Investigating the effects of acute intracranial pressure and brain oxygenation on neuropsychological outcomes 12 months after severe pediatric traumatic brain injury.

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Declaration

I hereby declare that this submission is my own work, both in concept and execution, and that to the best of my knowledge and belief it contains no material written by another person nor material that has been accepted for an award of any other degree or diploma of the university or other institute of higher learning, except where due acknowledgement has been made in the text.

Signed by candidate

Lydia Dodge (Mrs) Date

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By Your grace, for Your glory.

Abbreviations

ACSENT	Applied Cognitive Science and Experimental Neuropsychology Team
ADAPT	Approaches and Decisions in Acute Pediatric TBI Trial
AIDS	Acquired Immune Deficiency Syndrome
BRIEF	Behaviour Rating Inventory of Executive Function
BRI	Behavioural Recognition Index
CBCL	Child Behaviour Checklist
CBF	Cerebral Blood Flow
CI	Confidence Intervals
CMS	Children's Memory Scale
CNS	Central Nervous System
CPP	Cerebral Perfusion Pressure
CT	Computed Tomography
CVLT-C	California Verbal Learning Test- Children
DAI	Diffuse Axonal Injury
D-KEFS	Delis-Kaplan Executive Function System
DSM	Diagnostic and Statistical Manual of Mental Disorders
ED	Emergency Department
FSIQ	Full Scale IQ
GCS	Glasgow Coma Scale
GEC	Global Executive Composite
GHS	Groote Schuur Hospital
GOS	Glasgow Outcome Scale
GOS-E Peds	Glasgow Outcome Scale-Extended Pediatrics
Hb	Hemoglobin Concentration
HI	Head Injury
HIV	Human Immunodeficiency Virus
HRQOL	Health Related Quality of Life
ICP	Intracranial Pressure
IQ	Intelligence Quotient
MAP	Mean Arterial Pressure
MVA	Motor Vehicle Accident

MI	Metacognition Index
OECD	Organisation for Economic Co-operation and Development
PaO_2	Partial Pressure of Oxygen
$PbtO_2$	Partial Pressure of Brain Tissue Oxygen
PedsQL	Pediatric Quality of Life Inventory
PICU	Pediatric Intensive Care Unit
PIQ	Performance IQ
PSI	Processing Speed Index
pTBI	Pediatric Traumatic Brain Injury
QOL	Quality of Life
RXH	Red Cross War Memorial Children's Hospital
SES	Socio-Economic Status
TBI	Traumatic Brain Injury
TEA-Ch	The Test of Everyday Attention for Children
UCT	University of Cape Town
U.K.	United Kingdom
U.S.	United States of America
VIQ	Verbal IQ
WASI	Wechsler Abbreviated Scale of Intelligence
WISC	Wechsler Intelligence Scale for Children

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Abstract

Traumatic brain injury (TBI) is one of the major causes of mortality and morbidity among children and adolescents all over the world and studies suggest a higher incidence of pediatric TBI (pTBI), as well as poorer post-TBI outcomes, in countries with extreme levels of socioeconomic inequality such as South Africa. pTBI leads to a multitude of long-term adverse outcomes in a wide range of domains and in general, a dose-response pattern is evident. Multiple acute and post-acute stage predictors of outcome have been investigated, however acute stage neurological and neurosurgical variables are relatively absent from this knowledge base. This study was conducted to better understand the heterogeneity in outcomes of pTBI: it aimed to investigate the nature and severity of neuropsychological deficits in pTBI patients one year after injury and to investigate the association between acute stage physiological changes in intracranial pressure (ICP) and brain tissue oxygenation ($PbtO_2$) and neuropsychological outcomes one year after pTBI. Results of the study indicated that children who sustained TBI performed significantly poorer than healthy, matched controls on multiple cognitive, behavioural and quality of life domains, however, neither acute ICP nor $PbtO_2$ reliably predicted within-TBI group performance. The results of the study emphasise the poor relationship of ICP and $PbtO_2$, and the complexity of the relationship between acute physiological variables and outcomes after pTBI. Further studies of this kind should be done on large sample sizes and include multiple physiological variables.

Investigating the effects of acute intracranial pressure and brain oxygenation on neuropsychological outcomes 12 months after severe pediatric traumatic brain injury.

Traumatic brain injury (TBI) is one of the major causes of mortality and morbidity among children and adolescents across geographic and demographic boundaries all over the world (Dewan, Mummareddy, Wellons, & Bonfield, 2016). In countries such as the United States of America (U.S.), where diseases and nutrition are well controlled, unintentional injury, including TBI, is the leading cause of death in children aged between 1 and 14 years (Babikian & Asarnow, 2009; Bartlett, 2002, Ichkova, et al., 2017). Children and adolescents are especially vulnerable to injury and particularly to TBI; incidence of TBI in this age group (0-18 years) is much higher than in adults and the elderly, representing an exceedingly common disruption to normal development (Anderson & Yeates, 2010; Bartlett, 2002; Bruns & Hauser, 2003).

A recent study by Chen and colleagues (2017) found that between the years 2006 and 2013, over 6 million children and adolescent emergency department (ED) visits in the U.S. had a diagnosis of TBI[1] and although the rate of severe TBI decreased by 18.4% during this period, the overall rate of TBI increased by 34.1% during this time. This study also found that among their sample of 0- to 17-year-olds, children aged 1-4 years had the highest rate of TBI-related ED visits, and children under 4 had the highest incidence of severe TBI (Chen, et al., 2017). This is in keeping with an earlier study which found that between the years 2002 and 2006 in the U.S., children aged 0 to 4 years had the highest rate of TBI-related ED visits of all age groups (including ages 0 - ≥75 years) at 1 256 per 100 000 population, followed by children aged 15 to 19 years at 757 per 100 000 population (Faul, Xu, Wald, & Coronado, 2010).

It has been estimated that 98% of global pediatric accident-related deaths occur in the poorest countries of the world (UNICEF, 2001). While there remains an overall dearth of reported data in this domain, research suggests a higher incidence of childhood TBI in settings of socioeconomic deprivation (Bruns & Hauser, 2003; Dewan, et al., 2016; Hyder Wunderlich, Puvanachandra, Gururaj, & Kobusingye, 2007 et al., 2007). For example, studies that have been performed in the United Kingdom (U.K.) and U.S. suggest a higher incidence of TBI in children from poorer backgrounds (Dewan, et al., 2016; Parslow, Morris, Tasker, Forsyth, & Hawley, 2005; Reid, Roesler, Gaichas, & Tsai, 2001). In addition, research consistently suggests that outcomes of pediatric brain injury in countries such as

[1] When the ICD-9-CM diagnosis code for unspecified head injury (code 959.01) was included.

South Africa, with extreme levels of socioeconomic inequality among its people, are worse than in high income countries (Bartlett, 2002; Bruns & Hauser, 2003; Hyder, et al., 2007; D. Naidoo, 2013). Despite this, there is a great paucity of pediatric traumatic brain injury (pTBI) research emerging from such countries.

Defining TBI

TBIs are acquired injuries to the brain resulting from external forces, which cause an alteration in brain function, and which may manifest as changes in consciousness, confusion, seizures, or focal neurologic deficits. These injuries result in varying degrees of functional disability and/or psychosocial impairments which may persist many years after the injury (K.A Allen, 2016; Babikian, Merkley, Savage, Giza, & Levin, 2015; Bruns & Hauser, 2003; Faul, et al., 2007). The forces which produce TBIs are most commonly caused by falls and motor vehicle accidents (MVA). Causes of TBI are however, strongly related to individual demographic and geographic characteristics such as age, SES, sex, rural vs. urban settlement, type of housing, population density, and more (Bruns & Hauser, 2003; Dewan, et al., 2016; Faul, et al., 2010; Hyder, et al., 2007). For instance, passenger-related MVAs account for a larger proportion of pTBI in higher income countries, whereas pedestrian MVAs are the more likely mechanism of injury in lower income countries (Dewan, et al., 2016). Another example of this association is the greater proportion of violence-related TBIs being associated with areas of dense population, lower income, higher rates of unemployment, higher crime rates and substance use (Bruns & Hauser, 2003).

Traditionally, TBI is biomechanically characterised as either open, when the skull, meninges or the brain is penetrated by an external agent, or closed, when the brain moves abruptly within the skull, without being penetrated by an external force (Babikian, et al., 2015; Chua & Kong, 1999; Di Battista, Soo, Catroppa, & Anderson, 2012; Osborn, 2012). Another classification system commonly employed pertains to mechanisms of neuropathology and divides TBI into either 1) focal brain insults (insults to neurons and glia at specific locations) as a result of contact injury causing circumscribed areas of contusion, abrasion, laceration and intracranial hemorrhage, or 2) diffuse brain insults (insult to axons) resulting from acceleration or deceleration forces causing wide-spread axonal injury and edema (Marshall, 2000; Werner & Engelhard, 2007).

It is further important to understand the pathophysiology underlying TBI because knowledge of pathophysiological injury progression is crucial in preventing the development of secondary injuries associated with poorer outcome (K. A Allen, 2016).

Pathophysiology of TBI. TBI is pathophysiologically subdivided into primary and secondary injuries. Primary injuries can result from linear or rotational forces from direct, forceful head impacts applied to the brain at the point of impact. Primary injuries may also result from acceleration and deceleration forces in the absence of a physical head impact, causing diffuse axonal injury (DAI), characterised by widespread damage to axons from tearing and shearing sustained during the injury (K.A. Allen, 2016; Margulies & Coats, 2010; D. Naidoo, 2013; Osborn, 2012). The effects of the structural changes caused by primary injuries on long-term post-TBI outcomes are near impossible to isolate, however, given that secondary injuries are set in motion very rapidly post-injury in a complex molecular and physiological cascade (K.A. Allen, 2016).

Secondary injury refers to a range of effects set in motion by the primary injury which occurs hours, days or even weeks post-injury; an increased length of time spent in the secondary injury period increases the likelihood of long-term disability post-TBI (K.A. Allen, 2016). Secondary injuries include, among a multitude of possible effects, inflammatory responses, edema, hypoxic or anoxic events, mitochondrial and metabolic disruption, vascular damage, perfusion alterations, elevated intracranial pressure, and herniation, and add considerably to the severity of the TBI (K.A. Allen, 2016; Margulies & Coats, 2010; D. Naidoo, 2013; Osborn, 2012). Most prominent of these mechanisms in the development of secondary injury is cerebral edema and alterations in cerebral blood flow (CBF), the continued compromise of which results in cell damage and death (K.A. Allen, 2016; Mandera, Larysz, & Wojtacha, 2002).

Preventing or minimising this secondary damage and thereby improving prognostic outcome is the target of medical intervention and of research into establishing new, effective treatment strategies (Werner & Engelhard, 2007). Acute intervention according to pediatric-specific guidelines aimed at reducing the occurrence of secondary injuries is especially important in pTBI as it has been found that the child brain reacts differently to injury than the adult brain (K.A. Allen, 2016; Figaji, 2017; Margulies & Coats, 2010).

Pathophysiology of pTBI. Until very recently, researchers and clinicians operated under the assumption that the properties of the adult brain and child brain were equal. In reality, the skull, brain and spinal cord of children is different to that of adults in a variety of ways; these differences sometimes leave them more vulnerable to TBI (Figaji, 2017; Margulies & Coats, 2010). Generally, it has been found that children have 'stiffer' brain tissue, a thinner and less rigid skull, and proportionately larger, heavier heads with weaker cervical ligaments and muscles than adults (K.A. Allen, 2016; Calder, Hill, & Scholtz, 1984;

Figaji, 2017; Margulies & Coats, 2010). These factors all arguably make children more vulnerable to sustaining brain injury. In addition, there are physiological differences between adult and child brains which affect the way the child responds to brain injury and impact on treatment guidelines. These include differences in cerebral metabolism, CBF, general blood volume, susceptibility to hypothermia, intracranial pressure (ICP) and blood pressure, among others, which all change as the child ages (Figaji, 2017). Differences in mechanisms of TBI in children have also been noted between adult and child TBI patients (Figaji, 2017).

In summation, because the young brain develops so rapidly, pTBI cannot be compared to injuries to the adult brain, and the treatment and care regimes of adult injuries cannot be generalised to children. Additionally, because of the significant changes in the central nervous system (CNS) as children age, they must be treated as a heterogenous group themselves in the context of TBI (Figaji, 2017).

TBI Severity. Although multiple injury-related factors contribute to overall injury severity, TBI severity is most commonly delineated on a 3-tier scale (mild, moderate and severe) using the Glasgow Coma Scale (GCS)[2] score at the point of initial presentation (Dewan, et al., 2016).

In keeping with previous literature, Dewan, Mummareddy, Wellons III, and Bonfield (2016) found that mild TBI comprises >80% of pediatric brain injuries. Although most cases of TBI are mild and result only in minimal behavioural or neuropsychological changes, a portion of children and adults experience more severe TBI, which accounts for most of the long-term deficits and mortality associated with TBI (Bruns & Hauser, 2003; Hyder, et al., 2007; Moran, et al., 2016).

Severe pTBI. Severe TBI is characterised by a GCS score of 8 or less out of 15 (Babikian & Asarnow, 2009). Consistent with the widely recognised dose-response relationship between injury severity and outcome (Anderson & Catroppa, 2005; Anderson, Godfrey, Rosenfeld, & Catroppa, 2012, Babikian & Asarnow, 2009), research has reliably found that children who sustain severe TBI have the worst post-injury outcomes and are at an increased risk for persisting deficits and slower skill and functional development over time compared to children who sustain mild (GCS score of 13-15) and moderate (GCS score of 9-12) TBIs. This is true across multiple domains including attention, working memory, verbal

[2] The Glasgow Coma Scale (Teasdale & Jennett, 1974) is an instrument that is commonly used to classify injuries. The GCS assesses level of impaired consciousness or coma as a score out of 15 based on 3 factors: eye opening, verbal responses and motor responses.

memory, processing speed and IQ (Anderson, et al., 2012; Babikian & Asarnow, 2009; Babikian, et al., 2015; Lajiness-O'Neill, Erdodi, & Bigler, 2010).

Compared to adult TBI, childhood brain injury more often results in ongoing neuropsychological, educational, psychiatric, social and emotional impairments as development progresses. Effective acute and long-term intervention is therefore of highest importance to minimise the enduring effects of the "silent epidemic" (Semple, Bass, & Peter, 1998, p. 440) of childhood TBI. Acute and long-term management of pTBI is significantly complicated by the fact that insults to the developing brain are influenced by a wide range of different contextual and developmental factors than in adult TBI. These factors impact on the neuropathological mechanisms of injury, subsequent outcomes, recovery trajectory, and rehabilitation success (Anderson & Yeates, 2010). Effective protocols for the prevention and treatment of pTBI in South Africa therefore relies on epidemiological data specific to the unique context of the country (D. Naidoo, 2013).

pTBI in South Africa

Few epidemiological studies have been done on pTBI in South Africa. Some of these studies fail to differentiate between pediatric head injuries and pTBI more specifically[3]. The findings of these studies are summarised in Table 1. These studies reveal that pediatric (head- and) brain injury is one of the most devastating consequences of South Africa's exceptionally high incidence of MVAs. South Africa's road traffic fatality rate ranks among the top 10 countries in the world with a rate of 25.1/100 000 population, far above the global average of 17.4/100 000 (N. Naidoo & Muckart, 2015; World Health Organisation, 2015). The high rate of MVAs is however not the only risk factor which predisposes South Africa to a high rate of pTBI; the high incidence of interpersonal violence has also been identified as contributing to childhood TBI and its outcomes in South Africa (Levin, 2004).

[3] Head injury is a non-specific term which encompasses external injuries to the face, scalp and skull which may or may not include injury to the brain. TBI specifically refers to injuries to the head resulting in an alteration in brain function (Bruns & Hauser, 2003; Hyder, et al., 2007).

Table 1:

Summary of pTBI prevalence studies in South Africa

Study Characteristics	De Villiers, Jacobs, Parry and Botha (1984)	Semple, Bass, and Peter (1998)	Lalloo and van As (2004)	Schrieff, Thomas, Dollman, Rohlwink, and Figaji (2013)	Naidoo and Muckart (2015)
Time frame	1966-1981	1990-1993	1991-2001	2006-2011	2008-2012
Sample	Children under 15 years admitted to RXH* and Groote Schuur Hospital, Western Cape, with head injury (HI).	Children under 14 years admitted to RXH, Western Cape, with severe HI.	Children under 13 years presenting to RXH, Western Cape, with HI.	Children under 15 years admitted to RXH, Western Cape, with severe TBI requiring intracranial monitoring.	Children under 16 years of age admitted to Chief Albert Luthuli Central Hospital, KwaZulu-Natal, with traumatic injuries.
Sample size	1820	102	Total: 37 610; TBI patients: 3384 (9%)	137	Total: 181; TBI patients: 112
Mortality rate	22.5%	56.86%	Total: 0.2%	14.60%	Total: 14.4%; TBI patients: 20.54%
Most common cause	71.7% of HI in children under 1 year caused by falls. 53.3% of HI in children 1-14 years caused by transport related injuries	81.37% of HIs caused by pedestrian MVAs	41% of HIs caused by falls, 19% of HIs caused by traffic-related injuries	79.56% of severe TBIs caused by MVAs, most as a result of pedestrian MVAs.	88.4% of total deaths caused by MVAs, most as a result of pedestrian MVAs.

* *RXH: Red Cross War Memorial Children's Hospital*

Neuropsychological Outcomes of pTBI

Childhood brain injury can lead to a multitude of adverse outcomes which extend far beyond the acute injury phase. In addition to deficits evident immediately after injury, longitudinal studies of pediatric TBI have found that due to the disruption to rapid neural development, children who sustain TBI often experience a 'flatter' developmental trajectory than typically developing children leading to some deficits only becoming evident as the child ages. This has been found to be especially true when children sustain severe TBI at a younger age (Anderson, Catroppa, Morse, Haritou, & Rosenfeld, 2005). Long term impairments after pTBI have been noted in cognitive, social, behavioural, functional, developmental, psychiatric, familial, environmental and academic domains (Anderson, et al., 2012; Babikian & Asarnow, 2009; Babikian, et al., 2015; Catroppa, et al., 2009).

It is, however, important to note that these deficits, as they are reported in most research, are detected at the level of the group. Approaches that investigate outcomes of pTBI at the level of the individual, including clinical practice, often find significant heterogeneity in the outcomes of pTBI (Anderson & Yeates, 2010; Bigler, et al., 2013; Babikian & Asarnow, 2009; Fay, et al., 2009; Figaji, Fieggen, Mankahla, Enslin, & Rohlwink, 2017; Moran, et al., 2016).

Cognitive outcomes after severe pTBI. There is substantial evidence for within-group variability with regard to cognitive recovery post pTBI; research has suggested that a relatively small portion of children with more severe TBI experience significant impairment in the long-term (Fay, et al., 2009; Moran, et al., 2016). Researchers report that children who sustain severe TBI experience the most debilitating long-term deficits in the domain of cognition, above other outcome domains (Babikian & Asarnow, 2009; Anderson, et al., 2012). Whilst causing significant disability in its own right, cognitive impairments also amplify the adverse effects of TBI on academic performance, behaviour and social functioning (Babikian & Asarnow, 2009).

Multiple studies report evidence for substantial recovery of cognitive function within 1 to 2 years post-TBI after which recovery typically plateaus. Despite this, children who sustain moderate to severe TBI usually lag behind their peers in the cognitive domain (Anderson, et al., 2005; Babikian & Asarnow, 2009; Fay, et al., 2009; Moran, et al., 2016). Meta-analytic review findings have indicated that children who sustain moderate and severe TBI have greater long-term impairments across cognitive domains, and on average perform approximately 0.5 to 1 standard deviation below healthy controls and children who sustain an injury other than TBI (Babikian & Asarnow, 2009; Moran, et al., 2016).

Attention. Impairment in attention is one of the most commonly reported deficits after pTBI (D.N. Allen, et al., 2010; Babikian & Asarnow, 2009). Research suggests that attention is particularly susceptible to disruption by pTBI because it is a skill which remains in a stage of rapid development throughout childhood, with different components of attention developing at different rates. Some components of attention therefore remain, overall, less well-developed nor established throughout childhood, making them more vulnerable to disruption (Babikian, et al., 2015; Ewing-Cobbs, et al., 1998). In addition, attentional control is mediated by the pre-frontal cortex, a region which is particularly vulnerable to structural damage and disruptions of white-matter connections during TBI (Anderson & Catroppa, 2005).

Attention is a multi-dimensional construct and a crucial prerequisite for cognitive, behavioural, academic and social functioning; deficits in attention may especially interfere with the acquisition of new knowledge both within and outside of the schooling environment (Babikian, et al., 2015; Konigs, et al., 2015). Research has indicated that the different domains of attention, sustained-, selective-, shifting-, divided attention and attention span, have differing levels of vulnerability to brain injury. A recent review of attention deficits after pTBI found that divided and sustained attention are affected to a greater extent than other domains of attention (Babikian, et al., 2015).

In general, a dose-response pattern is evident for attention deficits after pTBI: children who sustain more severe TBI demonstrate the greatest and most persistent deficits in attention (Babikian, et al., 2015; Ginstfeldt & Emanuelson, 2010). In their study on the recovery of executive functions, including attentional control, after pTBI, Anderson and Catroppa (2005) found that children who had more severe injuries showed more significant attention deficits which persisted and progressed 2 years post-TBI. These findings were echoed in a more recent meta-analysis on neurocognitive outcomes after pTBI, with children with more severe pTBI showing moderate to large effects in attention persisting 2 years after injury (Babikian & Asarnow, 2009). In literature, attention is often considered as a component of executive function and is known to be closely related to other executive functions.

Executive function. Executive function is a term that encompasses a range of higher-order cognitive skills which enable "purposeful, goal-directed and appropriate behaviour" (Beauchamp, et al., 2011, p. 578). The components of executive functioning generally include attention, cognitive flexibility, abstraction and planning and problem-solving using strategy (Anderson & Catroppa, 2005). The neuronal underpinnings of executive functions

and the neuroanatomical positioning of the frontal lobes, the seat of these functions, make these skills more vulnerable to the adverse effects of pTBI. The frontal regions and associated pathways are common sites of pathology after TBI and disrupted development of white matter networks due to diffuse damage may also result in impairments in integration of information from different brain areas involved in executive functioning (Anderson & Catroppa, 2005; Levin & Hanten, 2005). Executive function skills continue developing throughout childhood and adolescence; disruption to the development of executive functions by pTBI may therefore result in the full extent of deficits only becoming evident many years after injury (Anderson & Catroppa, 2005).

Executive functions play a crucial role in cognition, behaviour, emotional regulation and social functioning (Babikian, et al., 2015). Deficits in this domain appear to conform to the dose-response pattern evident in other neurocognitive outcomes. A review of the recovery of executive functions after pTBI indicates that children who sustain more severe TBIs have increased executive difficulties which recovers only somewhat in the 2 years post-injury (Anderson & Catroppa, 2005). Significant evidence for deficits in these functions after pTBI have further been noted even as late as 10 years after injury (Babikian, et al., 2015). Specific deficits found to be commonly implicated post-pTBI include difficulties with problem solving, inhibition and working memory, with the greatest deficits identified in the dimensions of cognitive flexibility and abstraction (Anderson & Catroppa, 2005; Babikian, et al., 2015). These skills have also been found to be related to general intellectual functioning (IQ; Jacobs, Harvey, & Anderson, 2007).

General intellectual functioning. Depressed general intellectual functioning measured by standardised IQ tests has consistently been noted in children who sustain TBI, even 10 years post-injury (Anderson, Godfrey, Rosenfeld, & Catroppa, 2012). Injury severity appears to be a particularly important predictor of the presence of intellectual deficits post-TBI (Konigs, Engenhorst, & Oosterlaan, 2016). Post-TBI deficits in general intelligence have been found to be more prominent when the injury is more severe and is sustained at a younger age, consistent with the commonly observed dose-response pattern of outcome after pTBI (Babikian & Asarnow, 2009; Anderson, Catroppa, Morse, Haritou, & Rosenfeld, 2000). A recent meta-analytic review of intellectual deficits after TBI found that children who sustain mild TBI experience greater recovery in intellectual functioning than adults who sustain mild TBI, however, severe pTBI is associated with poorer recovery in IQ than severe TBI in adulthood (Konigs, et al., 2016). This study also found that severe pTBI was

associated with more impairments in full scale- and verbal IQ than adult TBI (Konigs, et al., 2016).

