Neuropsychological and Neuroimaging Outcomes Following Moderate to Severe Paediatric Traumatic Brain Injury in South Africa.

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Abbreviations

ACSENT	Applied Cognitive Science and Experimental Neuropsychology Team
ADHD	Attention deficit hyperactivity disorder
BRIEF	Behaviour Rating Inventory of Executive Function parent report
BRI	Behavioural Regulation Index
CBCL	Child Behaviour Checklist parent report
CL	Confidence level
CMS	Children's Memory Scale
CT	Computerised tomography
CTB	Computerised tomography brain scan
CUBIC	Cape Universities Body Imaging Centre
D-KEFS	Delis-Kaplan Executive Function System
DTI	Diffusion Tensor Imaging
FBI	Family Burden of Injury Self-report Questionnaire
FLAIR	Fluid-attenuated inversion recovery
fMRI	Functional magnetic resonance imaging
FRS	Family Resource Scale
GCS	Glasgow Coma Scale
GEC	Global Executive Composite
GSH	Groote Schuur Hospital
ICP	Intracranial pressure
LMIC	Low- to middle-income countries
LSEN	Learners with Special Educational Needs
MI	Metacognition Index
MRI	Magnetic resonance imaging

MRS	Magnetic Resonance Spectroscopy
MVA	Motor vehicle accident
$PbtO_2$	Partial pressure of brain tissue oxygen
pICU	Paediatric intensive care unit
pTBI	Paediatric traumatic brain injury
RAVLT	Rey Auditory Verbal Learning Test
RCI	Reliable Change Index
RXH	The Red Cross War Memorial Children's Hospital
SES	Socioeconomic status
TAI	Traumatic axonal injury
TBI	Traumatic brain injury
TMT	Trail Making Test
UCLA	University of California Los Angeles
UCT	University of Cape Town
USA	United States of America
USC	University of Southern California
WISC-IV	Weschler Intelligence Scale for Children Fourth Edition

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Abstract

Paediatric traumatic brain injury (pTBI) is a leading cause of mortality and disability. South Africa is predicted to have a high pTBI rate and an adverse socioeconomic environment for recovery. Despite this, few studies have investigated the neuropsychological and/or neuroimaging outcomes of pTBI in South Africa. The study was designed as a capacity-building exercise to demonstrate the successful collection of data from different sites involved in a developing international collaboration. The aims were therefore to 1) provide a detailed description of the premorbid factors and neuropsychological and neuroimaging outcomes of a sample of South African children with moderate to severe pTBI, and 2) investigate the barriers to the successful implementation of neuropsychological and neuroimaging research in this population. Five patients with severe pTBI were enrolled during the 6-month recruitment window. These participants presented with 6-month post-TBI outcomes that ranged from mild neuropsychological deficits and no visible abnormalities on neuroimaging to severe neuropsychological deficits and evidence of multifocal pathology on imaging. There was a relatively high occurrence of adverse developmental, socioeconomic, and neuropsychological histories, which will need to be considered when selecting an appropriate control group or combining with other populations in a potential future multi-centre study. Additional strategies will also be required to improve recruitment and increase the rate of successful imaging. Changes may need to be made to the neuropsychology assessment so as not to disadvantage this population, for example avoiding tests that are reliant on sequencing the alphabet. In conclusion, the study's findings will help to improve the likelihood of the much-needed large-scale research in this at-risk and understudied South African population.

Introduction

Traumatic brain injury (TBI) is a leading cause of childhood mortality and disability worldwide (Dewan et al., 2016). Based on previously reported TBI rates in the United States of America (USA), approximately 60 000 children are hospitalized per year following a TBI, 7 500 of which are fatal injuries (Thurman, 2014). Paediatric TBI (pTBI) can result in severe lifelong physical and neuropsychological disabilities (Babikian et al., 2015) and the resultant socioeconomic burden is substantial (van Dijck et al., 2019).

TBI Definition

Thurman (2014) detailed a TBI definition based on the United States Centers for Disease Control and Prevention and the World Health Organization classifications. In this definition, the criteria for TBI include "an occurrence of injury to the head from physical force, to which one or more of the following symptoms or findings is attributable: a) decreased or altered level of consciousness or amnesia; b) other neurologic or neuropsychological changes; c) skull fracture; d) traumatic intracranial lesions; or e) death" (Thurman, 2014, p. 20). The severity of TBI is most often classified according to the Glasgow Coma Scale (GCS) after resuscitation. The GCS investigates three categories of responsive actions, namely eye-opening, verbal response, and motor response, to provide a total score out of 15, which is used to indicate the level of consciousness (Teasdale et al., 2014). GCS scores of 13 to 15 are designated as mild TBI, those between nine and 12 as moderate TBI, and scores of eight and below are demarcated as severe TBI.

TBI Epidemiology

The annual worldwide TBI incidence was estimated at 691 injuries per 100 000 population across all age groups, with 9 injuries per 1000 resulting in death (Thurman, 2014). Looking specifically at pTBI, the published incidence rates vary dramatically between countries, with a range from 12 per 100 000 population reported in Sweden (Emanuelson & Wendt, 1997) to 486 per 100 000 population measured in Australia (Mitra et al., 2006). A qualitative review of pTBI epidemiology studies by Dewan et al. (2016) reported that the majority (<80%) of pTBIs are mild, while moderate (>10%) and severe (>10%) pTBIs are less common (Dewan et al., 2016). The review also stated that pTBI mortality rates from different countries ranged from 2.8 to 3.75 per 100 000 population. Mortality rates differ according to the availability and type of medical intervention (Dash & Chavali, 2018). For example, intracranial pressure (ICP) monitoring has been shown to reduce pTBI mortality rates (Farahvar et al., 2012; Kukreti et al., 2014).

Nell and Brown (1991) reported a TBI incidence of 316 per 100 000 population in South Africa (Nell & Brown, 1991), which is the only published South African TBI incidence. Children younger than 15 years were not included in this study and thus there are no reported pTBI incidence rates specifically in South Africa, although higher than average rates are expected here. The suspected heightened pTBI risk is supported by injury mortality data from the World Health Organisation. Specifically, South Africa has a three times greater childhood injury mortality rate, of which a large proportion would be TBI related, compared to the USA (World Health Organisation, 2019). The suspected heightened TBI risk in South Africa has been attributed to the higher rates of motor vehicle accidents (MVAs) and interpersonal violence (Parkinson et al., 2013).

PTBIs are most commonly caused by MVAs and falls (Dewan et al., 2016). In high-income countries, children are more likely to sustain pTBIs as a passenger in an MVA, while in low- to middle-income countries (LMICs) children are more frequently injured as pedestrians (Bowman et al., 2008; Mitra et al., 2006; Schrieff et al., 2013; Udoh & Adeyemo, 2013). Studies consistently report that male children have a higher pTBI risk (Dewan et al., 2016), which has been suggested to be due to increased contact sports participation and risk-taking propensity (Steinberg, 2008; Stracciolini et al., 2014).

There appears to be a bimodal distribution of pTBI risk when investigating the age at injury. Specifically, children under the age of three years and between the ages of 15 and 18 years old show the greatest pTBI incidence rates (Amaranath et al., 2014; Greene et al., 2014). This phenomenon is attributed to the high fall risk in younger children and increased sporting and risk-taking activities in older adolescents (Amaranath et al., 2014). PTBIs occur more commonly on the weekend, late afternoon or evening, and during the warmer months of the year (Dewan et al., 2016), coinciding with when children are more frequently out of school.

TBI Pathophysiology

The forces on impact cause immediate tissue distortion and induce biological processes that may last for years following a TBI (Wilson et al., 2017). TBIs can be caused by non-contact events, where the brain is exposed to high forces despite the head not encountering an object (Menon et al., 2010). TBIs are separated into open or closed injuries. Open injuries involve the skull and the dura being pierced by an object, while the skull and dura remain intact in closed injuries. TBI pathology can additionally be focal (e.g., contusions) or diffuse (e.g., swelling) and is often a combination of both in moderate to

severe TBI (Andriessen et al., 2010). TBI pathophysiological processes are further divided into primary and secondary injuries.

Primary Injuries

Primary injuries refer to the tissue damage caused by the mechanical forces on the skull and brain on impact. Primary injuries would therefore include skull fractures, haemorrhages, and brain contusions (Kaur & Sharma, 2017). The frontal bone is the most frequent location of skull fracture in pTBI (Bonfield et al., 2014). Depressed skull fractures pose a specific concern as the bone fragments can injure the underlying brain tissue and vasculature (Prakash et al., 2018).

Haemorrhages and haematomas are caused by the impact forces disrupting the brain's intricate vasculature. Resultant blood collections can form between the skull and dura mater (epidural haematoma), between the dura and the brain (subdural haematoma), or between the arachnoid and the pia mater (subarachnoid haemorrhage). Blood from the parenchyma or surrounding vessels can also collect in the ventricles. Contusions occur when the brain is forcibly moved within the skull and is pressed against the jagged bony inner surfaces of the skull. TBI imaging studies have indicated that contusions are most common in the superficial grey matter of the inferior frontal and temporal lobes due to their location above the sphenoidal ridges and the edge of the tentorium cerebelli (Bigler, 2007).

White matter damage, referred to as traumatic axonal injury (TAI), is induced and was proposed to significantly contribute to the TBI pathophysiology (Kinnunen et al., 2011; Werner & Engelhard, 2007). White matter refers to the myelinated axon fibres that transmit electrochemical signals to allow communication between areas of the brain. The axonal damage is caused by the acceleration and deceleration forces exerted during a TBI, which cause stretch and shear injuries to the long-tract fibres. This shear injury may cause a cascade of detrimental biological disruptions that can result in Wallerian-type degeneration and progressive neuronal loss.

Secondary Injuries

The secondary injuries encompass the biological processes initiated by the primary injuries and may include cerebral swelling, excitotoxicity, blood-brain barrier disruption, ischemia, and neuroinflammation (Pinto et al., 2012). Secondary injuries can have an immense influence on the outcome following TBI and the primary goal of neurocritical care is to limit these effects (Dash & Chavali, 2018).

Cerebral swelling is common following moderate to severe TBI (O'Phelan et al., 2009). As the brain is a fixed volume, brain swelling causes an increase in ICP, which may

cause a drop in cerebral perfusion pressure resulting in reduced oxygen supply and ischemia (Kinoshita, 2016; Weiner et al., 2010). Neuroinflammation in TBI was described as a "double-edged sword" because an appropriate inflammatory response is critical to recovery, but a dysregulated response can cause excessive damage to the surrounding brain tissue (Simon et al., 2017). There is evidence that certain individuals experience chronic neuroinflammation following TBI, which can lead to progressive neurodegeneration (Devoto et al., 2017; Faden & Loane, 2014).

PTBI Pathophysiology

There are several anatomical and physiological differences between adults and children in the response to TBI (Figaji, 2017; Giza et al., 2007). Children's head to body ratios are greater and therefore there is a higher likelihood of the head being directly hit and sustaining greater acceleration forces on impact (Pinto et al., 2012). Axon myelination increases from birth until the mid-twenties (Kinney & Volpe, 2018) and unmyelinated fibres are more susceptible to injury (Reeves et al., 2012), making the developing brain, with higher levels of unmyelinated fibres, more vulnerable to TAI.

In terms of secondary injuries, animal models have displayed altered gene expression, cerebral blood flow, metabolism, inflammatory response, neurogenesis, and apoptosis in younger animals (Babikian et al., 2010; Curvello et al., 2017; Semple et al., 2016). In human studies, children were more likely to experience brain swelling, TAI, and post-traumatic seizures post-TBI than adults (Aldrich et al., 1992; Arndt et al., 2013; Pinto et al., 2012). There is limited TBI research in paediatric populations (Figaji, 2017) and therefore the clinical guidelines for pTBI are largely based on adult data, which is inappropriate for this vulnerable group.

PTBI Neuroimaging Outcomes

TBI pathology is clinically investigated using neuroimaging, typically computerised tomography (CT) or magnetic resonance imaging (MRI). CT scans are used in the acute setting due to their lower cost, speed, and ability to identify skull fractures, haemorrhages, or cerebral swelling that might require surgical intervention (Amyot et al., 2015). MRI scans have greater resolution and better diagnostic sensitivity for non-haemorrhagic pathology, including contusions and TAI (Kim & Gean, 2011), and involve no radiation risks, which is beneficial for repeated imaging. However, MRIs are more costly and take longer, requiring sedation or general anaesthesia in young children and confused patients. Advanced MRI modalities, such as Diffusion Tensor Imaging (DTI), Magnetic Resonance Spectroscopy (MRS), and Functional MRI (fMRI), are increasingly being utilized in TBI research.

Emerging evidence is promising, however, the majority of studies are limited by small sample sizes (Mendoza et al., 2018).

Moderate to severe TBIs can present with a variety of pathologies on imaging. In the acute phase, haematomas, haemorrhages, contusions, oedema, and TAI may all be visible on CT or MRI and can be differentiated based on their appearance and location (Appendix A). TAI is difficult to identify on standard CT scans as only 10% of TAIs show the classical petechial haemorrhages at the grey-white matter junctions, brainstem, or corpus callosum and between 50% to 80% of patients with TAI have normal initial CT scans (Buttram et al., 2015; Thomas & Dufour, 2009). MRI provides better clarity to observe TAI as it can detect non-haemorrhagic TAI lesions (Kim & Gean, 2011) but can still under-detect injuries (Thomas & Dufour, 2009). In a study investigating the distribution of TAI pathology using MRI, it was found that lesions were most commonly located in the frontal and temporal lobes, corpus callosum, mesencephalon and upper pons within the brainstem, thalamus, basal ganglia, and internal capsule (Hamdeh et al., 2017).

Encephalomalacia is a loss or softening of brain parenchyma that can develop as a long-term consequence of both the primary and secondary injuries associated with pTBI (Bigler et al., 2013). This was documented in 30% of severe and 20% of moderate pTBI cases when imaged more than 6 months post-TBI, appearing most commonly in frontal and temporal regions (Bigler et al., 2013).

Imaging studies also show persistent white matter damage at chronic time points following TBI (Kinnunen et al., 2011). White matter signal abnormalities were found in 32% to 45% of children with moderate to severe TBI (Bigler et al., 2013). Abnormalities were located predominantly in the frontal and temporal regions and, in addition, 40% of children with severe and 9% of those with moderate TBI had visible corpus callosum pathology (Bigler et al., 2013). Longitudinal neuroimaging studies of TBI have additionally displayed progressive cortical and white matter atrophy over time (Dennis et al., 2016, 2017; Farbota et al., 2012), suggesting that TBI may cause prolonged brain degeneration.

The neuroimaging findings of pTBI differ from adult TBI even when the clinical severity is similar (Sarkar et al., 2014). Evidence suggests that focal injuries and contusions are most common in adult TBI, while diffuse injuries are more frequent in the pTBI (Figaji, 2017; Giza et al., 2007). There is a need to investigate the neuroimaging outcomes of pTBI. However, most imaging studies have been conducted in adult populations and those available in paediatric populations are frequently underpowered (Mendoza et al., 2018).

PTBI Neuropsychological Outcomes

PTBI has been associated with cognitive and psychosocial impairments at both acute and chronic assessments (Babikian et al., 2015; Babikian & Asarnow, 2009). PTBI during critical developmental stages may have long-term consequences on the maturation process and skills acquisition (Anderson et al., 2005). In most cases, post-TBI neuropsychological difficulties present with a dose-response relationship with TBI severity, such that those with severe TBI usually display the most pronounced difficulties (Anderson et al., 2012; Babikian & Asarnow, 2009). Deficits are typically most severe in the acute phase and there is some recovery in the first three years post-TBI (Anderson et al., 2012).

Observation of within-group variation suggests that a subset of pTBI cases display worse long-term cognitive deficits (Fay et al., 2009), suggesting an individual susceptibility to a poor neuropsychological outcome. There also appears to be heterogeneity in neuropsychological outcomes, such that there is no typical cognitive presentation (Allen et al., 2010). The resultant neuropsychological picture is a complex interaction of the TBI pathology, biological recovery, premorbid features, and environmental factors (Anderson et al., 2012; N. Ryan et al., 2014).

Attention

Attention is a multi-dimensional construct consisting of five domains, namely divided, sustained, selective, shifting, and attention span[1], that integrate to allow focused mental actions. Intact attention is a prerequisite for most cognitive processes and was therefore referred to as a "cornerstone" function (Burgoyne & Engle, 2020). The frontal lobes, and prefrontal cortex, in particular, play a critical role in attention (Rossi et al., 2009) and are also especially vulnerable to damage during a TBI (Babikian et al., 2015; Bigler et al., 2013). A large body of evidence has consistently described chronic attention deficits following pTBI (Babikian et al., 2015; Mathias & Wheaton, 2007). A prospective longitudinal study found that 46% of children with severe TBI had attentional deficits four years post-injury (Yeates et al., 2005). In addition, 62% of children who sustained a severe TBI developed secondary attention deficit hyperactivity disorder (ADHD) within 6 years post-TBI (Narad et al., 2018).

[1] Divided attention is the skill of integrating multiple parallel stimuli (Lacoboni, 2005), sustained attention is the ability to maintain focus on relevant stimuli with repeated presentation over time (Williams & Saunders, 1997), selective attention is the capacity to direct attention to a limited range of available sensory stimuli (Ploog, 2013), shifting attention is the timeous change in focus from one stimuli to another (Bridgeman, 2012), and attention span is the short-term, lasting just seconds, ability to hold information in mind (Baddeley, 2003).

Memory

Numerous studies have displayed memory difficulties[2] following pTBI (Babikian et al., 2015; Babikian & Asarnow, 2009). Persistent memory difficulties may affect a child's acquisition of knowledge, skills, and academic progression (Arnett et al., 2013).

For information to be successfully stored as declarative memory, it must first be held in short-term memory, which is reliant on the individual's attention span (Jones & Macken, 2015). The information then needs to be encoded into long-term memory storage, a process dependant on the functioning of the medial temporal lobe and several diencephalic structures (Budson & Price, 2005; Godefroy et al., 2009). For a successful memory performance, the information must be accurately retrieved from long-term storage. Retrieval is an active search procedure that is influenced by executive functions and the functioning of the prefrontal cortex (Faw, 2002; Tomita et al., 1999). Attention and executive deficits may therefore elicit memory dysfunction without damage to memory encoding structures. Patients with pTBI have previously been shown to have varying degrees of encoding and retrieval difficulties (Lajiness-O'Neill et al., 2010).

Processing Speed

Processing speed is the time required to process information or complete a cognitive task and is negatively affected following TBI (Felmingham, Baguley, & Green, 2004; Mathias & Wheaton, 2007). Processing speed is closely related to white matter integrity (Penke et al., 2010; Turken et al., 2008) and is, therefore, vulnerable following TAI (Felmingham et al., 2004; Rabinowitz et al., 2018). Slowed processing speed was frequently noted following moderate to severe pTBI and was often one of the most severe deficits reported in pTBI studies (Allen, Thaler, et al., 2010; Babikian et al., 2015). In addition, processing speed deficits have been noted at 10 years post severe pTBI (Beauchamp et al., 2011).

Executive Functions

Executive functions encompass several higher-order cognitive processes including working memory, abstract thinking, inhibition, self-monitoring, planning, and decision-making, all of which support goal-directed behaviour. Executive functions were frequently impaired in pTBI studies (Babikian & Asarnow, 2009). In addition, executive difficulties were noted 10 years after severe pTBI (Beauchamp et al., 2011), suggesting persistent

[2] Memory is separated into declarative, which can be consciously accessed, and non-declarative, which cannot be consciously retrieved (N. Cohen & Squire, 1980). Traditionally, research and neuropsychological assessment of patients with TBI have focused primarily on declarative memory (Lajiness-O'Neill et al., 2010).

deficits. Inhibitory control, problem-solving, cognitive flexibility, and goal-setting appeared to be some of the most vulnerable executive functions following moderate to severe pTBI (Babikian et al., 2015; Beauchamp et al., 2011; Resch et al., 2019).

Executive functions develop in non-linear growth spurts throughout childhood and are therefore susceptible to the developmental disruptions of pTBI (Sesma et al., 2008). It was suggested that skills undergoing rapid development at the time of injury were vulnerable to greater deficits post-pTBI (Ewing-Cobbs et al., 2004). The frontal lobe, and the prefrontal cortex, in particular, are most associated with executive functioning (Cristofori et al., 2015). However, connections with numerous brain regions are required for appropriate executive functioning and therefore focal frontal lobe damage, diffuse injuries, and white matter network disruptions can all cause executive deficits (Cristofori et al., 2015; Kinnunen et al., 2011).

Psychosocial

Substantial research has indicated that pTBI can cause psychiatric and behavioural changes (Li & Liu, 2013). A systematic review concluded that 50% of pTBI cases were at risk of developing behavioural problems and disorders (Li & Liu, 2013). For example, pTBI has been associated with an increased risk of anxiety, depression, and obsessive-compulsive disorder onset (Grados et al., 2008; Luis & Mittenberg, 2002; Max et al., 2011, 2012).

Other Measures

PTBI has been associated with deficits in other cognitive domains and functions, including general intelligence, language, visuospatial and perceptual skills, sensory and motor abilities, and quality of life (Anderson et al., 2011; Babikian et al., 2015; Babikian & Asarnow, 2009; Galvin et al., 2009), but these were deemed outside of the scope of the current study and were therefore not reviewed in detail.

PTBI Outcome Modifiers

Evidence from studies investigating the neuropsychological, psychiatric, and structural outcomes of TBI congruently suggests that there is heterogeneity in TBI outcomes, which is only partially explained by injury severity (Saatman et al., 2008). Potential predictors can be broadly classified into injury-related, intrinsic, and extrinsic factors[3], which interact to determine individual pTBI outcomes.

[3] Intrinsic factors are those that emanate from within the body, while extrinsic factors come from outside of the body and relate to the environment.

Injury-related Factors

Injury Severity. As noted, TBI severity is most frequently classified according to GCS score and less commonly as coma duration (Sherer et al., 2008). GCS scores are recorded at multiple time points to track changes in the level of consciousness following a TBI. GCS assessments at the accident site are routine but in-hospital assessments after patient stabilization are considered more reliable (Lesko et al., 2013; Marmarou et al., 2007). There is sufficient evidence to suggest a dose-response relationship with outcomes when looking at group differences between patients with mild, moderate, and severe pTBI (Babikian et al., 2015; Babikian & Asarnow, 2009). However, there is considerable variation in the individual outcomes within each of the GCS severity groups, such that two patients might have the same initial GCS but have very different outcomes (Fay et al., 2009). Therefore, initial injury severity can be considered a crude measure of likely outcomes but is not completely predictive of long-term consequences. Coma duration has been inconsistently correlated with TBI outcomes (Donders & Janke, 2008; Krasny-Pacini et al., 2017; Strong et al., 2010; Trivedi et al., 2007).

