cross-sectional observational study executed in a consecutive cohort of primary school aged children in the chronic phase of recovery from mild to severe TBI \( (n = 113; \text{on average 1.7 years post-injury}) \) and a comparison group of children with trauma control injury \( (n = 53) \). The study in chapter 4 focuses on attention processes in relation to daily life behavior problems as observed by parents and teachers. Attention processes are essential to neurocognitive and behavioral functioning, by selecting sensory information for perception and gating the information flow to and from memory (Logan & Etherton, 1994; Logan, 2002; Moran & Desimone, 1985). The Attention Network Test measures three well-known attention networks: alerting attention (i.e. the ability to achieve and maintain an alert state), orienting attention (i.e. the ability to spatially orient to environmental stimuli) and executive attention (i.e. the ability to resolve conflict between conflicting responses). The results reveal no evidence for an effect of pediatric TBI on these attention networks. Nevertheless, children with mild TBI and risk factors for complicated TBI (mild RF+ TBI) and children with moderate/severe TBI show slower performance in all task conditions. Ex-Gaussian analysis was subsequently adopted to study intra-individual variability in the reaction time of task performance. This approach models the mean and standard deviation of normally distributed reaction times (i.e. \( \mu \) and \( \sigma \), respectively) together with an exponential component describing the influence of extremely slow responses on processing speed (i.e. \( \tau \)). Thereby, Ex-Gaussian modeling allows researchers to delineate the influence of lapses of attention (i.e. short moments of attention loss) on processing speed. The results reveal that children with mild RF+ TBI or moderate/severe TBI have higher \( \tau \) \( (d = 0.49 \text{ and } d = 0.77) \) than children in the trauma control group, reflecting increased lapses of attention. Lapses of attention are not more frequent, but have longer duration in children with TBI as compared to children with TC injury. Since no effects of pediatric TBI on \( \mu \) and \( \sigma \) are found, increased lapses of attention fully account for the observed slowing of processing speed in task performance. Furthermore, increased lapses of attention are related to lower intelligence and higher parent ratings of attention problems after pediatric TBI. Interestingly, mediation analyses reveal that lapses of attention partly mediate the negative relation between intelligence and attention problems (in statistical terms).
Chapter 5 describes a study into the relation between feedback learning and behavior problems after pediatric TBI. Feedback learning is the ability to adapt future behavior in response to feedback on current behavior, and is crucially involved in typical behavioral development (Rushworth & Behrens, 2008). Impaired feedback learning may affect post-injury behavioral development in children with TBI, contributing to the increased risk of behavior problems as observed in children with mild to severe TBI (Li & Liu, 2013). The Probabilistic Learning Test was used to assess feedback learning, the influence of feedback consistency and generalization of learning to new contexts. Children with pediatric TBI show comparable performance to children with trauma control injury in terms of feedback learning and the ability to cope with feedback inconsistency. In contrast, children with moderate/severe TBI were found to have impaired generalization of learning (\(d = -0.51\)). In other words, these children had difficulty to transfer feedback learning from the learning context to other contexts. Interestingly, poorer generalization of learning was related to higher parent ratings of externalizing problems (together with SES, \(R^2 = 15\%\)). Furthermore, receiver-operating characteristic analysis revealed that generalization of learning had good sensitivity (86\%) and adequate specificity (72\%) for the identification of children with clinically significant externalizing behavior problems.

Chapter 6 and 7 describe the results of experimental studies into the role of sensory integration in neurocognitive impairments following pediatric TBI. The rationale for these studies relied upon the robust evidence for widespread detrimental effects of TBI on white matter integrity (Roberts, Mathias, & Rose, 2014), which harbors the structural connectivity of the brain. Given the high degree of functional specialization in the brain (Young, 1992), we hypothesized that the impact of TBI on white matter integrity would become evident in tasks that require efficient integration of sensory information. In chapter 6, a novel paradigm was designed to measure visual integration during goal-directed behavior. Visual integration refers to the efficient coupling of differential features of visual stimuli, in this case the identity (‘6’ or ‘9’) and location (i.e. left or right) of visually presented digits. The results showed no effects of pediatric TBI on the speed or accuracy of visual identification or localization, but did reveal reduced accuracy of task performance in children with mild\(^{RF-}\) TBI and children with moderate/severe TBI when the task required integration of visual identity and visual location (\(d = -0.60\) and \(d = -0.56\), respectively). These findings were extended by the subsequent study in chapter 7, which used a novel paradigm to assess multisensory integration. Multisensory integration refers to the coupling of information across sensory modalities, in this case the integration of visual information with auditory information (i.e. audiovisual integration). The results revealed poorer accuracy of task performance in children with mild\(^{RF+}\) TBI and children
with moderate/severe TBI, specifically when the task required audiovisual integration ($d = -0.51$ and $d = -0.60$, respectively). In both chapter 6 and chapter 7, the diffusion model was used to further delineate the deficiencies underlying impaired task performance in children with TBI. The diffusion model combines RT and accuracy to break down the decision process into *boundary separation* (a measure of task strategy), *drift rate* (i.e. efficiency of information processing) and *non-decision time* (i.e. extra-decisional processes; e.g. stimulus encoding, execution of the motor response). The results reveal no effects of TBI on *boundary separation* or *non-decision time*. In contrast, lower *drift rate* (indicative of reduced efficiency of information processing) was observed in terms of both visual integration and multisensory integration, in children with mild\textsuperscript{RF+} TBI ($d = -0.73$ and $d = -0.44$) as well as children with moderate/severe TBI ($d = -0.81$ and $d = -0.63$). Mediation analyses further show that poorer efficiency of visual integration and multisensory integration were both related to poorer intelligence, partially to fully mediating the detrimental effects of pediatric TBI on intelligence (in statistical terms).