While partial recovery from intellectual deficits have been noted, research findings show that intellectual functioning is one of the cognitive domains most sensitive to pTBI (Babikian & Asarnow, 2009). Depressed IQ has been associated with decreased learning, acquisition of skills as well as social development, which results in an expanding gap between injured children and their typically developing peers as time passes, both academically and socially (Anderson, Catroppa, Morse, Haritou, & Rosenfeld, 2009; Babikian & Asarnow, 2009; Babikian, et al., 2015). Studies on the outcomes of severe pTBI have found significant impairments in full scale IQ (FSIQ), but a few studies note more severe impairment in performance IQ (PIQ) compared to verbal IQ (VIQ) (Anderson, et al., 2009; Babikian & Asarnow, 2009). Gradual but substantial recovery is however noted in FSIQ and PIQ over time with relatively little improvement to VIQ, suggesting that children who sustain pTBI make developmental gains after a recovery period, but continue to struggle in the domain of language (Anderson, et al., 2009; Babikian & Asarnow, 2009). This is consistent with findings by Konigs and colleagues (2016) mentioned above.

Memory. Much like attention, executive function and IQ, memory impairment significantly impacts the ability to learn, retain information and acquire new skills (Lajiness-O'Neill, Erdodi, & Bigler, 2010). Research has consistently shown that children who sustain TBI earlier in life often experience chronic memory impairment post-injury (Babikian, et al., 2015). In addition, it has been found that the recovery and impact of long-term memory deficits post pTBI, depends on a wide variety of other factors such as injury severity, comorbidities, premorbid functioning, socioeconomic status, family dynamics, post-injury care and sex (Lajiness-O'Neill, Erdodi, & Bigler, 2011).

Memory is not a unitary construct. Traditionally, research has primarily investigated explicit memory which involves retrospective conscious awareness of past verbal and spatial learning experiences, and there is abundant evidence for explicit memory deficits after pTBI in the research base. Implicit memory has received far less attention; however, few existing studies suggest that implicit memory may be less vulnerable to pTBI and may be preserved (Schacter, Wagner, & Buckner, 2000; Ward, Shum, Dick, McKinlay, & Baker-Tweney, 2004; Ylvisaker, Szekeres, & Haarbauer-Krupa, 1998).

Research has shown that pTBI patients appear to perform on average one standard deviation below control participants in the domain of memory. Further analysis, however, revealed significant differences solely in the domain of verbal memory between the severe

pTBI group, and other severity groups as well as control participants. This suggests that verbal memory is more vulnerable to impairment after severe pTBI (Lajiness-O'Neill, Erdodi, & Bigler, 2011). This finding is consistent with previous research findings that both visual and verbal memory impairments are often evident for all severity groups in the acute phase after pTBI, but severe pTBI is associated with enduring impairments in the domain of audio-verbal memory (Anderson & Catroppa, 2007; Anderson, et al., 2000; Babikian, et al., 2015; Lajiness-O'Neill, Erdodi, & Bigler, 2011).

Behavioural and psychiatric outcomes after pTBI. Evidence also exists for chronic, maladaptive behavioural and emotional problems in children following TBI. Li and Liu (2013) found that up to 50% of children with mild, moderate and severe TBI are at risk for enduring behavioural problems after their injury. These impairments may appear in the acute phase after injury or several years thereafter and may even worsen with time (Li & Liu, 2013). Behavioural and psychiatric difficulties are often reported by parents and teachers as the most disruptive and problematic outcomes of pTBI and have been noted to persist even years after the injury into adulthood (Noggle & Pierson, 2010; Watson, Rutterford, Shortland, Williamson, & Alderman, 2001; Sariaslan, Sharp, D'Onofrio, Larsson, & Fazel, 2016).

Behavioural outcomes after pTBI may include conduct disorder, rule breaking, impaired social judgement, impulsivity, hyperactivity and aggression, and psychiatric outcomes such as depression, anxiety, personality change and obsessive-compulsive disorder (Babikian, et al., 2015; Noggle & Pierson, 2010; Ryan, et al., 2016). These problems are commonly characterised as either internalising (e.g. fearfulness, withdrawal, frustration, irritability, anxiety, etc.) or externalising (e.g. hyperactivity, aggression, impulsivity, anger outbursts, use of drugs, inappropriate sexual behaviour, etc.; Dykeman, 2003; Konigs, et al., 2016). Children who sustain TBI at a younger age are furthermore likely to exhibit internalising problems with the incidence of externalising problems increasing with age at injury. Multiple pre-injury factors such as premorbid problematic behaviour, being of the male sex and poor family environment have however been found to be contributors to post-TBI behavioural and psychiatric dysfunction (Dykeman, 2003; Li & Liu, 2013).

Quality of life. There is a relative dearth in prospective research investigating the consequences of pTBI on day-to-day functional outcomes such as quality of life (QOL). However, the existent research suggests significant, measurable declines in QOL after moderate to severe pTBI (McCarthy, et al., 2006; Wade, Zhang, Yeates, Stancin, & Taylor, 2016). Research focusing on QOL outcomes in children generally utilise the same outcome measure, the Pediatric Quality of Life Inventory (PedsQL; Varni, Seid, & Kurtin, 2001). The

PedsQL measures health related quality of life QOL (HRQOL) in 3 domains: physical health, psychosocial health and total health.

Studies show that 42% of children with TBI show impaired HRQOL 3 months after injury, and 40% of children show impaired HRQOL at 12 months after injury. In addition, for children with moderate to severe TBI, these impairments span multiple QOL domains and do not improve significantly over time (McCarthy, et al., 2006). Research has found that both parents- and pTBI patients themselves report similar or lower HRQOL post-injury when compared to orthopaedic- or chronic illness control groups. Impairments have been noted in multiple domains including psychosocial disorders, general health, and family impact, which results in severely reduced QOL in schooling and emotional contexts (Erickson, Montague, & Gerstle, 2010; Stancin, et al., 2002). These researchers also found that HRQOL was associated with social disadvantange and poorer premorbid behaviour and academic functioning. Injury-related factors during the first year post-injury have also been found to be associated with HRQOL, more so than acute-phase patient and family characteristics (McCarthy, et al., 2006). Overall, this research suggests that the complete impact of the pTBI might not be captured by individual tests of cognitive, behavioural and psychiatric outcomes alone.

The above review is a summary of some of the adverse outcomes of childhood TBI, but it reflects the relative progress that the field has made in describing the possible consequences of pTBI. However, it remains that, at the level of the individual, each child responds differently to their unique injury. Clinical reports and research studies confirm a vast amount of variability in the outcomes of pTBI, leading researchers and clinicians to question the relative contribution of a wide variety of factors in predicting outcomes (Anderson & Yeates, 2010; Babikian & Asarnow, 2009; Babikian, et al., 2015). Research has examined multiple acute and post-acute stage predictors of outcome of pTBI including age at injury, injury nature and severity, time since injury, premorbid functioning, family environment, SES and access to rehabilitation services (Anderson, et al., 2001; Anderson et al., 2000; Anderson, et al., 2012; Catroppa, et al., 2009; Fay, et al., 2009; Moran, et al., 2016). Acute stage neurological and neurosurgical variables are however relatively absent from research on neuropsychological outcomes of pTBI.

Acute Physiological Predictors of Neuropsychological Outcomes post pTBI

Acute brain monitoring after TBI. Carefully monitoring various neurological changes after TBI have become essentials of acute care in the pursuit of reducing mortality rates and preventing secondary injury. Effective acute care is complicated by significant

challenges in diagnosing and treating physiological dysfunction due to intra-individual variability and temporal heterogeneity (Figaji, 2009; Padayachy, Figaji, & Bullock, 2009; Wahlstrom, Olivecrona, Koskinen, Rydenhag, & Naredi, 2005). Despite this, acute brain monitoring has to date successfully informed intensive care and advanced treatment methods leading to an observable increase in survival rates after TBI (Stein, Georgeoff, Meghan, Mirza, & El Falaky, 2010; Wahlstrom, et al., 2005).

While intracranial pressure (ICP) and cerebral perfusion pressure (CPP) monitoring have become standard in post-TBI care, research and clinical evidence have increasingly emphasised the complexity of post-TBI secondary injury which has provided impetus for multi-modal monitoring. A wide range of modalities, including transcranial Doppler, partial pressure of brain tissue oxygen ($PbtO_2$) and cerebral microdialysis, are now being monitored to optimise secondary injury prevention and thereby improve outcomes for patients with TBI (Bouzat, Sala, Payen, & Oddo, 2013). Although clinical observation of outcome has demonstrated the importance of monitoring and managing acute neurological changes post TBI, research on the relationship between these variables and outcome has produced varying results and suggests a more complex picture.

One way in which the complex relationship between acute physiological variables has been examined is through the relationship between ICP and brain oxygenation: how these variables predict outcome independently, and how they interact to predict outcome. Although the management of raised ICP is a crucial part of post-TBI care to ensure sufficient CBF and brain oxygenation, hypoxia may occur in conditions of normal ICP. Research has found that the relationship between ICP and brain oxygenation is, in general, poor and that only very high ICP is associated with poor brain oxygenation (Padayachy, Figaji, & Bullock, 2009; Rohlwink, et al., 2012). In addition, it has been found that reduced brain oxygenation not only independently predicts poor outcome (on the Glasgow Outcome Scale; Jennett & Bond, 1975), but has a stronger relationship with outcome than conventional targets of intervention, including ICP. Findings in this area suggest that an increased understanding of how ICP and brain oxygenation predict outcome jointly and independently is necessary for the effective treatment of pTBI (Figaji, et al., 2009; Rohlwink, et al., 2012).

Intracranial pressure. ICP refers to the pressure within the skull and is measured in millimetres of mercury (mm Hg). Typically, the components of the cranium, blood, cerebrospinal fluid and the brain, remain at a fixed volume represented by a normal pressure of 20mm Hg. In the event that the volume of either of these components increases the pressure within the cranial vault increases causing the brain to herniate, disrupting the flow of

blood to the brain and causing damage to brain matter (Pinto & Adeyinka, 2018). Despite the absence of randomised trials to confirm the utility of ICP monitoring and management after TBI, the clinical evidence that does exist indicates that ICP monitoring-informed treatment improves outcome post-TBI for adults and children when part of protocol driven therapy (Padayachy, Figaji, & Bullock, 2009). In the context of TBI, raised ICP may result from hematomas, cerebral edema or changes in cerebral blood volume generating pressure gradients within the cranium, which may result in herniation of brain tissue causing varying clinical syndromes, depending on location. ICP may result in secondary injury by causing local tissue pressure effects, reduction in CPP and brain oxygenation, and compromised brain energy metabolism (Jagannathan, et al., 2008; Kukreti, Mohseni-Bod, & Drake, 2014; Padayachy, Figaji, & Bullock, 2009).

ICP and outcome. Multiple studies have provided evidence that raised ICP is associated with poorer outcomes on generalised measures such as the Pediatric Glasgow Outcome Scale-Extended (GOS-E Peds) in children after TBI (Chambers, et al., 2006; Jagannathan, et al., 2008; Kukreti, Mohseni-Bod, & Drake, 2014; Padayachy, Figaji, & Bullock, 2009; Rohlwink, et al., 2012; Wahlstrom, et al., 2005). Refractory elevated ICP has been found to be an extremely important predictor of death after severe pTBI, and, in children who survive their injuries, ICP control in the acute care phase is significantly correlated with improved QOL, general cognition and activities of daily living in the long term (Jagannathan, et al., 2008; Kukreti, Mohseni-Bod, & Drake, 2014; Wahlstrom, et al., 2005).

The degree and duration of raised ICP are both associated with poorer outcome: increases over 20mm Hg for periods greater than 5 minutes often require treatment, which may be done through a variety of techniques (Kukreti, Mohseni-Bod, & Drake, 2014). ICP elevated above 20mm Hg has been found to have a significant relationship with poorer neurological outcome. Catala-Temprano and colleagues (2007) retrospectively investigated raised ICP and CPP as risk factors after pTBI and report that 36% of patients with ICP higher than 20 mm Hg died or remained in a persistent vegetative state, while only 50% had minimal or no disabilities. This is compared to 80% of patients with normal acute ICP who had a good outcome with or without minimal disabilities, while only 12% died or remained in a persistent vegetative state (Catala-Temprano, et al., 2007). A more recent study similarly found that the duration of hours that ICP exceeded 20mmHg and CPP remained below 45mmHg, predicted poorer outcome in a sample of severe pTBI patients (Miller Ferguson, et al., 2016). Investigation of outcomes related to ICP after pTBI predominantly utilise broad,

non-specific outcome measures such as the Glasgow Outcome Scale (GOS); research on the relationship between neuropsychological outcomes and acute ICP after pTBI is immensely scarce.

ICP and neuropsychological outcome. The majority of the research that does investigate the relationship between ICP and neuropsychological outcomes focuses on adolescents or adults. The results of these studies are mixed. Uzzeli, Obrist, Dolinskas, and Langfitt (1986) report that patients with severe head injury experience greater memory deficits if they experienced ICP of 20mm Hg or higher. Other studies however find that raised ICP has little to no effect on memory and if it does, the effect diminishes within 12 months post-TBI and that, in fact, ICP appears to have no relationship with overall neuropsychological impairment in the post-acute stage of TBI (Levin, et al., 1991; Lannoo, et al., 1998).

One study that examined the effect of raised ICP on neuropsychological outcomes in a severe pTBI sample found enduring post-acute stage deficits in attention and executive function including working memory, decision-making and impulsivity (Slawik, et al., 2009). In contrast, a study investigating predictors of cognitive functioning after moderate and severe pTBI (with an average lowest GCS of 7) found that acute injury variables including the presence of increased ICP failed to predict cognitive performance either in the acute or chronic phase of injury (Moran, et al., 2016). Overall, existing research suggests that the relationship between ICP and neuropsychological outcome is characterised by great variation.

The primary aims of treating ICP are to prevent brain herniation, and to prevent ischemic damage after pTBI (Figaji, et al., 2017). The latter is done through ensuring sufficient CBF and brain oxygenation, however, the relationship between ICP and $PbtO_2$ is not linear. Studies have found that low brain oxygenation may still occur in the presence of normal ICP suggesting a more complex relationship between these variables, one which is generally poorly understood (Rohlwink, et al., 2012).

Brain oxygenation. Brain oxygenation refers the presence of oxygen within the brain tissue which is necessary for adequate brain function; poor oxygen supply or disruptions to the brain's ability to utilise the available oxygen, results in cerebral hypoxia/ischemia (Gajavelli, et al., 2015; Rohlwink & Figaji, 2010). Reduced brain oxygenation is associated with poorer outcome after TBI, both in terms of survival rate and functional outcome, in both adult and pediatric populations (Figaji, et al., 2009; Figaji, et al., 2017; Maloney-Wilensky, et al., 2009; Rohlwink, et al., 2012). Direct monitoring of brain oxygenation by brain tissue oxygen tension monitors are used frequently in adult TBI, and

there is a growing body of experimental and clinical brain oxygenation data for pediatric populations. $PbtO_2$ is a direct measure of brain oxygenation that captures various factors which affect oxygen supply and diffusion in brain tissue (Rohlwink & Figaji, 2010). Adult research has shown increased risk of death and poorer generalised outcomes associated with reduced $PbtO_2$ after severe TBI. However, remarkably few studies have considered the effect of $PbtO_2$ on outcome in pediatric patients (Maloney-Wilensky, et al., 2009; Figaji, et al., 2009).

In their paper on the early use of ICP and brain tissue oxygen monitoring in children with severe TBI, Stiefel and colleagues (2006) found significant correlations between reduced $PbtO_2$ and raised ICP with low CPP *as well as* episodes of reduced $PbtO_2$ in the presence of normal ICP and CPP, in keeping with adult literature. Another study echoed these results and found that reductions in $PbtO_2$ below the critical threshold still occurred in one third of children despite adequate management of ICP, CPP and systemic oxygen levels (Figaji, Fieggen, Argent, le Roux, & Peter, 2008). The paucity of published research on $PbtO_2$ and outcome after severe pTBI has been noted (Stiefel, et al., 2006). While few studies have been published examining the relationship between $PbtO_2$ and outcomes post pTBI, research in this area is markedly sparse.

Brain oxygenation and outcome. Figaji, Fieggen, Argent, le Roux, and Peter (2008) examined the association between $PbtO_2$ and outcome in severe pTBI patients and found a significant relationship between unfavourable outcome (measured on the GOS) and lowest $PbtO_2$ over a 6-hour period, as well as the duration of time that $PbtO_2$ dropped below 15 and 10 mm Hg. They also found that low $PbtO_2$ (<20 mm Hg) commonly occurred despite the maintenance of other management targets (ICP, CPP, haemoglobin and arterial partial pressure of oxygen). In the largest study of its kind to date, it was found that reductions in $PbtO_2$ (particularly when it dropped below 5mm Hg) had the strongest relationship with unfavourable outcome (on the GOS) and was the only included variable to independently predict outcome after severe pTBI (Figaji, et al., 2009).

Brain oxygenation and neuropsychological outcome. In a study on neuropsychological outcome after severe TBI in adults, Meixensberger and colleagues (2004) found that patients with reduced brain oxygenation performed worse on measures of intelligence and memory. More recently, Schrieff-Elson, Thomas, Rohlwink, and Figaji (2015) performed the first study investigating the relationship between $PbtO_2$ and neuropsychological outcomes after severe pTBI. They found that patients who experienced at least one episode during which $PbtO_2$ dropped to or below 10 mm Hg performed

significantly worse in domains of general intelligence, verbal memory, attention, executive function and expressive language than severe pTBI patients who had not. While their study was limited by a small sample size, their results suggest that low $PbtO_2$ may have a detrimental effect on neuropsychological outcomes after severe TBI in children. Research in this area is however markedly sparse and there exists a need in this research base for further studies on $PbtO_2$ and neuropsychological outcome.

Rationale, Aims and Hypotheses

The heterogeneity in cognitive, psychosocial and behavioural outcomes after pTBI is highlighted across the literature base and is often the central focus of studies which aim to enable early intervention to address and improve outcomes after childhood TBI. Many injury- and non-injury related factors have been shown to be predictive of outcome after pTBI in various domains, to varying degrees, however, very few predictors have been found to reliably identify patients who are most likely to experience long-term post-pTBI deficits (Moran, et al., 2016). More research is necessary to explore the relationship between various injury-related and non-injury related factors and long-term outcome after childhood TBI.

Careful monitoring of acute neurological changes post-TBI have been found to contribute to improved mortality rates and generalised outcomes by enabling early identification of neurological dysfunction and rapid, effective neurosurgical intervention (Figaji, et al., 2008; Wahlstrom, et al., 2005). Research studies which examine the relationship between acute-stage neurological dysfunction and long-term outcome after pTBI in multiple neuropsychological domains rather than a single non-specific outcome scale are however very scarce.

The current study is a local extension to an established international research study, Approaches and Decisions in Acute Pediatric TBI Trial (ADAPT), which aims to evaluate the efficiency of various acute interventions on the outcome of severe pTBI. The local site of the study is the Red Cross War Memorial Children's Hospital (RXH). The current study utilised acute injury data gathered as part of the ADAPT trial at RXH to investigate the association between acute-stage neurophysiological changes and long-term neuropsychological outcomes in English-, Afrikaans- and isiXhosa-speaking severe pTBI patients at 12 months post-injury. Specifically, the domains of intracranial pressure and brain oxygenation were investigated.

The current study had the following specific aims:

1) To investigate the nature and severity of neuropsychological outcomes 12 months after severe TBI in South African children, comparing their performance to a typically developing, matched control group.

2) To explore the relationship of acute injury variables, ICP and $PbtO_2$, with neuropsychological outcome 12 months after severe pTBI.
   The following hypotheses were investigated:

- The severe TBI patient sample will perform poorer on neuropsychological outcome measures of cognition, behaviour and QOL than the control sample.
- Higher ICP over the monitoring period (on the parameters detailed in Table 2 below) will be associated with poorer neuropsychological outcome. In particular, crossing the treatment threshold of 20mm Hg will be associated with poorer outcome.
- Lower $PbtO_2$ over the monitoring period (on the parameters detailed in Table 2 below) will be associated with poorer neuropsychological outcome. In particular, crossing the treatment threshold of 20mm Hg, and the hypoxic threshold of 10mm Hg, will be associated with poorer outcomes.

Method

Design and Setting

The design of this research study is quantitative and observational with a cross-sectional, case-controlled component. I conducted neuropsychological assessments with pTBI patients who consented to participate in the ADAPT trial 12 months post-pTBI and I subsequently assessed a group of closely matched, typically developing control participants using the same neuropsychological battery. The assessment battery included parent-report questionnaires as well as direct assessment of each participant using paper and pencil measures in the domains of QOL, behaviour, attention, processing speed, memory, executive function and general intellectual ability. The assessments were carried out at RXH, Groote Schuur Hospital (GSH) and various primary schools in Cape Town.

Sample

The patient sample for the current study comprised 15 English-, Afrikaans- and isiXhosa-speaking children aged 6 to 14 years who underwent intracranial monitoring for ICP and $PbtO_2$ at RXH pediatric intensive care unit (PICU) following severe TBI (GCS $\leq$8 after resuscitation) between April 2015 and October 2016. In addition, given that the assessments comprising the neuropsychological battery utilised in the trial do not have reliable local norms, I also assessed 15 typically developing matched control participants. The control participants were matched to the pTBI sample on age, sex, SES and home language.

Exclusion Criteria. Children younger than 6 years of age were excluded to ensure that the data collected is comparable for children across all ages. This is because the same test

battery can be used consistently with children aged 6 to 14 years. In addition, control group participants had not been previously diagnosed with any psychiatric or neurological conditions, or current or previous learning disability, and had not sustained a previous head injury that included loss of consciousness. Furthermore, pTBI patients with a GOS-E Peds (Beers, et al., 2012) score of 5 or above[4] at 12 months post-injury were excluded due to inability to complete the neuropsychological assessment battery following standardised administration.

Materials

I utilised a neuropsychological assessment battery consisting of measures of functional-, cognitive-, and behavioural outcomes all commonly used in pTBI research and clinical practice with pediatric patients.

The test materials are all originally published in English. To ensure that the language needs of the sample were catered to, the relevant subtests for each measure were translated into Afrikaans and IsiXhosa. This was done through the University of Stellenbosch's Language Centre through forward and back translations and an authentication process, and through local translation authenticated by a panel of neuropsychology researchers and community members fluent in Afrikaans or isiXhosa (Smith, Malcolm-Smith, & de Vries, 2016). See Table 24 in Appendix A for a summary of the assessment measures. I describe each of the measures in more detail below.

Quality of life.

Pediatric Quality of Life (PedsQL). The PedsQL (Varni, Seid, & Kurtin, 2001) measures three primary domains of HRQOL: Physical Health, Psychosocial Health (including school-, emotional- and social functioning) and Total Health and is suitable for children aged 2 to 18 years. The measure has both a self-report and a parent-proxy version; I used both forms in their appropriate capacities in the current research study. The PedsQL has high internal consistency, .89-.91 for each version. The measure has good reliability and validity, extensively demonstrated in pediatric patients with various health conditions (Erickson, Montague, & Gerstle, 2010; (Varni, Seid, & Kurtin, 2001). The PedsQL has previously been used on pTBI patients (Erickson, Montague, & Gerstle, 2010) and in a South African sample (Weedon & Potterton, 2010).

[4] The GOS-E Peds is a version of the Glasgow Outcome Scale-Extended that has been modified to provide a developmentally appropriate classification of outcome for children, toddlers and infants. Scores denote the following: 1-Upper Good Recovery, 2-Lower Good Recovery, 3-Upper Moderate Disability, 4-Lower Moderate Disability, 5-Upper Severe Disability, 6-Lower Severe Disability, 7- Vegetative State, 8-Death (Beers, et al., 2012).

Intellectual ability.

Wechsler Abbreviated Scale of Intelligence (WASI). The WASI (Wechsler, 1999) is a test of intelligence suitable for ages 6 to 89. It consists of 4 subtests, Block Design, Matrix Reasoning, Similarities and Vocabulary which provide scores of intellectual functioning in the domains of verbal comprehension (or verbal intelligence, VIQ) and perceptual reasoning (or performance intelligence, PIQ). It also provides two composite scores of general intelligence: full-scale IQ calculated using 4 subtests (FSIQ-4), and full-scale IQ using 2 subtests (FSIQ-2). The FSIQ-4 was utilised in this study along with the VIQ and PIQ scores. Internal consistency for the measure has been established, with reliability coefficients ranging on average between .81 and .97 across subtests in a child sample. Test-retest reliability ranges between .92-.95 for the subtests and the composite scores. The validity of the measure has also been established with extensive evidence (Wechsler, 1999). The WASI has been used in a South African sample of pTBI patients (Schrieff-Elson, Thomas, Rohlwink, & Figaji, 2015).

Memory.