Primary Injuries. The brain lesions resulting from pTBI are also considered heterogeneous, making prognosis difficult (Bigler et al., 2013). Generally, increased pathology on initial imaging has been associated with worse long-term outcomes (Puffer et al., 2019; Wong et al., 2011). Subcortical lesions, in particular, have been correlated with an increased risk of adverse outcomes (Bonnier, 2007; Grados et al., 2001). Looking specifically at TAI, the number of abnormalities found in the corpus callosum, brainstem, and thalamus predicted one-year post-injury outcomes in paediatric and adult patients (Moen et al., 2014).

The location of pathology has also been found to show some correlation with the pattern of cognitive deficits. For example, white matter damage to the fornix is more associated with memory deficits, injury to the tracts connecting the posterior areas of the brain to the frontal lobes with greater executive deficits, and damage to the corpus callosum with reduced working memory and processing speed (Kinnunen et al., 2011; Wilde et al., 2006; Wozniak et al., 2007). However, the expected neuropsychological picture is often less predictable from the macroscopic imaging pathology, as the brain works as a complex network and pTBI frequently involves diffuse microscopic injuries.

Secondary Injuries. Secondary injuries have a crucial role in TBI outcomes. Of the numerous TBI associated secondary injuries, brain oxygenation and ICP have been the most investigated as predictors of outcome.

Increased ICP exacerbates injury to the tissue through local pressure effects, a reduction in cerebral perfusion pressure, and subsequent alterations in metabolism (Kinoshita, 2016; Weiner et al., 2010). Elevated ICP was detrimental to general and neuropsychological pTBI outcomes in several studies (Badri et al., 2012; Jagannathan et al., 2008; Miller Ferguson et al., 2016; Slawik et al., 2009; Uzzell et al., 1986). Although there is no critical threshold known with certainty, it appears that ICP values above 20mm Hg are dangerous to the brain (Bratton et al., 2007; Jagannathan et al., 2008). The duration that ICP remains elevated also influences the extent of the damage as the number of hours that ICP was recorded at over 20mm Hg was found to be the best determinant of pTBI outcome (Miller Ferguson et al., 2016).

Hypoxia and ischemia are dangerous secondary injuries associated with TBI (Chang et al., 2009; Oddo et al., 2011). Reduced brain oxygenation, measured as the partial pressure of brain tissue oxygen ($PbtO_2$), following TBI was previously associated with worse functional and neuropsychological outcomes (Figaji et al., 2009; Maloney-Wilensky et al., 2009; Meixensberger et al., 2004; Schrieff-Elson et al., 2015; Valadka et al., 1998). Specifically, $PbtO_2$ levels below 20mm Hg were associated with an increased risk of poor outcomes, while 10mm Hg was described as the critical threshold, under which ischemia was more likely to occur (Maloney-Wilensky et al., 2009).

Intrinsic Factors

Age. It was previously hypothesised that younger children might have a greater capacity for neurological recovery due to their increased neuroplasticity (Anderson & Moore, 1995; Pascual-Leone et al., 2011). However, evidence indicates that TBIs sustained in early childhood have worse neuropsychological outcomes due to adverse interference with subsequent development (Anderson et al., 2005; Ewing-Cobbs et al., 2004; Verger et al., 2000).

The role of age on TBI outcomes in older children appears more complex, as studies inconsistently show associations between age and TBI outcome (Anderson et al., 2006, 2009; Formisano et al., 2004; Piomelli Daniele, 2013). As such, there is limited support for a linear relationship between age and TBI outcome. It was suggested that TBIs sustained during critical developmental periods might have greater detrimental effects. For example, children between the ages of seven and nine years old had worse neuropsychological outcomes post-TBI in comparison to younger and older children, which was attributed to the significance of this age range in attention and executive function development (Anderson & Moore, 1995;

Crowe et al., 2012). Therefore, the child's age and developmental stage need to be considered when assessing the potential neuropsychological TBI consequences.

Genetic Factors. Several studies have investigated genetic risk factors for TBI outcomes (Dardiotis et al., 2010; Lipsky & Lin, 2015). The *apolipoprotein E* (*APOE*) gene, which is postulated to be involved in neuronal repair (Horsburgh et al., 2000), is the most frequently investigated with regards to TBI. Several studies have reported an association between the *APOE* ε4 allele and worse TBI outcomes (Ariza et al., 2006; Crawford et al., 2002; Zhou et al., 2008). Other previously investigated genes include those involved in apoptosis (*TP53* and *B-cell lymphoma 2*), neuroinflammation (*interleukin-1* and *interleukin-6*), neuronal repair *(brain-derived neurotrophic factor*), and cognition and behaviour (*catechol-O-methyltransferase* and dopamine receptor genes) (Lipsky & Lin, 2015; McAllister, 2015). However, to date, outside of *APOE*, no polymorphisms or genes have consistently been associated with TBI outcomes. In addition, there is a shortage of genome-wide association studies and research into epigenetic factors. The field is still, however, in its infancy and is expected to have significant translational influence in the future.

Medical History. Previous or current medical conditions can influence premorbid neuropsychological and neuroimaging characteristics. For example, children with a history of seizure disorders, meningitis, infectious diseases, and brain tumours have an increased risk of worse neuropsychological functioning and structural brain differences in comparison to controls (Azeemuddin et al., 2019; Berg, 2011; Christie et al., 2017; Coryell et al., 2018; Hoare et al., 2014; Ravindran et al., 2014; Tonning Olsson et al., 2014). One would expect that conditions negatively affecting the nervous system would result in worse neuropsychological performances following pTBI due to potentially lower baselines. There is also a possibility that these conditions might also interact with the pTBI pathophysiology. However, there is an absence of studies investigating the influence of premorbid medical conditions on pTBI outcomes.

Developmental History. Exposure to alcohol, cigarettes, and harmful substances in utero and/or during breastfeeding have been associated with an increased risk of developmental delays, worse neuropsychological performance, behavioural and psychiatric disorders, and neuroimaging abnormalities later in life (Clifford et al., 2012; El Marroun et al., 2016; Kwiatkowski et al., 2014; Lebel et al., 2011; Lees et al., 2020) and would therefore presumably increase the odds of worse performance post-pTBI. Currently, to the best of our knowledge, no studies have investigated the influence of these exposures on pTBI outcomes.

Similarly, developmental disorders, such as autistic spectrum disorder, dyslexia, and genetic disorders, can influence premorbid neuropsychological and neuroimaging findings (Frith, 1998; Gioia et al., 2002; Greicius, 2003) and one would anticipate worse post-TBI outcomes in these groups. ADHD is the one developmental disorder that has received investigation in the context of pTBI. Unsurprisingly, premorbid ADHD was associated with increased attentional, memory, and executive deficits following pTBI (Donders et al., 2010; Farmer et al., 2002; Slomine et al., 2005).

Neuropsychological History. Premorbid neuropsychological functioning has been found to influence post-TBI outcomes (Farmer et al., 2002; Moran et al., 2016). Specifically, premorbid academic functioning was a stronger predictor of post-pTBI cognitive function than any of the investigated injury-related factors (Moran et al., 2016). In addition, children with pre-TBI learning disabilities performed worse on tests of memory and attention post-TBI (Farmer et al., 2002).

Pre-existing behavioural issues have consistently been linked to an increased risk of behavioural problems post-pTBI (Catroppa et al., 2008; Schwartz et al., 2003). For example, higher parents' ratings of behavioural concerns pre-TBI were associated with an increased risk of elevated behaviour problem ratings at multiple time-points following moderate to severe pTBI (Schwartz et al., 2003). Similarly, preinjury scores on a behavioural index[4] were found to be the strongest predictor of behavioural functioning at five years post-pTBI (Catroppa et al., 2008).

Extrinsic Factors

Family Environment. Given children's reliance on their caregivers, it is unsurprising that the family environment plays an important role in pTBI recovery (Durber et al., 2017; Narad et al., 2018; N. Ryan et al., 2016). Specifically, a more stable, supportive, and cohesive family dynamic appears to improve outcomes. For example, family dysfunction was associated with an increased risk of secondary ADHD following pTBI (Narad et al., 2018), while a less intimate family environment was correlated with an increased risk of poor sociocognitive function in adult survivors of pTBI (N. Ryan et al., 2014). In addition, the quality of the home environment predicted academic functioning and classroom behaviour more than five years after moderate or severe pTBI (Durber et al., 2017).

[4] The behavioural index consisted of undisciplined/poor self-control, social incompetence, internalization/somatic symptoms, cognitive development, and adaptive behaviour ratings.

The family dynamic can be significantly altered following pTBI due to the possible cognitive and behavioural changes and the extra care needed by a child with a TBI (Aitken et al., 2009; Wade et al., 2006). Elevated levels of parental distress were frequently noted following pTBI (Labrell et al., 2018; Prigatano & Gray, 2007) and this had a bidirectional influence on the child's behavioural outcomes (Gerry Taylor et al., 2001). Specifically, greater behavioural issues following pTBI led to greater parental distress, which in turn led to increased behavioural problems.

Social History. Previous childhood trauma and an adverse social history increase the risk of neuropsychological and psychiatric difficulties later in life in the absence of TBI (Draper & Hancock, 2011; Malarbi et al., 2017; Otowa et al., 2014) and therefore one would presume that it might exacerbate difficulties post-TBI. In support, Max et al. (2005) reported that children with greater pre-injury psychosocial adversity index scores had a greater risk of developing ADHD post-TBI. However, no other studies have investigated the effects of prior childhood trauma on outcomes following pTBI.

Socioeconomic Status (SES). Lower SES has consistently been shown to increase TBI risk (Amram et al., 2015; Bruns Jr. & Hauser, 2003) and the chance of poor outcomes post-TBI (Brown, 2010; Moran et al., 2016; N. Ryan et al., 2014). Socioeconomic disadvantage was predictive of elevated behaviour problem ratings at 6 months, 1 year, and four years after moderate and severe TBI (Schwartz et al., 2003). Similarly, children who developed new-onset ADHD following pTBI had lower SES scores (Max et al., 2005). Lower household income was associated with a decreased probability of a child receiving outpatient treatment after a TBI (Cook et al., 2004), which might be a contributing factor to the heightened risk of worse outcomes post-TBI. In addition, low SES has also been associated with worse neuropsychological test performance in the absence of TBI (Aran-Filippetti & Richaud de Minzi, 2012; Piccolo et al., 2016) and therefore might alter premorbid participant functioning.

Access to Rehabilitation. Cognitive and behavioural rehabilitation has been shown to improve post-pTBI outcomes (Kurowski et al., 2013; Wade et al., 2010; Woods et al., 2014). However, there is currently no gold-standard pTBI rehabilitation intervention and there is a high level of variability in the rehabilitation patients receive after hospitalization (Schrieff-Elson et al., 2017; Shah et al., 2019). Therefore, access to rehabilitation may greatly differ between individuals and influence post-TBI outcomes.

Rationale and Aims

Investigating the potential influencing factors and post-pTBI neuropsychological and neuroimaging outcomes is imperative to provide further information on the underlying pTBI pathophysiology, aid in the design of targeted therapeutic strategies, and identify individuals at risk of prolonged deficits who would benefit from the allocation of additional resources.

South Africa is conjected to have a high rate of TBI and an adverse socioeconomic environment for pTBI recovery (Jerome et al., 2017; Naidoo, 2013; Webster et al., 2015). Therefore, South African children are at increased risk of the long-term detrimental effects of pTBI. Despite this, few studies have investigated the neuropsychological outcomes of pTBI in South Africa. In addition, no study has investigated pTBI neuroimaging outcomes in a South African cohort.

Worldwide, the majority of neuroimaging studies have focused on adult TBI, however, paediatric populations have substantial anatomical and physiological differences to adults (Figaji, 2017), and therefore these findings are not transferable and research on paediatric patients is essential. In addition, studies using advanced neuroimaging techniques in populations with pTBI are frequently limited by small sample sizes (Mendoza et al., 2018). Large-scale, multi-site, collaborative studies are required to address this shortfall. An emerging collaboration between the University of California Los Angeles (UCLA), the University of Southern California (USC), the SARAH network (Brazil), and the University of Cape Town (UCT) aims to establish such a study. However, before the implementation of a large-scale study is warranted, a pilot study was required to provide an in-depth investigation of a South African pTBI cohort.

The current study has the following aims:

1. To provide a detailed description of the potential influencing factors and the neuropsychological and neuroimaging outcomes of South African children with moderate to severe pTBI.
2. To, thereafter, investigate the barriers to the successful implementation of research using neuropsychological and advanced neuroimaging techniques following moderate to severe pTBI in South Africa.

Method

Design and Setting

The study was designed as a capacity-building exercise to demonstrate the successful collection of data from different sites involved in a developing international collaboration. The study design was a consecutive case series with both observational and quantitative

constituents. Patients with pTBI admitted to the Red Cross War Memorial Children's Hospital (RXH) were enrolled in the study. There were two testing sessions. The first session was conducted at RXH three months post-injury (T1) and included several caregiver questionnaires. The second testing session took place six months post-injury (T2) at the Cape Universities Body Imaging Centre (CUBIC) at Groote Schuur Hospital (GSH) and involved a neuropsychological assessment, neuroimaging, and caregiver questionnaires.

Sample

Children, aged 8 to 12 years, admitted to RXH between June and November 2018 for treatment of moderate to severe TBI (GCS ≤12 after resuscitation) were invited to participate in the study.

Exclusion Criteria

Exclusion criteria included: 1) a history of neurological illness, including prior TBI, meningitis, brain tumour, or stroke and 2) if the TBI was because of suspected non-accidental injury. Patients with a history of neurological illness were excluded due to the potential confounding influence on neuropsychological and/or neuroanatomical measures. Patients with TBIs from non-accidental injuries were excluded due to the risk of previous unreported head injuries, as has been done in previous pTBI research (Levin et al., 2008).

Recruitment

The participant selection process is detailed in Figure 1. Briefly, 3924 individuals reported to RXH during the 6-month recruitment window. Of those, 23% presented with a head injury, but only 21% of those with a head injury fell within the required age range. Most (86%) of the head injuries sustained by children admitted to RXH were mild; leaving 14 individuals that met the age and severity inclusion criteria. A further patient was excluded for suspected non-accidental injury. Of the remaining 13 eligible patients, nine caregivers could be contacted. Six caregivers gave consent, while three declined. One consented participant was lost to follow-up before testing and therefore five participants were included in the study. The demographic details are shown in Table 1.

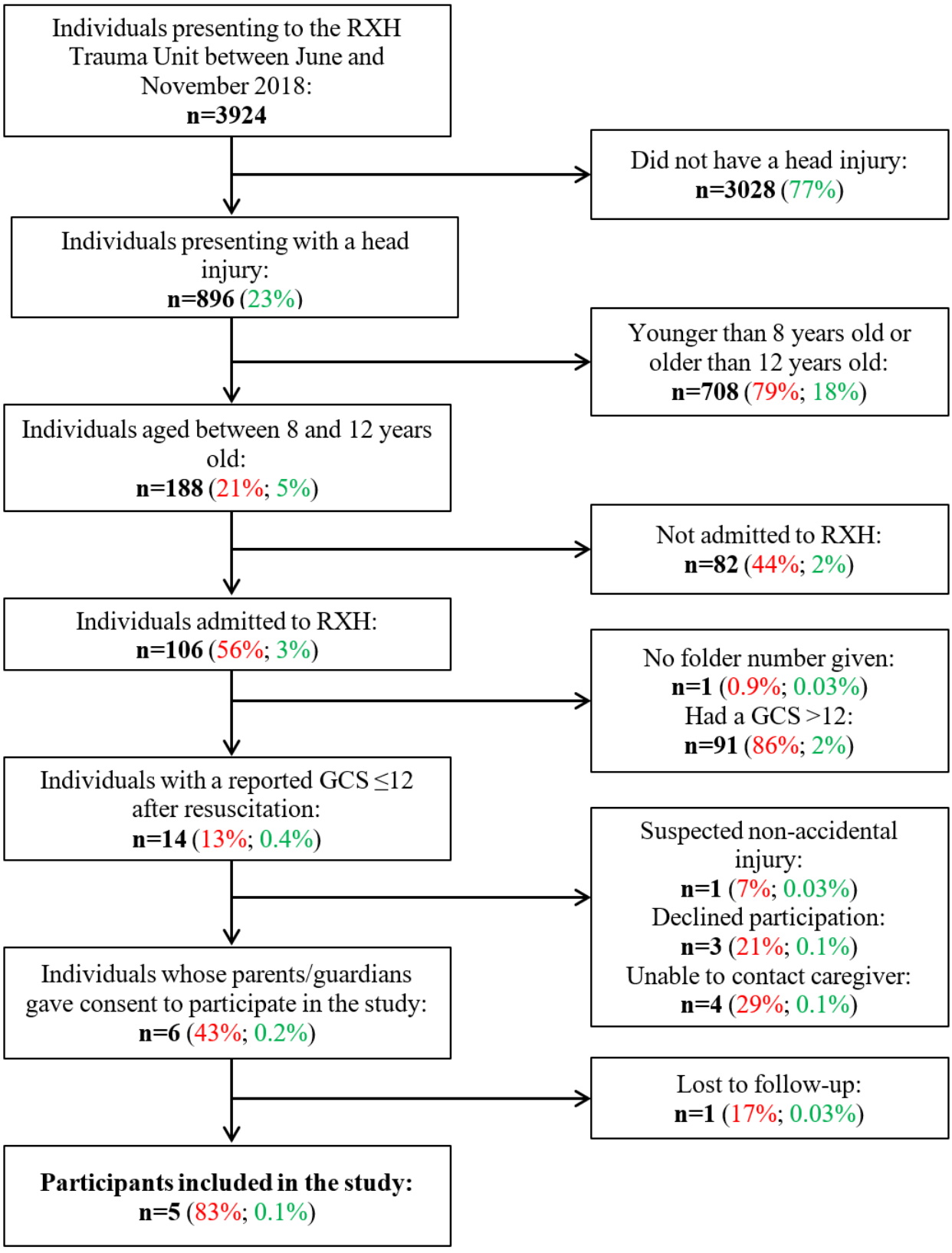

Figure 1. A flowchart summarising the participant selection. RXH: The Red Cross War Memorial Children's Hospital; n: the number of individuals, with the corresponding percentage of the previous step represented in red and the percentage of the original step represented in green; GCS: Glasgow Coma Scale.

Table 1

Demographic Characteristics of Included Participants

	Participant 1	Participant 2	Participant 3	Participant 4	Participant 5
Pseudonym	Alice	Ethan	Mia	Thando	Katlego
Sex	Female	Male	Female	Male	Male
Age at injury[a]	9:5	12:5	8:10	9:7	9:10
Home language	English/ Afrikaans	English/ Afrikaans	English	isiXhosa	isiXhosa/ English

Note. [a]Years: months.

Materials

The study included caregiver questionnaires, a neuropsychological assessment, and neuroimaging. Test instructions, questionnaires, and consent/assent forms were translated into Afrikaans and IsiXhosa by the Language Laboratory of the University of Stellenbosch. The translation process included forward and back translations and an authentication process.

Caregiver Questionnaires

Demographic Questionnaire and Asset Index. The Demographic Questionnaire and Asset Index (Appendix B) documented the demographic information, SES, and asset index of participants. Asset ownership was categorized into low (0 to 5), medium (6 to 12), or high (13 to 17) based on the Total Asset Index score (Myer et al., 2008).

Family Resource Scale (FRS). The FRS (Dunst & Leet, 1985) was designed to measure a family's access to a range of resources (Appendix C). The form consisted of 30 items that were rated on a five-point Likert-type scale, from 1 ("not at all") to 5 ("almost always") concerning the access that the family had to that item. Scores of 1 or 2 indicated that a need was not being met (Sexton & Rush, 2012). The FRS provided a total score and six subscales (Basic Needs, Housing/Utilities, Benefits, Social needs/Self-care, Child-care and Extra Resources; Brannan et al., 2006). See Appendix D for subscale descriptions. The items within each subscale were averaged to provide a score between 1 and 5 and the subscales were summed to provide a total score. The FRS was found to have good internal validity across economically diverse populations (Brannan et al., 2006).

Developmental Questionnaire. The Developmental Questionnaire (Appendix E) was used to investigate the participants' developmental history concerning pregnancy, birth, and any early separations or emotionally difficult periods. It is a shortened form of the developmental questionnaire used at the RXH Paediatric Neuropsychology Clinic.

Family Burden of Injury Self-report Questionnaire (FBI). The FBI (Burgess et al., 1999) was designed to assess the impact of a pTBI on a patient's family (Appendix F). The caregiver was asked to rate a list of potential concerns on a five-point Likert-type scale that ranged from 0 ("not at all stressful") to 4 ("extremely stressful"). The FBI had five subscales correlating to whom the burden relates (Child, Spouse, Siblings, Routines, and Extended Family/Friends). The average score for each subscale was used to provide an overall index of family burden. Subscale scores of three and four were considered to indicate a substantial burden. The FBI was shown to have good internal consistency (.90), as well as concurrent and predictive relationships to other validated family burden measures (Burgess et al., 1999).

Neuropsychological Measures

The neuropsychological assessment included a selection of tests from standardized neuropsychological batteries and was designed to test key components of cognition affected following moderate to severe pTBI, namely attention, memory, processing speed, and executive functions (Babikian & Asarnow, 2009).

Attention and Working Memory.

Working Memory Index from the Weschler Intelligence Scale for Children Fourth Edition (WISC-IV). The WISC-IV (Weschler, 2003) is a widely used measure of general intellectual functioning that evaluates the full-scale intelligence quotient and several subscales including working memory, processing speed, verbal comprehension, and perceptual reasoning. The WISC-IV was developed and normed in the USA.

The Working Memory Index score was obtained from the Digit Span and Letter-Number Sequencing subtests. The Digit Span subtest required participants to immediately recall a sequence of verbally administered digits, both forwards and backwards. The number of digits that could be recalled forwards indicated simple attentional capacity, while the number of digits that could be recalled backwards measured working memory. In the Letter-Number Sequencing subtest, the participants were given a sequence of letters and numbers and asked to recall them in ascending order. Similarly, the length of accurately recalled letters and numbers provided a measure of working memory. Both the Digit Span and Letter-Number Sequencing subtest had adequate reported internal consistencies (≥.88) (J. J. Ryan et al., 2009).