Driven by observed effects of mild\textsuperscript{RF+} TBI in chapter 4, 6 and 7, chapter 8 investigated the predictive value of risk factors for complicated mild TBI (i.e. mild TBI with the presence of intracranial pathology, not requiring neurosurgery) regarding functional outcome in terms of intelligence and behavior problems. These risk factors involve the presence of at least one of the following before or during admission in the trauma center: abnormal head CT-scan, impaired consciousness (i.e. GCS score = 14-13), persistent vomiting (i.e. ≥3 episodes), focal neurological deficits (e.g. anosmia, nystagmus, etc.), progressive headache and post-traumatic epileptic insult. Among children hospitalized for mild TBI, the most prevalent risk factors are abnormal head CT-scan (29%), impaired consciousness (25%) and persistent vomiting (24%). While no evidence is found for effects of mild\textsuperscript{RF-} TBI, children with mild\textsuperscript{RF+} TBI have poorer intelligence ($d = -0.52$) and more behavior problems ($d = -0.72$) as compared to children in the TC group. More specifically, the presence of impaired consciousness after mild TBI has modest predictive value for lower intelligence (together with SES, $R^2 = 30\%$) as well as more behavior problems (together with male gender and SES, $R^2 = 13\%$) in the chronic phase of recovery.

**GENERAL DISCUSSION**

Part II of this thesis describes the results of a cross-sectional observational study on a multicenter consecutive cohort of children in the chronic phase of recovery from mild to severe TBI. The results of part II reveal multiple neurocognitive deficits in the domains of attention, learning and sensory integration, which are likely to contribute to general neurocognitive impairment and behavioral dysfunction in children with TBI.
Although not directly relating to the primary aim of part II, a striking finding that is consistently reported in this part of the thesis relates to the outcome of children with mildRF+ TBI. In analyses on the outcome of mild TBI, children with mild TBI were differentiated according to the absence or presence of risk factors that are associated with an increased risk of complicated TBI. In contrast to mildRF− TBI, the results indicate that mildRF+ TBI affects neurocognitive functioning and behavioral functioning (chapter 8), even in the absence of clinical evidence of intracranial pathology. These findings contradict the outcome of two subsequent systematic reviews of the literature, performed by the World Health Organization Collaborating Center Task Force on Mild TBI (Carroll et al., 2004, 2014). These reviews conclude that mild TBI in children is associated with quick resolution of postconcussional symptoms, while no convincing evidence exists for persisting neurocognitive or behavioral deficits. Nevertheless, the observed impact of mildRF+ TBI on neurocognitive and behavioral functioning in children is in line with other existing evidence indicating that mild TBI may represent a spectrum of injury severity, where children with more severe forms of mild TBI may be at risk of relatively poor outcome (for a review, see Levin & Diaz-Arrastia, 2015). Taken together, part II of this thesis supports the routine follow-up of children with mildRF+ TBI for screening of neurocognitive and behavioral deficits associated with their injury.

The analyses aiming to elucidate neurocognitive mechanisms that underpin dysfunction in children with TBI, reveal several mechanisms that potentially play an important role in daily life function. Chapter 4 describes the impact of TBI on attention processes. The findings of that chapter indicate that TBI does not affect alerting attention, orienting attention or executive attention networks, but rather causes impaired consistency of processing as reflected by lapses of attention (i.e. short moments of attention loss). The study in chapter 4 is the first to report direct evidence for lapses of attention in children with TBI, which is in line with a study that reported increased inconsistency in attention performance after adult TBI (Kelly, Uddin, Biswal, Castellanos, & Milham, 2008). The results of chapter 4 further indicate that lapses of attention account for the observed slowing of processing speed in children with TBI. This is an important finding, since slowing of information processing is one of the most consistently observed neurocognitive deficits in patients with TBI (Mathias & Wheaton, 2007). The clinical relevance of lapses of attention is reflected by the observed relationships with poorer intelligence and more parent-rated attention problems in children with TBI. Mediation analysis furthermore reveals that lapses of attention mediate the previously reported negative relationship between intelligence and attention problems (Barriga & Doran, 2002). Although mediation analysis does not test causality, it may be speculated that increased lapses of attention after pediatric TBI may
have consequences for intelligence as well as hyperactive/inattentive behavior, therefore accounting for the relationship between these aspects of child functioning after TBI.

Chapter 5 describes the impact of pediatric TBI on feedback learning in relation to behavior problems. The results reveal no evidence for effects of mildRF- or mildRF+ TBI on feedback learning, or the ability to cope with inconsistency of feedback on behavior. In contrast, study findings indicate that moderate/severe TBI impairs generalization of feedback learning, reflecting difficulty to transfer learning to a novel context. These findings partly contrast with our expectations, since a previous study showed that children with raised intracranial pressure after severe TBI have impaired performance on a probabilistic reversal learning task, suggesting impaired feedback learning based on inconsistent feedback (Slawik, Salmond, & Taylor-tavares, 2009). Taken together, the results may implicate that only very severe forms of TBI affect the ability to learn from inconsistent feedback. In contrast, the observed deficit in generalization of learning is consistent with previous electrophysiological evidence for disturbed processing of changing feedback contexts in adults with severe TBI (Larson, 2007). Interestingly, the findings in chapter 5 show that poorer generalization of learning is predictive of more parent-rated externalizing behavior. Furthermore, generalization of learning has good sensitivity and adequate specificity for the identification of children with clinical levels of externalizing behavior problems. These findings suggest that generalization of learning may contribute to the emergence of post-injury externalizing problems in children with TBI, which is consistent with the involvement of frontostriatal networks in both feedback learning (Hämmerer & Eppinger, 2012; Maia & Frank, 2011) and the emergence of behavioral disorders after pediatric TBI (Max et al., 2012). We speculate that early assessment of feedback learning could potentially be used to identify children who may benefit from rehabilitation interventions aimed at the prevention or reduction of externalizing behavior problems after TBI.