California Verbal Learning Test-Children (CVLT-C). The CVLT-C (Delis, Kramer, Kaplan, & Ober, 1994a) is used to assess learning and memory in children aged 5 to 16 using a list-recall memory task. The test assesses recall performance, learning characteristics and areas of recall errors. The CVLT-C has high test-retest reliability ranging between .80-.84. The measure has been used extensively in the evaluation of children with TBI and has been shown to have construct and criterion validity as a sensitive measure of learning and memory in children (Delis, Kramer, Kaplan, & Ober, 1994b; Mottram & Donders, 2005; Woods, Delis, Scott, Kramer, & Holdnack, 2006). The CVLT-C has been used in a South African pediatric sample (Lewis, et al., 2015) and in patients with pTBI (Salorio, et al., 2005).

Children's Memory Scale (CMS): Dot Locations. The CMS (Cohen M. J., Children's Memory Scale, 1997) is a neuropsychological test battery which is used to assess multiple domains of learning and memory and is suitable for children between 5 and 16 years of age. The Dot Locations subtest is a measure of visual memory and learning in which the child is required to recall the location of an array of dots on a grid. The CMS has high internal consistency across age ranges and subtests. The median core index reliabilities range between .76 and .91. Construct validity has also been established for this measure and evidence is provided for its convergent validity through correlations with similar measures (Cohen, 2001). The CMS has been used in a South African sample of pTBI patients (Schrieff-Elson, et al., 2015).

Executive Function.

Delis-Kaplan Executive Function System (D-KEFS): Verbal Fluency. The D-KEFS (Delis, Kaplan, & Kramer, 2001) consists of 9 tests which assess verbal and spatial executive functions in individuals aged 8 to 89. The measure has high split-half reliability ranging between .50 - .90 for the various subtests and test-retest reliability ranging between .62-.80. Evidence for discriminant and convergent validity was given in the form of positive correlations between previously standardised tests measuring the same constructs. I used the Verbal Fluency subtest from the D-KEFS. This measure assesses verbal fluency in three domains: letter fluency, category fluency and category switching. The task requires participants to produce as many words as they can within a specific category and then switch between categories (Delis, Kaplan, & Kramer, 2001; Strong, Tiesma, & Donders, 2011). The D-KEFS has been used in a South African pediatric sample (Mattson, et al., 2013) and in a sample of pTBI patients (Tonks, Williams, Frampton, Yates, & Slater, 2007).

Attention.

The Test of Everyday Attention for Children (TEA-Ch): Sky Search. The TEA-Ch (Manly, Anderson, & Nimmo-Smith, 1999) is a neuropsychological test battery which assesses varying domains of attention in children and adolescents aged 6 to 15 years. The Sky Search subtest measures selective/focussed attention and has two components, an attention component and a motor control component, with test-retest reliability coefficients of .75 and .80 respectively (Pearson, n.d.). The TEA-Ch has been used in a South African sample of TBI patients (Schrieff-Elson, et al., 2015).

CMS: Numbers. The Numbers subtest of the CMS (Cohen M. J., 1997) has two components. Numbers forward is a measure of attention which requires the child to repeat a string of random digits of increasing length in the same order as is read by the examiner. Numbers backwards is a measure of working memory which requires the child to repeat the digits read backwards. See above for a description of the psychometric properties of the CMS. The CMS has been used in a South African sample of pTBI patients (Schrieff-Elson, et al., 2015).

Processing speed.

Wechsler Intelligence Scale for Children (WISC-IV): Processing Speed Index. The WISC-IV (Wechsler, 2003) is suitable for children aged 6 to 16 years. It measures Full Scale IQ and subdomains of Verbal Comprehension, Perceptual Reasoning, Working Memory and Processing Speed. The WISC-IV has high internal consistency, ranging between .82 to .94 across subtests and age groups. Test-retest reliability for the measure ranges between .86-.93

for the subdomains. Structural validity of the WISC-IV has been established by various factor-analytic studies.

The Processing Speed Index (PSI) consists of the Coding and Symbol Search subtests. The Coding subtest measures the rate of test-taking by evaluating the speed with which the child copies symbols using a key and the Symbol Search subtest measures perceptual speed by evaluating whether the child can identify the presence or absence of a target in a group within a specified time limit (Flanagan & Kaufman, 2009). The WISC-IV PSI has been used in a pTBI sample (Bigler, et al., 2013) and in a South African pediatric sample (Hoare, et al., 2012).

Behaviour.

Behaviour Rating Inventory of Executive Function (BRIEF). The BRIEF (Gioia, Isquith, Guy, & Kenworthy, 2000a) is a measure of executive function and self-regulation in children and adolescents aged 5 to 18 years. I used the parent form of this measure in the current study. Internal consistency for the BRIEF is high, ranging from .80 - .98 for both parent and teacher forms. Reliability of the measure has been shown (>.79) and its validity confirmed (Gioia, Isquith, Guy, & Kenworthy, 2000b; WPS, 2013). The BRIEF has been used in a South African sample of pTBI patients (Schrieff-Elson, et al., 2015).

Child Behaviour Checklist (CBCL). The CBCL (Achenbach & Rescorla, 2001) is a measure of emotional and behavioural problems suitable for children and adolescents aged 1.5 to 18 years. The test is made up of eight syndrome scales which are grouped to produce two higher-order factors, internalising and externalising. Additionally, the CBCL produces scores on six diagnostic scales which are based on the Diagnostic and Statistical Manual of Mental Disorders (DSM) IV-TR. I administered the parent version of this test. The CBCL has internal consistency ranging between .63 - .97, test-retest reliability ranging from .80 - .94 and inter-rater reliability ranging from .57 - .88. Tests for construct and criterion validity have indicated that the measure is valid across samples (The National Child Traumatic Stress Network, 2012). The CBCL has been used in a South African sample of pTBI patients (Schrieff-Elson, et al., 2015).

Procedure

Acute physiological monitoring and data collection. Patients were identified as requiring intracranial monitoring if their GCS was at or below 8/15 after resuscitation or deteriorated to that level while in the emergency room. Intracranial catheters for ICP (Codman ICP Express [Codman, Raynham, MA, USA] and Camino [Integra Neurosciences, Plainsboro, NJ, USA]) and $PbtO_2$ (Licox®, Integra Neurosciences) were subsequently

inserted according to convention into the right frontal lobe or in the hemisphere with greatest cerebral swelling or most significant lesions as seen on computed tomography (CT) scan. ICP catheters were inserted into brain parenchyma, and $PbtO_2$ catheters were placed in uninjured-appearing frontal white matter. A wide range of physiological variables were recorded during the period of monitoring. Physiological data were recorded hourly in the nursing records. For the current study, data from maximum 7 days post-injury were used, and $PbtO_2$ data for the first two hours of monitoring were excluded from analyses to avoid potential artefacts from stabilizing the catheter.

Standard critical care protocol was implemented in the PICU for all patients and patient care in general adhered to the current recommendations for the management of severe pTBI in children (Kochanek, et al., 2012). As is convention, treatment was targeted at maintaining ICP at less than 20 mm Hg and $PbtO_2$ at or above 20 mm Hg; treatment was unaffected by the monitoring and data collection process.

Recruitment and assessment of pTBI patients. Patients who underwent intracranial monitoring for ICP and $PbtO_2$ at RXH PICU following severe TBI were formally invited to participate in the ADAPT trial, which involves 3 follow up sessions post-injury, including the 12-month post-injury neuropsychological assessment relevant to the current study. Before being discharged, the details of the study were clearly explained after which the parents/caregivers of the pTBI patients had the opportunity to provide consent and patients had the opportunity to provide assent to participate in the study if they were able to (see appendix F and G). At this point, the relevant follow up sessions were scheduled.

While all patients matching this description were invited to participate in the ADAPT study at the RXH site, hence forming part of the current study, the 12-month post-injury neuropsychological assessment data for the Afrikaans- and isiXhosa-speaking children will not be utilised by the broader ADAPT trial. This is due to the ADAPT trial being an international, multi-site research study with comprising 1000 patients from various countries around the globe; for accurate, comparative analysis, the ADAPT trial will only utilise data from English-speaking participants from each international research site.

I conducted the 12-month post-injury neuropsychological assessments for the patient participants at RXH and the assessment session included parent-report questionnaires as well as direct assessment of each participant. The duration of the testing was approximately 2 hours. Non-English-speaking participants could elect to be assessed in their home-language, in which case the translated test battery was used to conduct the assessment. For Afrikaans-speaking participants I conducted the assessment in their home language as I am fluent in

Afrikaans, and for isiXhosa-speaking participants the services of a translator trained in neuropsychological assessment was utilised in the assessment.

Recruitment and assessment of control participants. After the patient sample was assessed, I recruited control participants matching the patient sample from a variety of sources: I contacted various primary schools in Cape Town, was aided by the University of Cape Town (UCT) SHAWCO Education Sector (a student-driven after-school tutoring initiative for school learners from various areas in Cape Town) and made use of personal communication for recruitment. Letters and consent forms were circulated to parents of prospective control participants explaining the study and providing them the opportunity to consent to participate (see appendix H and I). The control group included in this study consists of those children whose parents provided consent and who subsequently provided assent themselves. I contacted these participants telephonically to schedule the assessment. I then assessed the control participants using the same neuropsychological battery as the patient sample, at GSH or at their primary school. As with the patient group, these assessments were conducted in the preferred language of the participant by a fluent assessor or utilising a trained translator and the translated test battery where necessary.

Scoring Procedures and Data Analysis

Physiological data. Hourly readings for ICP and $PbtO_2$ for a maximum of 7 days post-injury were recorded for each patient (the average number of days of monitoring from which data was used was 5 days). Using this data, I calculated 10 values for statistical analyses in the current study, these are listed in Table 2 along with the association with outcome hypothesised for each of the variables.

Neuropsychological data. I followed the scoring procedures outlined in each test administration and scoring manual, or utilised the relevant scoring software when available, for each of the neuropsychological tests, and converted raw scores to age-adjusted scaled scores following appropriate conventions.

Data verification. All data, neuropsychological and neurophysiological were checked for accuracy by an independent PhD graduate and the Head of Pediatric Neurosurgery at UCT (Prof A. Figaji).

Statistical analysis. All analyses were carried out using SPSS Version 25.0.

Table 2:

ICP and $PbtO_2$ variables used in statistical analyses

Variables calculated for statistical analysis	Hypothesised association with outcome
Highest ICP over monitoring period	Higher → poorer outcome
Number of episodes* that ICP exceeded 20mm Hg	More episodes → poorer outcome
Number of episodes* that ICP exceeded 25mm Hg	More episodes → poorer outcome
Average ICP over the first 24hrs of monitoring	Higher → poorer outcome
Average ICP over monitoring period	Higher → poorer outcome
Lowest $PbtO_2$ over monitoring period	Lower → poorer outcome
Number of episodes* that $PbtO_2$ dropped below 10 mm Hg	More episodes → poorer outcome
Number of episodes* that $PbtO_2$ dropped below 20 mm Hg	More episodes → poorer outcome
Average $PbtO_2$ over the first 24hrs of monitoring	Lower → poorer outcome
Average $PbtO_2$ over monitoring period	Lower → poorer outcome

*These 'episodes' refer to the number of hourly averages which exceeded or dropped below these thresholds.

Deriving composite scores. Given that the neuropsychological assessment battery consisted of many tests and subtests, and in order to avoid a Type One statistical error, I used a hybrid method (see Ferret, Carey, Thomas, Tapert, & Fein, 2010) to create 5 composite variables: higher order attention, verbal fluency, visuospatial memory, verbal memory, and executive functioning. I did this by sorting the individual dependent variables into domains based on established categorizations and theoretical assumptions and through reliability analyses using Cronbach's α coefficients. Thereafter, I converted the dependent variables into z-scores which were averaged for each domain to create a composite z-score. The variables making up the composites are listed in Table 3 below.

Bootstrapping in analyses. Given the small size of the sample, the assumptions of normality and homogeneity of variance were violated for multiple variables in the dataset preventing accurate inferences regarding the shape of the sampling distribution. For this reason, I employed bootstrapping on the analyses described below using 95% bias corrected confidence intervals based on 1 000 replications, correcting for the inability to assume equal variances using the Welch correction (Welch, 1947).

Between group statistical analysis. I performed the following analyses comparing the patient and control groups: I investigated between-group differences in demographic

variables and neuropsychological outcomes using Chi Squared tests (for categorical variables) and independent samples t-tests (for continuous variables).

Within group statistical analysis. To investigate the presence of a relationship between the acute physiological variables and each neuropsychological outcome domain, I performed correlational analyses. I also used multiple descriptive statistics to comment on these relationships. I then performed correlation analyses between the physiological variables themselves to investigate possible significant relationships within and between the acute variables.

Table 3:

Creation of composite variables

Composite Variable	Component Variables Included	Cronbach's Alpha
Verbal fluency	D-KEFS Letter Fluency Total Correct	.75
	D-KEFS Category Fluency Total Correct	
	D-KEFS Category Switching Total Correct	
	D-KEFS Category Switching Total Accuracy	
Higher order attention	Sky Search Time per Target	.92
	Sky Search Attention	
Visuospatial memory	CMS Dot Locations Learning	.96
	CMS Dot Locations Short Delay	
	CMS Dot Locations Long Delay	
	CMS Dot Locations Total	
Verbal memory	CVLT-C Short Delay Free Recall	.91
	CVLT-C Short Delay Cued Recall	
	CVLT-C Long Delay Free Recall	
	CVLT-C Long Delay Cued Recall	
	CVLT-C Correct Recognition	
Executive Functions	CMS Numbers Backward	.74
	WASI Matrix Reasoning	
	WASI Blocks	

Ethical Considerations

The ADAPT Trial and the current study received ethical approval from UCT's Faculty of Health Sciences Ethics Committee. The current study also received ethical approval from the UCT Department of Psychology Research Ethics Committee and the Western Cape Education Department. See Appendix B – E for relevant documentation in this regard.

Informed Consent

According to the protocol of the ADAPT trial, the parents/caregivers of the pTBI patients received a detailed explanation of the nature of study and what participation will involve before providing informed consent to participate in the study. For non-English speaking participants, the services of a translator were utilised in this process. If the patient was able to do so, they provided assent as well. The parents/caregivers of the control sample were similarly informed regarding the study protocol and aims before being given the opportunity to consent and the participant to assent. See Appendix F-I for the consent and assent forms.

Confidentiality

Parents were made aware that all information obtained throughout the duration of the study would be confidential and used solely for research purposes. Data is stored securely at the ACSENT laboratory at UCT and at RXH.

Risks and Benefits

The current study posed no risks to the participants. To combat possible discomfort and fatigue during the lengthy assessment session regular breaks were provided. Participants' parents or caregivers were remunerated R150 to assist with transport costs.

Debriefing and Feedback

Children and their parents were debriefed upon completion of the assessment session. During this time, they also had the opportunity to ask questions and were provided with the contact details of the principal researcher should they have further queries at a later stage.

Results

In reporting the results of my analyses, I will adhere as far as is possible to the guidelines stipulated by the Journal Article Reporting Standards for Quantitative Research in Psychology Workgroup (Appelbaum, et al., 2018). I will, however, focus on confidence intervals and effect sizes along with *p* values when obtainable (due to the nature of bootstrapped analysis, it is not always possible to obtain a *p* value), when commenting on group differences and correlations rather than employing null hypothesis significance testing alone. This method of reporting statistical analyses has been increasingly favoured within the field of psychology over recent years, especially when commenting on clinical significance e.g., in the setting of neuropsychological rehabilitation (Krueger & Heck, 2018; Perdices, 2017).

Participant Characteristics

Demographic characteristics of the sample are presented in Table 4. Of the 30 participants included in the analyses (15 TBI patients and 15 controls), 18 participants (60%) were male. The age at assessment for the overall sample ranged from 7 to 13 years (87.06 to 165.14 months (m)) with a mean age at assessment of 10.32 years (123.7 m; SD = 2.39 y/ 28.31 m). Most of the participants (53.3%) were Afrikaans-speaking.

Various measures of SES are presented for each group in Table 5. The distribution across each of these measures suggest that the sample have neither a markedly low or high SES as the majority of participants fall within the middle category of each measure of SES. For example, on the material and financial resources index, 69% of participants fell within the 'medium' range. There were no differences in age, sex, home language or SES, with $p >$ 0.05 for each variable between the TBI and Control groups.

The average age at injury for the TBI group was 9.31 years (111.72 m; *Range* = 6.42-12.75y [77.1-153m]; *SD* = 2.47) and the average time between injury and assessment was 1.05 years (12.6 m; *Range* = 1.00-1.09y [12-13.1m]; *SD* = .04). 13 of the 15 TBI participants (87%) sustained their injury as a result of a road traffic accident, 8 (62%) of which were pedestrian MVAs and the rest passenger-related MVAs. 1 participant sustained their TBI through a gunshot, and 1 participant sustained a blow to the head. The post-resuscitation GCS of the TBI participants ranged from 3 to 8.

Table 4:

Sample Demographic Characteristics (N = 30)

Variable	Group		p
	TBI (n = 15)	Control (n = 15)	
Age: M (range; SD)	10.36 (7.50-13.75; 2.46)	10.28 (7.25-13.58; 2.41)	.848
Sex			
Male:Female	9:6	9:6	1.000
Home Language			1.000
Afrikaans	8	8	
isiXhosa	6	6	
English	1	1	

Between-Group Analysis (TBI vs Control): Hypothesis One

I used bootstrapped independent samples t-tests to investigate the nature and severity of neuropsychological outcomes 12 months after severe TBI by comparing the performance of the TBI group to the matched control group. These analyses were run for the cognitive variables, including the cognitive composite variables, as well as for each behavioural and QOL measures.

The results of the between group comparisons for each cognitive variable are provided in Table 6. As is evident by the bootstrapped *p* values and bias adjusted confidence intervals, there were significant between-group differences, all with large effect sizes, on all cognitive variables except for sustained attention. In each of the cognitive domains in which significant group differences were present, the performance of the TBI group was poorer than the control group. For between-group differences on the subtests making up the cognitive composite variables, see Appendix J.

Table 5:

Between Group (TBI vs Controls) Differences on Measures of SES (N = 30)

Variable	Group		*p*
	TBI	Control	
Annual household income			.271
0	0	1	
1 - 5 000	1	4	
5 001 - 25 000	3	5	
25 001 - 100 000	3	1	
100 001 +	3	1	
Unknown	5	3	
Parental education (father: mother: guardian)			.329; .519; a
0 years	0: 0: 0	0: 0: 0	
1-6 years	1: 2: 0	0: 0: 0	
7 years	0: 0: 0	0: 0: 0	
8-11 years	2: 7: 3	2: 8: 2	
12 years	4: 2: 0	0: 2: 0	
13 years +	1: 2: 0	1: 3: 0	
Unknown/Not Applicable	7: 2: 12	12: 2: 13	
Parental employment (father: mother: guardian)			.061; .095; .135
Higher executives, major professionals, owners of large businesses	0: 0: 0	0: 0: 0	
Business managers of medium sized businesses, lesser professions	0: 0: 0	0: 2: 0	
Administrative personnel, managers, minor professionals, owners / proprietors of small businesses	1: 0: 0	0: 0: 0	
Clerical and sales, technicians, small businesses	0: 2: 0	0: 2: 0	
Skilled manual – usually having had training	0: 0: 0	0: 2: 0	
Semi-skilled	3: 1: 0	0: 1: 0	
Unskilled	2: 5: 1	0: 1: 0	
Homemaker	0: 1: 2	1: 2: 0	
Student, disabled, no occupation	2: 4: 0	0: 0: 1	
Unknown/Not applicable	7: 2: 12	14: 7: 14	
Material and financial resources (Asset Index)			.861
0-5 assets (low)	2	1	
6-12 assets (medium)	10	10	
13-17 assets (high)	3	3	

a: Not computed because Guardian Education is a constant

The results of the between-group analyses on the behavioural and QOL measures (BRIEF, PedsQL and CBCL) are presented in Tables 7-10. On each behavioural and QOL measure, the TBI group had, on average, poorer scores than the control group on all subscales, however these did not always reach statistical significance. There were no significant differences between the groups on any of the BRIEF indices as is evidenced by all bias adjusted confidence intervals crossing zero with small effect sizes. On the PedsQL, there are significant differences between groups on three of the parent report scales, Physical QOL, Psychosocial QOL and Total QOL, however, in each case the confidence intervals cross zero suggesting that the null hypothesis should not be rejected for these variables. One of the PedsQL self-report scales, Physical QOL, was significantly different between the groups, with the TBI participants reporting lower physical QOL than the control group associated with a small effect size. With regard to the CBCL, there were significant differences between the groups on the following syndrome scales: Withdrawn/Depressed, Social Problems, Thought Problems and Rule-Breaking Behaviour, as well as for Internalising Problems, Externalising Problems and Total Problems. On each of these scales the parents of the TBI group reported higher levels of disordered behaviour than the parents of the control group associated with large effect sizes. This is further illustrated in Table 10 which shows that there were more TBI participants whose behaviour was classified in the 'clinical' or 'borderline' range, with more control participants' behaviour being classed as 'normal' on each syndrome scale.

Table 6

Between Group (TBI vs Control) Independent Samples T-Test (Bootstrapped) on Cognitive Variables (N = 30)

	TBI			Controls			Test statistics					
	N	Range	M (SD)	N	Range	M (SD)	t	df	p	η^2	Bias Adjusted CI	
											Lower	Upper
Sustained Attention	15	2-10	4.87 (2.07)	15	2-10	5.80 (2.27)	-.779	20.94	.223	.047	-2.781	1.266
General Intelligence												
VIQ	15	55-85	69.80 (8.50)	15	76-107	87.60 (8.27)	-4.065	20.55	**.001**	.547	**-23.668**	**-7.635**
PIQ	15	62-93	75.60 (9.23)	15	67-105	90.87 (11.24)	-3.517	20.65	**.001**	.371	**-26.388**	**-6.764**
FSIQ	15	58-86	70.04 (7.60)	15	71-102	87.93 (8.15)	-4.621	20.99	**.000**	.570	**-24.782**	**-9.399**
Processing Speed	14	50-106	68.43 (14.98)	15	68-118	88.60 (13.91)	-4.083	20.99	**.001**	.344	**-28.803**	**-9.364**
Verbal Learning	15	20-54	34.93 (9.02)	15	32-68	46.80 (10.23)	-2.993	20.92	**.004**	.288	**-20.981**	**-3.777**
Verbal Fluency Composite (α = .75)	11	-1.08-1.13	-.25 (.73)	12	-.67-1.17	.33 (.64)	-2.022	19.95	**.029**	.165	-1.177	.0184
Higher Order Attention Composite (α =.92)	15	-1.17-1.41	-.48 (.96)	15	-.49-2.07	.48 (.72)	-2.488	17.15	**.012**	.261	**-1.684**	**-.139**
Visuospatial Memory Composite (α = .96)	15	-1.94-1.15	-.60 (.80)	15	-.73-1.72	.60 (.68)	-3.581	20.63	**.001**	.399	**-1.772**	**-.469**
Verbal Memory Composite (α = .91)	15	-1.41-.63	-.52 (.75)	15	-.38-1.84	.52 (.62)	-4.049	19.85	**.001**	.165	**-1.547**	**-.494**
Executive Functions Composite (α =.74)	15	-1.28-.64	-.49 (.59)	15	-1.00-1.60	.49 (.69)	-3.329	20.55	**.002**	.379	**-1.576**	**-.363**

Note: VIQ: Verbal IQ, PIQ: Performance IQ, FSIQ: Full scale IQ.