Memory.

Rey Auditory Verbal Learning Test (RAVLT). The RAVLT (Schmidt, 1996) uses a list-recall memory task to assess audioverbal learning and memory. A list of nouns (List A) was verbally delivered to the participant, after which the participant recalled as many of the items as possible. The task consisted of five consecutive learning trials (List A), a distractor trial (List B), a short delay trial immediately after the distractor trial, a long delay trial following a 30-minute delay, and a recognition trial. "Turkey" was changed to "Chicken" on the word list due to South African cultural considerations. The RAVLT was shown to have good internal consistency (.80) and adequate convergent and divergent validity (Magalhães et al., 2012).

Dot Locations from the Children's Memory Scale (CMS). The CMS was designed to assess learning and memory in children (M. Cohen, 1997a). The CMS was developed and normed in the USA. The Dot Locations subtest required participants to recall the locations of dots placed on a grid and is a measure of visual learning and memory. The subtest consisted of three consecutive learning trials, followed by a distracter trial, and then a short delay recall trial. A long delay recall trial was conducted 25 minutes later. The internal consistency coefficients of the Dot Locations measures were reported to range from .73 to .76, indicating good internal consistency (M. Cohen, 1997b).

Processing Speed.

Processing Speed Index from the WISC-IV. The Processing Speed Index was obtained from the Coding and Symbol Search subtests of the WISC-IV (Weschler, 2003). Both tests were timed and scored to assess the participants' processing speed and accuracy. In the Coding subtest, participants were given a key on which numbers were paired with symbols. The participants placed the corresponding symbols below rows of numbers. The subtest score was determined by the number of correctly paired symbols completed within the two-minute trial. In the Symbol Search subtest, participants were provided with a page depicting several rows of symbols. The page had two columns, a target column consisting of two symbols, and a search column with five symbols. The participant had to quickly decide whether the symbols shown in the target column were present among the group of symbols in the search column. The score was derived from the number of correctly answered items, minus the number of incorrect items, within the two-minute trial. The reliability coefficient of the Processing Speed Index was reported to be .88 (Whechsler, 2003).

Executive Function.

Trail Making Test (TMT) from the Delis-Kaplan Executive Function System (D-KEFS). The D-KEFS battery (Delis et al., 2001b) was designed to assess a broad range of executive functions and consists of nine stand-alone tests. The D-KEFS was developed and normed in the USA. The TMT measured several executive function components including attention, sequencing, cognitive flexibility, and set-shifting ability. The TMT consisted of five trials. In the first trial (Visual Scanning), participants identified targets among numerous distractors. In the second (Number Sequencing) and third (Letter Sequencing) trials participants connected ascending numbers and letters, respectively, as quickly as they could without making errors. In the fourth trial (Number-letter Switching), participants alternated between connecting letters and numbers in ascending order. Participants traced a dotted line as fast as they could in the last trial (Motor Speed). The completion time and error count were utilized as the output scores. The reported internal consistency coefficients for the TMT ranged from moderate to high (≥.57) (Delis et al., 2001a).

Tower Test from the D-KEFS. The Tower Test (Delis et al., 2001b) was designed to investigate spatial planning, impulsivity, inhibition, and the ability to maintain an instructional set. The task required participants to build a series of towers of increasing complexity as efficiently as possible whilst adhering to a rule set. The time that was taken to complete the tower and the number of moves and rule violations were recorded for each trial. Successful constructions were awarded points to provide a Total Achievement Score. The subtest has a moderate to high reported internal consistency (≥.56) (Delis et al., 2001a).

Behaviour.

Behaviour Rating Inventory of Executive Function parent report (BRIEF). The BRIEF (Gioia et al., 2000) is a questionnaire that details a caregiver's assessment of their child's executive function and self-regulation. The BRIEF includes a Likert-type scale where caregivers rate their child's behaviour concerning 86 statements as "never a problem", "sometimes a problem", or "often a problem". The BRIEF measures eight clinical scales (Inhibit, Shift, Emotional Control, Initiate, Working Memory, Plan/Organize, Organization of Materials, and Monitor) grouped to provide two indices (Behavioural Regulation Index [BRI] and Metacognition Index [MI]) and one global composite from all eight clinical scales (Global Executive Composite [GEC]). The descriptions of the indices and clinical scales are listed in Appendix G. T-scores above 65 are in the clinical range and indicative of considerable problems. The BRIEF was found to have high internal consistency (≥.80) and test-retest reliability (.81) (Gioia et al., 2001).

Child Behaviour Checklist parent report (CBCL). The CBCL (Achenbach & Ruffle, 2000) was designed to document the caregiver's description of the presence of behavioural and emotional problems in children and adolescents. The CBCL includes a Likert-type scale where caregivers rated their child's behaviour as "never true", "somewhat or sometimes true", or "very often true" concerning 113 statements. The CBCL produces eight syndrome scales: Anxious/Depressed, Withdrawn/Depressed, and Somatic Complaints (which form the internalizing grouping), Rule-breaking Behaviour and Aggressive Behaviour (which form the externalizing grouping), and Social Problems, Thought Problems, and Attention Problems. In addition, the CBCL scores six diagnostic scales (Affective Problems, Anxiety Problems, Somatic Problems, Attention Deficit/Hyperactivity Problems, Oppositional Defiant Problems, and Conduct Problems) based on the Diagnostic and Statistical Manual of Mental Disorders (fourth edition). T-scores between 65 and 70 are considered to be in the borderline range, while scores of 70 and higher are designated to be in the clinical range (Achenbach & Ruffle, 2000). The CBCL had good reported internal consistency (≥.78) and test-retest reliability (≥.80) (Albores-Gallo et al., 2007).

MRI

The imaging protocol was designed to investigate structural, metabolic, and functional characteristics using MRI-based modalities. Specifically, participants underwent structural (T1-weighted, T2-weighted, and fluid-attenuated inversion recovery [FLAIR]), DTI, MRS, and resting-state fMRI sequences in one continuous scan. Given the scope of this study, only structural findings will be reported. Participants were imaged using a Siemens 3T Prisma scanner.

Acute Physiological Brain Monitoring

RXH routinely uses intracranial physiological monitoring as part of the clinical management of severe pTBI. Intracranial ICP (Codman ICP Express, Codman, Raynham, MA, USA; Camino, Integra Neurosciences, Plainsboro, NJ, USA) and $PbtO_2$ (Licox, Integra Neurosciences) catheters were placed in patients that met the clinical criteria for intracranial monitoring (GCS ≤8/15 after resuscitation). Monitors were removed based on clinical judgement. Several physiological measures were recorded on an hourly basis but only ICP and $PbtO_2$ will be reported in this study. Data from the first two hours of recording was excluded due to the risk of artefacts during catheter stabilization.

Procedure

RXH Trauma unit admission records were screened for potential participants between June and November 2018. Caregivers of eligible patients were given informed consent forms

and the study was explained to them. Caregivers were given several days, or longer if required, to make a consent decision.

Caregivers completed several questionnaires at T1 (Demographic and Asset Index, FRS, Developmental Questionnaire, BRIEF, and CBCL) and T2 (FBI, BRIEF, and CBCL). At T1, the caregivers completed the BRIEF and CBCL based on the functioning of participants six months before the TBI, while completion at T2 was regarding the functioning of participants at six months post-TBI.

The MRI scan and neuropsychological assessment took place at CUBIC during the T2 assessment. The CUBIC staff briefed participants and caregivers on the scanning process. Participants were screened for any potential MRI contraindications (e.g., metal implants). Participants were first placed in a mock scanner to familiarize themselves with the conditions in the scanner. Caregivers accompanied participants in the scanner room. Participants watched a children's movie while in the scanner. Neuropsychological assessments took place after the MRI scans in a private testing room and took approximately two hours to complete. Participants whose school language was not English were given the option to be assessed in their preferred language. Translators experienced in neuropsychological assessments were present when required.

Participants' medical folders and physiological brain monitoring data were reviewed to provide the participants' injury-related details. This information was supplemented by a history-taking interview with the caregivers at T2. The history-taking investigated the participants' medical, developmental, social, and academic history and queried the main caregiver concerns following the pTBI.

Scoring Procedures and Data Analysis

Neuropsychological Measures

The administration and scoring manuals were followed for all neuropsychological tests and questionnaires. Raw scores were converted to age-adjusted scaled scores, standard scores, T-scores, or percentiles for all the neuropsychological tests and behavioural questionnaires using the official test manuals, except for the RAVLT. Normative data for the RAVLT was obtained from Vakil et. al (1998), as the RAVLT does not have official normative data.

Neuroimaging Data

Dr Ebrahim Banderker, a consultant in RXH's Radiology Unit, reviewed the structural scans and provided a descriptive clinical report for each participant. Key images

were captured using Mango imaging software (Version 4.1, University of Texas Health Sciences Centre, San Antonio, TX).

Statistical Analysis

Analyses were completed using SPSS statistical software (Version 26, IBM®, Armonk, NY). Graphs were created using GraphPad Prism (Version 8, GraphPad Software, San Diego, CA).

Reliable Change Indices (RCI; Jacobson & Truax, 1991) were calculated using the Reliable Change Generator (Version 2.0, PsyTek Ltd.) to investigate meaningful differences between pre and post-TBI CBCL and BRIEF scores. The RCI took the standard deviation and test-retest reliability of a scale into account to assess whether there was a meaningful change between two scores at three confidence levels (68%, 95%, and 99%; Jacobson & Truax, 1991). A clinically statistically significant change was designated when confidence levels were equal to or greater than 95%.

Individual neuropsychological scores, designated to be in the same cognitive domain based on theoretical assumptions, were combined to create composite variables to provide an overall estimate of functioning within each investigated domain (audioverbal memory, visuospatial memory, processing speed, executive functions). Internal consistency was investigated for each composite variable by calculating Cronbach's α coefficients (Appendix H). Individual standard scores were converted to Z scores and averaged to provide a composite Z score for each composite variable.

Ethical Considerations

Ethical approval was obtained from UCT's Faculty of Health Science's Human Research Ethics Committee (HREC references: 764/2017 and 192/2018), UCT's Department of Psychology Research Ethics Committee and RXH for permission to access RXH medical folders. See Appendices I and J for the ethical approval letters.

Informed Consent and Assent

Caregivers were given comprehensive study information before they were asked to consent to their child's participation. It was emphasized that caregivers had every right to decline participation and that this would not compromise their child's current or future clinical management. Eligible children were given a simplified description of the study and the choice to provide assent before the T2 assessment if they were able to do so. The consent and assent forms are included in Appendices K and L, respectively.

Confidentiality and Anonymity

All information obtained throughout the study was only used for research purposes and was kept strictly confidential. Questionnaires, neuropsychological scoring sheets, and MRI scans were labelled with anonymised participant codes. Only caregivers were given a summary of their child's neuropsychological and MRI results. Pseudonyms were used in the reporting of results. Collected participant forms and questionnaires were securely stored at the UCT's Applied Cognitive Science and Experimental Neuropsychology Team (ACSENT) laboratory. Data was captured in an anonymised electronic database for analysis.

Risks and Benefits

The study posed minimal risks to the participants. MRI scans involve no radiation and were piloted on four adult volunteers before the commencement of the study. The MRI might have caused some discomfort, for example, claustrophobia or apprehension because of the enclosed space and noise. To reduce this, participants were placed in a mock scanner before the scan to familiarize them with the process. Caregivers were allowed into the scanner room with the participants to reduce any stress. If a participant was uncomfortable in the scanner, they were immediately removed from the scanner and the scan was discontinued.

All scans were reviewed by Dr Ebrahim Banderker. Anomalies (incidental or trauma-related) identified on MRI scans were immediately referred to Professor Anthony Figaji, head of RXH's Paediatric Neurosurgery Unit, and were managed clinically through the Neurosurgery Unit. The investigators were not responsible for any follow-up investigations; these were decided through the Neurosurgery Clinic or other clinical services to which the patient was referred. Professor Figaji was responsible for the coordination of this care. Trauma-related lesions were recorded and communicated to the caregivers by Professor Figaji. No incidental findings were noted on the scans.

Breaks were provided at the participant's request during the neuropsychological assessment to combat any fatigue. Caregivers were remunerated for travel expenses.

Debriefing and Feedback

The contact details of the principal investigator were provided to allow caregivers to contact with queries throughout and after study enrolment. Participants and caregivers were verbally debriefed after the assessment sessions and provided with a summary of their child's neuropsychological performance.

Results

Each participant will be presented as a separate case study. Participants' comprehensive injury-related (Table M1), physiological brain monitoring (Table M2), developmental (Table M3), socioeconomic (Table M4), academic (Table M5), family burden (Table M6), neuropsychological (Table M7), BRIEF (Table M8), and CBCL (Table M9) data are presented in Appendix M, while MRI images can be found in Appendix N.

Case Study 1: Alice

Medical History

Pre-TBI. Alice[5] had asthma, but no other notable medical history.

The TBI. Alice was a passenger in a head-on MVA on 01/06/2018 (aged 9 years). She was travelling with her grandmother, who sustained multiple limb fractures. Alice had a GCS of 6 on the scene, indicating a severe TBI. She was intubated and transferred to RXH, where she was admitted to the paediatric intensive care unit (pICU), and ICP and $PbtO_2$ monitors were placed (02/06/2018).

A CT brain scan (CTB; 05/06/2018) showed a right, depressed comminuted frontal fracture, facial fractures, and bilateral orbital injury, which resulted in right globe proptosis. Alice had bifrontal haemorrhagic contusions with generalized cerebral oedema evidenced by loss of surface sulci markings. Petechial haemorrhages were noted at the bifrontal grey-white matter junctions, suggestive of TAI. Grey-white matter differentiation was maintained and there was no midline shift or hydrocephalus.

Alice had two brief episodes[6] of ICP over 20mm Hg, but these quickly lowered and did not cross the 25mm Hg threshold (Table M2 and Figure M1 in Appendix M). There were no low $PbtO_2$ events (Table M2 and Figure M2 in Appendix M). She had the monitors removed on 05/06/2018, was extubated on 07/06/2018, and was discharged from the pICU on 08/06/2018.

Alice was moved to the Neurosurgery ward and her neurological functions gradually improved over the next two weeks. She received occupational and speech therapy rehabilitation while in the ward. By 15/06/2018, her GCS was 15 and she was mobilising with minor assistance. Alice was discharged from RXH on 20/06/2018, 19 days after the TBI, and moved to GSH for one month of continued Occupational Therapy and Speech Therapy rehabilitation (21/06/2018 – 19/07/2018). She was thereafter discharged home.

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[5] Pseudonym.
[6] Each episode denotes one hour of monitoring time.

Post-TBI. Alice was seen at RXH for Neurosurgery follow-up appointments at 3 and 6 months post-injury. At the first appointment (30/08/2018), it was noted that she was doing well and there were no new focal deficits. She was coping at school but had attention difficulties and occasional headaches. She had been diagnosed with ADHD by a GSH psychiatrist and was prescribed Ritalin (5mg bi-daily, since 10/07/2018). At the second appointment (05/12/2018), Alice was described as "generally doing well". However, there were behavioural issues at home, which were not specified at the time.

Developmental History

Alice's grandmother provided the developmental history. There were no complications during the pregnancy, birth, or new-born period. Alice's mother reportedly did not smoke or take any medication, alcohol, or illicit substances during the pregnancy. Alice's developmental milestone achievement was reportedly faster than other children's, but her grandmother was unsure of the milestone timelines.

Social Functioning

Pre-TBI. Alice was raised by her mother in the Eastern Cape. She has no contact with her father and has no siblings. Alice's mother was killed in an MVA in 2015 and thereafter, Alice (aged six years) was looked after by her grandmother in the Eastern Cape. She was reportedly popular at school and got on well with other children. Alice's grandmother was retired and received a pension. As a family, they had a medium asset index and most of their resource needs were reasonably met, except for Childcare, Benefits, and Extra Resources (Table M4 in Appendix M).

Post-TBI. Alice's grandmother was admitted to the hospital for several weeks and therefore Alice's 23-year-old aunt looked after Alice following the accident. Alice's aunt described major behavioural problems after the TBI. Specifically, Alice required constant supervision and would frequently act out, throw tantrums, push the boundaries, and break rules, which placed a strain on her caregivers.

Academic Functioning

Pre-TBI. Alice failed grade 2 in 2016 (aged 8 years). Her grandmother felt that this was because she was struggling with her mother's death. She passed all her subsequent grades, but there were concerns regarding her attention according to her aunt. Her grade 3 teacher moved her to the front of the class to try to focus her. Alice was not diagnosed with ADHD or given any treatment for ADHD-like symptoms before the TBI. Despite the attention concerns, Alice's grandmother described her as a "smart child", while her aunt

stated that she was above average in maths and languages, achieving 6's and 7's, and average scores across her other subjects, receiving 4's and 5's[7].

Post-TBI. Alice was in grade 3 when she sustained her TBI. The accident occurred in the latter half of the second term[8]. She returned to her previous school for the second half of the third term after discharge. Alice's aunt reported that her grades had dropped since the accident, now achieving mostly 3's and 4's. She passed grade 3 and could continue to grade 4 in 2019.

Caregiver Concerns

Both Alice's aunt and grandmother listed her behaviour as their greatest concern. Specifically, they felt that she was disobedient, socially inappropriate, emotionally labile, hyperactive, and childish. Alice was also experiencing frequent headaches and had started wetting the bed at night. Alice's aunt reported a high level of stress following the TBI on the FBI (Table M6 in Appendix M), with 13 of the 26 items scored as 3's ("quite stressful") or 4's ("extremely stressful"). The highest-rated burden categories were The Child and Family Routines/Planning.

Neuropsychology Assessment

Presentation. Alice was on Ritalin (5mg bi-daily) on the day of the assessment. Despite this, she was extremely distractible and needed to take breaks with every test. She disrupted the instructions, impulsively took the test apparatus, and would visibly not be paying attention. She became frustrated and defiant on tasks where she was corrected, on tasks that were too difficult, and on tasks that required sustained attention.

Attention. Alice had a forward digit span of four, which was lower than expected for her age (Figure 2). She had a haphazard search strategy and missed one of the targets on the TMT Visual Scanning condition (Visual Scanning errors: low average range; Table M7 in Appendix M). She did, nevertheless, finish the trial within a normal time limit (Figure 2). Her Visual Scanning condition performance suggested selective attention difficulties, as she missed a target. Collectively, Alice had an attention composite score in the low average range (Figure 3). However, qualitatively, Alice was highly distractible and struggled to direct and sustain her attention.

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[7] South African schooling grade classifications are as follows: 1: "Not achieved", 0 – 29%; 2: "Elementary achievement", 30 – 39%; 3: "Moderate achievement", 40 – 49%; 4: "Adequate achievement", 50 – 59%; 5: "Substantial achievement", 60 – 69%; 6: "Meritorious achievement", 70 – 79%; 7: "Outstanding achievement", 80 – 100%.

[8] The South African school year is divided into four quarters, which are referred to as "terms".

Memory. Alice scored poorly across all Dot Locations and RAVLT measures (Figure 2, Table M7 in Appendix M) and her audioverbal and visuospatial memory composite scores fell in the extremely low range (Figure 3). She did not adequately attend to the stimuli for either test and required constant cueing of her attention. Alice made an incorrect arrangement of dots on the first Dot Locations learning trial and she repeated the same placement on the remaining learning trials and both the short and long delay trials. She was certain that this was the correct placement. Although she scored poorly, this subtest provided evidence that Alice could encode and retain visuospatial information, however, her poor attentional focus and error monitoring lead her to encode and retain her arrangement, rather than the one she was asked to remember.

Alice became more distractible as the RAVLT wore on and would constantly interrupt the administrator. She had a flat learning curve over the five learning trials (2/16, 6/16, 7/16, 5/16, and 6/16 words; extremely low range; Figure 2). Alice would also add in her own words (often objects from around the room), resulting in 34 intrusions across the seven trials. Her short delay trial consisted of two words from List A and two words from List B, suggesting interference and/or poor error monitoring. She defiantly answered "no" to 46 of the 50 recognition items and it was clear that she was answering using a response set without trying to remember the words, thus invalidating the score. The RAVLT recognition trial was excluded from the audioverbal composite calculation.

Processing Speed. Alice performed in the low average and extremely low range for the Coding and Symbol Search tasks (Figure 2), respectively, which resulted in an overall Processing Speed composite score in the borderline range (Figure 3). The discordance between her Coding and Symbol Search scores was due to her high error rate on the Symbol Search task. Specifically, Alice attempted 18 items but made six errors. She impulsively selected the answers without error monitoring. Her high error count could have also been partly due to selective attention deficits causing her to miss the targets. On the Coding task, she started relatively fast but lost momentum and focus as the two-minute trial wore on. In contrast to her test scores, qualitatively, Alice's thinking was not markedly slow.

Executive Functions. Alice had substantial executive difficulties, as evidenced by her extremely low range executive functions composite score (Figure 3). In terms of working memory, Alice had a backward digit span of three (low average range; Figure 2). Alice performed especially poorly on the Letter-Number Sequencing subtest (extremely low range; Figure 2), where she lost the rule on several occasions. Overall, she had a Working Memory

Index in the extremely low range (Table M7 in Appendix M), indicating working memory deficits which were likely further confounded by attentional problems.

Alice struggled with both the TMT Letter Sequencing and Number-Letter Switching conditions (Figure 2). Although she could recite the alphabet as a song, she was unable to accurately order the letters after "H" on both conditions. Alice also lost the rule on the Number-Letter Switching condition and would impulsively connect a string of numbers or letters. She became frustrated when corrected, which led to further errors.

Alice's behavioural issues and executive deficits were clear on the Tower test. She was unable to form a strategy and would impulsively break the rules to get to the correct endpoint. She made 23 rule violations across the seven attempted towers (extremely low range; Figure 2). She became angry when her rule breaks were corrected, to the point where she refused to continue the task. Her reluctance to cooperate led to an extremely low time per move ratio (Table M7 in Appendix M). Alice was only able to build two of the seven attempted towers and thus had a Total Achievement score in the extremely low range (Figure 2).