The studies in chapter 6 and 7 used experimental paradigms to investigate sensory integration after TBI. Since sensory integration requires connectivity between specialized brain areas, while TBI has a detrimental impact on white matter integrity, we hypothesized that sensory integration should be sensitive for the effects of TBI. In line with this idea, the results show that mildRF+ and moderate/severe TBI affect both visual integration (Chapter 6) and multisensory integration (Chapter 7). These findings are in line with the existing literature, reporting impaired spatial grouping of visual stimuli in a group of patients with acquired brain injury (Kurylo, Larkin, Waxman, & Bukhari, 2014), which is thought to be caused by reduced integration of information in the visual cortex after axonal disruption. Likewise, a functional magnetic resonance imaging (MRI) study showed that increasing
the load on visual feature integration during an attention task, caused impaired task performance in a group of adult patients with TBI (Raja Beharelle, Tisserand, Stuss, McIntosh, & Levine, 2011).

Interestingly, a comparison of the observed impact of TBI on aspects of attention (chapter 4), feedback learning (chapter 5) and sensory integration (chapters 6 & 7), indicates that sensory integration has relatively high sensitivity for the effects of TBI ($d$s between -0.44 and -0.81) compared to the alerting, orienting and executive attention networks as assessed using the Attention Network Test ($d$s between 0.04 and 0.18) and aspects of feedback learning as assessed using the Probabilistic Learning Test (only sensitive to moderate/severe TBI: $d = -0.51$). The effects of TBI on sensory integration are comparable to the impact of TBI on processing speed (chapter 5; $d = 0.45$) and lapses of attention (chapter 5; $d$s 0.49 to 0.77). Taken together, these findings suggest that reduced efficiency of sensory integration may have a considerable role in the neurocognitive consequences of pediatric TBI.

Since sensory integration is crucial for the construction of a full neural representation of our (multi)sensory environment that in turn facilitates efficient interaction with that environment (Calvert, Hansen, Iversen, & Brammer, 2001), the relation between sensory integration and general neurocognitive functioning was investigated. The results of these analyses show that the efficiency of both visual integration and multisensory integration, partially to fully mediate the impact of TBI on general neurocognitive functioning, as defined by intelligence. These findings are consistent with a recent review stating that sensory integration deficits underlie the impact of TBI on neurocognitive functioning (Alwis, Johnstone, Yan, & Rajan, 2013) and studies showing that multisensory integration is predictive of the development of intelligence during childhood (Barutchu et al., 2011; Rose, Feldman, & Wallace, 1992; Rose & Feldman, 1998). Taken together, these findings indicate that reduced (multi)sensory integration may contribute to general neurocognitive impairment in children with TBI.

**IMPLICATIONS FOR CLINICAL PRACTICE**

Part II also has implications for clinical practice. Since it is generally assumed that mild TBI is associated with quick resolution of postconcussional symptoms without residual impairments (Carroll et al., 2004, 2014), it is important for clinical professionals to recognize that children with mild$^{RF+}$ TBI have increased risks of neurocognitive deficits and behavioral problems, even in the absence of evidence for intracranial pathology on conventional neuroimaging. Moreover, part II of this thesis supports the routine follow-up of children with mild$^{RF+}$ TBI using sensitive instruments to screen for symptoms of neurocognitive
and behavioral deficits. Empirical evidence indicates that psychoeducation may also be a useful early intervention to cushion nonspecific effects of mild TBI on postconcussional symptoms and perceived stress (Ponsford et al., 2001).

Part II also indicates that deficits in specific neurocognitive processes may contribute to dysfunction in children with TBI. Clinical professionals involved in the assessment of neurocognitive functioning after pediatric TBI, should be aware that computerized neurocognitive testing might contribute to the sensitivity and specificity of neurocognitive evaluations (Luciana, 2003). Furthermore, advanced modeling of task performance may aid in the interpretation of abnormal test scores. For example, the analysis of individual reaction time distributions in chapter 4 reveals that lapses of attention can account for slowed processing speed, one of the most consistently diagnosed neurocognitive impairments in patients with TBI (Mathias & Wheaton, 2007). These findings indicate that lapses of attention (i.e. short moments of attention loss) represent a core attention deficit in children with TBI, and likely contribute to reduced intelligence and increased attention problems in daily life.

Furthermore, the results indicate that children with moderate/severe TBI have impaired generalization of feedback learning (i.e. difficulty to transfer feedback learning to novel contexts). With regard to rehabilitation treatment, this finding suggests that children with moderate/severe TBI may benefit from context-specific relearning of skills. Given the importance of feedback learning for typical behavioral development (Rushworth & Behrens, 2008), the observed relation between poor generalization of feedback learning and more externalizing problems after pediatric TBI suggests that impaired generalization of feedback learning may contribute to the post-injury development of externalizing behavior. Therefore, children with impaired feedback learning may benefit from interventions aimed at the prevention or reduction of behavior problems after pediatric TBI (Brown, Whittingham, & Boyd, 2013). Lastly, the reported findings show that the Probabilistic Learning Test has good sensitivity and adequate specificity for the presence of clinically significant externalizing problems, potentially reflecting clinical potential for the identification of children at risk of developing externalizing behavior problems after TBI.