Table 7:

Between Group (TBI vs Control) Independent Samples T-Test (Bootstrapped) on the BRIEF (N = 25)

	TBI			Controls			Test statistics					
	N	Range	M (SD)	n	Range	M (SD)	t	df	p	η^2	Bias Adjusted CI	
											Lower	Upper
Inhibit	12	40 – 86	60.83 (14.65)	12	38 – 80	52.33 (12.67)	1.52	21.56	.076	.095	-2.449	19.167
Shift	12	38 – 74	58.08 (12.61)	13	40 – 74	53.00 (10.14)	.88	20.83		.034	-5.730	13.387
Emotional Control	12	38 – 83	61.25 (14.75)	13	38 – 75	55.15 (11.54)	.94	20.54		.038	-4.793	15.135
BRI	12	39 – 83	61.58 (15.18)	13	38 – 76	53.92 (11.35)	1.22	20.29	.120	.064	-3.853	17.667
Initiate	12	38 – 74	54.83 (11.47)	13	35 – 79	53.15 (12.94)	.28	21.45		.003	-9.070	11.815
Working memory	12	38 – 81	61.00 (13.77)	13	43 – 73	56.00 (8.92)	1.04	19.32	.163	.047	-4.380	14.073
Plan/organization	12	35 – 81	56.58 (15.36)	13	37 – 65	53.85 (10.35)	.43	19.65		.008	-7.904	13.208
Org. of materials	12	37 – 59	48.42 (8.61)	13	39 – 64	50.00 (9.93)	-.5	21.33		.011	-9.598	6.080
Monitor	12	31 – 76	54.75 (15.50)	13	35 – 69	51.31 (10.71)	.53	19.85		.013	-7.188	14.056
MI	12	33 – 76	55.92 (13.62)	13	37 – 68	54.92 (10.07)	.10	20.53		.000	-9.624	10.647
GEC	12	36 - 81	59.00 (14.83)	13	38 - 72	53.92 (11.79)	.81	21.17		.029	-6.462	16.201

Note: BRI: Behavioural Regulation Index, MI: Metacognition Index, GEC: Global Executive Composite

Table 8:

Between Group (TBI vs Control) Independent Samples T-Test (Bootstrapped) on the PedsQL (N = 26)

	TBI			Controls			Test statistics					
	N	Range	M (SD)	n	Range	M (SD)	t	df	p	η^2	Bias Adjusted CI	
											Lower	Upper
Parent Report Physical QOL	12	34.4-81.3	59.13 (15.62)	13	37.5-100.0	73.58 (23.99)	-1.86	20.00	**.040**	.130	-33.993	3.651
Parent Report Emotional QOL	12	25.0-80.0	51.25 (15.54)	14	25.0-95.0	66.79 (21.27)	-1.31	20.00		.070	-24.831	5.375
Parent Report Social QOL	12	20.0–90.0	55.83 (25.75)	14	40.0-100.0	71.07 (20.21)	-1.06	16.23		.055	-30.817	9.715
Parent Report School QOL	12	30.0-80.0	57.92 (17.51)	14	40.0-100.0	70.00 (18.61)	-1.66	16.78	.063	.123	-29.413	1.750
Parent Report Psychosocial QOL	12	45.0-68.3	55.00 (8.38)	14	43.3-95.0	69.29 (17.23)	-1.97	18.65	**.039**	.134	-22.370	.686
Parent Report Total QOL	12	41.3-66.3	56.43 (9.03)	13	41.3-96.7	69.98 (18.66)	-2.08	18.95	**.033**	.148	-25.597	.828
Self-Report Physical QOL	13	25.0-93.8	59.64 (19.29)	14	62.5-96.9	83.06 (9.39)	-2.44	11.08	**.020**	.270	**-26.621**	**-3.684**
Self-Report Emotional QOL	13	25.0-95.0	61.92 (23.94)	14	40.0-100.0	68.57 (16.69)	.22	13.18		.003	-16.440	19.145
Self-Report Social QOL	13	20.0-100.0	68.46 (24.53)	14	10.0-100.0	75.00 (19.81)	-.16	13.07		.002	-23.411	19.073
Self-Report School QOL	11	30.0-100.0	56.36 (18.85)	14	25.0-100.0	66.07 (19.03)	-.69	15.33		.025	-20.484	10.000
Self-Report Psychosocial QOL	11	43.3-93.3	63.18 (17.52)	14	41.7-95.0	69.89 (14.45)	-.26	13.55	.392	.004	-14.855	11.695
Self-Report Total QOL	11	45.7-93.5	63.55 (16.40)	14	46.9-95.7	74.46 (11.06)	-1.03	11.62	.153	.061	-17.528	5.137

Table 9:

Between Group (TBI vs Control) Independent Samples T-Test (Bootstrapped) on the Syndrome Scales of the CBCL (N = 19)

	TBI			Controls			Test statistics					
											Bias Adjusted CI	
	n[b]	Range	M (SD)	n	Range	M (SD)	t	df	p	η^2	Lower	Upper
Anxious/ Depressed	7	50-76	59.14 (10.75)	12	50-66	55.58 (6.32)	.80	8.48		.047	-5.139	13.465
Withdrawn/ Depressed	7	50-68	61.71 (7.06)	12	50-68	54.17 (6.12)	2.36	11.23		.262	**1.483**	**13.382**
Somatic Complaints	7	50-76	61.57 (10.47)	12	50-72	55.42 (6.16)	1.42	8.48		.135	-1.108	13.368
Internalising Problems	7	50-79	62.43 (10.47)	12	41-70	52.83 (9.05)	2.02	11.21		.207	**1.297[a]**	**18.383[a]**
Rule-Breaking Behaviour	7	57-67	62.29 (4.23)	12	50-66	54.58 (6.47)	3.13	16.64		.316	**3.103**	**12.049**
Aggressive Behaviour	7	50-81	65.71 (10.50)	12	50-75	57.00 (9.22)	1.82	11.36		.174	-.822	18.118
Externalising Problems	7	53-73	64.71 (7.72)	12	33-71	51.83 (12.18)	2.82	16.78		.269	**3.141[a]**	**21.881[a]**
Total Problems	7	53-75	65.29 (9.27)	12	34-73	51.42 (11.98)	2.82	15.41		.289	**3.818[a]**	**23.319[a]**
Social Problems	7	51-77	64.00 (10.34)	12	37-67	51.58 (6.72)	2.85	9.02		.374	**4.060**	**20.642**
Thought Problems	7	51-79	64.43 (8.60)	12	50-79	54.33 (8.19)	2.51	12.18		.276	**1.853**	**17.747**
Attention Problems	7	53-81	63.14 (11.75)	12	50-67	55.75 (6.62)	1.55	7.97		.162	-.698	16.276

a: Results are based on 999 samples
b: Results based on reduced sample size due to missing data as a result of participants failing to complete a sufficient number of items in the scale.

Table 10:

CBCL Diagnostic Categorizations: Between group Comparisons for TBI vs. Controls (N = 19)

		Group		
CBCL syndrome profiles		TBI (n = 7[a])	Controls (n = 12)	p
Anxious/Depressed	Normal	5	10	.097
	Borderline	0	2	
	Clinical	2	0	
Withdrawn/Depressed	Normal	3	11	**.020**
	Borderline	4	1	
	Clinical	0	0	
Somatic Complaints	Normal	5	11	.243
	Borderline	0	0	
	Clinical	2	1	
Internalising Problems	Normal	3	9	.198
	Borderline	1	2	
	Clinical	3	1	
Rule-Breaking Behaviour	Normal	4	10	.211
	Borderline	3	2	
	Clinical	0	0	
Aggressive Behaviour	Normal	4	9	.379
	Borderline	0	1	
	Clinical	3	2	
Externalising Problems	Normal	2	9	.100
	Borderline	1	0	
	Clinical	4	3	
Total Problems	Normal	2	9	.054
	Borderline	0	1	
	Clinical	5	2	
Social Problems	Normal	3	10	.091
	Borderline	2	2	
	Clinical	2	0	
Thought Problems	Normal	3	11	**.035**
	Borderline	3	0	
	Clinical	1	1	
Attention Problems	Normal	4	11	.120
	Borderline	1	1	
	Clinical	2	0	

a Results based on reduced sample size due to missing data as a result of participants failing to complete a sufficient number of items in the scale.

Within-Group Analysis (TBI Group): Hypotheses Two and Three

The next set of analyses aimed to investigate the association between acute-stage ICP and $PbtO_2$, and neuropsychological outcomes within the TBI group. To do this, multiple parameters of each of these variables were utilised in the analysis.

Descriptive statistics: ICP and $PbtO_2$. While all the TBI participants underwent ICP monitoring in the acute phase of their injury, $PbtO_2$ data was only available for 13 out of 15 participants. This was due to technical difficulties with the $PbtO_2$ monitoring equipment and data being unavailable at the time of the study. Descriptive statistics for these variables are presented in Table 11. The average ICP and $PbtO_2$ among the sample exceeded or fell below the therapeutic threshold of 20mm Hg for ICP and PbtO2 respectively, however, large ranges and outliers were evident in the dataset.

Table 11

Descriptive Statistics: ICP and $PbtO_2$ (N = 15)

	N	Range	Mean	Std. Deviation
Highest ICP	15	16.0 - 39.0	25.13	5.79
Episodes ICP >20	15	0 - 73	9.00	18.71
Episodes ICP >25	15	0 - 31.0	2.87	7.86
Mean ICP over first 24hrs	15	9.6 - 21.9	13.14	3.16
Mean ICP	15	7.5 - 20.4	11.71	3.44
Lowest $PbtO_2$	13	6.9 - 23.0	13.70	5.38
Episodes $PbtO_2$ <10	13	0 - 7	.85	1.95
Episodes $PbtO_2$ <20	13	0 - 46	12.92	14.02
Mean $PbtO_2$ over first 24hrs	13	18.6 - 39.1	27.85	6.76
Mean $PbtO_2$	13	19 - 47	30.99	8.51

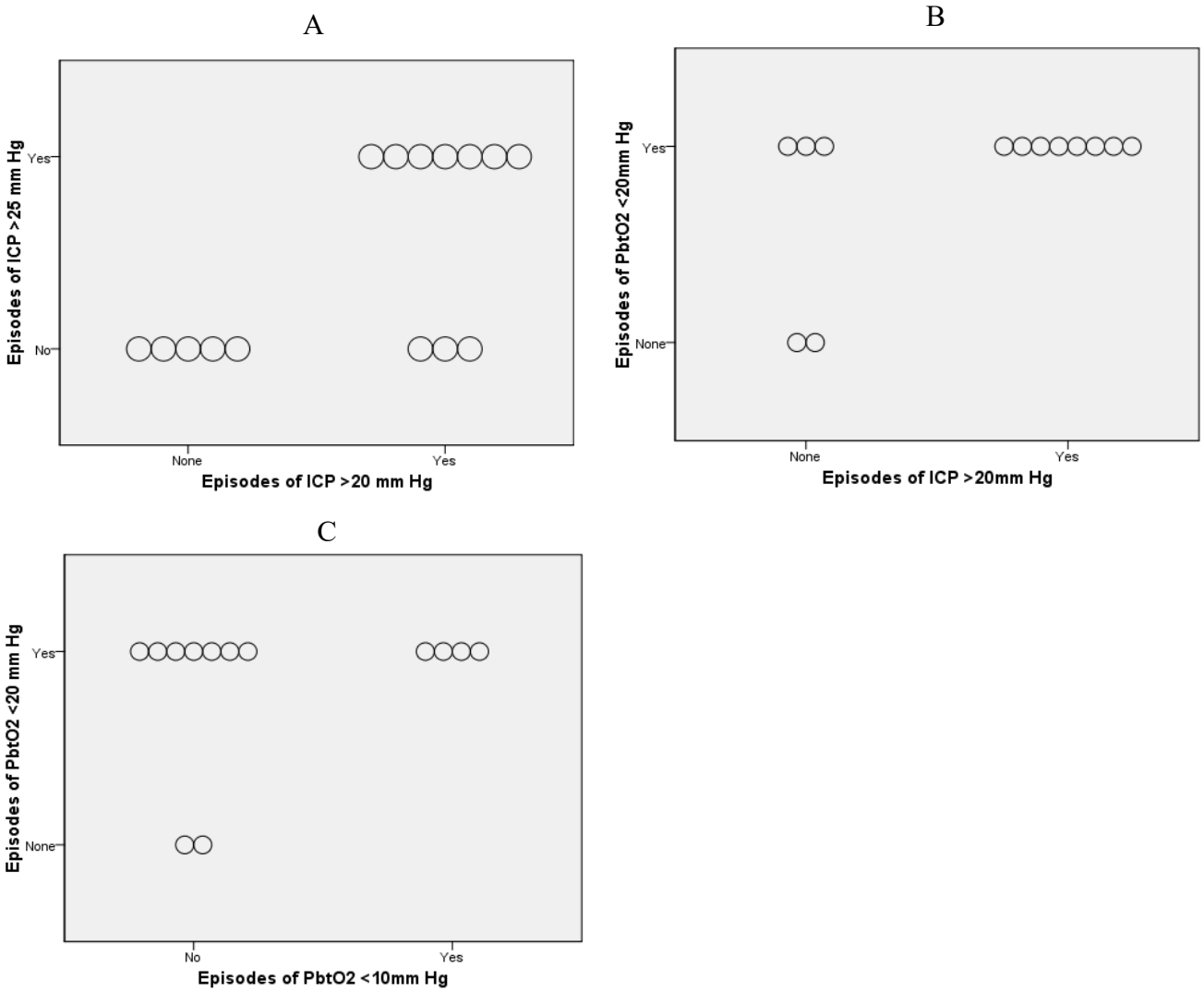
Note: ICP: Intracranial pressure, $PbtO_2$: Partial pressure of brain tissue oxygen

Individual data points for ICP and $PbtO_2$ for each TBI participant are presented in Table 12. 10 of the 15 participants (87%) experienced at least 1 episode during which ICP exceeded the therapeutic target of 20mm Hg and 7 of these patients experienced at least 1 episode during which ICP exceeded 25mm Hg (see Figure 1 A). All participants who experienced at least one episode of ICP raised to or above 20mm Hg experienced at least one episode during which $PbtO_2$ dropped to or below 20mm Hg (see Figure 1 B). In total, 11 of 13 participants (85%) experienced at least 1 episode during which brain oxygenation dropped

below the therapeutic threshold of 20mm Hg, and 4 of these participants (31%) experienced hypoxic episodes during which PbtO$_2$ dropped below the critical threshold of 10mm Hg (see Figure 1 C).

Figure 1

Illustration of participants who crossed treatment thresholds for PbtO$_2$ and ICP



Note: ICP: Intracranial pressure, PbtO$_2$: Partial pressure of brain tissue oxygen

Of the 13 participants who received both ICP and PbtO$_2$ monitoring, 8 participants (62%) crossed treatment thresholds for both ICP and PbtO$_2$ (>/< 20mm Hg respectively) during the monitoring period. It is further noteworthy that the participant with the highest overall ICP reading and highest number of episodes of ICP above 20 and 25mmHg (highlighted with red font colour in Table 12), did not experience even a single episode during which PbtO$_2$ dropped to or below the ischemic threshold of 10mmHg. Inversely, the

participant with the lowest overall $PbtO_2$ reading and highest number of episodes of $PbtO_2$ below 20 and 10mm Hg (highlighted with blue font colour in Table), did not experience a single episode during which ICP exceeded 20 or 25mm Hg.

Table 12

ICP and PbtO$_2$ data for each TBI participant (N = 15)

Participant	Highest ICP	Number of Episodes ICP >20	Number of Episodes ICP >25	Mean ICP over first 24hrs	Mean ICP	Lowest PbtO$_2$	Number of Episodes PbtO$_2$ <10	Number of Episodes PbtO$_2$ <20	Mean PbtO$_2$ over first 24hrs	Mean PbtO$_2$
1**	30	24	2	15.5	13.4	23.0	0	1	39.1	43
2[a]	28	7	2	14.0	13.4					
3**	24	1	0	14.0	11.9	14.0	0	11	24.4	24
4**	29	5	1	12.6	10.3	8.8	1	11	20.9	26
5*	**19**	**0**	**0**	**10.4**	**7.5**	**6.9**	**7**	**46**	**18.6**	**25**
6*	20	0	0	10.1	9.0	10.7	0	6	28.8	36
7[a]	26	4	0	16.6	15.2					
8**	25	3	0	11.0	12.5	10.0	0	14	34.1	29
9**	28	7	3	12.2	14.8	15.0	0	2	35.7	36
10**	**39**	**73**	**31**	**21.9**	**20.4**	**13.0**	**0**	**27**	**21.8**	**23**
11*	19	0	0	13.3	11.5	15.0	0	6	21.0	28
12	16	0	0	9.6	7.8	20.0	0	0	34.0	39
13	20	0	0	10.3	8.7	23.0	0	0	33.4	47
14**	26	5	3	13.2	10.5	9.0	2	32	23.3	19
15**	28	6	1	12.4	8.7	9.7	1	12	26.9	30

* Participants who crossed the treatment threshold (<20mm Hg) for PbtO$_2$. ** Participants who crossed the treatment threshold (</>20 mm Hg) for both ICP and PbtO$_2$. a No PbtO2 data available for these participants due to unavailability of data at the time of study and issues with equipment at the time of monitoring.

Note: ICP: Intracranial pressure, PbtO2: Partial pressure of brain tissue oxygen

Correlations between ICP and PbtO$_2$ variables. The relationship between the acute variables themselves was investigated using bootstrapped correlation analyses. These results are presented in Table 13. Both *p* values and bias adjusted confidence intervals indicate no significant relationship between ICP and PbtO$_2$ among the TBI participants. Figure 2 below also illustrates these relationships graphically. On graphs A and, particularly, B illustrated in Figure 2, it is notable that the participants' data does not follow an easily identifiable trend, instead the participants' scores (represented by the coloured lines on the graph) cross the variables in a largely random fashion. If there were a strong relationship between ICP and PbtO2, one would expect the lines for each of the participants to follow a similar trend (e.g. the dotted arrow indicated in black) when moving between ICP and PbtO$_2$. Unsurprisingly, the ICP variables themselves, and the PbtO$_2$ variables themselves, were however highly significantly correlated, as can be seen in Tables 14 and 15.

Figure 2

Illustration of correlations between ICP and PbtO$_2$ variables

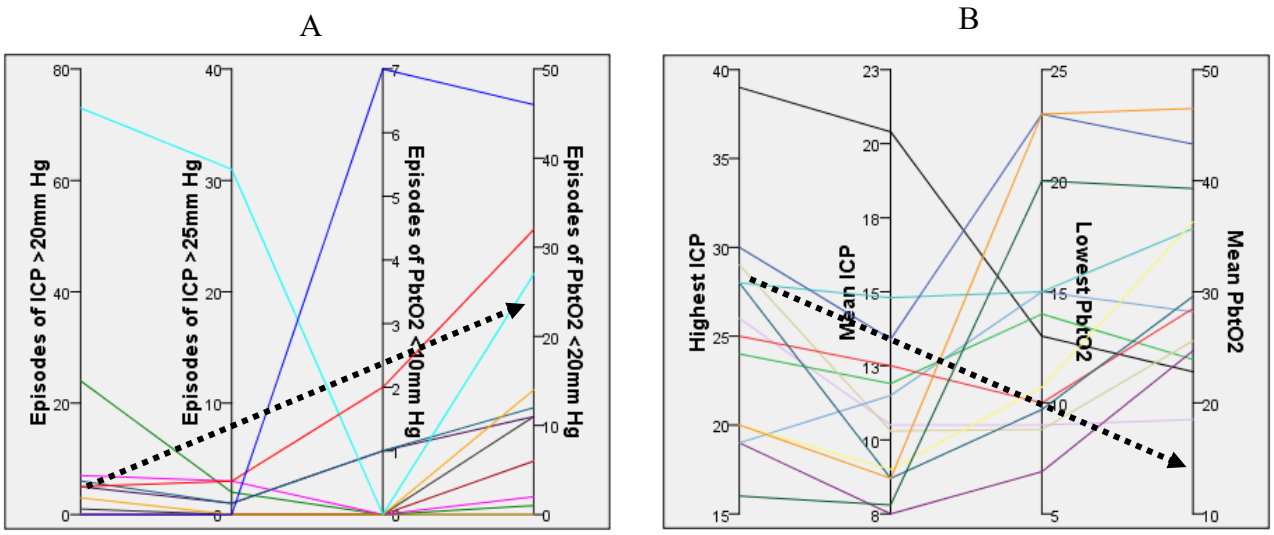


Table 13

Correlations between ICP and PbtO$_2$ (TBI Group N = 15)

			Lowest PbtO$_2$	Episodes PbtO$_2$ <10	Episodes Pbt0$_2$ <20	Mean PbtO$_2$ over first 24hrs	Mean PbtO$_2$
Highest ICP	Pearson Correlation		-.128	-.216	.167	-.056	-.308
	Sig. (1-tailed)		.338	.239	.293	.428	.153
	BCa 95% Confidence Interval	Lower	-.645	-.749[a]	-.542	-.592	-.679
		Upper	.424	.709a	.884	.540	.223
Episodes ICP >20	Pearson Correlation		.076	-.178	.220	-.101	-.186
	Sig. (1-tailed)		.403	.280	.235	.372	.272
	BCa 95% Confidence Interval	Lower	-.556	-.422[a]	-.418	-.582	-.601
		Upper	.727	.676[a]	.778	.809	.686
Episodes ICP >25	Pearson Correlation		-.041	-.135	.306	-.238	-.301
	Sig. (1-tailed)		.447	.330	.155	.217	.159
	BCa 95% Confidence Interval	Lower	-.417	-.394[a]	-.415	-.747	-.632
		Upper	.443	.831[a]	.855	.730	.420
Mean ICP over first	Pearson Correlation		.035	-.221	.214	-.237	-.356
24hrs	Sig. (1-tailed)		.455	.235	.242	.217	.116
	BCa 95% Confidence Interval	Lower	-.498	-.642[a]	-.478	-.670	-.712
		Upper	.728	.640[a]	.849	.358	.131
Mean ICP	Pearson Correlation		.085	-.387	.037	.036	-.219
	Sig. (1-tailed)		.391	.096	.453	.454	.236
	BCa 95% Confidence Interval	Lower	-.418	**-.701[a]**	-.634	-.502	-.630
		Upper	.784	**-.076[a]**	.782	.722	.409

* Correlation is significant at the 0.05 level ** Correlation is significant at the 0.01 level

a Results are based on 997 samples

Note: ICP: Intracranial pressure, PbtO2: Partial pressure of brain tissue oxygen

Table 14

Correlations between ICP parameters (TBI Group N = 15)

			Highest ICP	Episodes ICP >20	Episodes ICP >25	Mean ICP over first 24hrs	Mean ICP
Highest ICP	Pearson Correlation		1	.818**	.748**	.844**	.815**
	Sig. (1-tailed)			**.000**	**.002**	**.000**	**.000**
	BCa 95% Confidence Interval	Lower	.	**.651**	**.466**	**.423**	**.420**
		Upper	.	**.964**	**.951**	**.953**	**.954**
Episodes ICP >20	Pearson Correlation		.818**	1	.964**	.920**	.845**
	Sig. (1-tailed)		**.000**		**.000**	**.000**	**.000**
	Bca 95% Confidence Interval	Lower	**.651**	**.**	**.581**	**.379**	**.432**
		Upper	**.964**	**.**	**.998**	**.980**	**.951**
Episodes ICP >25	Pearson Correlation		.748**	.964**	1	.873**	.815**
	Sig. (1-tailed)		**.002**	**.000**		**.000**	**.000**
	Bca 95% Confidence Interval	Lower	**.466**	**.581**	**.**	**.286**	**.210**
		Upper	**.951**	**.998**	**.**	**.965**	**.937**
Mean ICP over first 24hrs	Pearson Correlation		.844**	.920**	.873**	1	.872**
	Sig. (1-tailed)		**.000**	**.000**	**.000**		**.000**
	Bca 95% Confidence Interval	Lower	**.423**	**.379**	**.286**	**.**	**.481**
		Upper	**.953**	**.980**	**.965**	**.**	**.983**
Mean ICP	Pearson Correlation		.815**	.845**	.815**	.872**	1
	Sig. (1-tailed)		**.000**	**.000**	**.000**	**.000**	
	Bca 95% Confidence Interval	Lower	**.420**	**.432**	**.210**	**.481**	.
		Upper	**.954**	**.951**	**.937**	**.983**	.

* Correlation is significant at the 0.05 level ** Correlation is significant at the 0.01 level

Note: ICP: Intracranial pressure

Table 15

Correlations between PbtO$_2$ parameters (TBI Group N = 15)

			Lowest PbtO$_2$	Episodes PbtO$_2$ <10	Episodes Pbt0$_2$ <20	Mean PbtO$_2$ over first 24hrs	Mean PbtO$_2$
Lowest PbtO$_2$	Pearson Correlation		1	-.523*	-.697**	.678**	.807**
	Sig. (1-tailed)			**.033**	**.004**	**.005**	**.000**
	BCa 95% Confidence Interval	Lower	.	**-.647^{a}**	**-.833**	**.304**	**.405**
		Upper	.	**-.511^{a}**	**-.554**	**.906**	**.934**
Episodes PbtO$_2$ <10	Pearson Correlation		-.523*	1	.813**	-.517*	-.380
	Sig. (1-tailed)		**.033**		**.000**	**.035**	.100
	BCa 95% Confidence Interval	Lower	**-.647^{a}**		**.138^{a}**	**-.728^{a}**	**-.574^{a}**
		Upper	**-.511^{a}**		**.961^{a}**	**-.317^{a}**	**-.322^{a}**
Episodes Pbt0$_2$ <20	Pearson Correlation		-.697**	.813**	1	-.687**	-.742**
	Sig. (1-tailed)		**.004**	**.000**		**.005**	**.002**
	BCa 95% Confidence Interval	Lower	**-.833**	**.138^{a}**	**.**	**-.889**	**-.873**
		Upper	**-.554**	**.961^{a}**	**.**	**-.415**	**-.679**
Mean PbtO$_2$ over first 24hrs	Pearson Correlation		.678**	-.517*	-.687**	1	.796**
	Sig. (1-tailed)		**.005**	**.035**	**.005**		**.001**
	BCa 95% Confidence Interval	Lower	**.304**	**-.728^{a}**	**-.889**	**.**	**.587**
		Upper	**.906**	**-.317^{a}**	**-.415**	**.**	**.936**
Mean PbtO$_2$	Pearson Correlation		.807**	-.380	-.742**	.796**	1
	Sig. (1-tailed)		**.000**	**.100**	**.002**	**.001**	
	BCa 95% Confidence Interval	Lower	**.405**	**-.574^{a}**	**-.873**	**.587**	.
		Upper	**.934**	**-.322^{a}**	**-.679**	**.936**	.