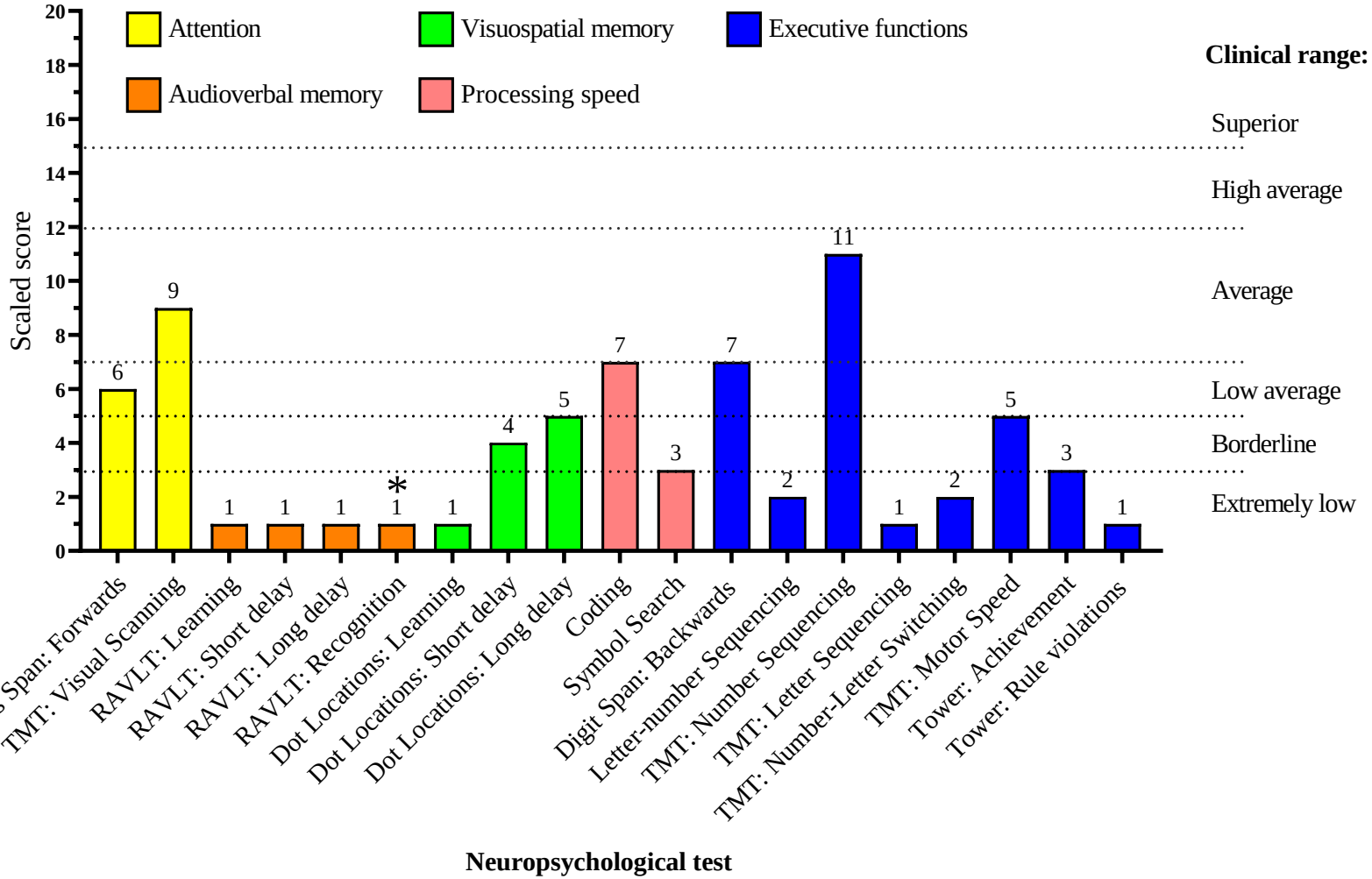

Figure 2. Alice's scaled scores for each of the neuropsychological tests. The bars are coloured according to which cognitive domain the test theoretically measures. The clinical scaled score descriptions are displayed on the right of the graph. *The score was invalidated by a response set. RAVLT: Rey Auditory Verbal Learning Test; TMT: Trail Making Test.

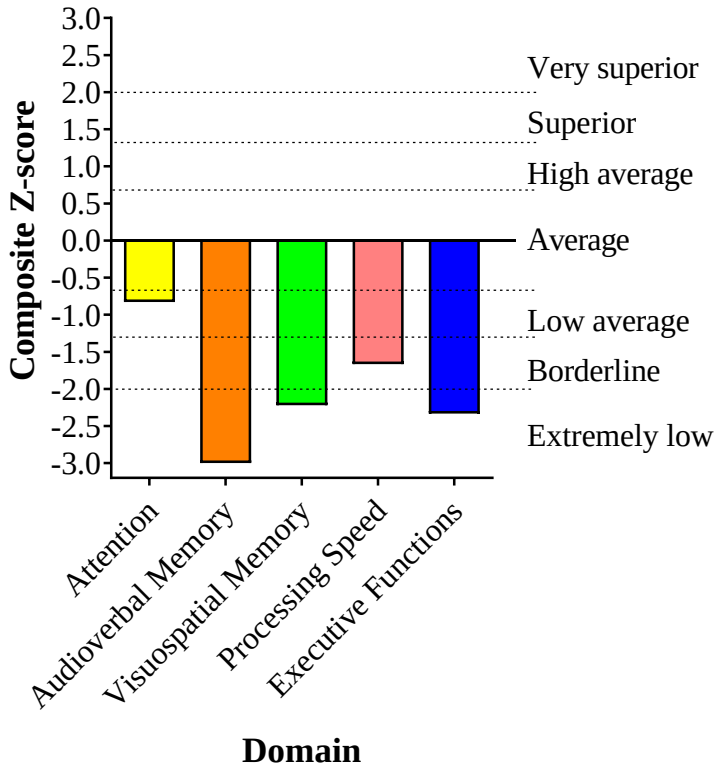

Figure 3. Alice's composite Z-scores for each of the assessed domains. The clinical Z-score descriptions are displayed on the right of the graph.

Behavioural Outcomes

BRIEF. Alice had BRI, Inhibit, and Plan/organize scores in the clinical range before the TBI, suggesting some premorbid behavioural problems (Figure 4). All BRIEF scores were higher post-TBI, which indicated greater executive and behavioural problems, resulting in a post-TBI GEC score that was clinically statistically significantly increased, with a 99% confidence level (CL), from her pre-TBI score (Figure 4). Alice displayed significant increases in both the BRI (95% CL) and the MI (99% CL). Investigation of the individual scales showed that the Shift, Initiate, Working Memory, Plan/organize, and Monitor scales were significantly increased from pre-TBI levels (≥95% CL) and in the clinical range post-TBI (Figure 4).

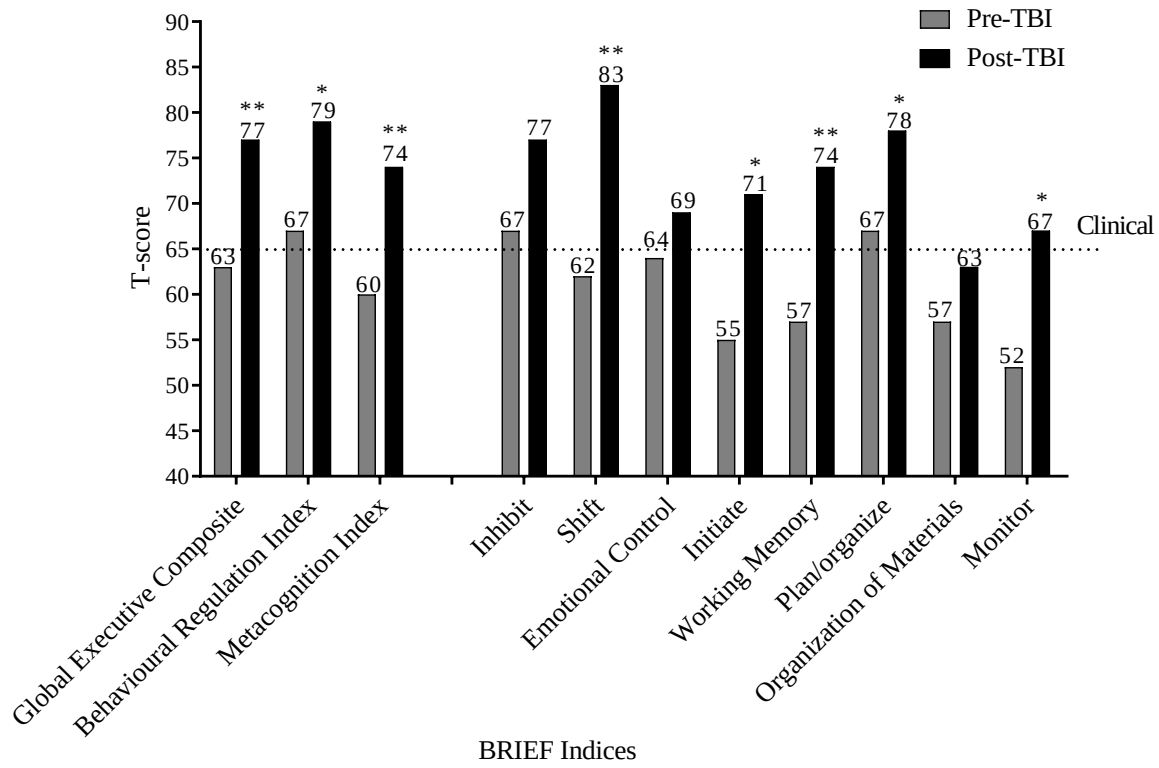

Figure 4. Alice's Behaviour Rating Inventory of Executive Function (BRIEF) indices before and after the traumatic brain injury (TBI). Scores equal to or greater than 65 are in the clinical range (Gioia et al., 2000). *a change with 95% confidence; **a change with 99% confidence.

CBCL. Alice's Externalising Problems grouping score fell into the clinical range and her Total Problems, Rule-breaking Behaviour, and Aggressive Behaviour scores were in the borderline range before the TBI, suggesting that she had some pre-TBI difficulties (Figure 5). All post-TBI CBCL syndrome groupings and individual profile scale scores, except for Anxious/Depressed and Withdrawn/Depressed, were clinically statistically significantly higher (≥95% CL) than the pre-TBI levels (Figure 5). All these increased measures fell into the borderline or clinical ranges post-TBI (Figure 5). Her post-TBI Internalizing Problems score was largely driven up by Somatic Complaints, which was likely due to residual injuries from the accident.

In terms of CBCL Diagnostic Scales, Alice had Conduct Problem scores in the clinical range and Attention Deficit/hyperactivity and Oppositional Defiant levels in the borderline range before the TBI, again indicating premorbid issues (Figure 6). All but Anxiety Problems were elevated into, or further into, the clinical range post-TBI but only Affective Problems, Somatic Problems, and Conduct Problems were significantly increased from the pre-TBI levels (≥95% CL; Figure 6).

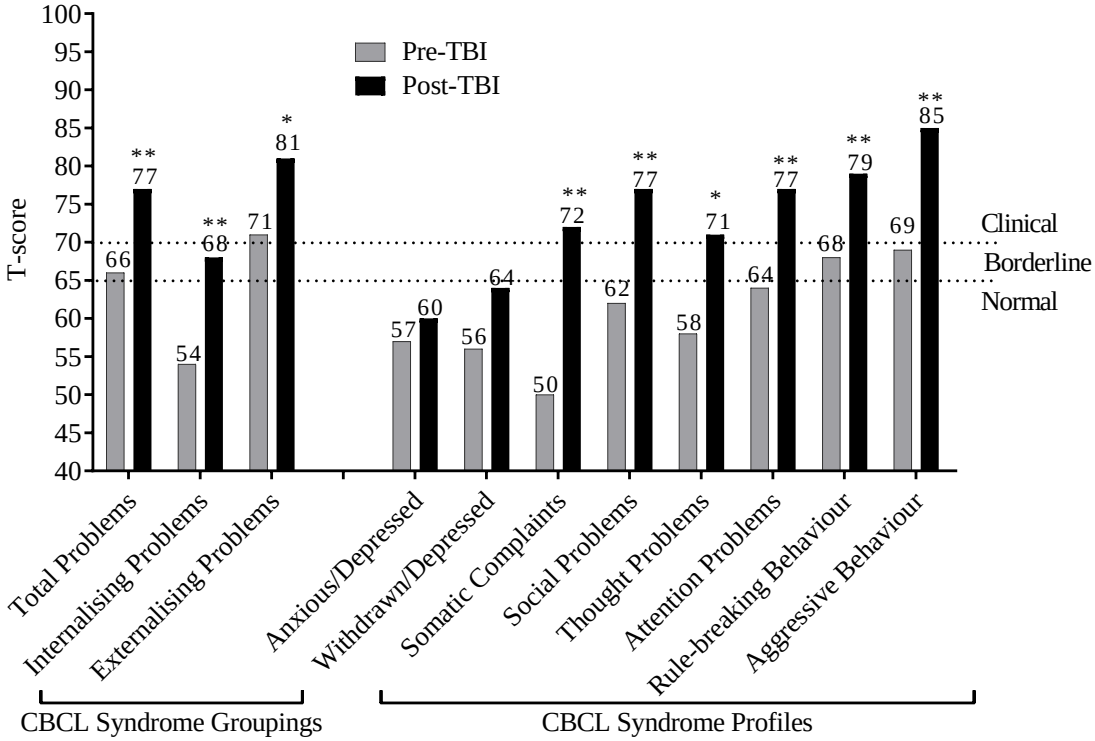

Figure 5. Alice's Child Behavioural Checklist (CBCL) syndrome profiles before and after the traumatic brain injury (TBI). T-scores between 65 and 70 are in the borderline range, while scores equal to or greater than 70 are in the clinical range (Achenbach & Ruffle, 2000). *a change with 95% confidence; **a change with 99% confidence.

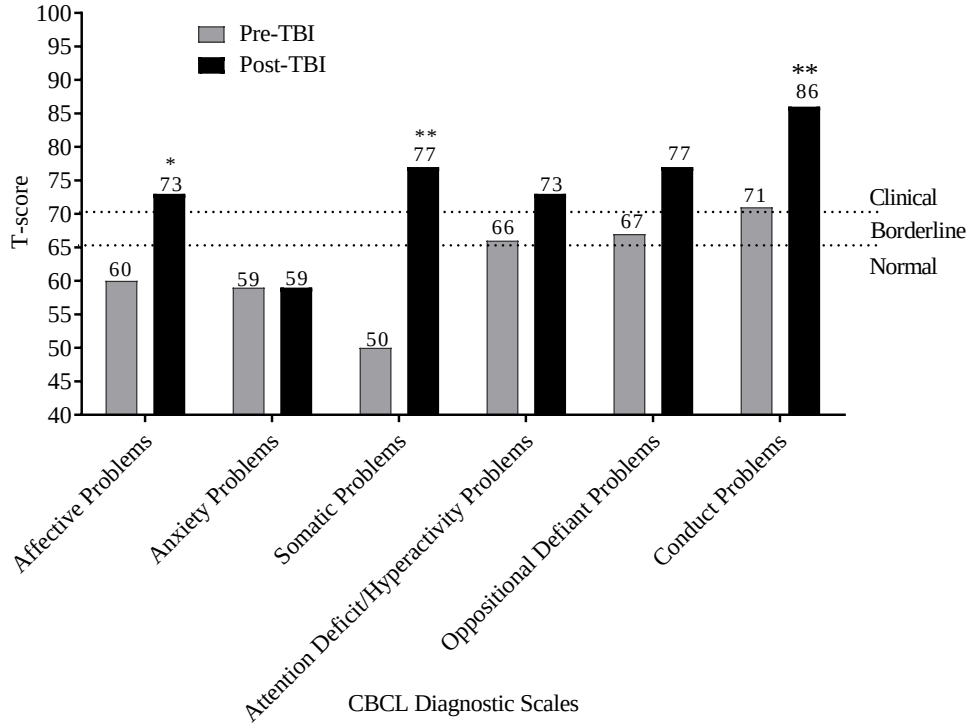

Figure 6. Alice's Child Behavioural Checklist (CBCL) diagnostic scales before and after the traumatic brain injury (TBI). T-scores between 65 and 70 are considered to be in the borderline range, while scores equal to or greater than 70 are designated to be in the clinical range (Achenbach & Ruffle, 2000). *a change with 95% confidence; **a change with 99% confidence.

MRI Results

Alice refused to undergo the MRI scan.

Summary of Outcomes

The standout features of Alice's assessment were her attention, executive, and behavioural deficits. Specifically, Alice had poor sustained attention, working memory, mental flexibility, impulse control, error monitoring, rule-adherence, and frustration tolerance. The executive and behaviour deficits that were seen in the assessment were mirrored in the CBCL and BRIEF. Her attention, executive, and behaviour problems impacted her performance across all other domains and made MRI unmanageable. A graphical summary of the potential factors influencing Alice's outcomes can be found in Appendix O (Figure O1).

Case Study 2: Ethan

Medical History

Pre-TBI. Ethan[9] had no noteworthy prior medical conditions.

The TBI. Ethan sustained a PVA (hit and run) on 30/06/2018 (aged 12 years). The accident was unwitnessed, and Ethan was found on the roadside near his home. He had one generalised tonic-clonic seizure at the scene. Ethan was first taken to a local hospital where his GCS was 10, indicating a moderate TBI. Ethan was intubated and sedated. CTB (30/06/2018) showed a large haematoma overlying the right parietal bone, generalised brain swelling, and evidence of subarachnoid haemorrhage in the lateral ventricles and basal cisterns.

Ethan was transferred to RXH the following day (01/07/2018). He had a GCS of 6T (now indicating a severe TBI) and no focal neurological deficits on pICU admission. Ethan did not meet the criteria for physiological brain monitors. Ethan was extubated and his sedation decreased on the first day in the pICU. He was disorientated, restless, and combative for 12 days (01/07/2018 – 13/07/2018), which was managed with sedation. Ethan underwent a follow-up CTB scan (02/07/2018), which found mild worsening of cerebral oedema.

Ethan was discharged from the pICU and moved to the Neurosurgery ward on 02/07/2018. His GCS scores fluctuated between 9 and 13 during his eight-day stay in the ward (02/07/2018 – 10/07/2018). Ethan was discharged from RXH on 10/07/2018, with a GCS of 10, and was admitted to GSH for several weeks of rehabilitation (10/07/2018 – 24/08/2018) before being discharged home (GCS was 15 at discharge).

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[9] Pseudonym.

Post-TBI. Ethan was described as clinically well and fully orientated at his three-month post-TBI Neurosurgery follow-up appointment (30/06/2018). Ethan's aunt reported that he was doing well at school, but there were some behavioural issues at home. Ethan was assessed as having an upper good recovery (full recovery) on the Glasgow Coma Outcome Scale Extended[10] version.

Developmental History

Ethan's aunt provided the developmental history. Ethan and his twin sister were born prematurely and had low birth weights (weight unknown). Ethan's aunt suspected that Ethan's mother had abused methamphetamine during the pregnancy. She did not think that Ethan was abnormally slow in any of his developmental milestone achievements, but she was unable to give details thereof, as she only became Ethan's caregiver when he was 8 years old.

Social Functioning

Pre-TBI. Ethan's father was jailed for fraud in 2014 and subsequently, the family lost their house. His mother, who had a history of substance abuse, then left Ethan (aged 8 years) and his five siblings (aged 9, 8, 5, 3 and 1 year) with their grandparents and disappeared. Ethan and his siblings were thereafter placed in the care of their aunt. Ethan's aunt described Ethan's father as a caring parent. Ethan had no further contact with his mother and her whereabouts remained unknown. Ethan's aunt reported that Ethan got on well with his siblings but would occasionally bully them. He also sometimes made friends with the "naughty children" and got into trouble at school. Ethan's aunt worked as a supervisor in a clothing factory. Ethan's family had a medium asset index, and their needs were reasonably met, except for Extra Resources (Table M4 in Appendix M).

Post-TBI. Ethan's aunt took unpaid leave and stayed with Ethan for the duration of his hospital stay, which caused financial and family burdens. Ethan's aunt reported that Ethan fought more with his siblings and was more irritable after discharge, but this improved to pre-TBI levels by 6 months post-TBI.

Academic Functioning

Pre-TBI. Ethan and his twin sister failed grade 1 (aged 7 years), which was the year leading up to his father's incarceration. Ethan's aunt believed that the stress at home influenced Ethan's academic performance that year. Ethan performed at an average academic

[10] The Glasgow Coma Outcome Scale Extended version has eight potential outcomes following brain injury, which are, in order of descending severity, "Death", "Vegetative state", "Lower severe disability", "Upper severe disability", "Lower moderate disability", "Upper moderate disability", "Lower good recovery", and "Upper good recovery".

level before the TBI, obtaining mostly 5's and 6's[11] for his subjects. He did however require additional support in grade 5 (2018). His teacher reported that he was disruptive in class and had been referred to the school psychologist for his behaviour but had not yet been seen. Ethan's aunt stated that Ethan struggled more with school in comparison to his siblings.

Post-TBI. Ethan was in grade 5 at the time of the TBI. He returned directly to school following his hospitalization but attended only half days for the first few weeks. Ethan's aunt reported that, despite some early difficulties, Ethan was back to his pre-TBI level of functioning at school by 6-months post-TBI and had passed grade 5.

Caregiver's Concerns

Ethan's aunt was initially worried about Ethan's irritability and aggressive behaviour and how he would cope at school. However, by the time of the 6-month assessment, she felt that Ethan had returned to his pre-TBI level of functioning. She was happy with his recovery and had no concerns to report. This was mirrored in the low level of burden recorded by the FBI (Table M6 in Appendix M).

Neuropsychological Assessment

Presentation. Ethan was initially reserved but warmed up quickly. He swiftly grasped instructions and worked conscientiously. He gave his full effort and required no breaks. However, he grappled with tasks that involved increased complexity and working memory load.

Attention. Ethan had a forward digit span of five (borderline range, Figure 7), but his ability to recall four- and five-digit sequences were inconsistent, suggesting fluctuating attention. Ethan systematically screened the TMT Visual Scanning page but required several screens to find all the items. Ethan's completion time, therefore, fell in the low average range (Figure 7) and his performance suggested some selective attention difficulties. His attention composite score fell into the borderline range (Figure 8).

Memory. Ethan showed a learning curve over the three Dot Locations learning trials (6/8, 7/8, and 8/8 correct; average range; Figure 7). He accurately recalled all eight locations following a short and long delay, resulting in above-average scores (Figure 7). Ethan similarly showed a good learning curve over the RAVLT learning trials (5/16, 7/16, 12/16, 14/16 and 14/16 words; average range; Figure 7). He recalled 12 of the words following a

[11] South African schooling grade classifications are as follows: 1: "Not achieved", 0 – 29%; 2: "Elementary achievement", 30 – 39%; 3: "Moderate achievement", 40 – 49%; 4: "Adequate achievement", 50 – 59%; 5: "Substantial achievement", 60 – 69%; 6: "Meritorious achievement", 70 – 79%; 7: "Outstanding achievement", 80 – 100%.

short and a long delay (average range) and performed well on the recognition trial (high average range; Figure 7). Based on these tests, Ethan's audioverbal and visuospatial memory composites were in the average range (Figure 8) and his memory capabilities appeared to be intact.