Finally, part II indicates that impaired sensory integration may play a relatively prominent role in the neurocognitive consequences of TBI. The effects of pediatric TBI on visual integration and multisensory integration are comparable to the impact on processing speed, one of the most consistently observed neurocognitive impairments in patients with TBI (Mathias & Wheaton, 2007). Since no validated neurocognitive tests of sensory integration currently exist for use in clinical practice, these findings may have modest direct implications for clinical neurocognitive assessments. However, clinical professionals
should be aware that children with TBI are at risk of sensory integration impairments, which may contribute to reduced general neurocognitive functioning (chapter 6 and 7) as well as difficulties in daily life tasks that require efficient coupling of information between multiple sensory modalities (e.g. getting dressed; Galvin, Froude, & Imms, 2009). In the absence of validated psychometric tests for sensory integration, sensory processing in daily life activities may be explored using validated questionnaires such as the Sensory Profile (Dunn, 2014).

LIMITATIONS & STRENGTHS

The research described in part II has some limitations. First, the results are derived from a cross-sectional study. Therefore, patients in the study sample differed in terms of time since injury, introducing heterogeneity in the measurement of neurocognitive and behavioral functioning. Furthermore, the cross-sectional design prevents robust analyses of recovery and post-injury development after pediatric TBI. Second, part II is based on a multi-center study, which may have introduced heterogeneity into the study sample relating to medical treatment differences between centers. Simultaneously, the multi-center patient sample increases the generalizability of the presented results. Third, hospital admission was part of the criteria for inclusion in this study. Since not all children with mild TBI are typically admitted to a hospital, the derived sample of children with mild TBI may be more representative for the more severe end of the mild TBI severity spectrum than for the general mild TBI population. Likewise, children with moderate or severe TBI have been assigned to the moderate/severe TBI group. As a consequence, the reported effect sizes for the effects of moderate/severe TBI may be liberal for children with moderate TBI and conservative for children with severe TBI. Fourth, the study sample of children with mild RF-TBI is relatively small (n = 24). As a consequence, group comparisons involving the mildRF-TBI group may have been subject to limited statistical power. Fifth, the sample of patients with TBI had lower socio-economic status as compared to the TC group. This premorbid difference between study samples may potentially have confounded group comparisons on neurocognitive and behavioral functioning. Therefore, each chapter features analyses that explore the potential influence of socio-economic status differences on the reported group differences. Although socio-economic status is consistently related to poorer neurocognitive performance and more behavior problems, all reported effects of TBI in part II of this thesis are replicated after matching the involved groups on socio-economic status. Although we cannot not completely rule out a potential contribution of socio-economic status to the reported effects of TBI, the results of confounding analyses consistently show that socio-economic status does not account for the reported effects of TBI. Sixth and last, the findings in part II are derived from the same sample of patients.
As a consequence, potential, but unidentified, idiosyncratic characteristics of this patient sample may influence the representativeness of the reported effects for the general TBI population.

The research reported in part II also has strengths. First, children with a hospital admission for traumatic injury not involving the head were included in the trauma control group. This strategy is adopted to account for the influences of premorbid risk factors for traumatic injury, potential psychological effects of hospitalization and effects of surgical treatment (Max, Koele, & Smith Jr., 1998). Second, neurocognitive functioning was assessed using accurate and sensitive computerized tests with in-built control conditions that account for potential confounding influences (e.g. deficits in processing speed or visuomotor control) in the assessment of isolated neurocognitive processes (e.g. lapses of attention, sensory integration). The value of computerized neurocognitive testing is reflected by the results described in chapter 4, where the absence of evidence for deficits in the assessed attention networks contrast findings in the literature (for a review, see Ginstfeldt & Emanuelson, 2010). A compelling explanation for these contrasting findings lies within the widespread use of paper and pencil tasks to measure attention, which often not control for deficits in information processing speed and visuomotor functioning that may co-occur after TBI (Kuhtz-Buschbeck et al., 2003; Mathias & Wheaton, 2007). The Attention Network Tests controls for these confounding factors, and revealed no evidence for an impact of pediatric TBI on alerting, orienting or executive attention. Third, advanced mathematical modeling of task performance was used to study the impact of TBI on neurocognitive functioning. In chapter 4, Ex-Gaussian analysis extends the traditional analysis of task performance by studying the impact of TBI on individual reaction time distributions of correct responses. Consequently, adoption of Ex-Gaussian analysis exposes the presence of increased lapses of attention in children with TBI and reveals that increased lapses of attention account for slowed information processing. In chapter 6 and 7, the diffusion model was used to analyze task performance in sensory integration paradigms. The diffusion model combines reaction time distributions with accuracy data, to break down task performance into the independent contributions of task strategy (i.e. individual speed-accuracy trade-off settings), efficiency of information processing (i.e. sensory integration) and extra-decisional processes (i.e. stimulus encoding as well as preparation and execution of the motor response). The use of the diffusion model exposes the impact of TBI on the efficiency of visual and multisensory integration. Fourth and last, differentiation of mild TBI into mildRF- and mildRF+ TBI reveals for the first time that children with mildRF+ TBI have relatively poor neurocognitive and behavioral outcome in the chronic phase of recovery.
PART III - THE NEUROIMAGING SECTION