* Correlation is significant at the 0.05 level ** Correlation is significant at the 0.01 level

a Results are based on 997 samples

Note: PbtO2: Partial pressure of brain tissue oxygen

Correlations between ICP and $PbtO_2$ and neuropsychological variables. Bootstrapped correlation analyses were utilised to investigate the association between ICP and $PbtO_2$ and the cognitive, behavioural and QOL neuropsychological outcome variables. The results of these analyses are included in Tables 16 - 19.

ICP. Table 16 shows that acute stage ICP was not significantly related to any of the cognitive outcome measures, including the cognitive composite variables. This is true for all of the measured parameters of ICP. In addition, ICP was not significantly related to any of the BRIEF indices. One of the scales of the PedsQL, the parent report of Emotional QOL, was significantly correlated with all 5 parameters of ICP with the correlation indicating a positive linear relationship. In addition, a number of the syndrome scales of the CBCL were significantly correlated with some of the parameters of ICP. One of these scales is somatic problems which is significantly correlated with a positive linear relationship with 4 of 5 of the parameters of ICP. In addition, mean ICP was significantly correlated with most of the syndrome scales on the CBCL, including the three higher-order factor groupings of the syndrome scales, Internalising, Externalising and Total Problems.

$PbtO_2$. Across analyses, $PbtO_2$ significantly correlated with more variables, including cognitive, behavioural and QOL, than ICP. Table 20 shows that few of the parameters of acute stage $PbtO_2$ significantly correlate with some of the cognitive neuropsychology variables. Sustained attention significantly correlated with number of episodes of $PbtO_2$ below 10mm Hg and below 20mm Hg as well as average $PbtO_2$. The average $PbtO_2$ over the first 24 hours of monitoring significantly correlates with verbal IQ, full scale IQ, the higher order attention composite and the executive functions composite. Each of these relationships are however, not in the expected direction, suggesting that a higher average $PbtO_2$ over the first 24 hours of monitoring is associated with poorer outcome on these cognitive variables. Two scales of the BRIEF, the Initiate and Plan/Organise scales, are significantly correlated with number of episodes of $PbtO_2$ below 10 mm Hg, however, the bias adjusted confidence intervals suggest that the null hypothesis should not be rejected for these variables. A number of scales of the PedsQL, most of which are parent-report surveys, significantly correlate with various parameters of $PbtO_2$, however, these were mostly against the expected direction, again seemingly suggesting poorer QOL associated with improved $PbtO_2$. Two syndrome scales of the CBCL are also significantly correlated with parameters of $PbtO_2$. The Withdrawn/Depressed scale significantly correlates with the number of episodes of $PbtO_2$ below 10mm and Attention Problems significantly correlates with the mean $PbtO_2$ over the first 24 hours of monitoring, however, both of these relationships are not in the expected

direction, as with the PedsQL scales. It is interesting to note that across the analyses, the lowest $PbtO_2$ did not significantly correlate with any of the variables, cognitive, behavioural and QOL.

Table 16
Correlations between cognitive neuropsychological variables and ICP (TBI Group N = 15)

			Highest ICP	Episodes ICP >20	Episodes ICP >25	Mean ICP over first 24hrs	Mean ICP
Sustained Attention	Pearson Correlation		.011	.007	.184	.009	-.055
	Sig. (1-tailed)		.488	.493	.306	.490	.440
	BCa 95% Confidence Interval	Lower	-.746	-.894	**.092[a]**	-.013	-.024
		Upper	.621	.807	**.374[a]**	.331	.329
IQ: VIQ	Pearson Correlation		.134	.315	.443	.458	.283
	Sig. (1-tailed)		.356	.187	.100	.091	.214
	BCa 95% Confidence Interval	Lower	-.659	-.740	-.450[a]	-.323	-.682
		Upper	.748	.762	.804[a]	.828	.754
IQ: PIQ	Pearson Correlation		-.401	-.284	-.163	-.038	-.126
	Sig. (1-tailed)		.126	.213	.327	.459	.364
	BCa 95% Confidence Interval	Lower	**-.795**	-.745	-.678a	-.475	-.559
		Upper	**-.006**	.011	.130a	.699	.534
IQ: FSIQ	Pearson Correlation		-.137	.022	.164	.247	.093
	Sig. (1-tailed)		.353	.476	.325	.246	.399
	BCa 95% Confidence Interval	Lower	-.684	-.754	-.567a	-.297	-.549
		Upper	.503	.571	.667a	.773	.687
Processing Speed	Pearson Correlation		-.443	-.192	-.032	-.124	-.220
	Sig. (1-tailed)		.100	.297	.465	.367	.271
	BCa 95% Confidence Interval	Lower	**-.899**	-.848	-.747a	-.603	-.737
		Upper	**-.051**	.153	.336a	.332	.144
Verbal Learning	Pearson Correlation		-.009	.145	.114	.400	.318
	Sig. (1-tailed)		.490	.345	.377	.126	.186
	BCa 95% Confidence Interval	Lower	-.518	-.468	-.332a	**.119**	**.014**
		Upper	.624	.718	.670a	**.842**	**.760**

Table 16

Correlations between cognitive neuropsychological variables and ICP (TBI Group N=15) continued

			Highest ICP	Episodes ICP >20	Episodes ICP >25	Mean ICP over first 24hrs	Mean ICP
Higher Order Attention Composite	Pearson Correlation		-.235	-.216	-.123	.074	-.079
	Sig. (1-tailed)		.256	.275	.367	.419	.414
	BCa 95% Confidence Interval	Lower	-.670	-.661	-.544a	-.392	-.499
		Upper	.393	.251	.382a	.874	.655
Visuospatial Memory Composite	Pearson Correlation		-.358	-.251	-.259	-.009	-.190
	Sig. (1-tailed)		.155	.242	.235	.491	.299
	BCa 95% Confidence Interval	Lower	-.689	-.638	-.633a	-.484	-.555
		Upper	.265	.446	.758a	.674	.546
Verbal Memory Composite	Pearson Correlation		-.030	.086	.030	.355	.217
	Sig. (1-tailed)		.467	.407	.467	.157	.273
	BCa 95% Confidence Interval	Lower	-.486	-.461	-.349a	**.006**	-.100
		Upper	.536	.629	.599a	**.852**	.802
Verbal Fluency Composite	Pearson Correlation		-.150	.251	.310	.146	.110
	Sig. (1-tailed)		.340	.242	.192	.344	.381
	BCa 95% Confidence Interval	Lower	-.862	-.525	-.419a	-.630	-.767
		Upper	.885	.929	.944a	.886	.873
Executive Functions Composite	Pearson Correlation		-.140	-.019	.081	.229	.150
	Sig. (1-tailed)		.350	.479	.412	.262	.339
	BCa 95% Confidence Interval	Lower	-.693	-.681	-.627a	-.298	-.392
		Upper	.583	.677	.718a	.811	.762

*. Correlation is significant at the 0.05 level (1-tailed). **. Correlation is significant at the 0.01 level (1-tailed).

a. Based on 995 samples Note: ICP: Intracranial pressure

Table 17

Correlations between the BRIEF and ICP variables (TBI Group N=15)

			Highest ICP	Episodes ICP >20	Episodes ICP >25	Mean ICP over first 24hrs	Mean ICP
Inhibit	Pearson Correlation		-.049	.468	.077	.100	.036
	Sig. (1-tailed)		.440	.062	.406	.379	.456
	BCa 95% Confidence Interval	Lower	-.617	-.410	-.468	-.568	-.574
		Upper	.538	.814	.607	.676	.649
Shift	Pearson Correlation		-.160	.097	-.132	.106	-.042
	Sig. (1-tailed)		.310	.383	.342	.371	.449
	BCa 95% Confidence Interval	Lower	-.608	-.426	-.652	-.399	-.516
		Upper	.356	.468	.432	.548	.526
Emotional Control	Pearson Correlation		-.143	.210	-.220	.198	.030
	Sig. (1-tailed)		.329	.257	.246	.269	.463
	BCa 95% Confidence Interval	Lower	-.610	-.462	-.757	-.415	-.603
		Upper	.442	.578	.487	.822	.765
BRI	Pearson Correlation		-.098	.318	-.074	.150	.018
	Sig. (1-tailed)		.381	.157	.409	.321	.478
	BCa 95% Confidence Interval	Lower	-.588	-.410	-.631	-.418	-.595
		Upper	.474	.688	.567	.724	.690
Initiate	Pearson Correlation		.090	.284	.296	.046	.169
	Sig. (1-tailed)		.390	.185	.175	.444	.299
	BCa 95% Confidence Interval	Lower	-.448	-.299	-.343	-.505	-.518
		Upper	.660	.766	.837	.607	.849
Working Memory	Pearson Correlation		.316	.415	.137	.286	.136
	Sig. (1-tailed)		.158	.090	.336	.183	.336
	BCa 95% Confidence Interval	Lower	-.153	-.155	-.435	-.297	-.400

Table 17:

Correlations between the BRIEF and ICP variables (TBI Group N=15) continued

			Highest ICP	Episodes ICP >20	Episodes ICP >25	Mean ICP over first 24hrs	Mean ICP
		Upper	.691	.801	.707	.760	.674
Plan/Organisation	Pearson Correlation		.049	.275	-.088	.192	-.107
	Sig. (1-tailed)		.440	.194	.392	.275	.370
	BCa 95% Confidence Interval	Lower	-.475	-.315	-.539	-.498	-.696
		Upper	.585	.665	.453	.916	.784
Organisation of Materials	Pearson Correlation		-.038	.042	-.324	.435	.295
	Sig. (1-tailed)		.453	.449	.152	.079	.176
	BCa 95% Confidence Interval	Lower	-.668	-.477	-.840	-.111	-.228
		Upper	.533	.401	.246	.851	.795
Monitor	Pearson Correlation		.266	.378	.073	.331	.102
	Sig. (1-tailed)		.201	.113	.411	.147	.376
	BCa 95% Confidence Interval	Lower	-.261	-.116	-.408	-.434	-.538
		Upper	.710	.778	.592	.922	.863
MI	Pearson Correlation		.169	.340	.017	.276	.085
	Sig. (1-tailed)		.300	.140	.480	.193	.396
	BCa 95% Confidence Interval	Lower	-.363	-.227	-.465	-.364	-.487
		Upper	.669	.712	.556	.857	.822
GEC	Pearson Correlation		.070	.352	-.005	.228	.059
	Sig. (1-tailed)		.414	.131	.494	.238	.427
	BCa 95% Confidence Interval	Lower	-.457	-.270	-.499	-.414	-.548
		Upper	.613	.721	.548	.812	.793

*. Correlation is significant at the 0.05 level (1-tailed).**. Correlation is significant at the 0.01 level (1-tailed). Note: ICP: Intracranial pressure

Table 18:
Correlations between the PedsQL and ICP variables (TBI Group N=15)

			Highest ICP	Episodes ICP >20	Episodes ICP >25	Mean ICP over first 24hrs	Mean ICP
Parent-Report Physical QOL	Pearson Correlation		-.283	-.100	.015	-.104	-.299
	Sig. (1-tailed)		.231	.399	.485	.395	.217
	BCa 95% Confidence Interval	Lower	-.855	-.792	-.843	-.612	-.862
		Upper	.262	.149	.218	.372	.226
Parent-Report Emotional QOL	Pearson Correlation		.790**	.800**	.669*	.775**	.759**
	Sig. (1-tailed)		**.006**	**.005**	**.024**	**.007**	**.009**
	BCa 95% Confidence Interval	Lower	**.436**	.	**.151**	**.286**	**.376**
		Upper	**.950**	.	**.958**	**.980**	**.971**
Parent Report Social QOL	Pearson Correlation		-.046	.157	.354	.123	-.032
	Sig. (1-tailed)		.453	.343	.175	.376	.467
	BCa 95% Confidence Interval	Lower	-.744	-.874	-.701	-.692	-.820
		Upper	.483	.647	.711	.688	.530
Parent-Report School QOL	Pearson Correlation		-.393	-.396	-.318	-.440	-.574
	Sig. (1-tailed)		.148	.146	.202	.118	.053
	BCa 95% Confidence Interval	Lower	-.834	-.878	-.868	-.781	**-.856**
		Upper	.304	.424	.539	.023	**-.190**
Parent-Report Psychosocial	Pearson Correlation		.131	.314	.468	.239	.001
QOL	Sig. (1-tailed)		.369	.206	.102	.268	.499
	BCa 95% Confidence Interval	Lower	-.693	-.759	-.814	-.628	-.880
		Upper	.683	.743	.827	.701	.604
Parent-Report Total QOL	Pearson Correlation		-.086	.126	.281	.079	-.171
	Sig. (1-tailed)		.413	.374	.232	.420	.330
	BCa 95% Confidence Interval	Lower	-.835	-.882	-.840	-.719	-.931
		Upper	.546	.579	.613	.581	.390

Table 18:
Correlations between the PedsQL and ICP variables (TBI Group N=15) continued

			Highest ICP	Episodes ICP >20	Episodes ICP >25	Mean ICP over first 24hrs	Mean ICP
Self-Report Physical QOL	Pearson Correlation		.251	.226	.192	.196	.500
	Sig. (1-tailed)		.257	.279	.310	.307	.085
	BCa 95% Confidence Interval	Lower	-.116	-.155	-.484	-.407	**.022**
		Upper	.652	.763	.712	.760	**.922**
Self-Report Emotional QOL	Pearson Correlation		.237	.415	.393	.406	.611*
	Sig. (1-tailed)		.270	.134	.148	.139	**.040**
	BCa 95% Confidence Interval	Lower	-.445	-.118	-.655	-.346	**.107**
		Upper	.724	.707	.720	.883	**.951**
Self-Report Social QOL	Pearson Correlation		.095	.307	.227	.232	.399
	Sig. (1-tailed)		.404	.211	.278	.274	.144
	BCa 95% Confidence Interval	Lower	-.379	-.149	-.522	-.466	-.047
		Upper	.643	.639	.549	.704	.841
Self-Report School QOL	Pearson Correlation		.320	.047	.120	.045	.361
	Sig. (1-tailed)		.201	.452	.380	.455	.170
	BCa 95% Confidence Interval	Lower	-.826	-.599	.	-.735	-.203
		Upper	.957	.959	.	.814	.888
Self-Report Psychosocial QOL	Pearson Correlation		.270	.359	.334	.314	.607*
	Sig. (1-tailed)		.241	.171	.190	.205	**.041**
	BCa 95% Confidence Interval	Lower	-.340	-.047	-.476	-.403	**.180**
		Upper	.708	.835	.793	.958	**.979**
Self-Report Total QOL	Pearson Correlation		.277	.331	.301	.288	.601*
	Sig. (1-tailed)		.235	.192	.215	.226	**.043**
	BCa 95% Confidence Interval	Lower	-.249	-.032	-.529	-.389	**.179**
		Upper	.657	.861	.803	.886	**.955**

*. Correlation is significant at the 0.05 level (1-tailed).**. Correlation is significant at the 0.01 level (1-tailed), Note: ICP: Intracranial pressure,

Table 19
Correlations between the CBCL Syndrome Scales and ICP variables (TBI Group N=15)

			Highest ICP	Episodes ICP >20	Episodes ICP >25	Mean ICP over first 24hrs	Mean ICP
Anxious/Depressed	Pearson Correlation		.261	-.203	.334	.224	.629
	Sig. (1-tailed)		.286	.331	.232	.315	.065
	BCa 95% Confidence	Lower	-.656	-.781	-.613[a]	-.736	-.238
	Interval	Upper	.872	.931	1.000[a]	.921	.981
Withdrawn/Depressed	Pearson Correlation		.025	.314	.044	.212	.552
	Sig. (1-tailed)		.479	.246	.463	.324	.100
	BCa 95% Confidence	Lower	-.948	-.986	-.894[a]	-.783	-.654
	Interval	Upper	.987	.929	.959[a]	.947	.983
Somatic Problems	Pearson Correlation		.784*	.799*	.771*	.654	.926**
	Sig. (1-tailed)		**.019**	**.016**	**.021**	.056	**.001**
	BCa 95% Confidence	Lower	**.173**	.	**.240[a]**	-.010	**.768**
	Interval	Upper	**.996**	.	**.997[a]**	.981	**.997**
Social Problems	Pearson Correlation		.456	.604	.467	.503	.788*
	Sig. (1-tailed)		.152	.076	.145	.125	**.018**
	BCa 95% Confidence	Lower	-.922[a]	-.997[a]	-.347[b]	-.338[a]	-.053[a]
	Interval	Upper	.999[a]	.989[a]	.907[b]	.961[a]	.997[a]
Thought Problems	Pearson Correlation		.601	.747*	.297	.723*	.682*
	Sig. (1-tailed)		.077	**.027**	.259	**.033**	**.046**
	BCa 95% Confidence	Lower	-.705	-.614	-.440[a]	-.476	**.048**
	Interval	Upper	.937	.981	.808[a]	.989	**.988**
Attention Problems	Pearson Correlation		.469	.735*	.501	.371	.725*
	Sig. (1-tailed)		.144	**.030**	.126	.206	**.033**
	BCa 95% Confidence Interval	Lower	-.525[a]	-.825[a]	-.383[b]	-.552[a]	-.352[a]

Table 19:

Correlations between the CBCL Syndrome Scales and ICP variables (TBI Group N=15) continued

			Highest ICP	Episodes ICP >20	Episodes ICP >25	Mean ICP over first 24hrs	Mean ICP
		Upper	.982[a]	1.000[a]	.943[b]	.861[a]	.947[a]
Rule Breaking Behaviour	Pearson Correlation		.481	.478	.241	.859**	.391
	Sig. (1-tailed)		.137	.139	.302	**.007**	.193
	BCa 95% Confidence	Lower	-.488	-.227	-.536[a]	**.297**	-.496
	Interval	Upper	.962	.906	.928[a]	**1.000**	.977
Aggressive Behaviour	Pearson Correlation		.290	.372	.421	.423	.814*
	Sig. (1-tailed)		.264	.206	.174	.172	**.013**
	BCa 95% Confidence	Lower	-.632	-.790	-.409[a]	-.506	-.945
	Interval	Upper	.975	.998	.994[a]	.995	1.000
Internalising Problems	Pearson Correlation		.515	.375	.532	.536	.923**
	Sig. (1-tailed)		.118	.204	.109	.107	**.002**
	BCa 95% Confidence	Lower	-.498	-.481	-.244[a]	-.399	-.205
	Interval	Upper	.995	.992	.971[a]	.983	1.000
Externalising Problems	Pearson Correlation		.343	.408	.416	.568	.795*
	Sig. (1-tailed)		.225	.181	.177	.092	**.016**
	BCa 95% Confidence	Lower	-.564	-.467	-.563[a]	-.378	-.325
	Interval	Upper	.980	.959	.973[a]	1.000	1.000
Total Problems	Pearson Correlation		.497	.524	.436	.631	.858**
	Sig. (1-tailed)		.128	.114	.164	.065	**.007**
	BCa 95% Confidence	Lower	-.675	-.579	-.407[a]	-.456	.
	Interval	Upper	.984	.960	.912[a]	.996	.

*. Correlation is significant at the 0.05 level (1-tailed). **. Correlation is significant at the 0.01 level (1-tailed).

a. Based on 999 samples. b. Based on 998 samples

Note: ICP: Intracranial pressure

Table 20

Correlations between cognitive neuropsychological variables and PbtO$_2$ (TBI Group N=15)

			Lowest PbtO$_2$	Episodes PbtO$_2$ <10	Episodes Pbt0$_2$ <20	Mean PbtO$_2$ over first 24hrs	Mean PbtO$_2$
Sustained Attention	Pearson Correlation		-.443	.757**	.716**	-.444	-.564*
	Sig. (1-tailed)		.100	**.006**	**.010**	.099	**.045**
	BCa 95% Confidence	Lower	-.813	-.048a	-.104	-.795	-.915
	Interval	Upper	.425	.964a	.955	.274	.256
IQ: VIQ	Pearson Correlation		-.034	.155	.299	-.734**	-.423
	Sig. (1-tailed)		.463	.334	.201	**.008**	.112
	BCa 95% Confidence	Lower	-.685	-.196a	-.366	**-.931**	**-.787**
	Interval	Upper	.601	.591a	.778	**-.418**	**-.022**
IQ: PIQ	Pearson Correlation		-.146	-.112	-.012	-.535	-.374
	Sig. (1-tailed)		.344	.380	.487	.056	.144
	BCa 95% Confidence	Lower	-.639	-.472a	-.475	-.878	-.740
	Interval	Upper	.797	.327a	.525	.026	.152
IQ: FSIQ	Pearson Correlation		-.150	.071	.204	-.743**	-.490
	Sig. (1-tailed)		.339	.423	.285	**.007**	.075
	BCa 95% Confidence	Lower	-.698	-.326a	-.267	**-.932**	**-.832**
	Interval	Upper	.735	.516a	.704	**-.370**	**-.071**
Processing Speed	Pearson Correlation		-.089	.047	.093	-.402	-.116
	Sig. (1-tailed)		.403	.448	.399	.125	.374
	BCa 95% Confidence	Lower	-.772	-.713a	-.485	-.887	-.661
	Interval	Upper	.626	.612a	.609	.351	.489
Verbal Learning	Pearson Correlation		.141	-.183	.063	-.261	-.240
	Sig. (1-tailed)		.349	.306	.432	.234	.252
		Lower	-.473	-.733a	-.343	-.881	-.732

	BCa 95% Confidence Interval	Upper	.867	.249a	.631	.441	.300

Table 20:

Correlations between cognitive neuropsychological variables and PbtO$_2$ (TBI Group N=15) continued

			Lowest PbtO$_2$	Episodes PbtO$_2$ <10	Episodes Pbt0$_2$ <20	Mean PbtO$_2$ over first 24hrs	Mean PbtO$_2$
Higher Order Attention Composite	Pearson Correlation		-.146	.190	.141	-.588*	-.510
	Sig. (1-tailed)		.343	.299	.348	**.037**	.066
	BCa 95% Confidence	Lower	-.660	-.198a	-.371	**-.865**	**-.820**
	Interval	Upper	.635	.820a	.650	**-.117**	**-.011**
Visuospatial Memory Composite	Pearson Correlation		.189	.149	-.099	-.248	-.076
	Sig. (1-tailed)		.301	.341	.393	.245	.418
	BCa 95% Confidence	Lower	-.330	-.523a	-.668	-.787	-.549
	Interval	Upper	.748	.711a	.537	.551	.584
Verbal Memory Composite	Pearson Correlation		.200	-.087	.018	-.211	-.177
	Sig. (1-tailed)		.289	.405	.481	.280	.312
	BCa 95% Confidence	Lower	-.441	-.691a	-.432	-.906	-.706
	Interval	Upper	.819	.378a	.533	.485	.405
Verbal Fluency Composite	Pearson Correlation		.127	-.181	-.040	-.127	-.010
	Sig. (1-tailed)		.363	.308	.457	.364	.489
	BCa 95% Confidence	Lower	-.458	-.532a	-.626	-.784	-.600
	Interval	Upper	.849	.203a	.738	.475	.619
Executive Functions Composite	Pearson Correlation		-.112	-.131	.113	-.568*	-.485
	Sig. (1-tailed)		.379	.360	.378	**.043**	.078
	BCa 95% Confidence	Lower	-.600	-.511a	-.341	**-.863**	-.841
	Interval	Upper	.857	.248a	.867	**-.095**	.037

*. Correlation is significant at the .05 level (1-tailed).**. Correlation is significant at the .01 level (1-tailed).

a. Results based on 891 samples

Note: PbtO2: Partial pressure of brain tissue oxygen

Table 21*:*
Correlations between the BRIEF and PbtO$_2$ variables (TBI Group N=15)