Processing Speed. Ethan worked carefully, but not particularly speedily, on the Coding test and thus his score fell into the low average range (Figure 7). He made one mistake, possibly due to a lapse in concentration. Ethan performed well in the Symbol Search task and his score was in the average range (Figure 7). His processing speed composite score was therefore in the low average range (Figure 8). However, Ethan's completion times were slower than expected for his age on the TMT Number Sequencing (low average range) and Letter Sequencing conditions (borderline range; Figure 7), which might have indicated some reduced processing speed. Collectively, given his performance on Coding and the TMT, there was some evidence that Ethan had mild processing speed deficits.

Executive Functions. Ethan had a backward digit span of four but his ability to reverse three- and four-digit sequences fluctuated and therefore his score fell in the low average range (Figure 7). Ethan maintained the rule on the Letter-number Sequencing test but had difficulty with sequences of four or more (low average range; Figure 7). Both tests indicated that Ethan had some working memory difficulties, which were most likely also influenced by his attentional deficits.

Ethan was able to connect ascending numbers and letters without error on the TMT Number Sequencing and Letter Sequencing conditions, respectively. However, as mentioned previously, his times on both were slower than expected (Figure 7). Ethan laboured through the Number-Letter Switching trial and his time fell in the extremely low range (Figure 7). Ethan also made two errors as he lost the rule. Ethan's Motor Speed time was in the average range (Figure 7), suggesting no motor slowness to account for his performance on the other conditions. His TMT performance thus indicated difficulties with working memory and cognitive flexibility.

Ethan was able to complete all of the Tower test constructions but struggled to form an efficient strategy and therefore scored in the low average range (Figure 7). He made four rule violations (average range, Figure 7). For each rule break, Ethan briefly lost the rule and somewhat impulsively made a move before quickly apologizing, indicating potential impulsivity or working memory lapses. Collectively, Ethan's executive functions composite score fell into the borderline range (Figure 8).

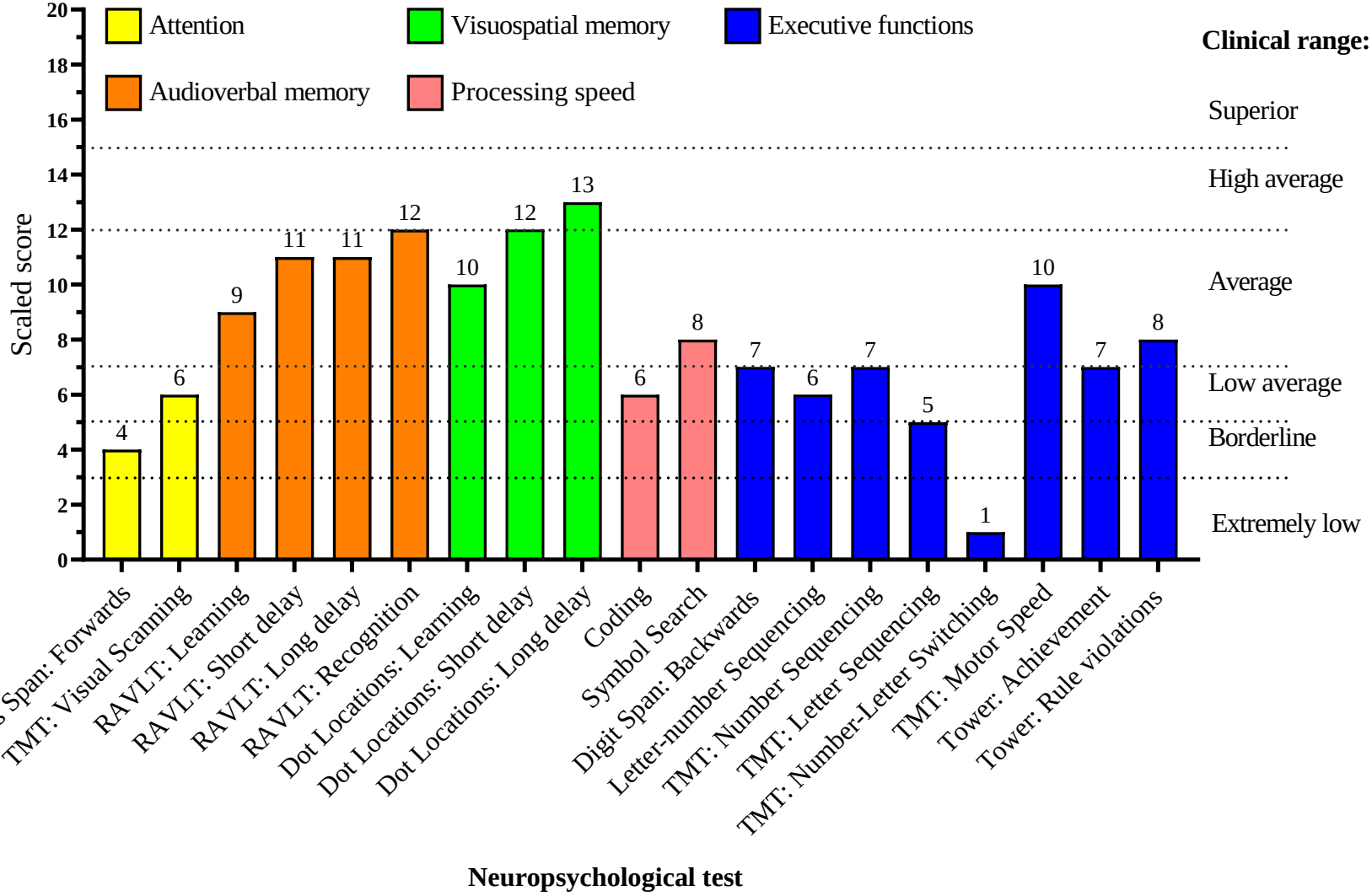

Figure 7. Ethan's scaled scores for each of the neuropsychological tests. The bars are coloured according to which cognitive domain the test theoretically measures. The clinical scaled score descriptions are displayed on the right of the graph. RAVLT: Rey Auditory Verbal Learning Test; TMT: Trail Making Test.

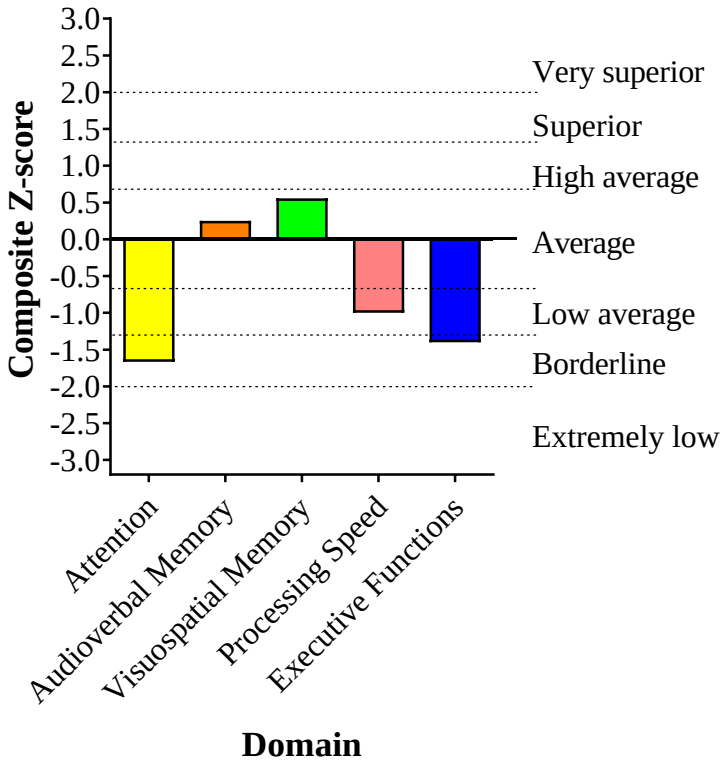

Figure 8. Ethan's composite Z-scores for each domain. The clinical Z-score descriptions are displayed on the right of the graph.

Behavioural Outcomes

BRIEF. Ethan showed no clinically statistically significant post-TBI changes in any of the BRIEF measures (Figure 9). Only Ethan's pre-TBI Shift score was in the clinical range, possibly suggesting some premorbid cognitive flexibility difficulties. Unexpectedly, his post-TBI Shift score was in the normal range.

CBCL. There were no clinically statistically significant post-TBI changes in Ethan's CBCL scores and all measures fell below the clinical range (Figures 10 and 11). Only Ethan's Conduct Disorder scores fell into the borderline range both pre- and post-TBI, indicating some issues emanating from before the TBI.

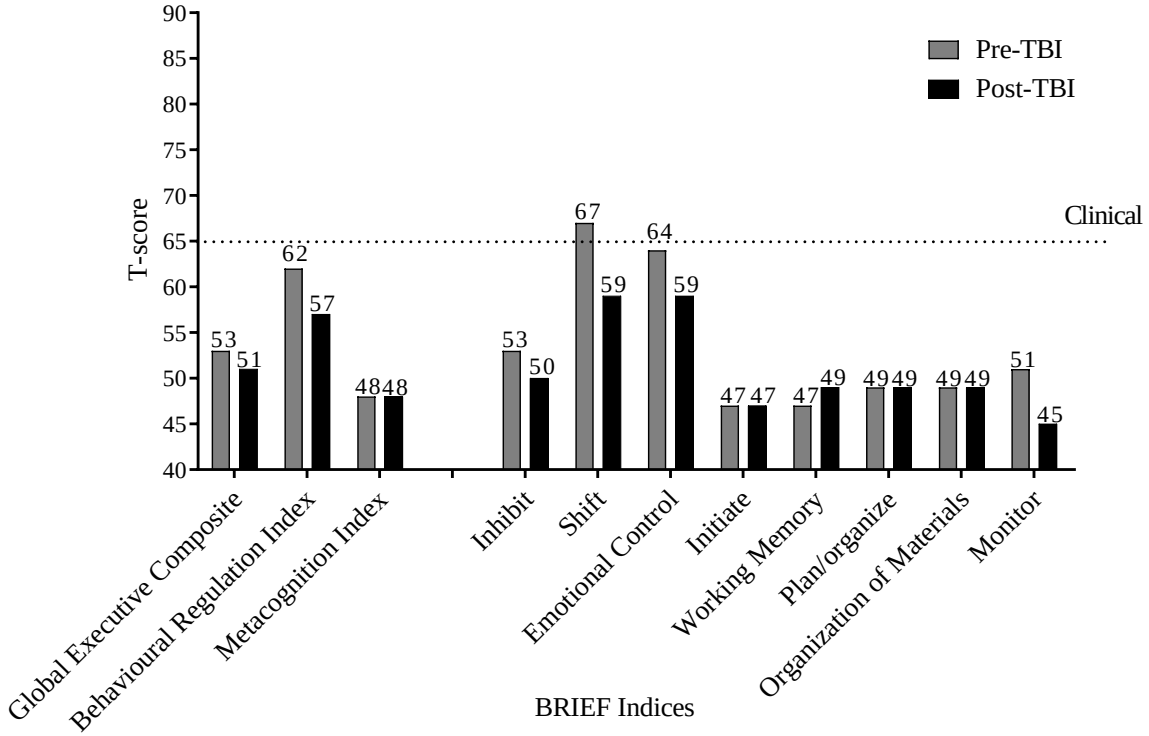

Figure 9. Ethan's Behaviour Rating Inventory of Executive Function (BRIEF) indices before and after the traumatic brain injury (TBI). Scores equal to or greater than 65 are in the clinical range (Gioia et al., 2000).

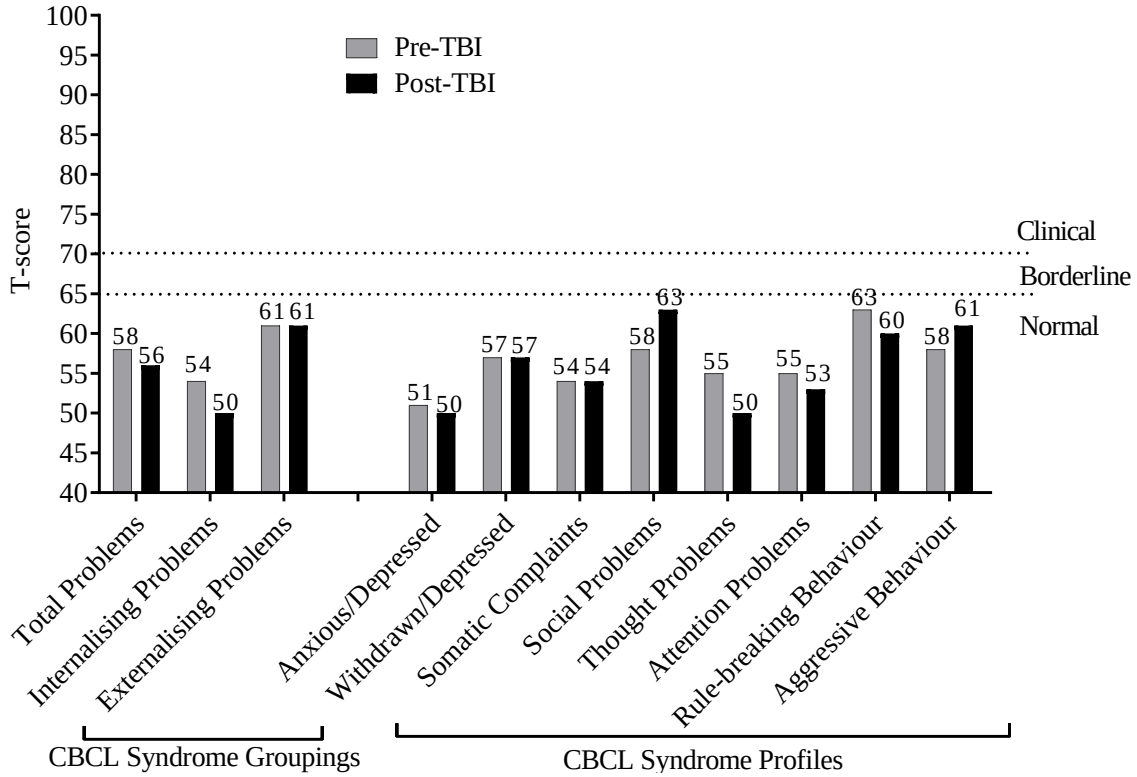

Figure 10. Ethan's Child Behavioural Checklist (CBCL) syndrome profiles before and after the traumatic brain injury (TBI). T-scores between 65 and 70 are in the borderline range, while scores equal to or greater than 70 are in the clinical range (Achenbach & Ruffle, 2000).

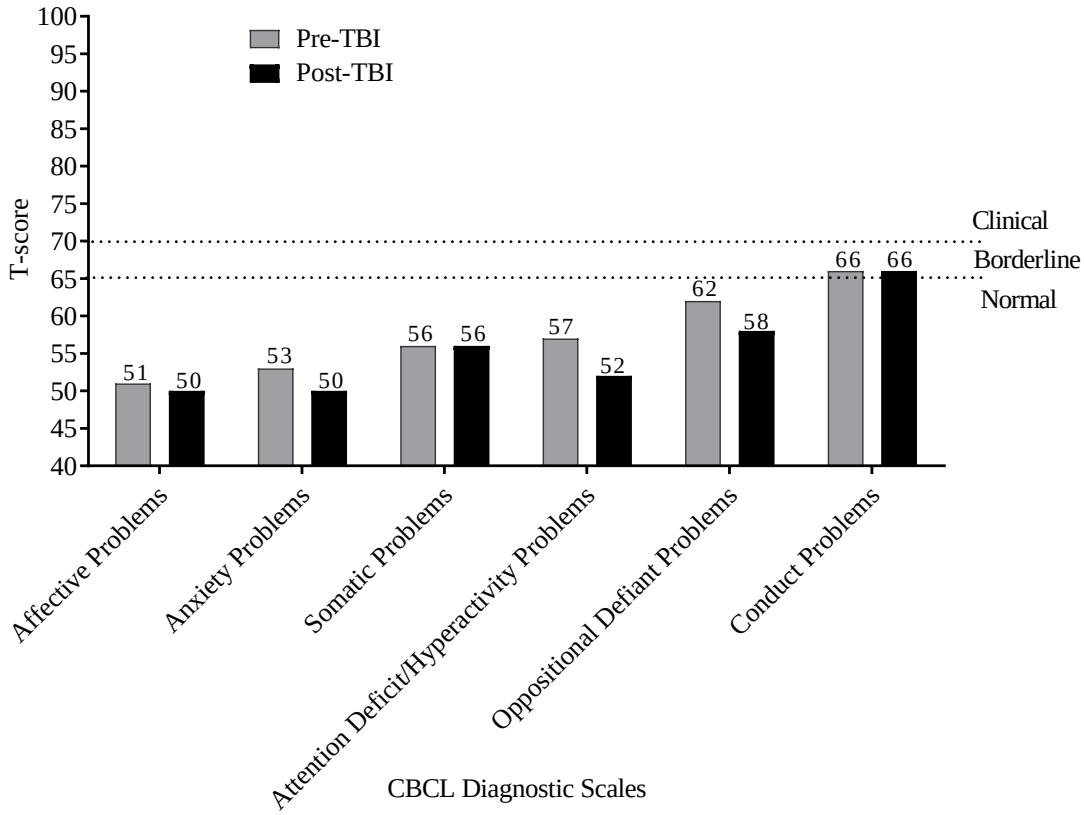

Figure 11. Ethan's Child Behavioural Checklist (CBCL) diagnostic scales before and after the traumatic brain injury (TBI). T-scores between 65 and 70 are in the borderline range, while scores equal to or greater than 70 are in the clinical range (Achenbach & Ruffle, 2000).

MRI Results

No abnormalities were found on the 6-month post-TBI MRI scan (See Figure N1 in Appendix N).

Summary of Outcomes

Ethan presented with mild to moderate difficulties, most notably in attention, processing speed, working memory, and cognitive flexibility. Ethan's audioverbal and visuospatial memory was intact. In addition, Ethan had no significant post-TBI behavioural changes on the BRIEF or CBCL, no caregiver concerns, and his MRI scan showed no visible evidence of pathology. A graphical summary of the potential factors influencing Ethan's outcomes can be found in Appendix O (Figure O2).

Case Study 3: Mia

Medical History

Pre-TBI. Mia[12] was first seen at RXH with a suspected head injury when she was two years old (07/10/2011). She had fallen from a 0.5m height and had vomited. Mia was not admitted or diagnosed with a TBI at that time. Mia had no other notable premorbid medical issues.

The TBI. Mia sustained a TBI on 28/07/2018 (aged 8 years). She was walking with her grandmother when she was hit by a car while crossing the road. Mia vomited and her GCS was 3 at the scene. Mia was intubated and admitted to RXH where she was diagnosed with a severe TBI, multiple facial fractures, mild left proptosis, and a right femur fracture. CTB (28/07/2018) showed bifrontal haemorrhagic contusions, generalised brain swelling, and potential TAI.

Mia had a slow neurological recovery and spent 15 days in the pICU (28/07/2018 – 13/08/2018). Mia was intubated, ventilated, and sedated for 13 days (28/07/2018 - 10/08/2018). Mia's GCS began to slowly improve after extubation but remained low. Specifically, her GCS scores stayed between 6 and 9 for the remainder of her RXH stay (11/08/2018 - 29/08/2018). MRI was conducted (13/08/2018) to assess the reason for the persistently low GCS and it showed features of TAI predominantly affecting the frontal lobes, corpus callosum, and brachium pontis.

Mia had physiological brain monitors placed for 158 hours (29/07/2018 – 04/08/2018). During that time, she had 38 episodes[13] of ICP over 20mm Hg, nine of which were over 25mm Hg (Table M2 and Figure M3 in Appendix M). Mia had three episodes where her $PbtO_2$ was less than 20mm Hg (Table M2 and Figure M4 in Appendix M). However, these low $PbtO_2$ incidents were brief and did not cross the 10mm Hg threshold.

Mia developed nosocomial sepsis with staphylococcus aureus bacteria evident on tracheal aspirate (30/07/2018). The infection was treated with antibiotics and active cooling. However, Mia continued to have temperature spikes and therefore loss of autoregulation was postulated as a possible cause of the temperature fluctuations. Mia was discharged from RXH on 29/08/2018, 32 days after the TBI. She was moved to GSH for two months of rehabilitation (29/08/2018 – 29/10/2018). Mia was discharged to an intermediate care facility for chronically ill children, three months after her TBI (29/10/2019).

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[12] Pseudonym
[13] Each episode denotes one hour of monitoring time.

Post-TBI. Mia was next seen for her 6-month post-TBI follow-up appointment (23/01/2019). She presented with right-sided weakness, dysmetria (right > left), left facial palsy, and dysarthria. Mia's grandmother reported personality changes. Specifically, Mia was previously shy but was now extroverted, short-tempered, and hyperactive. It was concluded that Mia had made good progress since her discharge, but still had some way to go.

Developmental History

Mia's grandmother provided the developmental history. There were no complications during the pregnancy, birth, or new-born period. Mia's grandmother did not think that Mia's mother was taking illicit substances during the pregnancy, but she did smoke cigarettes. It was, however, noted in Mia's medical folder that Mia had been exposed to illicit substances in utero. Mia's grandmother did not recall any developmental delays but could not give milestone details.

Social Functioning

Pre-TBI. Mia had a turbulent childhood. She was sent to live with her grandmother when she was two years old because of her parents' substance abuse. Mia's mother would take her back into her care every few months, but this never lasted for more than three weeks. Mia has one brother who is three years younger than her. Mia's grandmother reported that Mia acted as the primary caregiver to her brother because of their parent's substance abuse.

When Mia was four years old, she was sexually assaulted by their landlord's 14-year-old son. The case was reported to the police and Mia was then permanently placed in her grandmother's care. Mia received monthly counselling sessions for six months. Mia's grandmother reported that after the incident Mia began re-enacting sexual acts with other children. Mia was reprimanded and the behaviour stopped over the next few months. Her grandmother believed that Mia had not fully dealt with the trauma.