SUMMARY OF MAIN FINDINGS

Part III of this thesis aims at elucidating the neuropathological mechanisms that underpin dysfunction following pediatric TBI. This part describes the results of a MRI follow-up study on children with mild\textsuperscript{RF+} TBI or moderate/severe TBI. The study in chapter 9 investigates the predictive values of innovative neuroimaging (i.e. DTI performed in the post-acute phase) and conventional clinical neuroimaging (i.e. acute CT-scans and post-acute conventional MRI). The results show that the impact of mild\textsuperscript{RF+} TBI and moderate/severe TBI primarily manifests on the brain's white matter. Volumetric analysis on post-acute conventional MRI scans show that children with mild\textsuperscript{RF+} TBI or moderate/severe TBI have smaller white matter volume than children in the trauma control group ($d = -0.74$ and $d = -0.80$, respectively). Using tract-based spatial statistics on DTI scans, children with moderate/severe TBI are found to have widespread white matter abnormalities (i.e. lower fractional anisotropy, FA, $d = -1.88$) thought to reflect demyelization and/or axonal degeneration. Interestingly, among the assessed conventional and innovative neuroimaging parameters, lower FA is most consistently related to poorer neurocognitive and behavioral functioning (i.e. intelligence, attention and working memory, encoding in verbal memory and internalizing problems). Voxel-wise regression further shows that FA in parts of the corpus callosum (i.e. genu and body) is consistently related to neurocognitive functioning.

The last study of this thesis, chapter 10, describes how the detrimental impact of TBI on white matter integrity alters the organization of structural connectivity in the brain (i.e. the structural connectome). Probabilistic tractography in combination with graph theory was used to study the impact of pediatric TBI on differential aspects of the connectome, as defined by streamline density (SD; i.e. the connectivity probability network) or FA (i.e. the connectivity integrity network). The findings of this study indicate that various network definitions capture differential aspects of the connectome. The connectivity probability network primarily captured intrahemispheric connectivity, while the connectivity integrity network had higher sensitivity for interhemispheric connectivity. Analyses concerning the impact of pediatric TBI reveal no evidence for effects of mild\textsuperscript{RF+} TBI on the structural connectome. In contrast, children with moderate/severe TBI had higher transitivity ($d = 0.70$) and assortativity ($d = 0.70$) in the connectivity probability network than children in the trauma control group. These findings indicate that moderate/severe TBI increases local clustering (i.e. connectivity between small groups of nodes) and hierarchy (i.e. the tendency of nodes to connect to other nodes with similar importance in the network).
in a network of high probability connections. Simultaneously, children with moderate/severe TBI had increased characteristic path length ($d = 0.75$) in the connectivity integrity network as compared to children in the trauma control group. This finding indicates that moderate/severe TBI decreases structural integration (short distance connections) in a network of high integrity connections. Longer characteristic path length was further related to intelligence and working memory in children with TBI, suggesting that reduced structural integration may be implicated in neurocognitive dysfunction.

**GENERAL DISCUSSION**

Part III of this thesis describes the results of a MRI follow-up on children with mild RF+ or moderate/severe TBI. The results of part III show that various aspects of the brain’s white matter are crucially involved in the neuropathology of pediatric TBI, and are likely implicated in the neurocognitive and/or behavioral consequences that are frequently observed in the chronic phase of recovery.

The results of chapter 9 show that children with mild RF+ TBI and children with moderate/severe TBI have decreased white matter volume as compared to children in the trauma control group. Since no effects of pediatric TBI on grey matter volume were observed, these findings confirm the idea that white matter pathology is a central aspect of the neuropathology associated with TBI (Hayes, Bigler, & Verfaellie, 2016; Sharp, Scott, & Leech, 2014). Chapter 9 is the first study to show that mild RF+ TBI has a detrimental impact on white matter volume. Nevertheless, this finding is consistent with the impact of mild RF+ TBI on neurocognitive and behavioral functioning as reported in part II of this thesis.

Analysis that used DTI to study white matter integrity (chapter 9) additionally show that moderate/severe TBI has widespread detrimental impact on FA, affecting all of the assessed white matter tracts. Analyses assessing the relations between neuroimaging parameters and functional outcome further show that FA relates to intelligence, working memory, encoding in verbal memory and ratings of internalizing problems. In contrast, intracranial abnormality on acute CT-scans is only related to higher internalizing problems, while white matter volume shows no significant relations to the assessed aspects of functional outcome. Taken together, these findings indicate that post-acute DTI is superior in the prediction of functional outcome of pediatric TBI as compared to conventional neuroimaging (i.e. acute CT-scan or post-acute volumetric analysis). These findings extend the current literature showing that DTI has higher sensitivity for white matter pathology following TBI as compared to conventional neuroimaging parameters (Mac Donald et al., 2011; Niogi & Mukherjee, 2010), and further add to the existing literature indicating that white matter pathology importantly contributes to neurocognitive deficits and behavior problems after pediatric TBI (Roberts, Mathias, & Rose, 2016).
Voxel-wise regression analysis between white matter integrity and functional outcome further revealed that FA in the corpus callosum (i.e. genu and body) is consistently related to neurocognitive functioning (intelligence, working memory and encoding in verbal memory). These findings may be suggestive of a pivotal role of the corpus callosum in a range of neurocognitive deficits after pediatric TBI. Alternatively, DTI parameters may have superior sensitivity to the impact of TBI in the corpus callosum. As compared to the kissing and crossing tracts in the intrahemispheric white matter, the corpus callosum harbors interhemispheric tracts with relatively uniform directionality (Basser, Pajevic, Pierpaoli, Duda, & Aldroubi, 2000). This relatively uniform directionality of tracts is likely to be associated with lower variability in the directionality of water diffusion, which may in turn decrease the measurement error of DTI parameters in the corpus callosum. According to this reasoning, the relatively high sensitivity of DTI parameters in the corpus callosum to the impact of TBI (Aoki & Inokuchi, 2016) and functional outcome after TBI (Roberts et al., 2016), may be the result of intrinsic physical properties of the corpus callosum, in addition to its implication in the structural and functional consequences of TBI.