			Lowest PbtO$_2$	Episodes PbtO$_2$ <10	Episodes Pbt0$_2$ <20	Mean PbtO$_2$ over first 24hrs	Mean PbtO$_2$
Inhibit	Pearson Correlation		.460	.332	.093	.347	.444
	Sig. (1-tailed)		.091	.175	.399	.163	.099
	BCa 95% Confidence Interval	Lower	-.535	-.536[a]	-.659	-.575	-.378
		Upper	.970	.714[a]	.609	.916	.914
Shift	Pearson Correlation		.094	.315	.170	-.042	.170
	Sig. (1-tailed)		.398	.187	.319	.454	.320
	BCa 95% Confidence Interval	Lower	-.549	-.437[a]	-.413	-.672	-.733
		Upper	.794	.663[a]	.575	.824	.856
Emotional Control	Pearson Correlation		.343	.438	.209	.098	.241
	Sig. (1-tailed)		.166	.103	.281	.394	.251
	BCa 95% Confidence Interval	Lower	-.518	-.684[a]	-.713	-.679	-.528
		Upper	.974	.767[a]	.697	.869	.873
BRI	Pearson Correlation		.351	.409	.179	.189	.328
	Sig. (1-tailed)		.160	.120	.310	.300	.178
	BCa 95% Confidence Interval	Lower	-.525	-.565[a]	-.628	-.673	-.614
		Upper	.964	.743[a]	.643	.904	.893
Initiate	Pearson Correlation		.163	.599*	.363	.184	.191
	Sig. (1-tailed)		.326	**.034**	.151	.305	.299
	BCa 95% Confidence Interval	Lower	-.597	-.496[a]	-.709	-.710	-.458
		Upper	.912	.878[a]	.768	.955	.921
Working Memory	Pearson Correlation		.117	.378	.156	.101	.203
	Sig. (1-tailed)		.373	.140	.333	.391	.287
	BCa 95% Confidence Interval	Lower	-.587	-.403[a]	-.560	-.644	-.634
		Upper	.844	.756[a]	.577	.776	.868

Table 21

Correlations between the BRIEF and PbtO$_2$ variables (TBI Group N=15) continued

			Lowest PbtO$_2$	Episodes PbtO$_2$ <10	Episodes Pbt0$_2$ <20	Mean PbtO$_2$ over first 24hrs	Mean PbtO$_2$
Plan/Organise	Pearson Correlation		.027	.575*	.413	.006	.075
	Sig. (1-tailed)		.471	**.041**	.118	.493	.418
	BCa 95% Confidence Interval	Lower	-.700	-.169[a]	-.319	-.688	-.648
		Upper	.916	.862[a]	.779	.824	.833
Organisation of Materials	Pearson Correlation		.098	.305	.212	-.212	-.097
	Sig. (1-tailed)		.394	.196	.278	.278	.395
	BCa 95% Confidence Interval	Lower	-.694	-.711[a]	-.552	-.867	-.959
		Upper	.915	.685[a]	.680	.624	.535
Monitor	Pearson Correlation		-.020	.545	.382	.054	.071
	Sig. (1-tailed)		.479	.052	.138	.441	.423
	BCa 95% Confidence Interval	Lower	-.732	-.096[a]	-.319	-.686	-.622
		Upper	.845	.862[a]	.774	.812	.764
MI	Pearson Correlation		.087	.531	.326	.048	.127
	Sig. (1-tailed)		.405	.057	.179	.448	.363
	BCa 95% Confidence Interval	Lower	-.652	-.374[a]	-.540	-.690	-.636
		Upper	.926	.831[a]	.733	.845	.884
GEC	Pearson Correlation		.200	.495	.276	.125	.223
	Sig. (1-tailed)		.290	.073	.220	.366	.268
	BCa 95% Confidence Interval	Lower	-.610	-.463[a]	-.571	-.635	-.586
		Upper	.951	.799[a]	.703	.866	.871

*. Correlation is significant at the 0.05 level (1-tailed). **. Correlation is significant at the 0.01 level (1-tailed).

a. Based on 997 samples

Note: PbtO2: Partial pressure of brain tissue oxygen

Table 22
Correlations between the PedsQL *and PbtO$_2$ variables (TBI Group N=15)*

			Lowest PbtO$_2$	Episodes PbtO$_2$ <10	Episodes Pbt0$_2$ <20	Mean PbtO$_2$ over first 24hrs	Mean PbtO$_2$
Parent-Report Physical QOL	Pearson Correlation		-0,253	-0,026	0,053	-0,502	-0,291
	Sig. (1-tailed)		0,273	0,475	0,451	0,102	0,242
	BCa 95% Confidence Interval	Lower	-0,894	-.812a	-0,981	-0,956	-0,923
		Upper	0,883	.762a	0,996	0,668	0,784
Parent-Report Emotional QOL	Pearson Correlation		0,161	-0,062	0,296	0,147	0,104
	Sig. (1-tailed)		0,352	0,442	0,239	0,364	0,403
	BCa 95% Confidence Interval	Lower	-0,632	-.420a	-0,720	-0,577	-0,664
		Upper	0,732	.545a	0,874	0,784	0,828
Parent Report Social QOL	Pearson Correlation		-0,574	0,170	0,600	-.789**	-.800**
	Sig. (1-tailed)		0,068	0,344	0,058	**0,010**	**0,009**
	BCa 95% Confidence Interval	Lower	-0,893	-.346a	-0,079	**-0,947**	**-0,991**
		Upper	0,236	.534a	0,976	**-0,204**	**-0,412**
Parent-Report School QOL	Pearson Correlation		-0,328	.649*	0,155	-0,223	-0,138
	Sig. (1-tailed)		0,214	**0,041**	0,357	0,298	0,372
	BCa 95% Confidence Interval	Lower	-.999b	**.276a**	-.580b	-.716f	-.770b
		Upper	.947b	**.987a**	.789b	.435f	.660b
Parent-Report Psychosocial QOL	Pearson Correlation		-0,611	0,547	.771*	-.728*	-.704*
	Sig. (1-tailed)		0,054	0,080	**0,013**	**0,020**	**0,026**
	BCa 95% Confidence Interval	Lower	**-0,903**	**.163a**	-0,052	**-0,920**	**-0,948**
		Upper	**-0,097**	**.923a**	0,995	**-0,249**	**-0,258**
Parent-Report Total QOL	Pearson Correlation		-0,498	0,302	0,477	-.707*	-0,573
	Sig. (1-tailed)		0,104	0,233	0,116	**0,025**	0,069
	BCa 95% Confidence Interval	Lower	-0,960	-.437a	-0,658	-0,988	-0,950
		Upper	0,423	.788a	0,980	0,518	0,534
Self-Report Physical QOL	Pearson Correlation		0,250	-0,478	-0,408	0,362	0,474

Table 22:
Correlations between the PedsQL *and PbtO$_2$ variables (TBI Group N=15) continued*

			Lowest PbtO$_2$	Episodes PbtO$_2$ <10	Episodes Pbt0$_2$ <20	Mean PbtO$_2$ over first 24hrs	Mean PbtO$_2$
	Sig. (1-tailed)		0,275	0,115	0,158	0,189	0,117
	BCa 95% Confidence Interval	Lower	-0,427	-.905a	-0,937	-0,286	-0,183
		Upper	0,737	.057a	0,615	0,742	0,902
Self-Report Emotional QOL	Pearson Correlation		0,512	-.764*	-0,259	0,471	0,400
	Sig. (1-tailed)		0,097	**0,014**	0,267	0,119	0,163
	BCa 95% Confidence Interval	Lower	-0,475	**-.934a**	-0,888	-0,159	-0,319
		Upper	0,936	**-.642a**	0,669	0,916	0,907
Self-Report Social QOL	Pearson Correlation		0,608	-0,563	-0,436	0,520	.676*
	Sig. (1-tailed)		0,055	0,073	0,140	0,093	**0,033**
	BCa 95% Confidence Interval	Lower	**.208g**	**-1.000a**	-.961g	**.054c**	**.316c**
		Upper	**.916g**	**-.151a**	.195g	**.937c**	**.942c**
Self-Report School QOL	Pearson Correlation		-0,231	0,129	0,178	0,277	-0,087
	Sig. (1-tailed)		0,291	0,380	0,337	0,253	0,419
	BCa 95% Confidence Interval	Lower	-0,629	-.519a	-0,460	-0,464	-0,904
		Upper	0,084	.850a	0,944	0,848	0,486
Self-Report Psychosocial QOL	Pearson Correlation		0,459	-0,585	-0,276	0,595	0,502
	Sig. (1-tailed)		0,127	0,064	0,254	0,060	0,102
	BCa 95% Confidence Interval	Lower	-0,263	**-.793a**	-0,914	**0,102**	-0,033
		Upper	0,986	**-.491a**	0,445	**0,955**	0,953
Self-Report Total QOL	Pearson Correlation		0,412	-0,583	-0,341	0,549	0,524
	Sig. (1-tailed)		0,155	0,065	0,204	0,079	0,091
	BCa 95% Confidence Interval	Lower	-0,314	**-.876a**	-0,987	**0,035**	-0,019
		Upper	0,963	**-.375a**	0,494	**0,919**	0,986

*. Correlation is significant at the 0.05 level (1-tailed). **. Correlation is significant at the 0.01 level (1-tailed).

a. Results based on 884 samples. b. Results based on 999 samples. c. Results based on 996 samples. Note: PbtO2: Partial pressure of brain tissue oxygen

Table 23
Correlations between the CBCL Syndrome Scales and PbtO$_2$ variables (TBI Group N=15)

			Lowest PbtO$_2$	Episodes PbtO$_2$ <10	Episodes Pbt0$_2$ <20	Mean PbtO$_2$ over first 24hrs	Mean PbtO$_2$
Anxious/Depressed	Pearson Correlation		-0,184	-0,068	0,123	-0,091	-0,370
	Sig. (1-tailed)		0,347	0,443	0,396	0,423	0,207
	BCa 95% Confidence Interval	Lower	-0,863	-.628a	-0,571	-0,892	-0,981
		Upper	0,955	.992a	0,995	0,707	0,197
Withdrawn/Depressed	Pearson Correlation		0,499	-.694*	-0,467	0,658	0,524
	Sig. (1-tailed)		0,127	**0,042**	0,145	0,054	0,114
	BCa 95% Confidence Interval	Lower	-.431b	**-.910a**	**-.883b**	-.110b	-.301b
		Upper	.965b	**-.666a**	**-.117b**	.975b	.951b
Somatic Problems	Pearson Correlation		0,362	-0,095	-0,166	0,549	0,283
	Sig. (1-tailed)		0,212	0,419	0,361	0,101	0,269
	BCa 95% Confidence Interval	Lower	-0,865	-.854a	-0,996	-0,946	-0,980
		Upper	0,910	.956a	0,985	0,969	0,870
Social Problems	Pearson Correlation		0,346	-0,348	-0,207	0,583	0,366
	Sig. (1-tailed)		0,223	0,222	0,328	0,085	0,210
	BCa 95% Confidence Interval	Lower	-0,698	**-.866a**	-0,962	-0,287	-0,461
		Upper	0,926	**-.011a**	0,472	0,992	0,920
Thought Problems	Pearson Correlation		0,297	-0,253	-0,133	0,379	0,276
	Sig. (1-tailed)		0,259	0,292	0,388	0,201	0,275
	BCa 95% Confidence Interval	Lower	-.819b	-.781a	-.877b	-.709f	-.772b
		Upper	.986b	.063a	.619b	.974b	.948b
Attention Problems	Pearson Correlation		0,486	-0,404	-0,428	.768*	0,628
	Sig. (1-tailed)		0,134	0,184	0,169	**0,022**	0,065
	BCa 95% Confidence Interval	Lower	-0,498	-.881a	-0,999	**0,136**	**0,086**
		Upper	0,949	.036a	0,747	**0,999**	**0,949**
Rule Breaking Behaviour	Pearson Correlation		0,060	0,257	0,461	-0,140	-0,349
	Sig. (1-tailed)		0,450	0,289	0,149	0,382	0,222

Table 23

Correlations between the CBCL Syndrome Scales and PbtO$_2$ variables (TBI Group N=15) continued

			Lowest PbtO$_2$	Episodes PbtO$_2$ <10	Episodes Pbt0$_2$ <20	Mean PbtO$_2$ over first 24hrs	Mean PbtO$_2$
	BCa 95% Confidence Interval	Lower	-0,822	-.645a	-0,746	-0,930	-0,962
		Upper	0,762	.968a	1,000	0,569	0,557
Aggressive Behaviour	Pearson Correlation		0,439	-0,427	-0,243	0,577	0,257
	Sig. (1-tailed)		0,162	0,170	0,300	0,087	0,289
	BCa 95% Confidence Interval	Lower	-0,433	**-.854a**	-0,783	-0,166	-0,534
		Upper	0,994	**-.155a**	0,268	0,942	0,878
Internalising Problems	Pearson Correlation		0,208	-0,269	-0,102	0,376	0,061
	Sig. (1-tailed)		0,328	0,280	0,414	0,203	0,449
	BCa 95% Confidence Interval	Lower	-0,610	-.736a	-0,803	-0,590	-0,718
		Upper	0,984	.150a	0,663	0,888	0,655
Externalising Problems	Pearson Correlation		0,380	-0,306	-0,076	0,453	0,115
	Sig. (1-tailed)		0,200	0,252	0,436	0,153	0,403
	BCa 95% Confidence Interval	Lower	-0,469	-.862a	-0,749	-0,467	-0,679
		Upper	0,990	.092a	0,471	0,969	0,866
Total Problems	Pearson Correlation		0,305	-0,317	-0,113	0,440	0,169
	Sig. (1-tailed)		0,253	0,244	0,404	0,162	0,359
	BCa 95% Confidence Interval	Lower	-0,642	-.870a	-0,768	-0,532	-0,653
		Upper	0,982	.035a	0,461	0,966	0,812

*. Correlation is significant at the 0.05 level (1-tailed). **. Correlation is significant at the 0.01 level (1-tailed).

a. Results based on 907 samples b. Results based on 999 samples

Note: PbtO2: Partial pressure of brain tissue oxygen

Discussion

TBI is one of the major causes of mortality and morbidity among children and adolescents all over the world. Multiple predictors of outcome post pTBI have been investigated, however acute stage neurological and neurosurgical variables are relatively absent from this knowledge base. This study had two specific aims: 1) to investigate the nature and severity of neuropsychological deficits in pTBI patients one year after injury, comparing their performance to a typically-developing control group matched to the pTBI sample on age, sex, home language and SES, and 2) to investigate the association between acute stage physiological changes in ICP and $PbtO_2$ and neuropsychological outcomes one year after pTBI. In researching these specific aims, I hoped to better understand the heterogeneity in outcomes of pTBI, a broader aim of this research. I investigated various cognitive, behavioural and QOL outcomes using pencil and paper measures and parent- and self-report questionnaires and included multiple parameters of ICP and $PbtO_2$ in my analyses. Due to the comparatively low rate of patients who present with severe pTBI requiring ICP monitoring as well as time constraints associated with the scope of this project, the final sample size of the study was low. This had implications for statistical analysis and bootstrapped analyses were employed to compensate for non-normality and heterogeneity in the data. The results of these investigations were inconsistent. While the pTBI participants generally performed poorer than the control group (pertaining to the first aim), only a select few of the parameters of the acute variables significantly correlated with some of the neuropsychological variables (pertaining to the second aim). While the sample size of the study certainly played a role (see study limitations), the inconsistent nature of the results is in keeping with the current literature base on acute physiological variables and neuropsychological outcomes (measured on multiple scales): results found are typically mixed, and often contradictory (see Lannoo et al., 1998; Levin et al., 1991; Meixensberger, et al., 2004; Moran, et al., 2016; Schrieff-Elson, et al., 2015; Slawik, et al., 2009; Uzzeli, Obrist, Dolinskas, & Langfitt, 1986). These results are discussed in detail below.

Participant Demographic Characteristics

The demographic characteristics of the current sample is typical of pTBI samples described in literature, both internationally and in South Africa (Amaranath, et al., 2013; Dewan, et al., 2016; Schrieff, Thomas, Dollman, Rohlwink, & Figaji, 2013; Thurman, 2016). It is commonly observed that there is a higher rate of TBI among male children, although this rate differs across regions. For the current sample, the ratio of male to female pTBI was 1.5:1 which is in keeping with reported local and international estimates (Dewan, et al., 2016;

Schrieff, et al. 2013). With regard to home language, most participants, TBI and Controls, were Afrikaans-speaking (16 participants, 53%), followed by isiXhosa-speaking (12 participants, 40%), and 1 participant (3%) was English-speaking. This is reflective of the language profile of the Western Cape (Statistics South Africa, 2014) and similar to what was found in a study on the demographic profile of severe pTBI patients at the same hospital at which the patients of the current study were recruited (Schrieff, et al., 2013). The majority of the TBI participants, 13 out of 15, sustained their TBI by means of a road traffic accident, 8 of which (61.5%) were pedestrian-related MVAs and the rest passenger-related. This is unsurprising given the high rate of MVAs in South Africa and is consistent with both local and international epidemiological data in which MVAs are the most common mechanism of injury reported with the greatest proportion of MVAs in African countries being pedestrian-related (Dewan, et al., 2016; Schrieff, et al., 2013).

SES was measured using multiple factors and the results of these surveys revealed that the majority of participants fell neither into a low or high SES bracket, but rather into the middle range. This may be slightly misleading, however. The average monthly income in South Africa estimated by the Organisation for Economic Co-operation and Development (OECD) in February 2017 is R18 687, equating to approximately R224 000 per year (BusinessTech, 2017), while the highest income bracket available on the SES survey employed is R100 000+ per year. Though this is only one of the measures of SES, only 4 out of 22 participants for whom annual household income data was available fell within this bracket, suggesting that the majority of the participants may, in fact, be classified as below-average, and in some cases far below average, in terms of average household income. Additionally, only 7 of the 42 parents or guardians (for all participants) for whom data was available had completed education beyond high school level, with most having completed 8-12 years of education, and the great majority (27 out of 36) of parents/guardians indicated that they were employed in semi-skilled or unskilled jobs, were homemakers or were students/disabled/unemployed. This is in keeping with the fact that RXH serve mostly patients from socially disadvantaged backgrounds.

Hypothesis One: Between Groups Analysis (TBI vs Control)

The first hypothesis I tested was that the pTBI group would perform significantly poorer than the control group on all neuropsychological variables. In order to control for the commonly reported effects of age, sex, home language and SES on neuropsychological performance (Babikian & Asarnow, 2009) the groups were carefully matched on these variables. This hypothesis was largely upheld as the TBI group had significantly poorer

mean scores than the control group on most of the cognitive, behavioural and QOL outcome measures.

Between-group differences in cognitive outcomes. The TBI group performed significantly poorer than the control group on all of the cognitive variables except for sustained attention. Each cognitive domain in which a significant group difference was observed, VIQ, PIQ, FSIQ, processing speed, verbal learning, higher order attention, visuospatial memory, verbal memory, verbal fluency and executive functioning, was associated with a large effect size. These group differences are in keeping with the long-term cognitive outcomes of pTBI described across the literature base (Anderson & Catroppa, 2007; Anderson, et al, 2005; Anderson, et al., 2000, 2009; Babikian & Asarnow, 2009; Babikian, et al., 2015; Lajiness-O'Neill, Erdodi, & Bigler, 2011).

While the mean for the TBI group was marginally lower than the control group in the domain of sustained attention, the mean fell within the borderline range for both the TBI and control groups. The lack of a significant difference between groups is especially noteworthy as attention is one of the most commonly reported deficits after pTBI with sustained attention previously having been found to be impaired more consistently than other domains of attention (Babikian, et al., 2015). The small difference between groups may be a product of the high rate of attention deficits among typically-developing children, and especially among typically developing children from low SES backgrounds which has been found in multiple studies (Hackman & Farah, 2009; Mezzacappa, 2004; Russell, Ford, Williams, & Russell, 2016; Schrieff-Elson, Ockhuizen, During, & Thomas, 2017). The results of these studies suggest that environmental, developmental and social factors associated with socioeconomically disadvantaged backgrounds have a significant effect on the development of foundational-level cognitive skills such as attention, resulting in attention deficits which often go undiagnosed (Mezzacappa, 2004; Russell, et al., 2016). Furthermore, attention is a notoriously difficult construct to measure psychometrically because it "cannot be measured unless a person is asked to do *something*" (Manly, et al., 2001, p. 1066). As such, it is inevitably influenced by other cognitive faculties, level and quality of education, and differences in the recruitment of neural systems (Hackman & Farah, 2009; Manly, et al., 2001; Stevens, Lauinger, & Neville, 2009).

Between-group differences in behavioural and QOL outcomes. Although the TBI group had poorer average scores, there were no significant between-group differences on any of the BRIEF subscales. While this finding is not what was expected, it has previously been found that executive functioning deficits only become evident many years after injury as

these skills continue developing late into adolescence and beyond (Anderson & Catroppa, 2005). It may be that deficits in executive functions may become evident in this sample of pTBI patients as they age. It may also be that the method of data collection of this data (parent-report) had an effect on these results in accordance with the well-known finding that self-report measures tend to correlate weakly with true behaviour (as can be assessed using direct pencil-and-paper measures e.g. those of the executive functions composite score used in analyses) (Kormos & Gifford, 2014).

Consistent with existing literature which has shown that 40% of children with TBI experience impaired HRQOL at 12 months post-injury (McCarthy, et al., 2006), the results of the PedsQL revealed significant between-group differences on the three primary parent-report scales, physical QOL, psychosocial QOL and total QOL, with the parents of the TBI group reporting lower QOL for their children than the parents of the control participants. Previous research has found that lower psychosocial QOL among pTBI patients is significantly related to school functioning, which is one of the subsections making up the psychosocial QOL scale. Poorer school functioning due to cognitive deficits after pTBI is common and given that the pTBI patients in the current sample have cognitive deficits compared to the control group, it is likely that this contributed to their parents' rating of their psychosocial QOL (Erickson, Montague, & Gerstle, 2010). Self-reported physical QOL was also significantly different between the groups with the TBI patients reporting lower physical QOL than the control group. The significant between-group differences in physical QOL on both parent-report and self-report surveys is unsurprising. This is because many of the participants sustained multiple physical injuries in addition to their TBI (polytrauma is common in MVAs), which would have significant effects on their day-to-day physical functioning. The results also indicated that parents rated the QOL of their children as poorer in each domain than the children themselves did. This likely contributed to the significant group differences on the parent-report measures not present on the self-report measures. This finding is in keeping with previously recognised trends in this literature which have identified that family members of children who sustain TBI often experience a greater amount of distress than the child themselves (Di Battista, et al., 2012; Erickson, Montague, & Gerstle, 2010).

Finally, the TBI group had significantly poorer scores than the control group on multiple syndrome scales of the CBCL including Withdrawn/Depressed, Social Problems, Thought Problems and Rule-Breaking Behaviour. All three higher-order factor groupings of the syndrome scales, Internalising Problems, Externalising Problems and Total Problems, were also significantly different between groups. All of these outcomes are commonly

reported behavioural and psychiatric sequelae of pTBI (Babikian, et al., 2015; Noggle & Pierson, 2010; Ryan, et al., 2016). It was also observed that the behaviour of more TBI participants than control participants was classified in the 'clinical' or 'borderline' range while there were more control participants whose behaviour was classified in the 'normal' range.

In summary, the TBI group performed significantly poorer than the control group on multiple cognitive, behavioural and QOL domains which largely confirms the first hypothesis.

Hypothesis Two: Within Group Analysis (TBI Group)

The second hypothesis pertained to the acute stage physiological variables, ICP and $PbtO_2$. I expected that higher ICP and lower $PbtO_2$ over the monitoring period would be associated with poorer neuropsychological performance among the TBI participants. I included multiple parameters of ICP and $PbtO_2$ in the analyses to explore possible nuances within these acute physiological changes. I was particularly interested in the possible effects of exceeding or dropping below the treatment targets of 20mm Hg for ICP and $PbtO_2$ respectively. I expected that participants with a higher number of episodes during which ICP exceeded 20 mm Hg and $PbtO_2$ dropped below 20mm Hg would have poorer neuropsychological performance. In addition, I expected that participants who experienced episodes of $PbtO_2$ below 10mm Hg, the hypoxic threshold, would perform poorer on the neuropsychological tests. This hypothesis was investigated using multiple descriptive statistics and bootstrapped correlation analyses. In keeping with current literature on the relationship between acute stage physiological variables and various outcome domains, in which there is little consistency within- and across studies, the results of these analyses varied.