Mia's mother overdosed and died in May 2018, two months before Mia's TBI. Mia's grandmother reported that this was an emotionally difficult time. Mia had relatively frequent contact with her father, but her grandmother described him as being "always on the road" due to his substance abuse.

In terms of financial stability, Mia's grandparents were both employed as skilled labourers and had a high asset index (Table M4 in Appendix M). Most of their needs were met, except for Extra Resources on the FRS (Table M4 in Appendix M).

Post-TBI. Mia's TBI has had a detrimental impact on the family's environment. Her grandmother retired from her job to look after Mia who required constant supervision after the TBI. Mia had become disobedient and fought more with her brother. Mia's grandmother

also reported that Mia was acting in an inappropriately sexual manner towards her brother, for example trying to kiss him, lying on top of him, and calling him her boyfriend.

Academic Functioning

Pre-TBI. Mia's grandmother reported that Mia enjoyed school and was an excellent student before the TBI. She received 7's[14] for all her subjects in grade 2 before the TBI (2018).

Post-TBI. Mia had severe academic difficulties and required special needs schooling following the TBI. She started school at an intermediate facility for chronically ill children while applications were made for placement in a Learners with Special Educational Needs (LSEN) school.

Caregiver's Concerns

Mia's grandmother had many concerns relating to Mia's functioning. Mia's behaviour was her biggest concern. She reported that Mia was child-like, impulsive, disinhibited, and socially inappropriate. In terms of cognition, Mia's grandmother reported that Mia was forgetful and would lose her train of thought easily. Her language was also impaired as she spoke slowly and in short sentences. Mia's grandmother's high level of concern was evident in the FBI, where she scored 10 items above three, indicating a high burden (Table M6 in Appendix M).

Neuropsychological Assessment

Presentation. Mia was child-like and spoke slowly in basic sentences. Her thinking was slow, and she would often stare for several seconds before answering questions. Mia was socially inappropriate and overly familiar. She needed breaks between every task and became tired easily. Mia was initially cooperative, but some tasks were too difficult, which made her defiant and upset. Mia became inconsolable during the TMT and the assessment ended without completing the TMT or Tower test.

Attention. Mia had a forward digit span of three (borderline range; Figure 12), which suggested attention and concentration difficulties. She identified all the targets on the TMT Visual Scanning condition, however, her search was haphazard and slow and thus she scored in the extremely low range (Figure 12). Her attention composite score fell into the extremely low range (Figure 13). Qualitatively, she struggled to focus and sustain her attention.

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[14] South African schooling grade classifications are as follows: 1: "Not achieved", 0 – 29%; 2: "Elementary achievement", 30 – 39%; 3: "Moderate achievement", 40 – 49%; 4: "Adequate achievement", 50 – 59%; 5: "Substantial achievement", 60 – 69%; 6: "Meritorious achievement", 70 – 79%; 7: "Outstanding achievement", 80 – 100%.

Memory. Mia made a pattern instead of trying to replicate the configuration of discs on the first learning and the long delay trials of Dot Locations, thus invalidating her scores as accurate measures of her visuospatial memory capabilities. However, for both trials, she stated that she could not remember where the dots were before resorting to making a pattern. She attempted to reproduce the dot locations on the other trials but was unable to place the dots in the correct pattern. Therefore, it was evident that Mia had visuospatial memory deficits, but the severity could not be determined. The visuospatial memory composite was not calculated due to the invalidated test performance. She also struggled to sustain her attention during the trials, which would have further impacted her memory performance.

Mia battled to attend to the RAVLT learning trials and showed a flat learning curve (2/16, 3/16, 8/16, 5/16 and 5/16 words; extremely low range; Figure 12). Mia could recall only two of the words following a short and a long delay (extremely low range; Figure 12). She also made 19 intrusions across the trials. Mia did slightly better on the recognition task (Figure 12), suggesting that her memory recall was aided by prompts. Her audioverbal composite score fell into the extremely low range (Figure 13), indicating audioverbal memory difficulties that were likely exacerbated by her attentional deficits.

Processing Speed. Mia completed seven items of the Coding task in the two-minute trial. She made no errors but was exceptionally slow and therefore her score fell in the extremely low range (Figure 12). She struggled with fine motor control, but over and above her motor deficits, her thinking was laborious, and she took time looking between the numbers and the key and deciding which symbol to draw. Mia was similarly slow on the Symbol Search task, again falling in the extremely low range and resulting in a composite score in the extremely low range (Figures 12 and 13). Qualitatively, Mia's thinking was slow across all tasks and in conversation.

Executive Functions. Mia had a backward digit span of two (borderline range; Figure 12), which indicated working memory difficulties. Mia struggled with the Letter-number Sequencing task and was only able to correctly manipulate two-item sequences resulting in an extremely low score (Figure 12). She was also unable to recite the alphabet after the letter E.

Mia only connected the numbers up to seven before running out of time in the TMT Number Sequencing condition (extremely low range; Figure 12). She also made one mistake. Mia became increasingly emotional at the difficulty of the tasks and therefore the TMT and the assessment were discontinued. Based on the tests that were completed, Mia's executive functions composite score fell into the extremely low range (Figure 13).

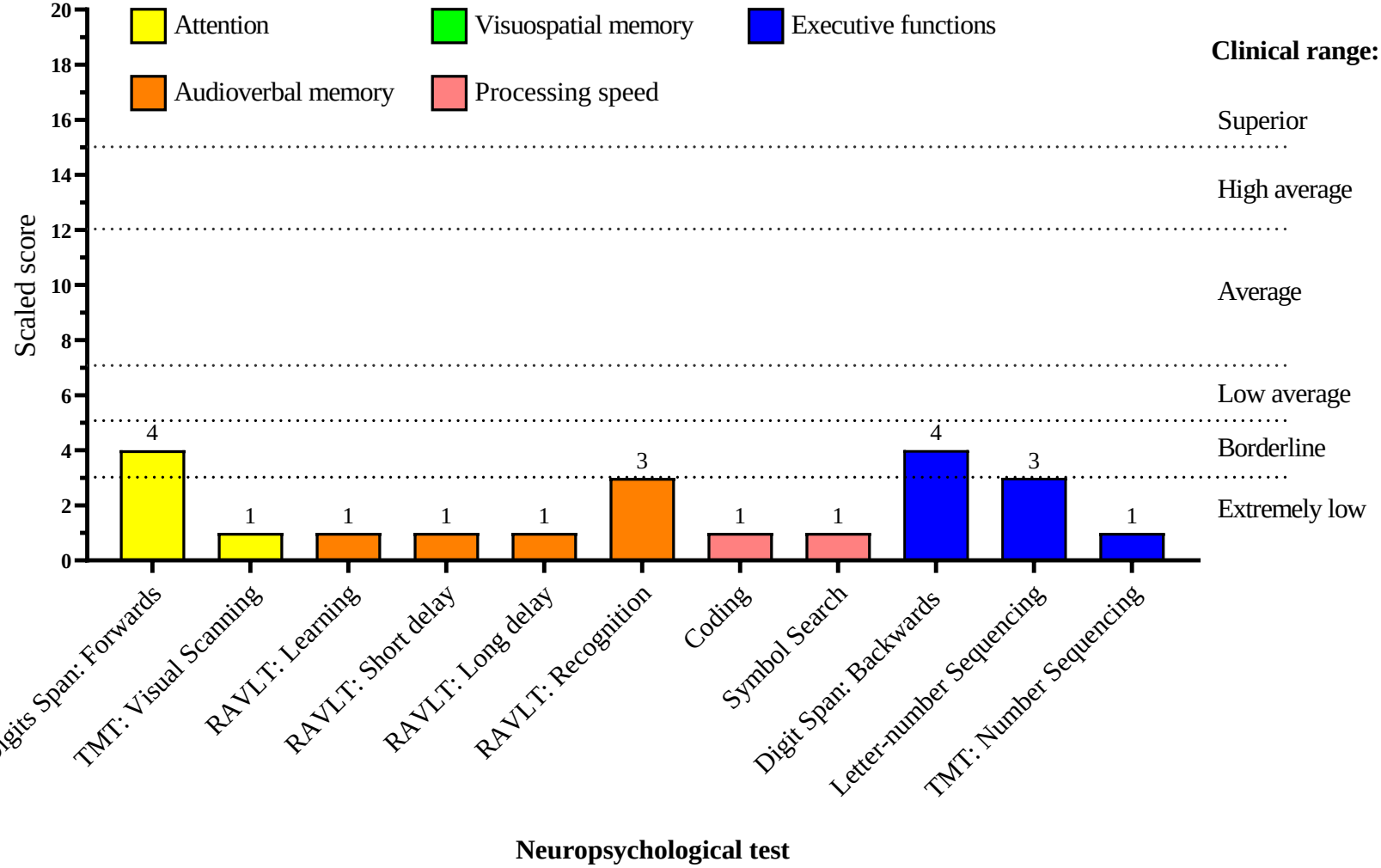

Figure 12. Mia's scaled scores for each of the neuropsychological tests. The bars are coloured according to which cognitive domain the test theoretically measures. The clinical scaled score descriptions are displayed on the right of the graph. The Dot Locations subtest scores were invalidated by the participant and therefore were not included. RAVLT: Rey Auditory Verbal Learning Test; TMT: Trail Making Test.

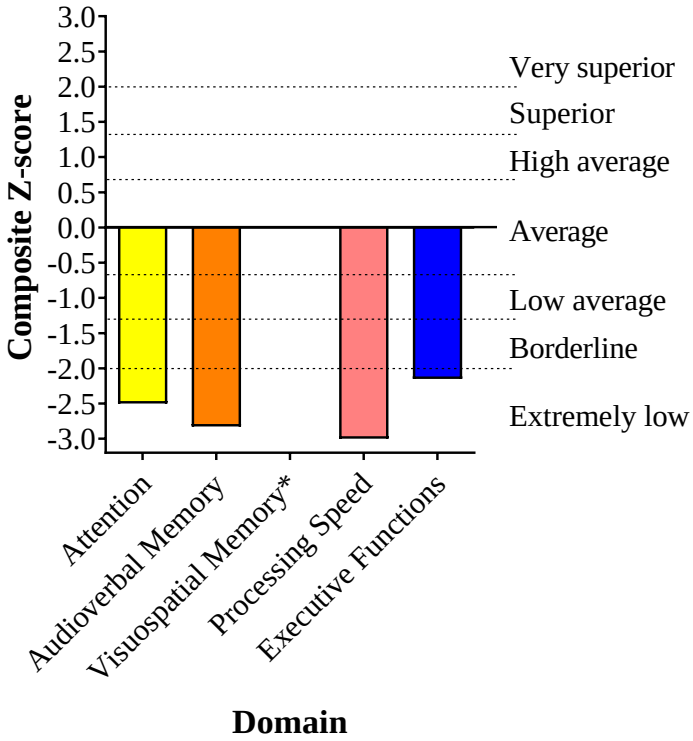

Figure 13. Mia's composite Z-scores for each of the assessed domains. The clinical Z-score descriptions are displayed on the right of the graph. *Visuospatial memory scores were invalidated by the participant and therefore were not included in the composite analysis.

Behavioural Outcomes

BRIEF. Mia's post-TBI GEC, both the BRI and MI, and all individual scales were in the clinical range and showed clinically statistically significant increases (99% CL) from her pre-TBI levels, indicating drastic deterioration of behavioural regulation and executive functions following the TBI (Figure 14). Mia's post-TBI BRIEF Negativity score was six, suggesting that Mia's grandmother had a negative perception of Mia's behaviours following the TBI (Table M8 in Appendix M).

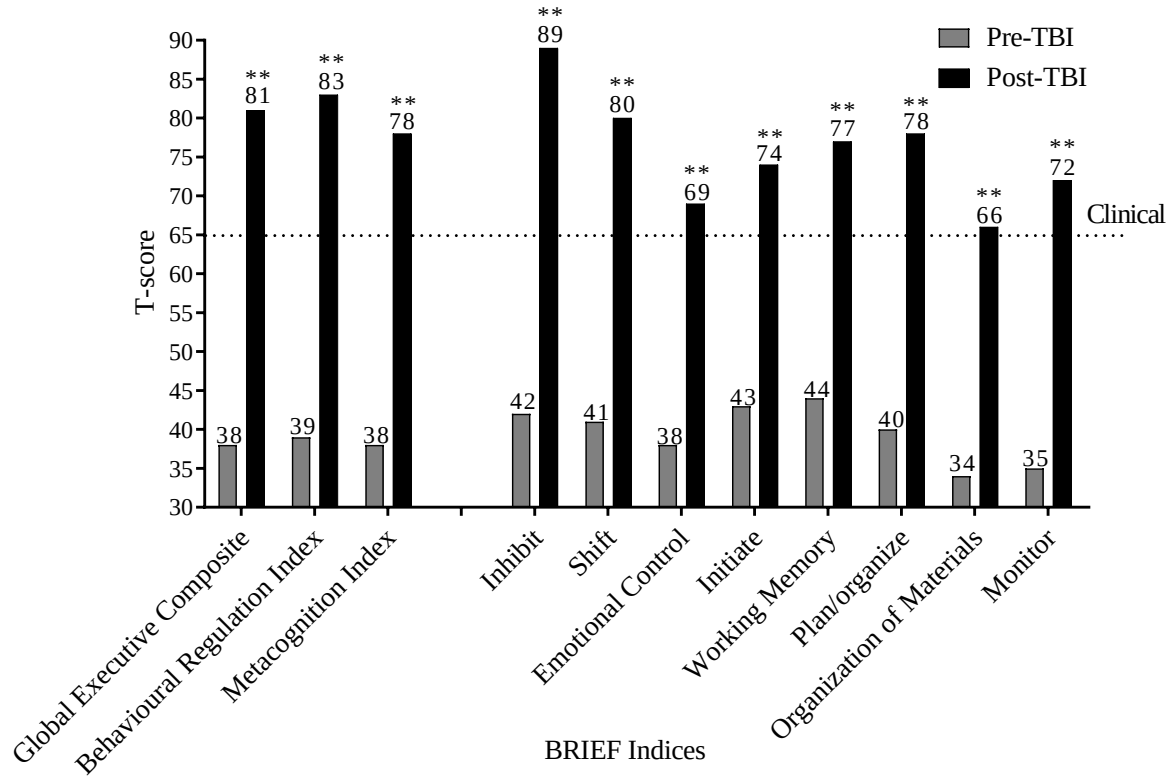

Figure 14. Mia's Behaviour Rating Inventory of Executive Function (BRIEF) indices before and after the traumatic brain injury (TBI). Scores equal to or greater than 65 are in the clinical range (Gioia et al., 2000). **a change with 99% confidence.

CBCL. Mia showed dramatic post-TBI increases in the majority of CBCL syndrome groupings, profiles, and diagnostic scales (Figures 15 and 16). The only scales to not reach clinically statistically significant differences were the Anxious/Depressed and Withdrawn/Depressed syndrome profiles, and the Anxiety Problems diagnostic scale. For all other measures, the post-TBI scores were in the clinical range and showed a significant increase with a 99% CL from the pre-TBI levels, suggesting substantial problems after the TBI.

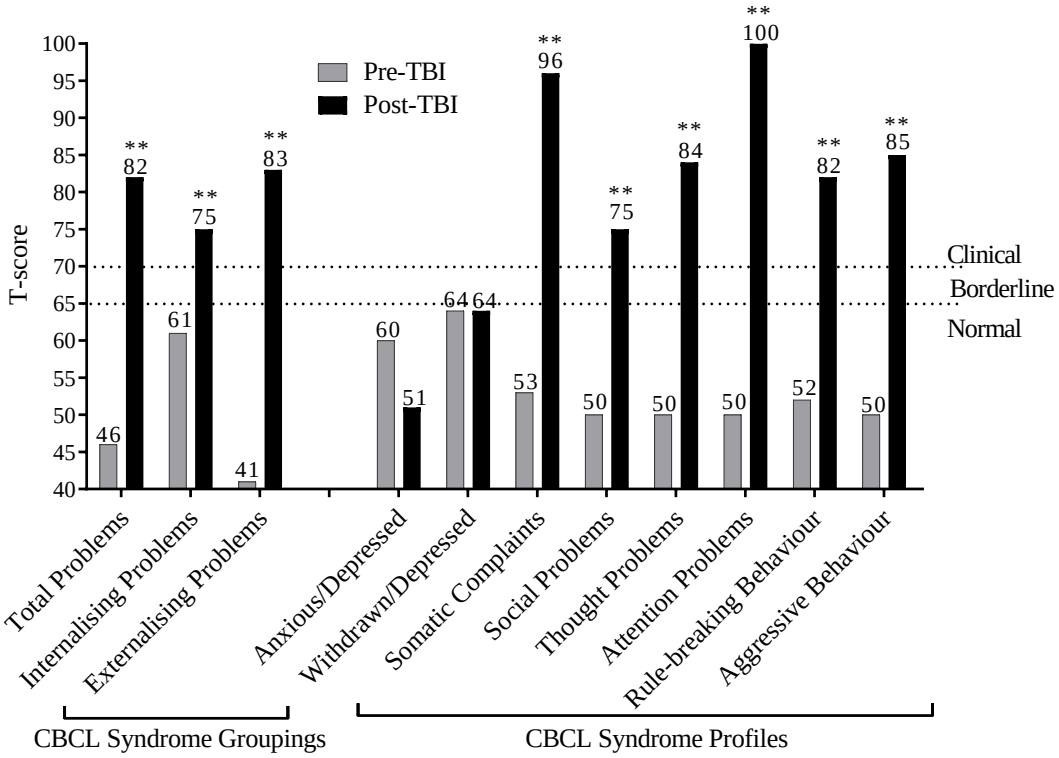

Figure 15. Mia's Child Behavioural Checklist (CBCL) syndrome profiles before and after the traumatic brain injury (TBI). T-scores between 65 and 70 are in the borderline range, while scores equal to or greater than 70 are in the clinical range (Achenbach & Ruffle, 2000). **a change with 99% confidence.

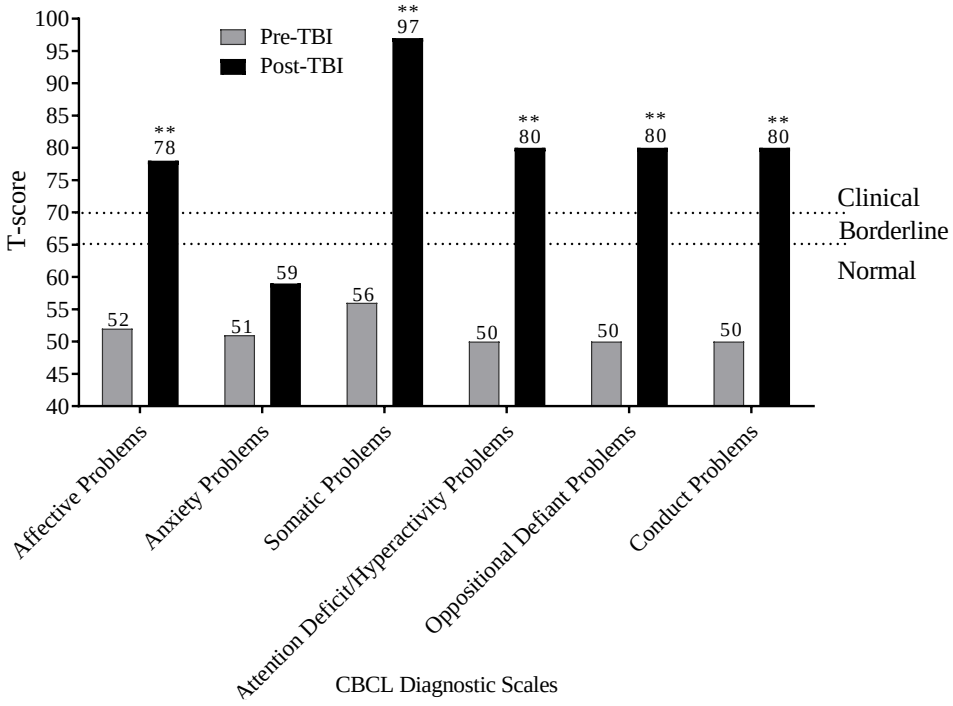

Figure 16. Mia's Child Behavioural Checklist (CBCL) diagnostic scales before and after the traumatic brain injury (TBI). T-scores between 65 and 70 are in the borderline range, while scores equal to or greater than 70 are in the clinical range (Achenbach & Ruffle, 2000). **a change with 99% confidence.

MRI Results

Mia was only able to stay in the MRI machine for the structural scans and did not complete the full scan as she was scared. Mia's 6-month post-TBI MRI (12/03/2019) revealed multifocal areas of encephalomalacia (See Figures N2 - N5 in Appendix N). Specifically, there was bilateral frontal lobe encephalomalacia and associated volume loss, with the left frontal lobe more affected than the right. There were multifocal areas of cystic encephalomalacia in the body and splenium of the corpus callosum. In addition, there were several areas of lacunar encephalomalacia in the left external capsule extending into the left corona radiata and in the deep white matter of the right postcentral gyrus.

Summary of Outcomes

Mia presented with severe neuropsychological deficits across all domains. Her deficits in the "gate-keeper" functions of attention, working memory, and processing speed affected her performance across all tests, while the severity of her deficits made some tests impossible to complete. The findings of the assessment supported the post-TBI executive and behavioural problems recorded in the BRIEF and CBCL. Qualitatively, Mia was impulsive, disinhibited, socially inappropriate, had poor monitoring, and reduced insight. Mia's MRI showed multifocal areas of encephalomalacia in line with the severity of her neuropsychological difficulties. A graphical summary of the potential factors influencing Mia's outcomes can be found in Appendix O (Figure O3).

Case Study 4: Thando

Medical History

Pre-TBI. Thando[15] had no notable medical history.

The TBI. Thando was involved in a PVA (hit and run) on 02/08/2018 (aged 9 years) while playing on the side of the road. He lost consciousness and vomited after the impact. His GCS was 7 on the roadside. Thando was intubated, ventilated, and transferred to RXH, where he was admitted to the pICU (03/08/2018). CTB (03/08/2018) showed generalized cerebral oedema and a sliver of subdural blood along the tentorium cerebelli. There were no signs of hydrocephalus, contusions, or skull fractures, and the grey/white matter interface was intact. No physiological brain monitors were placed. Thando was extubated and moved from the pICU to the Neurosurgery ward (03/08/2018).