The study in chapter 10 assesses the impact of TBI on the structural connectome. Various network definitions were used to reconstruct the structural connectome, showing that the measure that is used to define connectivity greatly influences the characteristics of the reconstructed network, both in terms of sensitivity to interhemispheric connectivity and sensitivity to the impact of TBI. More specifically, the use of SD captures a network of high probability connections (i.e. the connectivity probability network) that is primarily sensitive to intrahemispheric connectivity. Accounting for FA in the connectivity probability network increases the sensitivity of this network for interhemispheric connectivity. Furthermore, the use of FA captures a network of high integrity connections (i.e. the connectivity integrity network) that is predominantly sensitive to interhemispheric connectivity. Although it is known that network definition can influence network properties (Qi, Meesters, Nicolay, Romeny, & Ossenblok, 2015), the study in chapter 10 is the first to show the impact of network definition on the representation of interhemispheric connectivity in the reconstructed structural connectome.

The analyses in chapter 10 reveal no evidence for an impact of mildRF+ TBI on the structural connectome. This finding partly contrasts the results from chapter 9, where children with mildRF+ TBI show to have smaller white matter volume than children with trauma control injury. Taken together, these findings suggest that mildRF+ TBI may have a direct detrimental impact on white matter volume and/or post-injury white matter development, but does not affect the organization of structural connectivity.
Contrasting with the findings on mild\textsuperscript{RF+} TBI, the findings of chapter 10 show that moderate/severe TBI alters structural connectivity in the child’s connectome. More specifically, children with moderate/severe TBI have higher \textit{transitivity} and higher \textit{assortativity} in the connectivity probability network, indicating increased local clustering and increased hierarchy in a network of high probability connections. These findings may be primarily attributable to intrahemispheric connections, given the observed sensitivity of the connectivity probability network for intrahemispheric connectivity. When accounting for white matter integrity in the connectivity probability network, children with moderate/severe TBI also have increased \textit{characteristic path length}, indicative of reduced structural integration. The study in chapter 10 is the first to show the impact of moderate/severe TBI on the structural connectome in children. The observation of increased \textit{characteristic path length} converges with previous studies on adult TBI (Caeyenberghs et al., 2012, 2014; Kim et al., 2014) and is consistent with the idea that TBI shifts the structural connectome away from a small-world topology (Sharp et al., 2014).

With regard to the connectivity integrity network, children with moderate/severe TBI also have longer \textit{characteristic path length} than children in the trauma control group, indicating that moderate/severe TBI reduces structural integration in this network of high integrity connections. This effect of moderate/severe TBI on \textit{characteristic path length} is also observed in the backbone of the connectivity integrity network, as exposed using the minimum spanning tree (an acyclic network connecting all nodes in a network, while minimizing network cost, i.e. maximizing the sum of the total link weight; see Stam et al., 2014). Given the relative sensitivity of the connectivity integrity network for interhemispheric connectivity, the impact of moderate/severe TBI on \textit{characteristic path length} may be primarily applicable to interhemispheric connections. \textit{Transitivity} and \textit{assortativity} in the connectivity probability network and \textit{characteristic path length} in the connectivity integrity network shared only moderate relationships, indicating that these measures reflect aspects of the TBI neuropathology.

Lastly, chapter 10 also assesses the relations between network parameters and functional outcome after pediatric TBI. The findings show that longer \textit{characteristic path length} is related to poorer intelligence (in the connectivity probability network) and working memory (in the connectivity probability and connectivity integrity networks). These findings indicate that reduced structural integration may be implicated in the neurocognitive deficits that are frequently observed in children with TBI. The results reveal no evidence for relations between network parameters and ratings of behavior problems, for which a clear explanation remains to be found. Possibly, behavioral functioning after pediatric TBI is not related to global connectivity, but is rather dependent on more
SUMMARY & GENERAL DISCUSSION

Specific (e.g. frontostriatal) subnetworks (Max, Wilde, & Bigler, 2012). Interestingly, longer characteristic path length in the backbone of the connectivity integrity network is related to better working memory performance. The counter-intuitive direction in this relationship suggests that increased characteristic path length in the backbone of the connectivity integrity network may reflect an adaptive plasticity response, attempting to reconnect the disintegrated network by reorganizing its structural backbone (with high integrity connections) in a more distributed fashion.

IMPLICATIONS FOR CLINICAL PRACTICE

The findings presented in part III of this thesis support the notion that the impact of TBI primarily manifests on the child’s white matter. The results in chapter 9 show that presence of intracranial pathology on acute CT-scans has predictive value for more internalizing problems. Likewise, the results indicate that post-acute white matter volume derived from conventional structural MRI (i.e. T1 scans) has no predictive value for neurocognitive or behavioral functioning. These findings indicate that conventional neuroimaging methods have limited predictive value for the functional outcome of pediatric TBI. In contrast, DTI had superior sensitivity for functional outcome after pediatric TBI, showing predictive value for neurocognitive functioning (i.e. intelligence, working memory, and encoding in verbal memory) and behavioral functioning (i.e. internalizing problems). Taken together, clinicians should acknowledge the limited predictive value of conventional neuroimaging parameters for functional outcome of pediatric TBI, and facilitate (research aimed at) the implementation of diffusion weighted imaging in clinical practice.