Before considering the relationship between the acute physiological variables and the neuropsychological variables however, it is of note that there was no significant relationship between ICP and $PbtO_2$ in this sample. While the management of ICP is crucial in ensuring adequate cerebral oxygenation, research has found a generally poor relationship between ICP and $PbtO_2$ and the current study is no exception (Padayachy, Figaji, & Bullock, 2009; Rohlwink, et al., 2012). The parameters of ICP significantly correlated with each other, and the parameters of $PbtO_2$ significantly correlated with each other, but there were no significant correlations between the ICP and $PbtO_2$ parameters. While all the participants who crossed the treatment threshold of 20mm Hg for ICP experienced at least one episode of $PbtO_2$ reduced below 20mm Hg, the inverse was not true; 3 participants experienced episodes of

$PbtO_2$ below 20mm Hg in the absence of elevated ICP. In addition, the participant who experienced the lowest overall $PbtO_2$ across parameters, did not experience a single episode during which ICP exceeded 20 mm Hg. This is in keeping with previous studies which have found that reduced $PbtO_2$ may occur in conditions of normal ICP (Figaji, et al., 2008; Padayachy, Figaji, & Bullock, 2009; Rohlwink, et al., 2012).

While various parameters of $PbtO_2$ significantly correlated with a higher number of neuropsychological variables than the ICP parameters, many of these correlations were against the direction that would be expected, and bias adjusted confidence intervals often crossed zero for these correlations indicating non-significance despite significant *p*-values. This is discussed further below.

ICP and cognitive outcomes. The results of correlation analysis indicated no significant relationship between the parameters of ICP and the cognitive outcome variables which suggests that acute-stage ICP has no relationship with neurocognitive impairment in the post-acute stage of injury for this sample. While this finding is contrary to what was hypothesised (I hypothesised that poorer ICP would be related to poorer neuropsychological outcome because it has been shown to be related to poorer generalised outcome), it is in keeping with a small number of studies on ICP and neuropsychological outcomes. These studie have found that increased ICP in the acute stage generally does not predict cognitive performance after pTBI, and when an effect is present, it diminishes within the first year post-injury (Levin, et al., 1991; Lannoo, et al., 1998; Moran, et al., 2016). Given that the current sample was assessed 1 year post-injury, the absense of an effect is reasonable. The current research therefore suggests that while elevated ICP may increase the risk of death and persistent vegetative state after pTBI (Catala-Temprano, et al., 2007; Miller Ferguson, et al., 2016), it is not related to long-term cognitive effects in the children who survive their injuries. This conjecture is of course tentative, given that the study is underpowered, and requires a more robust evaluation in future studies.

ICP and behavioural and QOL outcomes. ICP was also not significantly related to any of the BRIEF subscales; this is likely in keeping with what was discussed above regarding ICP and cognitive outcomes, given that executive functions are cognitive in nature. However, one must remember that the mean scores on the BRIEF among the pTBI group did not fall into the clinical range on any of the indices and no differences were observed between the TBI and control groups on this measure. This suggests no marked impairments in this domain within the TBI group on average, making the absence of a difference due to ICP unsurprising.

One of the scales of the PedsQL, the parent-report of emotional QOL, was significantly correlated with all 5 parameters of ICP in a positive fashion. This suggests that higher ICP, and a higher number of ICP readings above 20mm Hg, is associated with poorer emotional QOL after pTBI in this sample. Emotional QOL is one of the 3 items in the scale which make up the psychosocial QOL primary score which was significantly poorer in the pTBI sample than the control sample. There is a dearth of previous research on the relationship of ICP with domains of outcome outside of cognition, such as QOL, however, research has previously found lower emotional QOL in pTBI patients when compared to chronically ill patients, who would be comparable to them in terms of physical dysfunction (Erickson, Montague, & Gerstle, 2010).

The results of the CBCL indicated significant correlations between various scales of the CBCL and various parameters of ICP. In particular, somatic problems, which pertain to physical complaints e.g. nausea, aches and pains, reduced energy etc, significantly correlated with 4 parameters of ICP suggesting increased physical dysfunction related to elevated ICP in this sample. With regard to emotional and behavioural dysfunction, mean ICP significantly correlated with Internalising, Externalising and Total problems, suggesting an increase in behavioural/psychiatric problems associated with elevated ICP. However, the bias adjusted confidence intervals associated with these correlations all cross zero, indicating that care should be taken in interpreting these results as significant.

When considered together, the results of the PedsQL and CBCL may suggest a persistent effect of ICP on physical, behavioural and emotional domains rather than cognitive domains. These findings are a new addition to the literature base which lacks data on the effect of ICP on behavioural outcomes after pTBI and therefore need to be further investigated before conclusions may be drawn in this regard.

Due to the significantly increased risk of death and disability observed in pTBI patients who experience elevated ICP, I expected that participants who experienced higher ICP would have poorer outcomes across cognitive, behavioural and QOL domains. This was not true for cognitive outcomes, which is largely in keeping with previous research which suggests raised ICP has no enduring effect on cognition. However the hypothesis held for behavioural and QOL outcomes. It must be noted that the biggest difference between the data on cognitive outcomes and that for behavioural and QOL outcomes, is the method in which the data was collected: direct measurement using pencil-and-paper assessments vs. self-report, of which the latter is a traditionally less reliable indication of true behaviour (Kormos & Gifford, 2014). While, the results of the investigation into behavioural and QOL

outcomes may provide some impetus for future research into the possible enduring effects of elevated acute-stage ICP on behavioural and emotional outcomes, given that these results are not based on clinical assessments of these outcomes, interpretations should be made with extreme caution due to the well-known limitations of self-report and, by extention, proxy-report measures of behaviour and emotion.

$PbtO_2$ and cognitive outcomes. A number of parameters of $PbtO_2$ correlated significantly with various cognitive outcome variables. Results indicated poorer sustained attention was associated with a higher number of episodes of $PbtO_2$ below 20mm Hg and 10mm Hg, and a lower mean $PbtO_2$ over the monitoring period. For each of these significant correlations, however, the bias adjusted confidence intervals crossed zero which suggests that caution should be employed in interpreting the relationship as significant based on the *p*-value. Additionally, between-group analyses indicated that the pTBI group did not differ from the control group on sustained attention. Significant correlations were also observed between the mean $PbtO_2$ over the first 24 hours of monitoring and VIQ, FSIQ, higher order attention and executive function, however, these relationships were not in the expected direction, suggesting improved scores in these domains associated with lower $PbtO_2$ values. This finding is not in line with what would be expected based on the existing $PbtO_2$ knowledge base; when one considers that these variables did not significantly correlate with any other measure of $PbtO_2$, as would be expected if a relationship were present in the population, it is likely that this result is an artefact of the small sample size used in analysis. However, this is worth noting, as the majority of the $PbtO_2$ significant correlations were against the expected direction. This is discussed further below.

Overall, while the cognitive variables mentioned above correlated significantly with $PbtO_2$, the reliability and validity of the effect implied by these results is questionable due to the reasons mentioned above and it is likely that these findings would not be significant in a different sample. It is also particularly of note that episodes of hypoxia ($PbtO_2$ <10 mm Hg), which was expected to be a strong predictor of outcome, was not associated with poorer outcome across cognitive variables. However, only 4 participants in this study crossed this threshold during their monitoring period, which limits the power of the correlation analyses to detect a possible effect that may be present in the population of patients who experience $PbtO_2$ below 10mm Hg.

The results of the current study are notably different to a recent study on $PbtO_2$ and neuropsychological outcome after severe pTBI (Schrieff-Elson, et al., 2015) despite having both been performed in the same local setting with similar samples. This difference is worth

interrogating and may have occurred for a variety of reasons. The study by Schrieff-Elson and colleagues (2015) found that pTBI patients who sustained hypoxic episodes had significantly more cognitive impairment across multiple domains than pTBI patients who did not. One likely reason for the difference in results between this study and that one, is the fact that $PbtO_2$ levels were overall lower in the 2015 study by Schrieff-Elson and colleagues and a greater proportion of the participants in that study experienced episodes of $PbtO_2$ below the hypoxic threshold (5 out of 11, roughly 45%, compared to 4 out of 13 in the current sample, roughly 30%). Furthermore, the current study had less variation within the TBI group (lower standard deviations and smaller ranges) on these variables than the previous study did. That study was, however, also limited by a small sample size as is the case for the current research and the dissimilar results of the studies emphasise the need for research with larger samples.

$PbtO_2$ and behavioural and QOL outcomes. Two scales of the BRIEF, Initiate and Plan/Organise, correlated significantly with the number of episodes of $PbtO_2$ below 10mm Hg, suggesting increased levels of impairment in these domains associated with a greater number of hypoxic episodes. For both of these correlations, however, the bias adjusted confidence intervals cross zero which indicates that the null hypothesis should not be rejected in this case. A number of the PedsQL subscales were significantly correlated with various parameters of $PbtO_2$ supported by the bias adjusted confidence intervals, however, all but one of these were against the expected direction; lower $PbtO_2$ was significantly associated with improved QOL on the parent report measures of social QOL and psychosocial QOL, and the self-report measure of emotional QOL. The self-report measure of social QOL however, correlated significantly with mean $PbtO_2$ in a positive fashion, indicating poorer social QOL for participants with a lower average $PbtO_2$. Given the context of this result, however, it is unlikely that this is a true indication of an effect in this population. A similar trend was however, found on the CBCL in which the Withdrawn/Depressed syndrome scale significantly correlated with number of episodes of $PbtO_2$ below 10mm Hg and Attention Problems significantly correlated with the mean $PbtO_2$ over the first 24 hours, however, both of these relationships were not in the expected direction.

The repetitive findings of significant relationships between $PbtO_2$ and neuropsychological variables in the unexpected direction is somewhat irregular. The existing knowledge base of studies on $PbtO_2$ as discussed in the introduction section of this thesis, overwhelmingly suggests that that lower $PbtO_2$, and particularly $PbtO_2$ below the hypoxic threshold of 10mm Hg, results in poorer outcomes after TBI.

There are a variety of possible reasons for the discrepant findings of this study including those already discussed in relation to a previous local study of a similar nature (Schrieff et al., 2015). Other reasons include the large amount of variance in $PbtO_2$ data in the sample and the presence of outliers (factors known to influence correlational analyses) and the possibility that the relationship between $PbtO_2$ and neuropsychological outcome is more complex than can be captured on simple correlational analyses. Should the study have had a larger sample size, alternate statistical analysis, such as regression analysis, could have been used to investigate the presence of a more complex relationship between these variables, one possibly mediated by other variables. However, the findings of this study might also be in line with research on mitochondrial dysfunction after TBI.

Mitochondria in the brain are the sites of oxidative phosphorylation, a process involving the production of adenosine triphosphate (ATP) from glucose and oxygen. ATP provides for the brain's high energy demand and in conditions of insufficient ATP supply, homeostasis cannot be maintained and cell death results (Diringer, 2008; Verweij, et al., 2000). Research suggests that the process of ATP production is impaired after TBI; while it is possible that this occurs due to inadequate *supply* of oxygen to brain tissue, which has been found to occur after TBI, it may also occur due to impairment in mitochondrial function which results in inadequate oxygen *utilisation* by the brain (Ragan, McKinstry, Benzinger, Leonard, & Pineda, 2013; Verweij, et al., 2000). Studies have found impairment in mitochondrial function following TBI in both animals and humans, adults and children (Gajavelli, et al., 2015; Ragan, et al., 2013; Verweij, et al., 2000). The damage to mitochondria caused by TBI causes metabolic crisis which has been found to contribute to secondary injury (Gajavelli, et al., 2015).

Simply put, research in this area indicates that even in conditions of adequate, or even super-normal, brain tissue oxygenation (measured using $PbtO_2$), mitochondrial damage may result in the brain being unable to utilise, and therefore benefit from, its oxygen supply. This may be the case for the current sample in which an explicit measure of oxygen *consumption* was not included in analyses. In addition, it has been found that an oversupply of oxygen e.g. in the case of ventilation and other methods used to treat brain injury, may result in the formation of free radicals associated with a variety of adverse effects including edema, gas exchange dysfunctions, and inflammatory processes which have toxic effects and may even lead to death (Diringer, 2008). When excluding metabolic measures e.g. the cerebral metabolic rate of oxygen (CMRO2) from analysis in cases such as these, higher $PbtO_2$ would correlate with poorer outcome as in the current study. Given that metabolic abnormalities are

beyond the scope of the current study, as well as the limitations detailed below, caution should be taken in interpreting these results.

Very little research exists on $PbtO_2$ and outcome after pTBI. Of the few studies that have been done, all have identified poorer outcomes related to reduced $PbtO_2$ on both generalised and specific outcome measures (Figaji, 2009; Figaji, et al., 2008; Schrieff-Elson, et al., 2015). For this reason, I expected participants with lower $PbtO_2$ to have poorer neuropsychological outcomes. Results were overall not consistent with this hypothesis.

Limitations and Directions for Future Research

The most significant limitation to this study is the small sample size which reduces the power of the research to detect effects and limits the generalisability of the results that are found. This study consisted of a small sample size due to the time constraints associated with a Masters dissertation, the relatively low rate of patients presenting with severe TBI requiring ICP monitoring and the attrition associated with longitudinal studies. In addition, because it formed part of the ADAPT trial, the sample was limited to the group of patients being recruited and followed up on through the ADAPT trial. The scope of the current project did not allow for a lengthier data collection period which would have increased the sample size. The small sample size of the current study makes the probability of making errors in analysis very high, increasing the chance that what is observed in the results of this sample is not true for the population. To attempt to combat the limitation of small sample size and its effects on the interpretation of the data, care was taken to report multiple statistics instead of focussing on *p*-values alone. It is however imperative that future studies of this kind include larger sample sizes to increase the power of this research to detect true effects.

The restraints of the project further did not allow multiple other physiological variables, which are usually monitored alongside ICP and $PbtO_2$, to be included in analyses. These include CPP, mean arterial pressure (MAP), partial pressure of oxygen (PaO2) and haemoglobin concentration (Hb), and cerebral microdialysis measures of metabolic abnormalities, among others. Including multiple physiological variables as they are monitored in the acute phase of injury would be advisable in research of this kind in order to identify nuances in the relationship between acute stage physiological brain changes and longer-term outcome after pTBI. The small sample size in the study also did not allow for a design that would investigate the ability of ICP and $PbtO_2$ to *predict* neuropsychological outcome using regression analyses, which would be the preferred method of statistical analysis for a study of this kind. Instead, correlations were used to investigate the presence of a relationship between the acute variables and neuropsychological variables. This method of

analysis represents a suitable starting point from which to investigate the presence of an effect of these acute variables on long term neuropsychological outcome. This effect can then be studied in more detail in future studies using analyses that allow for multiple variables to be controlled for and precise investigation of the ability of various parameters of ICP and $PbtO_2$, as well as other physiological variables, to predict neuropsychological outcomes post-pTBI both independently and together.

Another possible limitation is the inclusion of patients with both open and closed TBI in the sample. While most existing studies on ICP and $PbtO_2$ and generalised outcome do not exclude participants based on injury mechanism, neuropsychological outcomes after open and closed TBI are known to differ due to the focal vs. diffuse nature of open vs. closed TBI. In this study, the injury mechanism did not however, influence the results.

In addition to these, the use of parent-report measures of behaviour as well as parent- and self-report measures of QOL is also a limitation to the current study. Self-report measures of behaviour have been reported to correlate weakly with true behaviour (Kormos & Gifford, 2014). This may be due to a number of reasons including the tendency to over-report pro-environmental, socially-desirable behaviour, the introduction of subjectivity in interpreting survey items and responses, and the increased likelihood of providing answers that reflect individual perceptions, beliefs, attitudes and memory rather than actual behaviour (Kormos & Gifford, 2014). While this may affect the validity of the results of these surveys, each measure I used has been shown to have good reliability and validity and the results obtained from them are generally accepted in psychological research.

A final limitation of this study pertains to the large amount of missing data on the behavioural and QOL measures which were parent-report pencil-and-paper surveys. A lot of data could not be included in analyses due to incomplete surveys prohibiting scores from being calculated. A few reasons for this problem include varying levels of literacy among the parents of the participants, unwillingness on the part of the parents to complete the questionnaires and children being brought to the assessment session by individuals who were not their parent or caregiver and therefore not able to complete the surveys.

Summary and Conclusion

TBI among children and adolescents remains a global public health concern representing a common disruption to normal childhood development resulting in enduring neuropsychological sequelae in cognitive, emotional, behavioural and QOL domains (Anderson & Yeates, 2010; Babikian, et al., 2015; Bruns & Hauser, 2003; Dewan, et al., 2016). Research has however emphasised the significant within-group variation in the

outcomes of pTBI with markedly few predictors reliably identifying which patients are most likely to endure long-term deficits (Moran, et al., 2016). In trying to better understand the variation in outcome after childhood TBI, a growing body of research has provided evidence of the association between acute stage physiological changes and outcome (Lannoo, et al., 1998; Levin, et al., 1991; Meixensberger, et al., 2004; Moran, et al., 2016; Schrieff-Elson, et al., 2015; Slawik, et al., 2009; Uzzeli, et al., 1986). This research study aimed to contribute to this knowledge base through its investigation of the relationship of acute-stage changes in ICP and $PbtO_2$ and long-term outcome after pTBI in multiple neuropsychological domains.

Overall, the results of this study highlighted two points which have been alluded to in previous research: 1) that ICP and $PbtO_2$ are not linearly related to each other and do not have the same impact on outcomes in the context of pTBI, and 2) the relationship between these acute variables and neuropsychological outcomes is a complex and inconsistent one. These results reflect the heterogeneity present in the pTBI population which has historically represented a challenge to the interpretation of the effectiveness of clinical interventions (Figaji, et al., 2017). A recent study which has described the inconsistencies observed in a variety of acute physiological variables (including ICP, CPP, $PbtO_2$ and others) and the effect of these inconsistencies on treatment, has argued that it is time to integrate heterogeneity into the treatment of pTBI instead of attempting to find a model or treatment procedure that is applicable to the *average* patient (Figaji, et al, 2017). This heterogeneity is not specific to acute physiological variables, it has also been highlighted by significant variability in the literature on neuropsychological outcomes after pTBI (Babikian & Asarnow, 2009). The results of the current study provide impetus for research that focuses on understanding the heterogeneity in pTBI population and investigating the effect of variables such as ICP and $PbtO_2$ in context of other physiological and social factors within individuals. This will require studies of a larger scale with large, representative samples.

Significance

A major shortcoming in the literature base on outcomes after pTBI is that it has traditionally comprised narrowed, field- and domain-specific research studies. As a result, little progress has been made in establishing associations between injury-related physiological variables, including ICP and brain oxygenation, and neuropsychological outcomes after pTBI (Anderson & Yeates, 2010). To date, only a handful of studies have examined the effects of acute neurological changes on multiple neuropsychological domains rather than a single non-specific outcome scale.

Studies of this kind aim to further characterise the increasingly popular finding that, at the level of the individual, only a select subgroup of pTBI patients experience significant long-term neuropsychological deficits (Moran, et al., 2016). The factors which reliably predict which children experience the greatest deficits post-pTBI remain unclear. The current study aimed to contribute to this gap in the pTBI knowledge base by means of a multi-dimensional, cross-disciplinary investigation of the factors associated with neuropsychological outcome after pTBI. The results of the study however, echoed the heterogeneity associated with TBI, both in terms of outcome and predictors. In particular, it provided motivation for broader, more in-depth investigation into the relationship between acute physiological variables, as well as the effect of these variables on long-term outcome post-pTBI.

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Appendices

Appendix A: Summary of Assessment Measures

Table 24

Summary of Assessment Measures

Domain Assessed	Measure	Applicable Age Range	Completed By
Quality of Life	PedsQL	2y - 13y	Parent/Caregiver (2-8 years) Patient (>8 years)
Intellectual Ability	WASI FSIQ	≥6y	Patient
Memory	CVLT-C	5y – 13y	Patient
	CMS Dot Locations	5y – 13y	Patient
Executive Function	BRIEF	6y – 13y	Parent/Caregiver
	DKEFS Verbal Fluency	≥8y	Patient
Attention	TEA-Ch Sky Search	6y – 15y	Patient
	CMS Digit Span	6y – 16y	
Processing Speed	WISC-IV PSI	6y – 16y	Patient
Behaviour	CBCL- Child	6y – 18y	Parent/Caregiver

Appendix B: Faculty of Health Sciences Ethical Approval: ADAPT Trial

UNIVERSITY OF CAPE TOWN

FACULTY OF HEALTH SCIENCES
Human Research Ethics Committee

FHS016: Annual Progress Report / Renewal

HREC office use only (FWA00001637; IRB00001022)			
This serves as notification of approval, including any documentation discussed below.			
☑ Approved	Annual progress report	Approved until/next renewal date	30/12/2017
☐ Not approved	See attached comments		
Signature Chairperson of the HREC		Date Signed	24/11/2016

Comments to PI from the HREC

Principal Investigator to complete the following:

1. Protocol Information

Date (when submitting this form)	10 November 2016		
HREC REF Number	016/2014	Current Ethics Approval was granted until	30/12/2017
Protocol title	Approaches and Decisions for Acute Pediatric TBI (ADAPT)		
Protocol number (if applicable)	NA		
Are there any sub-studies linked to this study?	☐ Yes ✓ No		
If yes, could you please provide the HREC Ref's for all sub-studies? Note: A separate FHS016 must be submitted for each sub-study.			
Principal Investigator	Professor Anthony Figaji		
Department / Office Internal Mail Address	6th Floor ICH Building, Red Cross War Memorial Children's Hospital, Klipfontein Road, Rondebosch, 7700		

1.1 Does this protocol receive US Federal funding?	✓ Yes	☐ No
1.2 If the study receives US Federal Funding, does the annual report require full committee approval?	☐ Yes	✓ No
1.3 Has sponsorship of this study changed? If yes, please attach a revised summary of the protocol.	☐ Yes	✓ No

HUMAN RESEARCH ETHICS COMMITTEE
18 NOV 2016
HEALTH SCIENCES FACULTY
UNIVERSITY OF CAPE TOWN

(Note: Please complete this Closure form (FHS016) if the study is completed within the approved period)

Appendix C: Faculty of Health Sciences Ethical Approval: Current Study

UNIVERSITY OF CAPE TOWN
Faculty of Health Sciences
Human Research Ethics Committee

Room E53-46 Old Main Building
Groote Schuur Hospital
Observatory 7925
Telephone [021] 406 6626
Email: shuretta.thomas@uct.ac.za
Website: www.health.uct.ac.za/fhs/research/humanethics/forms

20 April 2017

HREC REF: 163/2017

Dr L Schrieff-Elson
Psychology
Humanities Graduate School Building
Upper Campus

Dear Dr Schrieff-Elson

PROJECT TITLE: INVESTIGATING ACUTE PREDICTORS OF NEUROPSYCHOLOGICAL OUTCOME 12 MONTHS AFTER SEVERE PAEDIATRIC TRAUMATIC BRAIN INJURY (Ma-candidate-L Wepener) sub-study linked to 915/2014

Thank you for submitting your response to the Faculty of Health Sciences Human Research Ethics Committee dated 11 April 2017.

It is a pleasure to inform you that the HREC has **formally approved** the above-mentioned study.

Approval is granted for one year until the 30 April 2018.

Please submit a progress form, using the standardised Annual Report Form if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period.
(Forms can be found on our website: www.health.uct.ac.za/fhs/research/humanethics/forms)

Please quote the HREC REF in all your correspondence.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Please note that for all studies approved by the HREC, the principal investigator **must** obtain appropriate institutional approval before the research may occur.

The HREC acknowledge that the student, Lydia Wepener will also be involved in this study.

Yours sincerely

pp TBurgess
PROFESSOR M BLOCKMAN
CHAIRPERSON, FHS HUMAN RESEARCH ETHICS COMMITTEE
Federal Wide Assurance Number: FWA00001637.
Institutional Review Board (IRB) number: IRB00001938

Appendix D: UCT Department of Psychology Ethical Approval

DEPARTMENT OF PSYCHOLOGY

REPORT OF THESIS COMMITTEE

Student Name: Lydia Wepener

Student #: WPNLYD001

Degree: MA Neuropsychology

Title (as proposed) Investigating acute predictors of neuropsychological outcomes 12 months after severe pediatric TBI

Supervisor: Dr Leigh Schrieff-Elson

Co-supervisor: Prof Anthony Figaji

Committee members: Lauren Wild

Susan Malcolm-Smith

Progress Njomboro

WE:

1. Approve the proposal, and recommend that the student continue with the research.

(2.) Approve the proposal, and recommend that the student may continue with the research. However, we recommend that change(s), as noted below, be incorporated in the research, to the satisfaction of the supervisor.

(3.) Approve the proposal in terms of its ethical implications. If necessary, explanatory notes appear below.

4. Find the proposal unsatisfactory, for the reason(s) listed below. The student is hereby requested to re-present the proposal to a departmental thesis committee by ________________.