Thando had a gradual neurological recovery. His GCS was 10 post-extubation and stayed between 10 and 13 for the first week of admission (03/08/2018 – 10/08/2018). He was

[15] Pseudonym.

extremely restless and needed to be restrained and sedated. By 10/08/2018 Thando began to respond to questions and follow commands (GCS: 14), although he was still drowsy and irritable. On 10/08/2018 it was noted that Thando was showing new-onset left-sided weakness and decreased tone. A CTB (14/08/2018) found an ill-defined area of hypo-attenuation within the left basal ganglia and to a lesser extent in the left centrum semi-ovale, which did not align with the reports of left-sided weakness.

Thando started experiencing double vision and was seen by Ophthalmology (16/08/2018). His GCS score returned to 15 on 14/08/2018, 12 days after the TBI. He was discharged from RXH on 16/08/2018 and was moved to the GSH rehabilitation unit for several weeks (16/08/2018 – 07/09/2018) before being discharged home.

Post-TBI. Thando was seen at his first Neurosurgery follow-up appointment on 28/11/2018. He was back in grade 4 at his previous school and was confirmed to move into grade 5 the following year. There were still concerns about his double vision. Thando was described as clinically much improved at his 6-month post-TBI appointment (20/02/2019). He was doing well at school and had generally good behaviour, normal speech, and no neurological deficits. There were some complaints about increased hyperactivity, fatigue, and occasional headaches but these were reportedly not disruptive to normal life.

Developmental History

Thando's mother provided the developmental history. She did not smoke, drink alcohol, or take illicit substances during the pregnancy. There were no complications during the pregnancy, birth, or new-born period. She reported that there were no noticeable developmental delays but could not give milestone details.

Thando was sent to live with his grandparents in the Eastern Cape for 18 months when he was between two and four years old. His mother reported that this was difficult for her and Thando. She reported no other separations or emotionally difficult periods during his childhood.

Social Functioning

Pre-TBI. Thando lived with his biological parents, uncle, and younger sister (aged 1 year old). His mother reported that he had lots of friends. As a family, they had significant financial troubles and sometimes had insufficient money for food. His father was unemployed while his mother worked intermittently as a domestic worker. They relied on social grants. The FRS scores indicated that none of the categories of needs were being sufficiently met, although Thando's family's asset index fell into the medium range (Table M4 in Appendix M).

Post-TBI. Thando's mother stated that he had become more emotional since the TBI. She said that he struggled with their poverty and could not understand why other children had nicer things. This had not bothered him before the TBI. When asked about the accident, Thando said that the accident had made him scared and that he was having nightmares about it. He had not been seen by any health professional regarding these fears. Thando's mother had not noticed any other differences in how Thando interacted with friends or family after the TBI. Thando went back to live with his grandparents in the Eastern Cape after his 6-month post-TBI appointment, due to his parents' financial constraints.

Academic Functioning

Pre-TBI. Thando's mother reported that he was an above-average student and received 6's and 7's[16] for all his subjects. He had never failed a grade and was particularly strong in languages and mathematics.

Post-TBI. Thando was in grade 4 at the time of the TBI and returned to his previous school after the hospitalization. Thando's mother reported that he was still coping and passing at school but was not doing as well as before. He was now achieving 3's and 4's for his subjects. He passed grade 4 and progressed to grade 5 in 2019.

Caregiver's Concerns

Thando's parents' primary concern was that Thando had become forgetful following the TBI. For example, he would forget conversations and events. He also required instructions to be repeated. Thando's mother was also worried about his schooling. Thando's father rated five of the 26 FBI items as three or higher, indicating a substantial burden for those items (Table M6 in Appendix M). Of those five items, two were related to Thando (The Child) and three were related to Family Routines/Planning.

Neuropsychological Assessment

Presentation. Thando was assessed with an isiXhosa translator. He was quiet and serious. He did not appear nervous or anxious, but rather focused and contemplative. He took pride in his work and the only time he would smile was after being given praise or doing well in a task. He worked carefully and conscientiously through tasks and preferred not to take breaks. His deliberate nature caused him to be slow on several tasks as he appeared to value

[16] South African schooling grade classifications are as follows: 1: "Not achieved", 0 – 29%; 2: "Elementary achievement", 30 – 39%; 3: "Moderate achievement", 40 – 49%; 4: "Adequate achievement", 50 – 59%; 5: "Substantial achievement", 60 – 69%; 6: "Meritorious achievement", 70 – 79%; 7: "Outstanding achievement", 80 – 100%.

not making mistakes above speed. Thando enjoyed the tasks, especially ones that he performed well in.

Attention. Thando had a forward digit span of five but could not consistently recite the four- or five-digit spans, resulting in a borderline range score (Figure 17) and indicating fluctuating attention. Thando identified all the TMT Visual Scanning Condition search items (average range; Table M7 in Appendix M) but the time taken to complete the trial fell in the extremely low range (Figure 17). He was careful and systematic in his search. He rechecked the page several times causing him to take longer than needed. He did not appear to have selective attention difficulties; he was just careful and therefore slow. Thando's attention composite score was in the extremely low range (Figure 18) but his slow approach on the TMT was a confounding factor.

Memory. Thando had a flat learning curve on the RAVLT learning trials (6/16; 8/16; 8/16; 8/16; 8/16 words; borderline range; Figure 17). He repeated the same eight words on the last four learning trials. However, Thando could only recall one of the words on the short delay trial (extremely low range; Figure 17). He recalled three items from List B suggesting that his recall was affected by interference from the preceding distractor trial. Thando did better on the long delay trial and was able to recall five words (borderline range; Figure 17). He performed in the average range on the recognition trial (Figure 17), which suggested that he had encoded the words and his recall was improved by prompts. Overall, Thando's audioverbal memory composite was in the borderline range (Figure 18).

In contrast, Thando did well on the Dot Locations subtest. He correctly placed 7/8, 7/8, and 8/8 discs on the learning trials (high average range; Figure 17). He placed all eight discs correctly on both the short and long delay trials (high average range; Figure 17). Thando scored in the high average range for his visuospatial memory composite (Figure 18), which demonstrated that he had no visuospatial memory difficulties.

Processing Speed. Thando scored in the average range for the Coding subtest and the high average range for the Symbol Search subtest, resulting in a Processing Speed Composite score in the average range (Figure 17). Thando worked efficiently and made no errors on either subtest. Thando, therefore, had no processing speed deficits supporting the idea that his meticulous nature was subserved more by the need for accuracy and neatness, than slowness per se.

Executive Functions. Thando had a backward digit span of four (average range; Figure 17) but like his forward digit span task his attention fluctuated. Thando performed poorly on the Letter-Number Sequencing subtest (Figure 17). He was unable to manipulate

more than two alphanumeric digits and lost the rule. Thando's Working Memory Index thus fell in the borderline range (Table M7 in Appendix M).

Thando made no errors on the TMT Number Sequencing or Letter Sequencing conditions but took longer than expected to complete the tasks, resulting in scores in the extremely low range (Figure 17). Again, he was meticulous and in no rush. Thando performed better on the Number-Letter Switching task (borderline range; Figure 17). He made no errors and was again careful. Thando cautiously traced the lines of the Motor Speed condition and his completion time fell into the extremely low range (Figure 17), suggesting that it was his careful approach, rather than cognitive load, that caused his slow completion times on the previous conditions. When taking this into account, there was no clear evidence that Thando had sequencing or switching deficits despite his poor scoring.

Thando did well on the Towers test. He was able to build eight of the nine constructions (average range; Figure 17). However, he built the towers with a trial-and-error approach, rather than planning ahead, resulting in a move accuracy ratio in the borderline range (Table M7 in Appendix M) and suggesting some planning difficulties. Thando made no rule violations (average range; Figure 17). Thando's executive functions composite was limited by his deliberate approach but still fell into the average range (Figure 18).

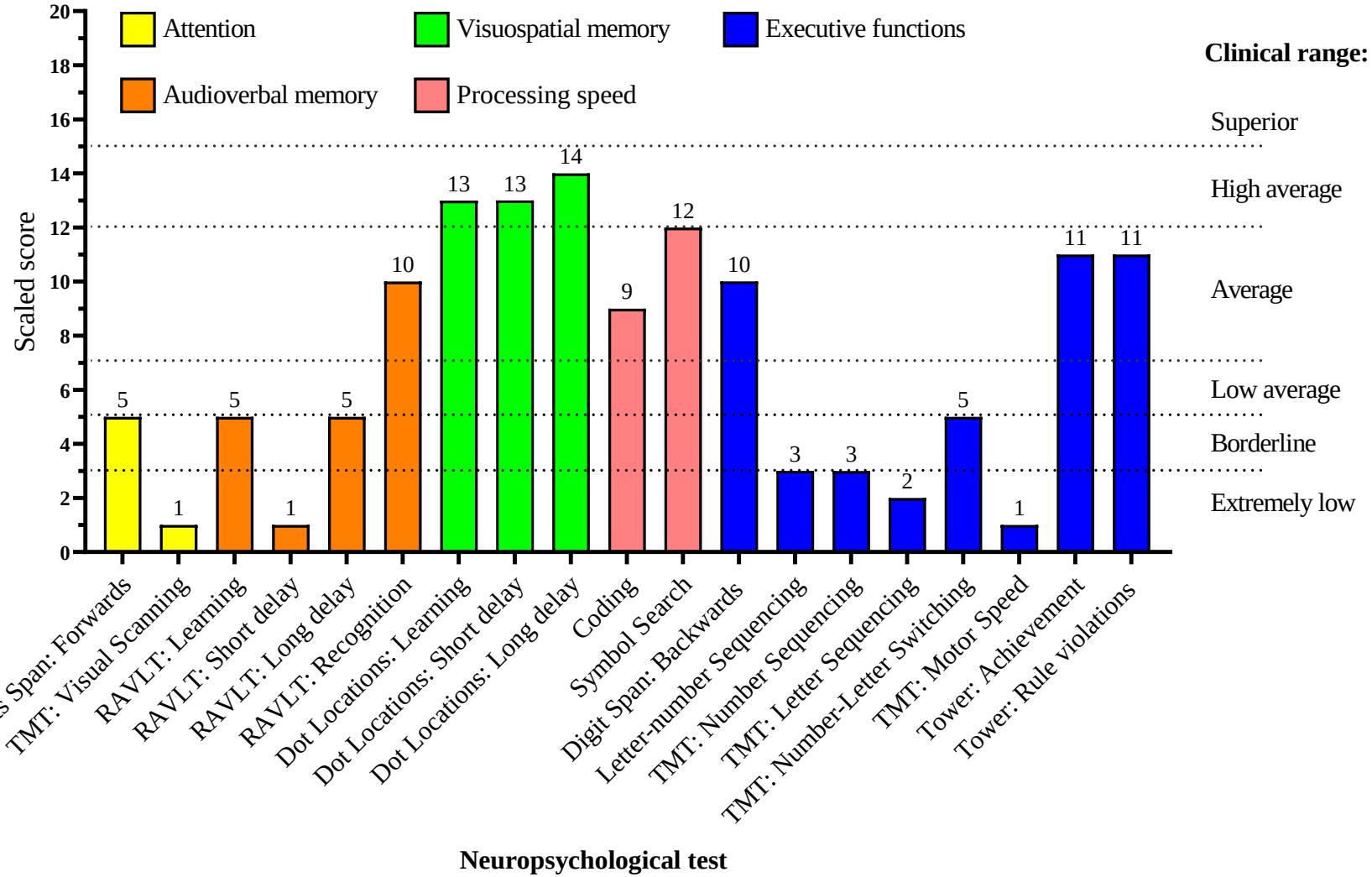

Figure 17. Thando's scaled scores for each of the neuropsychological tests. The bars are coloured according to which cognitive domain the test theoretically measures. The clinical scaled score descriptions are displayed on the right of the graph. RAVLT: Rey Auditory Verbal Learning Test; TMT: Trail Making Test.

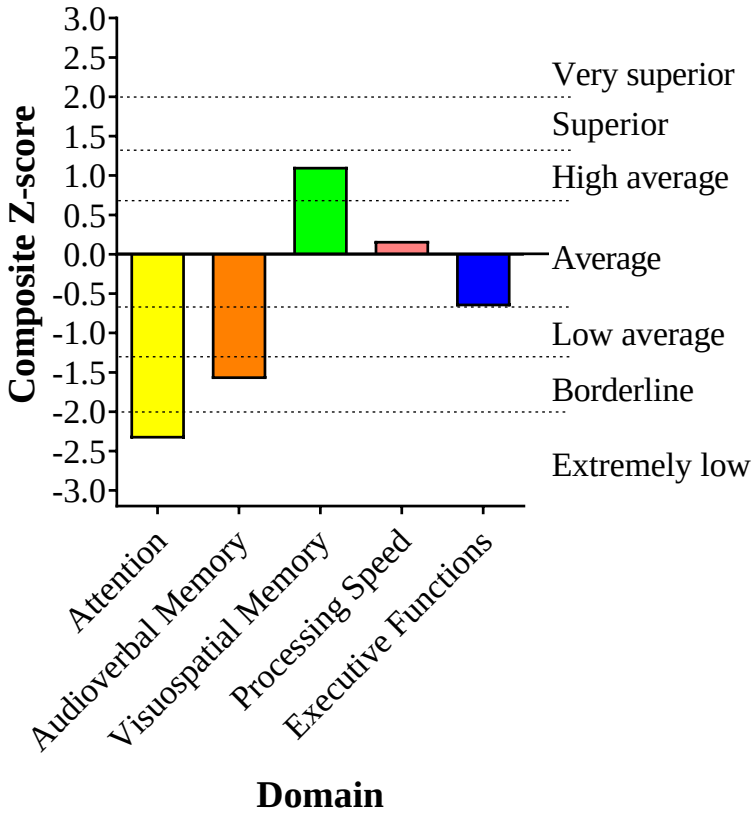

Figure 18. Thando's composite Z-scores for each of the assessed domains. The clinical Z-score descriptions are displayed on the right of the graph.

Behavioural Outcomes

BRIEF. Thando had no clinically statistically significant changes in any of the BRIEF measures post-TBI (Figure 19). Only Thando's pre-TBI Inhibit and Shift scales, and resultant BRI, were in the clinical range. Only Shift remained in the clinical range post-TBI. One thing to note was that the pre-TBI BRIEF was completed by his mother, while his post-TBI BRIEF was completed by his father and therefore the comparability of the pre- and post-TBI scores was reduced. In addition, the pre-TBI BRIEF had an Inconsistency score of 7 (questionable range; Table M8 in Appendix M), which suggested that the pre-TBI behaviours were inconsistently reported across items.

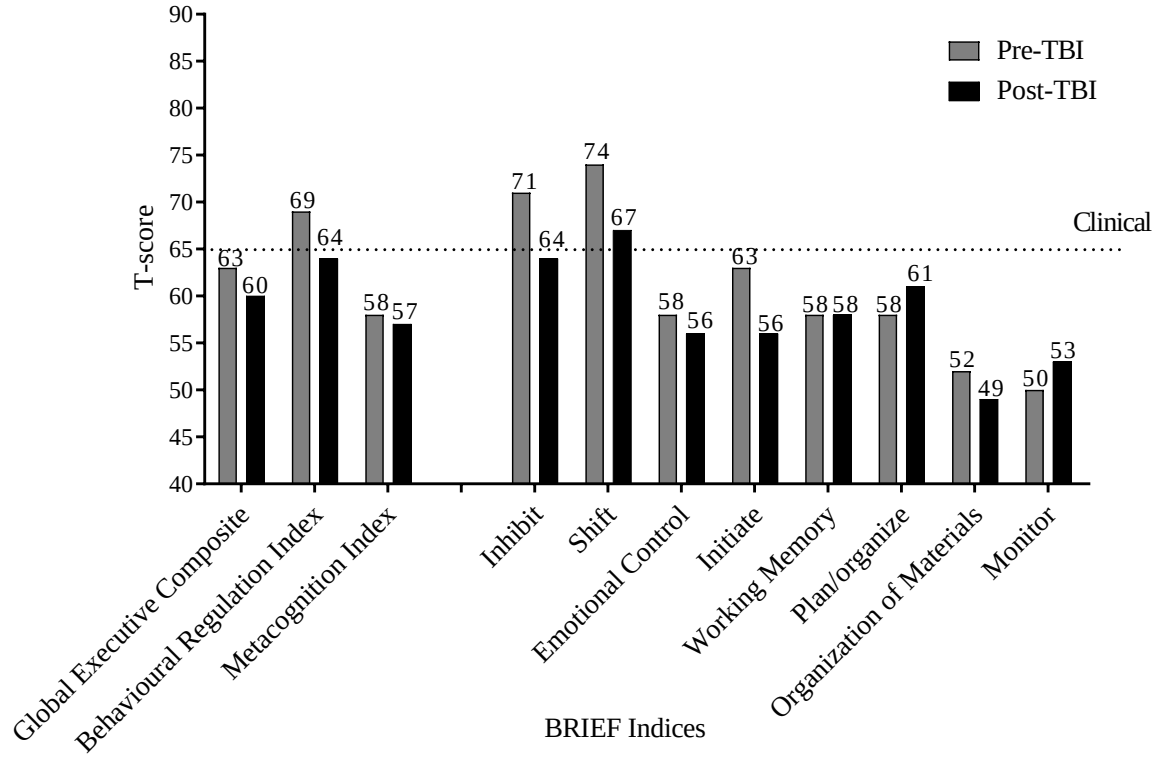

Figure 19. Thando's Behaviour Rating Inventory of Executive Function (BRIEF) indices for before and after the traumatic brain injury (TBI). Scores equal to or greater than 65 are in the clinical range (Gioia et al., 2000).

CBCL. Thando displayed a clinically statistically significant increase (95% CL) in the Internalising Problems grouping following the TBI, which was largely due to the increase in Somatic Complaints (99% CL) post-TBI (Figure 20). Within the individual syndrome profiles, Thando's Thought Problems and Attention Problems scores were significantly increased (95% CL) post-TBI but only Attention Problems reached the clinical range (Figure 20). The other measures had similar pre- and post-TBI scores. However, a number of these measures were in the borderline or clinical ranges before and after the TBI (Figure 20), potentially suggesting premorbid behavioural difficulties that were unchanged by the TBI.

In terms of the CBCL Diagnostic Scales, Thando had a significant increase (99% CL) in Somatic Problems post-TBI, while all other indices were unchanged (Figure 21). However, his pre- and post-TBI Affective and Conduct Problems fell into the clinical range, suggesting premorbid issues. Like the BRIEF, the pre-TBI CBCL was completed by Thando's mother, while the post-TBI CBCL was completed by his father.

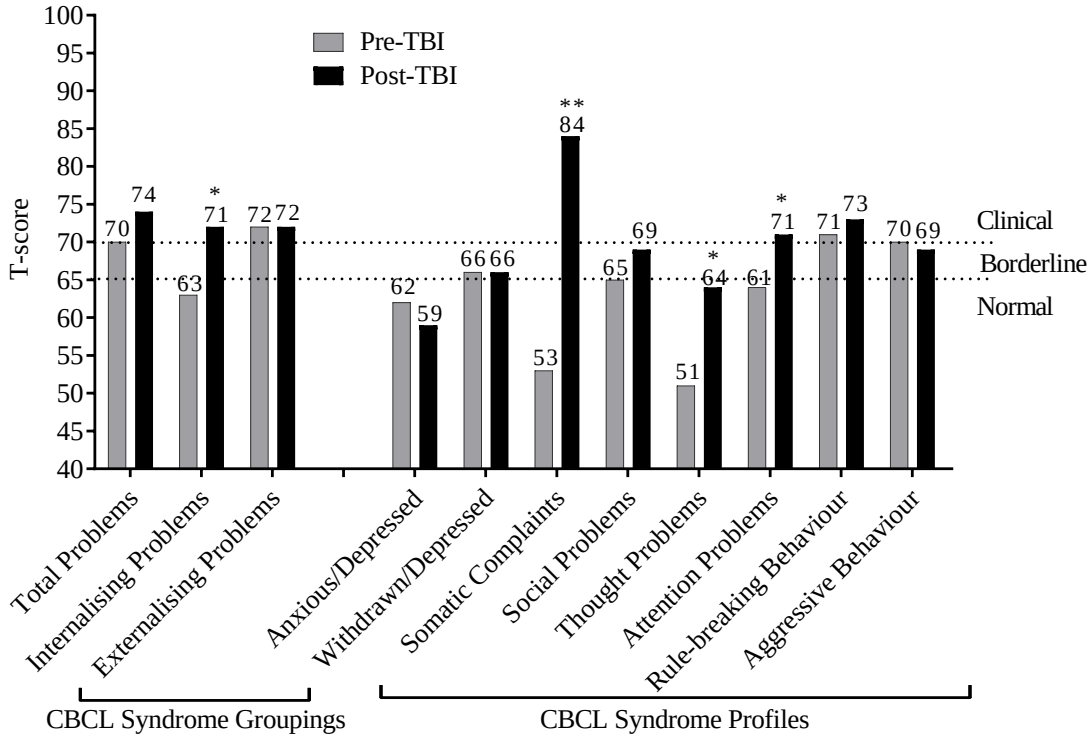

Figure 20. Thando's Child Behavioural Checklist (CBCL) syndrome profiles for before and after the traumatic brain injury (TBI). T-scores between 65 and 70 are in the borderline range, while scores equal to or greater than 70 are in the clinical range (Achenbach & Ruffle, 2000). *a change with 95% confidence; **a change with 99% confidence.