LIMITATIONS & STRENGTHS

Part III describes the results of a follow-up on a patient subsample derived from the larger cohort described in part II of this thesis. Therefore, most of the limitations of part II also apply to part III. In addition, part III has some specific limitations. First, the investigated patient sample has a relatively small sample size ($n = 63$), especially in terms of the moderate/severe TBI group ($n = 16$). Consequently, the described group comparisons had modest statistical power, and the results should be replicated to confirm their representativeness for the general pediatric TBI population. Second, the adapted cross-sectional study design is suboptimal to investigate the predictive value of neuroimaging parameters for functional outcome. Although the described associations between neuroimaging parameters and aspects of functional outcome provide clear evidence supporting the superior prognostic potential of DTI as compared to more conventional neuroimaging parameters, the true prognostic value of post-acute DTI for long-term
functional outcome should be elucidated in a longitudinal study design. Third and last, a limited set of instruments was used to measure outcome in terms of neurocognitive and behavioral functioning.

The research described in part III also has some specific strengths. First, the use of innovative neuroimaging methodology in combination with measures of functional outcome has revealed the relevance of specific aspects of the TBI neuropathology. This type of research is critical to guide the translation of neuroscientific findings into clinical practice. Second, innovative neuroimaging methodology was applied to investigate the neuropathology of TBI. For example, the study in chapter 9 is the first to use tract-based spatial statistics (TBSS) as a model-free method to study the impact of pediatric TBI on white matter integrity. TBSS overcomes the selection of regions of interest, which is highly heterogeneous between studies, is prone to investigator bias and may provide incomplete information about the regional effects of TBI on white matter integrity. Furthermore, the study in the chapter 10 is the first to study the impact of pediatric TBI on the structural connectome in the chronic phase of recovery. The use of probabilistic tractography in combination with graph theory contributes to our understanding of the white matter pathology of pediatric TBI. Third and last, the instruments that were used to measure neurocognitive and behavioral outcome are in line with the recommendations for the use of Common Data Elements in the assessment of outcome after pediatric TBI (McCauley et al., 2012). This strategy answers to a recent call for more homogeneous outcome measurement in research on the relation between DTI and neurocognitive functioning (Roberts et al., 2016) and maximizes the scientific and clinical utility of the reported study findings.
RESEARCH AGENDA

To conclude this thesis, the reported findings are translated into directions for future research.

STANDARDIZED DUTCH INSTRUMENT FOR PTA DURATION IN CHILDREN

Part I of this thesis shows that the GCS score, LOC duration and PTA duration have strong predictive value for long-term general neurocognitive outcome in patients with TBI. Nevertheless, marked heterogeneity is observed in the definition of PTA and methodology used to measure PTA duration. These findings indicate that prospective measurement of PTA duration using a standardized instrument may increase the validity and reliability of PTA recording. Multiple standardized and validated instruments for the measurement of PTA duration are available in English, such as the Galveston Orientation and Amnesia Test (Levin, O’Donnell, & Grossman, 1979), Children’s Orientation and Amnesia Test (Ewing-Cobbs, Levin, Fletcher, Miner, & Eisenberg, 1990) Orientation Group Monitoring System (Mysiw, Bogner, Arnett, Clinchot, & Corrigan, 1996), Orientation Log (Jackson, Novack, & Dowler, 1998), Westmead PTA Scale (Ponsford et al., 2004) and Westmead PTA scale for children (Rocca, Wallen, & Batchelor, 2008). For clinical practice in the Netherlands, a Dutch version of the Orientation Log is available for adults with TBI (Schmand, 2001). However, no instrument is available for the assessment of PTA duration in Dutch children. Future research should therefore be aimed at the development of a Dutch version of an existing and validated measure of PTA duration for use in children with TBI. The Common Data Elements for the measurement of injury severity recommend use of the Children’s Orientation and Amnesia Test for the measurement of PTA duration in children (McCauley et al., 2012), which would therefore be a useful instrument to translate into the Dutch language.

ADVANCED NEUROCOGNITIVE TESTING

As in clinical practice, advanced neurocognitive testing may importantly contribute to the accuracy and reliability of measurement in empirical research. Computerized neurocognitive testing allows researchers to isolate specific neurocognitive processes and control for the confounding influences of commonly co-occurring neurocognitive deficits after TBI (e.g. slowed processing speed or reduced visuomotor control). The interpretation of task performance in clinical research can also be importantly improved by the application of mathematical methods that take inter-individual data distributions into account. For example, Ex-Gaussian analysis has also proven its value to study the
consistency of task performance in other clinical pediatric populations (Conklin et al., 2010; de Kieviet, van Elburg, Lafeber, & Oosterlaan, 2012; Leth-Steensen, Elbaz, & Douglas, 2000). As a more holistic alternative in the analyses of task performance, the diffusion model combines reaction time distributions and accuracy data to break down task performance into the independent contributions of task strategy (i.e. individual speed-accuracy trade-off settings), efficiency of information processing and extra-decisional processes (e.g. stimulus encoding as well as the preparation and execution of the motor response). The diffusion model is a compelling tool to solve the problematic differential interpretation of reduced performance on the reaction time vs. accuracy metric, and is additionally sensitive to the spread of effects of interest over the reaction time and accuracy metrics (Voss, Nagler, & Lerche, 2013).

In addition to the use of computerized neurocognitive testing and advanced modeling of task performance for empirical purposes, future research may also contribute to the implementation of these methods in clinical practice to complement traditional neurocognitive testing. Therefore, the psychometric properties of computerized neurocognitive tests should be comprehensively assessed and, if necessary, improved to meet guidelines for clinical testing in individual patients (see Evers, Lucassen, Meijer, & Sijtsma, 2009 for Dutch guidelines). Other challenges to the implementation of computerized neurocognitive testing in clinical practice lie within the design of easy-to-administer computer tests that are compatible with a wide range of available hardware and operating systems, while still producing consistent results.