NOTES:

Edits to consent form for controls:

Simplify language

Add Ros' details

UNIVERSITY OF CAPE TOWN

FACULTY OF HUMANITIES

DC: HUM /

PROPOSAL APPROVAL FORM

DOCTORATE (A research proposal must accompany this form)	RESEARCH MASTERS (A research proposal must accompany this form)	C/W MASTERS X

SECTION A: (To be completed by candidate)
Please complete this form and return it to the Faculty Office once you have obtained the signatures of the supervisor(s) and Head of Department.

Surname	Wepener			First Name(s)	Lydia
Title	Mr.	Ms.	Mrs. Miss	Student No	WPNLYD001
Address	26 Irene Court Irene Road Newlands, 7700				
Telephone(Home)				Work/Cell	0716771182

Note: Your UCT Email address is the default email address for all official communication – make sure that you access it regularly.

Department	Psychology
Title of Dissertation:	Investigating acute predictors of neuropsychological outcomes 12 months after severe pediatric traumatic brain injury.

Qualifications held			
Degree/Diploma	Major(s) &) Subjects	Month/Year awarded	University
BSocSci	English & Psych	December 2014	UCT
BSocSci (Hons) Psychology	Psychology	December 2015	UCT

Signature of candidate: _____ Date: 23/2/2017

SECTION B:

	Name	Signature	Date
Supervisor	Leigh Schrieff-Elson		23/02/2017
Co-supervisor (if applicable)			
HOD	A/Prof Wilma		3/3/2017
Deputy-Dean: Research			
Ethics approval obtained where applicable	on behalf of Departmental Ethics Committee		24/02/2017

Appendix E: Western Cape Education Department Ethical Approval

Western Cape Government
Education

Directorate: Research

Audrey.wyngaard@westerncape.gov.za
tel: +27 021 467 9272
Fax: 0865902282
Private Bag x9114, Cape Town, 8000
wced.wcape.gov.za

REFERENCE: 20170508 –609
ENQUIRIES: Dr A T Wyngaard

Ms Lydia Wepener
26 Irene Court
Irene Road
Rondebosch
7700

Dear Ms Lydia Wepener

RESEARCH PROPOSAL: INVESTIGATING ACUTE PREDICTORS OF NEUROPSYCHOLOGICAL OUTCOMES 12 MONTHS AFTER SEVERE PEDIATRIC TRAUMATIC BRAIN INJURY

Your application to conduct the above-mentioned research in schools in the Western Cape has been approved subject to the following conditions:

1. Principals, educators and learners are under no obligation to assist you in your investigation.
2. Principals, educators, learners and schools should not be identifiable in any way from the results of the investigation.
3. You make all the arrangements concerning your investigation.
4. Educators' programmes are not to be interrupted.
5. The Study is to be conducted from **02 May 2017 till 28 February 2018**
6. No research can be conducted during the fourth term as schools are preparing and finalizing syllabi for examinations (October to December).
7. Should you wish to extend the period of your survey, please contact Dr A.T Wyngaard at the contact numbers above quoting the reference number?
8. A photocopy of this letter is submitted to the principal where the intended research is to be conducted.
9. Your research will be limited to the list of schools as forwarded to the Western Cape Education Department.
10. A brief summary of the content, findings and recommendations is provided to the Director: Research Services.
11. The Department receives a copy of the completed report/dissertation/thesis addressed to:

    The Director: Research Services
    Western Cape Education Department
    Private Bag X9114
    CAPE TOWN
    8000

We wish you success in your research.

Kind regards.
Signed: Dr Audrey T Wyngaard
Directorate: Research
DATE: 08 May 2017

Appendix F: ADAPT Trial Consent Form (TBI Participants)

CONSENT FOR A CHILD TO ACT AS A PARTICIPANT IN A RESEARCH STUDY

TITLE: Approaches and Decisions for Acute Pediatric TBI (ADAPT) Trial

PRINCIPAL INVESTIGATOR: Professor Anthony Figaji

Paediatric Neurosurgery Unit, Ward D1
Red Cross War Memorial Children's Hospital
Klipfontein Road
Rondebosch
7700
Tel: +27 21 658 5049

SOURCE OF SUPPORT: National Institute of Health, US

What are my child and I being asked to do?

DESCRIPTION: _____ (name and relationship) is being invited to participate in this clinical research project because he/she has had a severe head injury.

What is this study about?

Your child has been admitted to the intensive care unit because he/she has a serious brain injury. He/she will receive the very best care during this time, which involves monitoring his/her brain function. This monitoring is necessary to understand how the brain is injured and what we need to do to treat the injury properly.

The purpose of this research is to compare the effectiveness of different medical therapies for traumatic brain injuries. These therapies have formed part of the routine care your child has received at Red Cross Children's Hospital. We have collected information about these therapies from all children who are being treated for a severe head injury at this hospital - including your child – and from other children at hospitals around the world. We have already looked at your child's medical records and recorded the therapies that your child's doctor used to help your child recover from his/her injury. This information was recorded in a confidential database. To help us know which therapies are most effective, we need to see how children who have suffered from a serious head injury do after they leave the hospital.

Who is being asked to participate in this study?

All children, age 0 – 13 years old, who are being treated for a severe traumatic brain injury at this hospital are being asked to participate in this study. In total, 1000 children will be included in this study from 50 hospitals all over the world.

What will my child's participation in this study involve?

The treatment your child receives will not be affected by this study. As part of routine clinical follow up, your child will be assessed at 3, 6, and 12 months after injury to see how he/she is

recovering from his/her head injury. This is part of the normal follow up your child would receive anyway. At 12 months your child will be tested by a trained neuropsychologist. This testing session will take about 1 to 1 ½ hours to complete, depending on the age of your child**.** The tests will measure your child's behaviour, attention, and general thinking. If your child is able, he/she will be asked to play with toys or to do paper and pencil tests. We will examine your child's ability to learn lists of words, remember designs, and build with blocks. We will try our best to plan these assessments at the same time that you come to see the doctor. At the 12 month appointment we will ask you questions about how your child is acting and behaving at home and/or at school after his/her injury.

What are the possible risks of my child's participation in the study?

There are no risks of physical injury associated with your child's participation in the study.

Participation does involve the possible risk of information about your child's health becoming known to people outside of the study. We will do several things to try to prevent this. First, no information with your child's name on will leave this hospital. Only de-identified information (information that cannot be traced back to your child) will be sent to the central database in America. To do this, we will give a special research code number to your child and no personal information (for example, your child's name and medical record number) will be sent out of Red Cross Children's hospital. Second, any information linking the research code number to your child's name will be stored in a secure location at this hospital. Access to this linking information will be limited to Professor Figaji and Neurosurgery staff who are working on this study. Lastly, the de-identified information that is sent to the Epidemiology Database Center (EDC) at the University of Pittsburgh in America will be stored in a password-protected, fully secured database. This Centre has many years experience with similar studies and has taken the appropriate steps necessary to insure the protection and confidentiality of all patient records and information.

The neuropsychology testing requires effort and your child may find this to be tiring or stressful. To minimize this, we will work together with you and your child and take breaks as needed. The testing will be kept as short as possible. We will answer any questions about the assessment or the results. Upon your request, we will provide feedback about these assessments to your child's doctor and refer your child to other clinics in the hospital who can help with their recovery if that is needed. We will be available to answer any questions you may have about the testing.

There will be no additional costs for participating in this study.

Benefits

There is no guarantee of a direct benefit to participation in this study. However, we hope that this information may help us to find better ways of treating children who have serious head injuries in the future. The neuropsychology testing is useful and may provide information that would be helpful to your child's further recovery. It helps us know what problems your child may still have and is relevant to future schooling options. Specifically, if you wish to discuss your child's testing results, the neuropsychologist will be available at a convenient time (either by phone or in person), should you wish.

Will I be paid for my child's participation in the study?

In order to compensate you for the neuropsychology evaluation at the 12 month visit, you will be paid R150 for participation in this study.

May I refuse to participate in the follow-up testing that is part of this research study?

You may choose to not participate in the neuropsychology testing at 12 months. If you choose not to participate this will not affect your child's care in any way.

How will my child's privacy rights be protected?

As part of this study we will record information about your child's treatment and share that information with the study centre in America. Your child's name will be taken away from their information and they will be given a special number to ensure their privacy. No information that can be linked to your child will be sent outside of Red Cross Children's Hospital. De-identifiable information (information that cannot be linked to your child) will be shared with other groups, including authorized officials from the National Institutes of Health (the agency that is paying for this study), the University of Pittsburgh Research Conduct and Compliance Office (who are monitoring the study) and possibly other agencies. This number that your child will be given will be able to link the de-identified information from this study with other studies your child may decide to join in the future. This number, however, can never be linked to your child or their medical records.

Is my child's participation in the study voluntary?

Your child's participation in this study is voluntary. Whether or not you provide your permission for participation in this study will have no effect on your child's current or future medical care at this hospital or other local hospitals.

For how long will my child's medical record information continue to be placed in the study and for how long will this information be used for research purposes?

The investigators will be permitted to use your child's de-identified health information within the study database until your child is 18 years old. When he/she turns 18, we will ask his/her permission to continue to use their information.

May I withdraw, at a future date, my consent for participation in this study?

You may withdraw, at any time, your consent for your child's participation in the study. To formally withdraw your permission for participation in the study, you need to write a letter to Professor Figaji at the address listed on the first page of this consent form.

****

Voluntary Consent and Authorization

The above information has been explained to me and all of my questions have been answered. Any future questions I have about this research registry will be answered by one of the investigators listed on the first page of this consent document at the telephone number(s) given.

The UCT FHS Human Research Ethics Committee can be contacted on 021 406 6338 in case participants have any questions regarding their rights and welfare as research subjects on the study

_____
Participant's (Child's) Name (print)

I understand that, as a minor (age less than 18 years), the above-named child is not permitted to participate in this research registry without my consent. Therefore, by signing this form, I give my consent for his/her participation in this research registry. A copy of this consent form will be given to me.

_____ _____
Parent or Guardian's Name (Print) Relationship to Participant (Child)

_____ _____
Parent's or Guardian's Signature Date

Certification of Informed Consent

I have explained the nature and the purpose of this research and the disclosure of the child's medical information to the parent(s) or legally authorized guardian(s). He/she/they have had the opportunity to ask questions. Based on this conversation, I believe that he/she/they understand what this research project involves. The physicians and research staff will be available to address future questions as they arise.

_____ _____
Printed Name of Person Obtaining Consent Role in Study

_____ _____
Signature of Person Obtaining Consent Date

Explanation of Lack of Assent: **(**For children who are not capable of understanding the registry procedures and their potential discomforts and benefits**).**

I do not believe my child is capable of giving assent for participation.

_____
Signature of Parent(s) or Guardian(s)

Appendix G: ADAPT Trial Assent Form (TBI Participants)

TITLE: Approaches and Decisions for Acute Pediatric TBI (ADAPT) Trial

PRINCIPAL INVESTIGATOR: Professor Anthony Figaji

Paediatric Neurosurgery Unit, Ward D1
Red Cross War Memorial Children's Hospital
Klipfontein Road
Rondebosch
7700
Tel: +27 21 658 5049

SOURCE OF SUPPORT: National Institute of Health, US

What am I being asked to do?

You, _____ (name) are being invited to participate in this clinical research project because you have had a severe head injury.

What is this study about?

This study looks at different ways to treat children in hospital with a severe injury to the head, like you have had. We also want to know how children who have had head injuries are getting better after they leave the hospital.

Why am I being asked to be a part of this study?

We are asking all children like you who are 0 – 13 years old and who are being treated for a severe head injury at Red Cross Children's Hospital to be a part of this study. In total, 1000 children will be included in this study from 50 hospitals in America and in other countries.

What will happen to me as part of this study?

After you leave the hospital you will come back for check-ups with the doctor after 3, 6, and 12 months to see how you are doing after your injury. These are normal check-ups that you would have anyway as you get better. At 12 months after your injury you will also see a neuropsychologist who will do activities with you like building with blocks, learning a list of words or doing pencil and paper exercises to measure your attention, behaviour and thinking. These activities will take approximately 1 to 1 ½ hours to finish. This will help us to understand what areas you may still be struggling with. We will share some information about how you are doing with the hospital in charge of this study in America. To make sure that we keep your information private you will be given a special number and only this number will be sent with your information.

Will I be harmed if I take part in this study?

Nothing in this study will hurt or harm you. No-one else except us will know you are in this study. The activities with the neuropsychologist may make you tired or make you feel stressed but they will work with you all the way and you will be able to take breaks when you feel you need them. The assessment will be kept as short as possible. If the neuropsychologist sees that you need some more help with getting better she will share that with your parents and your doctors who will try to help you have the best recovery. You are free to ask questions at any time.

For how long will my information be kept?

The information with your special number will be kept in a special computer until you are 18 years old. We will ask you again when you are 18 if we can still keep your information.

Do I have to be in the study?

It is your choice to be in the study. Your parents have said that you can take part if you want to but it's still up to you to decide. If you say 'no' it won't affect how you are treated in hospital.

Can I leave the study if I decide I don't want to take part anymore?

You can tell us at any time if you want to leave the study. If you decide you don't want to be in the study any longer, you can tell Professor Figaji or write him a letter saying you want to stop being in the study.

****

Assent for Participation in the Study:

This research has been explained to me, and I agree to participate.

_____ _____

Signature of Child-Subject Date

_____

Printed Name of Child-Subject

Verification of Explanation: (For children who are capable of understanding the registry procedures and their potential discomforts and benefits but physically unable to sign)

I certify that I have carefully explained the purpose and nature of this research study to the child-subject in age appropriate language. He/she has had an opportunity to discuss it with me in detail. I have answered all his/her questions and he/she has provided affirmative agreement (i.e., assent) to participate in this study.

_____ _____

Investigator's Signature Date

I believe my child understands what this research involves and that he/she has given his/her assent for participation.

_____

Appendix H: Control Participant Consent Form

Parent/Guardian's Informed Consent Document

University of Cape Town
Psychology Department
Telephone: +27 21 650-3430
Fax: +27 21 650-4104

Investigating acute predictors of neuropsychological outcomes 12 months after severe pediatric traumatic brain injury.

Informed Consent to Allow Participation in Research and Authorization for Collection, Use, and Disclosure of Cognitive Performance and Other Personal Data

You are being asked to allow your child to take part in a research study. This form provides you with information about the study and seeks your authorization for the collection, use and disclosure of your child's cognitive performance data, as well as other information necessary for the study. The Principal Investigator (the person in charge of this research) or a representative of the Principal Investigator will also describe this study to you and answer all of your questions. Your participation is entirely voluntary. Before you decide whether or not to take part, read the information below and ask questions about anything you do not understand. By refusing participation in this study you or your child will not be penalized or lose any benefits to which you would otherwise be entitled.

My research will be conducted in a manner that adheres to the ethical guidelines and principles of the International Declaration of Helsinki.

1. **Title of Research Study**

Investigating acute predictors of neuropsychological outcomes 12 months after severe pediatric traumatic brain injury.

2. **What is the purpose of this research study?**

The purpose of this research study is to investigate the nature and severity of neuropsychological outcomes 12 months after severe TBI in South African children, comparing their performance to a typically developing, matched control group. In addition, the ability of acute injury variables to predict poor outcome after brain injury will be explored.

3. **How many people are expected to participate in the research?**

50

4. **Principle Investigator(s) and Telephone Number(s)**

Leigh Schrieff-Elson, Ph.D. (PI and supervisor)

Psychology Department

University of Cape Town

0216503708

Lydia Wepener (Masters student)

Psychology Department

University of Cape Town

0716771182

5. **What will be done if you provide consent for your child to part in this research study?**

During this study, you will be required to complete a number of questionnaires and scales to obtain demographic information and information regarding your child's behaviour and emotional state. In addition, your child will undergo a neuropsychological assessment which consists of various cognitive measures of attention, intelligence, memory and processing speed. This will take place at the University of Cape Town or at a hospital in the Cape Town area.

6. **If you choose to allow your child to participate in the study, how long will they be involved in the research?**

Participation will involve one neuropsychological assessment session which will take approximately 2 hours, regular breaks will be provided.

7. **What are the possible discomforts and risks to your child?**

There is minimal risk associated with this study. Due to the assessment being a more lengthy process, participants may feel fatigued or irritable during testing as the tasks require concentration. Each participant will be given a break mid-way through the assessment in addition to regular breaks when they would like breaks.

8. **What are the possible benefits of this study?**

This research aims to contribute to the knowledge base on what factors predict outcome after severe traumatic brain injury in children. In order to do so it is necessary to compare the results of our traumatic brain injury sample to those of children who have not sustained a previous head injury. Upon the conclusion of the study, you will receive feedback on your child's neuropsychological assessment.

9. **If you choose to allow your child to take part in this research study, will it cost you anything?**

The assessment will not cost you anything. The assessment will take place at your child's school, the University of Cape Town, or at a hospital in the Cape Town area. Should you be required to travel, you will be compensated R150 for this travel expenditure.

10. Can you or your child withdraw from this research study and if you withdraw, can information about you still be used and/or collected?

You or your child may withdraw your consent or assent and stop participation in this study at any time without any penalty. Information already collected may still be used.

If you have a complaint or complaints about your rights and welfare as research participants, please contact the Human Research Ethics Committee.

Tel: 021 406 6492

E-mail: sumaya.ariefdien@uct.ac.za

11. Once information is collected, how will it be kept confidential in order to protect your privacy and what protected health information about you may be collected, used and shared with others?

The information gathered from you and your child will be demographic information, records of his/her performance on neuropsychological tests and questionnaires on their emotional and behavioural state. Information collected will be stored in locked filing cabinets and on computers with security passwords. Only certain people - the researchers for this study and certain University of Cape Town officials - have the legal right to review these research records. Your research records will not be released without your permission unless required by law or a court order.

12. What should you tell your child?

You may wish to discuss the study with your child to find out whether he/she feels comfortable taking part. The assessment takes the form of games and puzzles. Your child should know that he/she can choose not to participate in the study. Your child should also know that if he/she does choose to participate, he/she can withdraw at any time during the study with no negative consequences.

13. How will the researcher(s) benefit from your child being in the study?

In general, presenting research results helps the career of a scientist. Therefore, the Principal Investigator and others attached to this research project may benefit if the results of this study are presented at scientific meetings or in scientific journals.

14. Signatures

As a representative of this study, I have explained to the participant the purpose, the procedures, the possible benefits, and the risks of this research study; the alternatives to being in the study; and how the participant's protected health information will be collected, used, and shared with others:

_____ _____

Signature of Person Obtaining Consent Date

You have been informed about this study's purpose, procedures, possible benefits, and risks; and how your child's performance and other data will be collected, used and shared with others. You have received a copy of this form. You have been given the opportunity to ask questions before you sign, and you have been told that you can ask other questions at any time.

You voluntarily consent to allow your child to participate in this study. You hereby authorize the collection, use and sharing of your child's performance and other data. By signing this form, you are not waiving any of your legal rights.

_____ _____

Signature of Person Consenting Date

Name of Participant (your child)

_____

Appendix I: Control Participant Assent Form

Assent Form for Participants

University of Cape Town
Psychology Department
Telephone: +27 21 650-3430
Fax: +27 21 650-4104

I am doing a study with school-aged children at primary schools in Cape Town who speak English, Afrikaans and isiXhosa. I want to see if how they do on some tasks is different to how children with brain injuries do on the same tasks.

You are going to be asked to play some games and do some puzzles. The person who is going to ask you the questions has told you that you can stop if you are feeling tired and need to take a break, and that nobody else will be told your answers to the questions.

Signing this paper means that you want to be in the study. If you don't want to be in the study, you don't have to sign the paper. No one will be angry if you don't sign this paper, and no one will be angry if you change your mind later and want to stop.

You can ask any questions that you have about the study. If you have a question later that you didn't think of now, you can call me on (071 677 1182) or ask me next time.

_____ _____

Signature of Child Date

_____ _____

Signature of Researcher Date

Name of Participant (your name)

_____

Appendix J: Between Group analysis for each of the variables making up the cognitive composites

Table 25

Between Group (TBI vs Control) Independent Samples T-Test (Bootstrapped) on variables comprising the Verbal Fluency Composite

	TBI			Controls			Test statistics					
	N	Range	M (SD)	N	Range	M (SD)	t	df	p	η^2	Bias Adjusted CI	
											Lower	Upper
D-KEFS Letter Fluency	11	2-9	5.36 (2.014)	12	3-10	7.25 (2.050)	-2.225	20.889	.034	.190	**-3.446**	**-.409**
D-KEFS Category Fluency	11	3-12	7.09 (2.700)	12	7-14	9.67 (2.229)	-2.482	19.485	.030	.256	**-4.641**	**-.669**
D-KEFS Category Switching	11	2-11	6.73 (2.649)	12	4-11	7.50 (2.276)	-.747	19.851	.419	.052	-2.818	1.033
D-KEFS Category Switching Accuracy	11	1-14	6.09 (3.562)	12	2-11	6.92 (3.260)	-.578	20.346		.034	-3.374	1.801

Table 26

Between Group (TBI vs Control) Independent Samples T-Test (Bootstrapped) on variables comprising the Higher Order Attention Composite

	TBI			Controls			Test statistics					
	N	Range	M (SD)	N	Range	M (SD)	t	df	p	η^2	Bias Adjusted CI	
											Lower	Upper
Sky Search Time Per Target	15	1-11	3.00 (3.024)	15	4-13	6.93 (2.520)	-3.870	27.120	.003	.348	**-5.892**	**-1.806**
Sky Search Attention Score	15	1-16	4.20 (4.523)	15	3-13	7.40 (2.898)	-2.307	23.838	.053	.160	**-5.899**	**-.279**

Table 27

Between Group (TBI vs Control) Independent Samples T-Test (Bootstrapped) on variables comprising the Visuospatial Memory Composite

	TBI			Controls			Test statistics					
	N	Range	M (SD)	N	Range	M (SD)	t	df	p	η^2	Bias Adjusted CI	
											Lower	Upper
Dot Locations Learning	15	1-13	6.47 (3.378)	15	5-16	10.20 (2.783)	-3.304	27.010	.003	.281	**-5.819**	**-1.455**
Dot Locations Short Delay	15	3-13	7.73 (2.463)	15	7-14	11.53 (2.100)	-4.547	27.317	.001	.425	**-5.361**	**-2.196**
Dot Locations Total	15	2-13	6.53 (3.137)	15	6-16	11.07 (2.963)	-4.069	27.910	.001	.372	**-6.606**	**-2.400**
Dot Locations Long Delay	15	3-13	7.53 (3.021)	15	6-14	11.47 (2.386)	-3.957	26.577	.001	.359	**-5.723**	**-1.895**

Table 28

Between Group (TBI vs Control) Independent Samples T-Test (Bootstrapped) on variables comprising the Verbal Memory Composite

	TBI			Controls			Test statistics					
	N	Range	M (SD)	N	Range	M (SD)	t	df	p	η^2	Bias Adjusted CI	
											Lower	Upper
CVLT-C Short Delay Free Recall	15	-3.5-.0	-1.467 (1.187)	15	-1.5-2.0	-267 (.942)	-3.066	26.629	.009	.251	**-1.986**	**-.467**
CVLT-C Short Delay Cued Recall	15	-3.5-.5	-1.533 (1.141)	15	-1.5-1.0	-.067 (.821)	-4.041	25.428	.001	.368	**-2.183**	**-.785**
CVLT-C Long Delay Free Recall	15	-3.0-.0	-1.233 (1.067)	15	-1.5-2.0	-.167 (1.012)	-2.810	27.922	.015	.220	**-1.778**	**-.367**
CVLT-C Long Delay Cued Recall	15	-3.0-.5	-1.367 (1.008)	15	-1.5-1.5	.033 (.876)	-4.060	27.460	.001	.371	**-2.067**	**-.690**
CVLT-C Recognitions Correct	15	-4.0-.5	-.633 (1.202)	15	-.5-1.0	.233 (.417)	-2.638	17.319	.060	.199	**-1.567**	**-.264**

Table 29

Between Group (TBI vs Control) Independent Samples T-Test (Bootstrapped) on variables comprising the Executive Functions Composite

	TBI			Controls			Test statistics					
	N	Range	M (SD)	N	Range	M (SD)	t	df	p	η^2	Bias Adjusted CI	
											Lower	Upper
CMS Numbers Backwards	15	2-10	6.13 (2.3556)	15	5-13	7.93 (2.789)	-1.909	27.239		.115	-3.692	.067
WASI Block Design	15	3-10	5.40 (2.063)	15	4-12	8.60 (2.131)	-4.178	27.971	.001	.384	**-4.679**	**-1.651**
WASI Matrix Reasoning	15	1-9	4.80 (2.678)	15	3-12	8.07 (2.738	-3.304	27.986	.005	.280	**-5.190**	**-1.420**