The findings of chapter 6 and 7 further suggest that measures of sensory integration are relatively sensitive to the impact of TBI. Since reduced efficiency of sensory integration also is related to intelligence in children with TBI, sensory integration deficits may have a relatively prominent role in the neurocognitive consequences of pediatric TBI. Future research could test the hypothesis that disrupted neural connectivity underlies impaired reduced sensory integration in children with TBI (e.g. in terms of white matter integrity, structural and functional connectivity). Likewise, research into the relation between sensory integration and daily life functioning (e.g. parent and teacher reports on the Sensory Profile; Dunn, 2014), could clarify the ecological validity of sensory integration testing. If future research adds to the evidence that currently supports the value of sensory integration, this domain may potentially be considered to complement the neurocognitive assessment of children with TBI in clinical practice.
LONGITUDINAL COHORT STUDIES

The results of this thesis identify several neuropathological and neurocognitive mechanisms that are likely to contribute to dysfunction in children with TBI. These findings call for the execution of longitudinal research testing the contributions of reduced white matter integrity, changes in the structural connectome, lapses of attention, impaired generalization of feedback learning and reduced efficiency of sensory integration for the initial recovery and long-term post-injury development of neurocognitive and behavioral functioning after pediatric TBI. The ecological validity of such studies can be further extended by the inclusion of academic functioning as one of the outcome measures. In order to improve the representativeness of the study sample for the general TBI population, longitudinal studies should ideally be based on consecutive cohorts recruited from a multicenter network of trauma level I centers, where measurements are part of routine outcome monitoring (Boswell, Constantino, Kraus, Bugatti, & Oswald, 2016) and align with recommendations for the use of Common Data Elements (McCauley et al., 2012). Furthermore, premorbid functioning should be assessed as detailed as possible. Although premorbid measurements of neurocognitive functioning are very difficult (if not impossible) to obtain systematically, premorbid behavioral functioning of children with TBI can be investigated by administering parent and teacher questionnaires shortly after hospital admission. The existence of standardized pupil monitoring systems that are often implemented in primary schools, further provide a unique opportunity to systematically collect psychometrically robust measurements of premorbid as well as post-injury academic functioning (Glas & Geerlings, 2009). Lastly, the recruitment of a trauma control group is essential to account for premorbid risk factors for trauma and psychological effects of hospitalization on the outcome of TBI (Max et al., 1998). Longitudinal research with a robust design not only contributes to a better understanding of functional outcome and post-injury development, but also can importantly contribute to the accuracy and reliability of the prognosis for pediatric TBI.

MULTIMODAL PROGNOSTIC MODELS

The neuropathological and neurocognitive abnormalities in children with pediatric TBI described in the current thesis are consistently related to general neurocognitive functioning (e.g. intelligence) and/or behavioral functioning (e.g. parent and teacher reports of behavior problems), validating the clinical relevance of our findings. At the same time however, the strength of these relations between neuroimaging parameters (e.g. FA or network parameters) and specific neurocognitive functions (e.g. lapses of attention, generalization of learning, sensory integration) on one hand, and general
neurocognitive and behavioral functioning on the other hand; is modest in most cases (typically not accounting for more than 30% in the variance of the assessed outcome variables). This is consistent with the available evidence indicating that TBI is a complex disorder, where neurological, neurocognitive and behavioral mechanisms interact with premorbid functioning, post-injury development and environmental factors to influence functional outcome of TBI (Catroppa et al., 2016).

The complexity of TBI requires the construction of innovative prognostic models, combining the strongest predictors within the domains of demographics, premorbid functioning, injury severity, neuroimaging, acute neurocognitive functioning and family functioning to predict long-term outcome of pediatric TBI in terms of neurocognitive, behavioral and academic functioning. The accuracy and reliability of traditional prognostic models may be importantly improved by the use of machine learning algorithms for variable selection and prediction model construction. For example, the elastic net (Zou & Hastie, 2005) is a powerful and flexible method to improve variable selection in regression models (Cleophas & Zwinderman, 2013b). Furthermore, support vector machine learning revealed its high potential to improve patient classification in medical research (Cleophas & Zwinderman, 2013a) and recently in the field of adult TBI (Fagerholm, Hellyer, Scott, Leech, & Sharp, 2015).

Although often overlooked in clinical research, prognostic models require external validation to replicate their prognostic value for in independent patients samples (Maas et al., 2015). The CRASH and IMPACT databases have produced the only externally validated prognostic models for adult TBI (Roozenbeek, Lingsma, Lecky, & Lu, 2012), which can be used for mortality prognosis and prognosis of unfavorable outcome based on the Glasgow Outcome Scale. Unfortunately, no prognostic models are available for more fine-grained but highly relevant aspects of functional outcome, such as general neurocognitive functioning, behavioral functioning or return to work. Likewise, no externally validated prognostic models are available for children with TBI, while there is strong evidence for differential recovery patterns after pediatric and adult TBI (chapter 3 of this thesis).

DIFFUSION TENSOR IMAGING IN CLINICAL PRACTICE

The existing literature indicates that DTI has superior sensitivity for essential aspects of the TBI neuropathology (i.e. diffuse axonal injury) as compared to conventional neuroimaging methodologies (Mac Donald et al., 2011; Niogi & Mukherjee, 2010). Part III of this thesis further supports the existing literature indicating that DTI also has superior sensitivity for the prediction of functional outcome after pediatric TBI (Roberts et al., 2016). However, the actual implementation of DTI as a prognostic tool is currently hampered by systematic
between-scanner differences in DTI parameters (Fischer et al., 2012). Future research should therefore aim at reducing these differences, for example by further standardizing imaging protocols (e.g. voxel size, repetition time, echo time, gradients) between scanning sites. Diminishing between-scanner differences in DTI parameters could pave the way for the development of clinical cut-offs with high sensitivity and specificity for the prediction of functional outcome after TBI.
REFERENCES