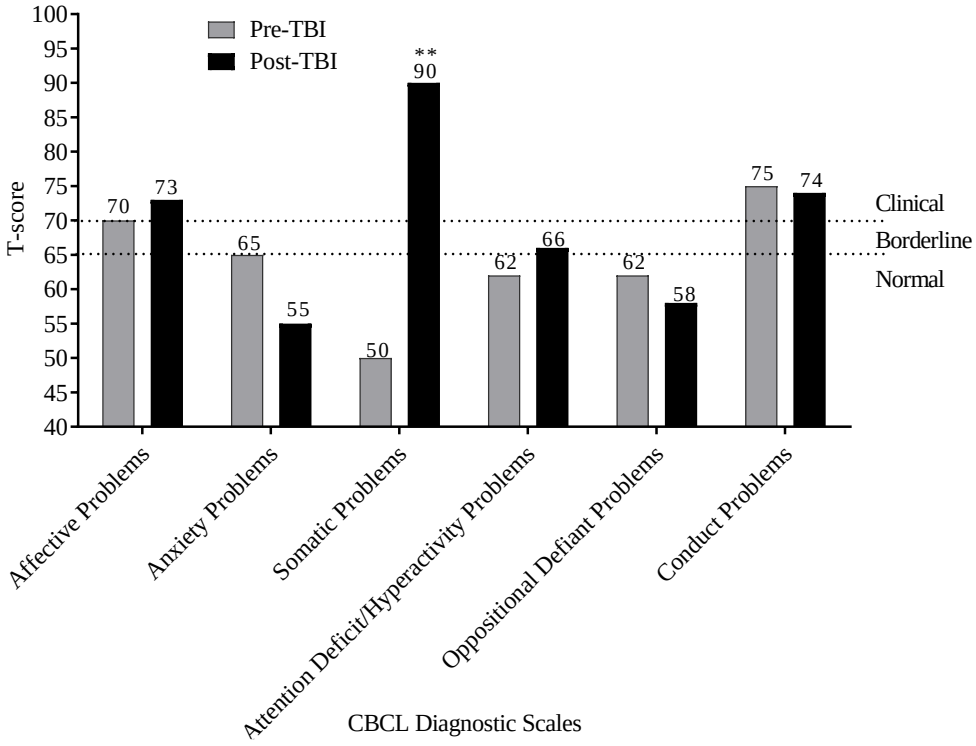

Figure 21. Thando's Child Behavioural Checklist (CBCL) diagnostic scales for before and after the traumatic brain injury (TBI). T-scores between 65 and 70 are in the borderline range, while scores equal to or greater than 70 are in the clinical range (Achenbach & Ruffle, 2000). **a change with 99% confidence.

MRI Results

Thando's 6-month post-TBI MRI scan revealed multifocal areas of pathology (See Figures N6 – N9 in Appendix N). Specifically, T2 and FLAIR signal abnormalities were found in both thalami, with extension posteriorly into the cerebral peduncles, as well as in the cerebellar white matter (greater expression in the left hemisphere). Small areas of cystic encephalomalacia were noted in the posterior aspect of the body and isthmus of the corpus callosum and the left dorsolateral area of the midbrain.

Summary of Outcomes

Thando presented with some mild to moderate cognitive difficulties in sustained attention, audioverbal memory, and planning but his visuospatial memory, processing speed, cognitive flexibility, problem-solving, and rule adherence were relatively intact. Thando showed no changes on the BRIEF but did have more Attention Problems, Thought Problems, and Somatic Complaints post-TBI on the CBCL. Thando's CBCL Rule-breaking Behaviour and Conduct Problems scores fell into the clinical range both before and after the TBI. However, Thando was able to adhere to the Towers' ruleset and was well-behaved throughout the assessment. Thando's MRI showed evidence of multifocal subcortical white matter abnormalities, which was at odds with his relatively good neuropsychological performance. A graphical summary of the potential factors influencing Thando's outcomes can be found in Appendix O (Figure O4).

Case Study 5: Katlego

Medical History

Pre-TBI. Katlego[17] was born prematurely and with an atrial septal defect, which did not require treatment. There were other significant medical issues.

The TBI. Katlego was involved in a PVA while crossing the street on 03/10/2018 (aged 9 years). He had a GCS of 3 on the scene and was taken to RXH and admitted to the pICU. On arrival, he was intubated and had a GCS of 8T, a tibia/fibula fracture, a left periorbital haematoma, and a dilated left pupil. CTB (03/10/2018) showed cerebral oedema and signs of TAI. Specifically, Katlego had haemorrhagic contusions at the grey/white matter interface of the left frontal lobe, subdural haemorrhage in the left hemisphere, a slight subdural haematoma in the interhemispheric fissure, and minimal subarachnoid haemorrhage in the interpeduncular fossa. There was some mild rightward midline shift at the third ventricle, but no signs of hydrocephalus. Katlego had physiological brain monitors placed on

[17] Pseudonym.

04/10/2018. During the five days of monitoring, there were two episodes[18] where Katlego's ICP briefly reached but did not exceed 20mm Hg (Table M2 and Figure M5 in Appendix M). Katlego's $PbtO_2$ levels remained above 20mm Hg (Table M2 and Figure M6 in Appendix M).

Katlego was extubated, had the monitors removed, and was discharged from the pICU on 08/10/2018. He had a relatively fast neurological recovery. His GCS improved to 15 on 11/10/2018 (eight days post-TBI) and by this time he was answering questions appropriately and in full sentences, although he spoke with a soft voice and took time to respond. The Occupational Therapist reported that Katlego could cut in a neat line, say the months of the year, and count backwards from 10 on assessment (11/10/2018). Several days later (16/10/2018) the Occupational Therapist reported that Katlego could solve 24-piece puzzles with minimal assistance and that his memory was good but required prompts. Katlego was also reportedly very distractible. Katlego was discharged home on 17/10/2018, 14 days after the TBI. He did not go for further rehabilitation at GSH due to his good recovery.

Post-TBI. Katlego was seen for a Neurosurgery follow-up appointment on 05/12/2018. It was reported that Katlego was still experiencing headaches three times a week. There were also concerns about his poor functioning at school and whether he would be able to cope in grade 4 the following year.

Developmental History

Katlego's mother provided the developmental history. Katlego's mother developed preeclampsia and Katlego was delivered two months prematurely via caesarean section. He weighed 800g at birth and his lungs were underdeveloped. Katlego spent a month in the hospital before being discharged home. His mother reported that he had delayed developmental milestone achievement compared to his siblings. He began walking at 18 months. She could not remember the exact age when he started talking but she knew that it was later than his siblings. He also struggled with fine motor skills, for example, he battled to do his buttons and tie his shoelaces until grade 1 (aged 7 years). Katlego's mother took him to an Occupational Therapist in grade 1 and she recalled that the Occupational Therapist noted poor fine motor skills and somatosensory functioning. Katlego had no separations from his parents and no notably difficult emotional childhood experiences.

Social Functioning

Pre-TBI. Katlego lived with his parents and his three sisters (aged 19, 8, and 6 years). Katlego's mother reported that he was a bit disobedient and distractible at home. Katlego was

[18] Each episode denotes one hour of monitoring time.

outgoing at school and had lots of friends. Katlego's parents worked as unskilled labourers. However, they were both inconsistently employed. His family had a medium asset index score, but their Social/Self-care, Childcare, and Extra Resources needs were not always met (Table M4 in Appendix M).

Post-TBI. Katlego's mother reported that Katlego was more disobedient and childish at home following the TBI. He required more supervision post-TBI; Katlego's mother thinks that this had negatively influenced the care given to his siblings. Katlego's mother also reported that she struggled emotionally to come to terms with Katlego's TBI and that the time since the accident had been difficult for the family. The family did not receive counselling for this.

Academic Functioning

Pre-TBI. Katlego has struggled at school since grade R (2014, aged 6 years). He repeated grade 1 in 2016 (aged 7 years) and obtained mostly 3's and 4's[19] for his subjects in the subsequent grades. Katlego was in the grade 3 LSEN unit at a mainstream public school and received remedial classes. Katlego was on the waiting list to be seen by an educational psychologist for a potential LSEN school placement. In contrast, Katlego's sisters did well in school.

Katlego's attention was the greatest concern according to his mother. He was diagnosed with ADHD and placed on Concerta (dosage unknown) by his family doctor in Grade R. After a year, his parents could not afford Concerta and Katlego was put on Ritalin (dosage unknown) in grade 1. Katlego's parents did not like Ritalin's side effects and chose to stop the medication and manage Katlego's attention through his diet from grade 2.

Post-TBI. Katlego was in grade 3 at the time of the TBI. He returned to his previous school after hospital discharge, but the teacher sent him back home for the remainder of the year as he was not coping. Katlego was promoted[20] to grade 4 in 2019. Katlego's mother reported that Katlego was performing worse at school following the TBI and he was obtaining 1's and 2's for all his subjects. She reported that he could read well before the TBI but struggled to read and write after the injury. The school organized a scribe to help him

[19] South African schooling grade classifications are as follows: 1: "Not achieved", 0 – 29%; 2: "Elementary achievement", 30 – 39%; 3: "Moderate achievement", 40 – 49%; 4: "Adequate achievement", 50 – 59%; 5: "Substantial achievement", 60 – 69%; 6: "Meritorious achievement", 70 – 79%; 7: "Outstanding achievement", 80 – 100%.

[20] The South African public school policies dictate that a learner can repeat "one year per school phase where necessary" (Department of Education, 1998). Each school phase consists of three or four school grades (years) and therefore if a learner has already repeated a grade in that phase they could be promoted through subsequent failed grades.

read and write his schoolwork. Katlego's mother reported that Katlego was going to be assessed by an educational psychologist for potential LSEN school placement. She also wanted to see a psychiatrist about putting Katlego back on ADHD medication.

Caregiver's Concerns

Katlego's mother's primary post-TBI concerns were Katlego's academic functioning and behaviour. She reported that Katlego was forgetful, distractible, impulsive, childish, and needed instructions to be repeated. Her concerns were also shown on the FBI (Table M6 in Appendix M), where she scored five of the items as three or higher, indicating a substantial burden. The items were distributed between the Child, Spouse, and Family Routines/planning measures.

Neuropsychological Assessment

Presentation. Katlego was friendly and outgoing; he laughed and joked throughout the assessment. Katlego was, however, highly distractible, talkative, and fidgety. He tried his best to steer the conversation away from the task at hand. Katlego would also impulsively interrupt instructions. He required constant encouragement to maintain focus. Katlego was not on any ADHD medication.

Attention. Katlego had a forward digit span of four (borderline range; Figure 22), suggesting difficulties with attention and concentration. Katlego performed poorly on the TMT Visual Scanning condition (borderline range; Figure 22). He had a haphazard search strategy and missed three of the targets (extremely low range; Table M7 in Appendix M) despite scanning the page several times. Katlego also frequently struggled to locate the desired letters or numbers in the subsequent TMT trials. His performance suggested that he had selective attention difficulties. Collectively, Katlego had an attention composite score in the borderline range (Figure 23).

Memory. Katlego required constant reminders to attend to the Dot Locations test stimuli. He haphazardly placed the discs during the recall trials. He, therefore, scored poorly on the Dot Locations' learning (6/8; 3/8; 5/8 correct; low average range), short delay (3/8 correct; borderline range), and long delay (4/8 correct; low average range) trials (Figure 22). Katlego's visuospatial memory composite fell into the borderline range (Figure 23) but his performance was strongly influenced by his poor attentional focus.

Katlego showed a relatively flat learning curve until the last RAVLT learning trial (5/16; 7/16; 7/16; 6/16; 11/16 words; borderline range; Figure 22). He recalled nine words following a short delay (average range) and 10 following a long delay (average range, Figure 22). Katlego also scored in the average range on the Recognition trial (Figure 22) despite

visibly losing attention toward the end of the trial. Katlego's RAVLT performance resulted in an average range audioverbal memory composite score (Figure 23) and showed that he could encode and retain audioverbal information. This result was of course achieved in the context of his attention being regularly cued in a relatively distraction-free setting.

Processing Speed. Katlego started quickly but soon lost attentional focus and impetus during the Coding and Symbol Search tasks resulting in scores in the borderline range for both tasks and the Processing Speed Composite (Figures 22 and 23). Qualitatively, his thinking did not appear slow but rather unfocused and disorganised. In addition, Katlego made two errors in the 15 attempted items of the Symbol Search task, which might have been due to impulsivity and/or selective attention deficits.

Executive Functions. Katlego had a backward digit span of two (borderline range; Figure 22). Similarly, he could only manipulate two-item sequences in the Letter-Number-Sequencing subtest (extremely low range, Figure 22). Both tasks indicated working memory difficulties (collectively shown in the Working Memory Index; Table M7 in Appendix M).

Katlego's completion time and error count scores fell in the extremely low range for the TMT Number Sequencing, Letter Sequencing, and Number-Letter Switching trials (Table M7 in Appendix M and Figure 22). He made two errors while connecting the numbers 1 to 13 before running out of time on the Number-sequencing condition. He impulsively connected adjacent numbers rather than finding the correct number. Katlego made four errors in connecting the letters A to J before the time limit expired on the Letter Sequencing condition. He could recite the alphabet as a song but could not accurately sequence the letters. Katlego frequently lost the rule and would connect a string of letters or numbers on the Number-Letter Switching trial. He took his time to trace the line in the TMT Motor condition, but his lines often veered away from the dotted line, suggesting difficulties with fine motor skills.

Katlego could not adhere to the Tower test's rules and made 10 rule breaks on the four attempted items (extremely low range; Figure 22). He was only able to construct the first tower, which consisted of just two discs, resulting in a Total Achievement score in the extremely low range (Figure 22). He could not form a strategy without breaking the rules. Katlego's executive functions composite score fell within the extremely low range (Figure 23).

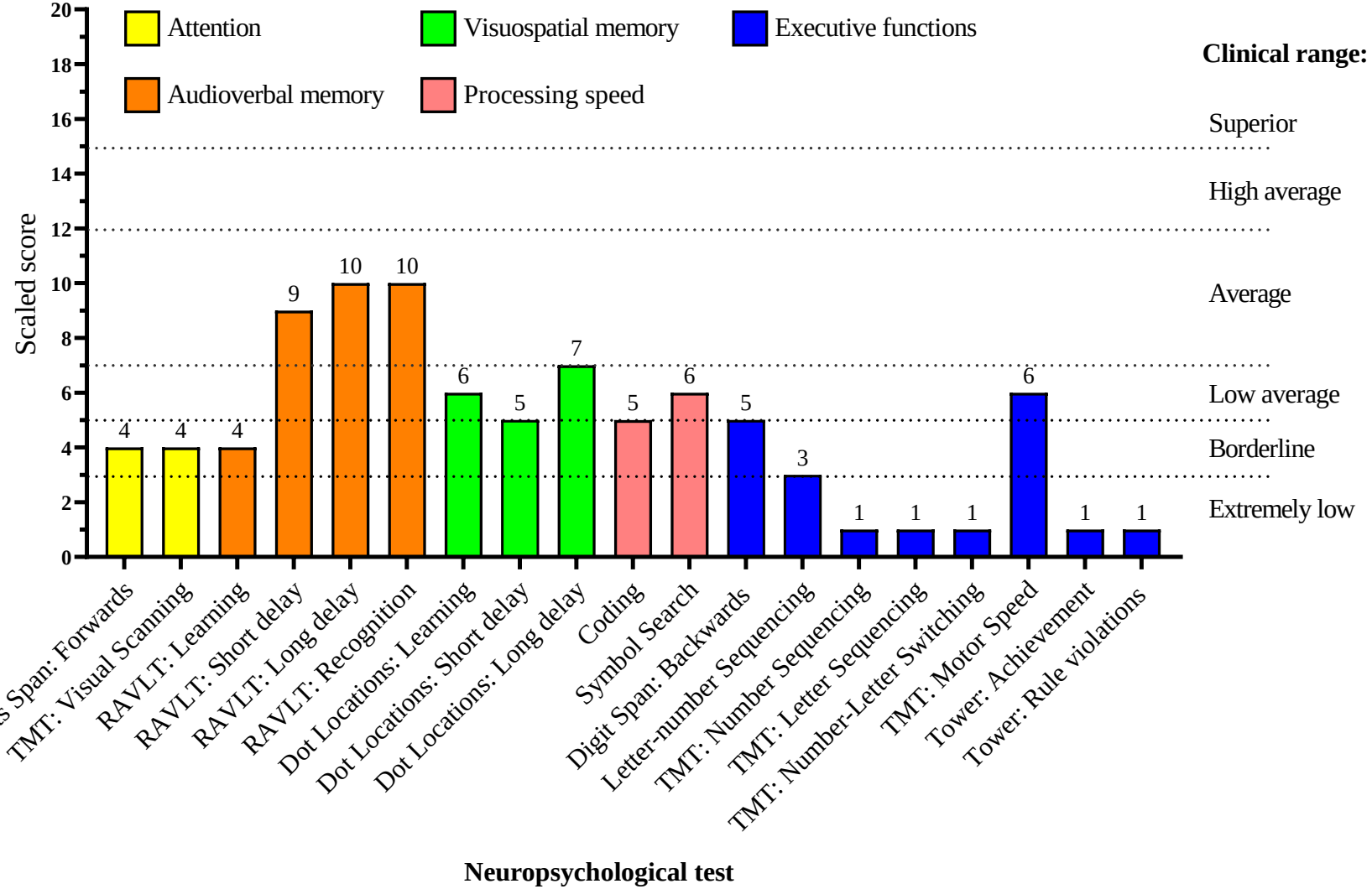

Figure 22. Katlego's scaled scores for each of the neuropsychological tests. The bars are coloured according to which cognitive domain the test theoretically measures. The clinical scaled score descriptions are displayed on the right of the graph. RAVLT: Rey Auditory Verbal Learning Test; TMT: Trail Making Test.

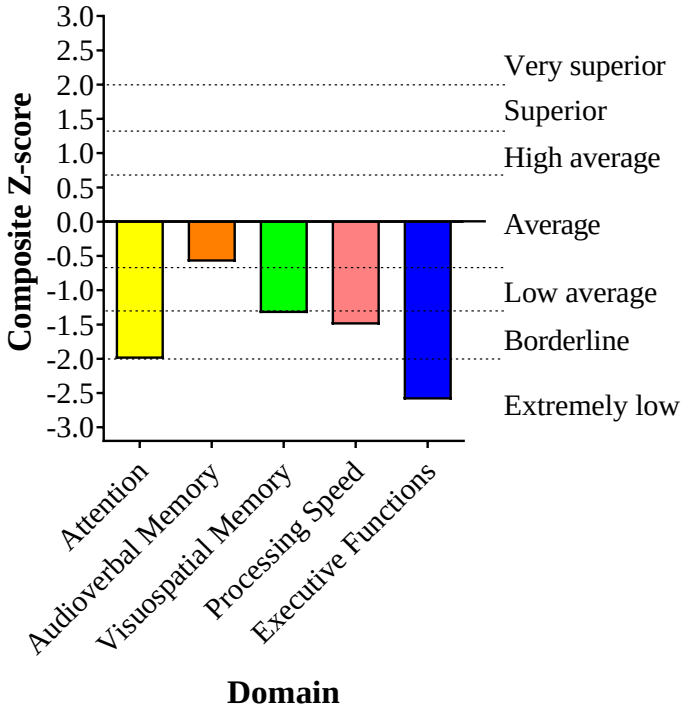

Figure 23. Katlego's composite Z-scores for each of the assessed domains. The clinical Z-score descriptions are displayed on the right of the graph.

Behavioural Outcomes

BRIEF. Katlego scored in the clinical range for all BRIEF measures, except for Organisation of Materials, both pre-and post-TBI (Figure 24). However, there were no clinically statistically significant differences between pre- and post-TBI scores. Katlego's mother might have had a negative view of Katlego's behaviour following the TBI as the post-TBI BRIEF Negativity score was 6 (elevated range, Table M8 in Appendix M).

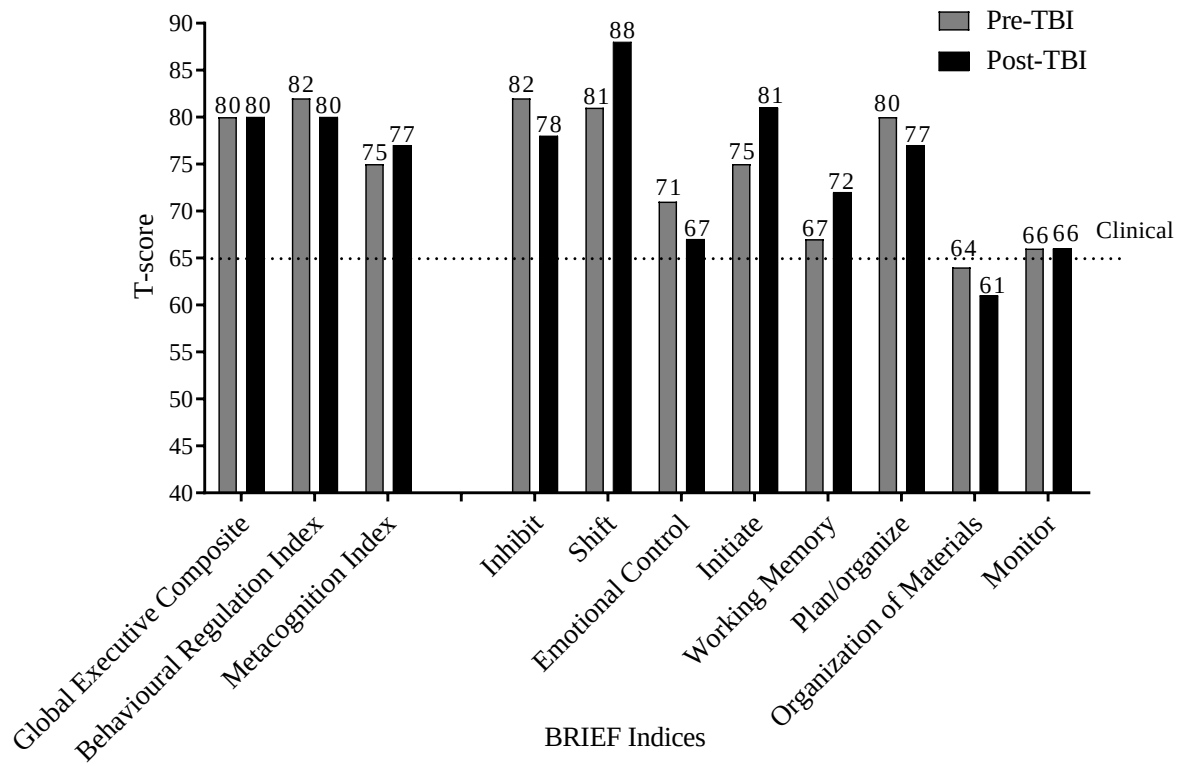

Figure 24. Katlego's Behaviour Rating Inventory of Executive Function (BRIEF) indices before and after the traumatic brain injury (TBI). Scores equal to or greater than 65 are in the clinical range (Gioia et al., 2000).

CBCL. Katlego had a clinically statistically significant increase (99% CL) in the Internalising Problems grouping score post-TBI (Figure 25). The increase in the Internalising Problems syndrome grouping was largely due to the significant increases in the Anxious/depressed (95% CL) and Somatic Complaints (99% CL) syndrome profiles post-TBI (Figure 25). Social Problems was the only other syndrome profile to be significantly higher following the TBI (95% CL). All four of these increased measures fell in the borderline range post-TBI (Figure 25). Katlego's post-TBI Attention Problems score was also in the borderline range but not significantly higher than the pre-TBI level (Figure 25). In terms of the diagnostic scales, Katlego had no clinically statistically significant changes post-TBI and only his post-TBI Anxiety Problems fell into the borderline range (Figure 26).

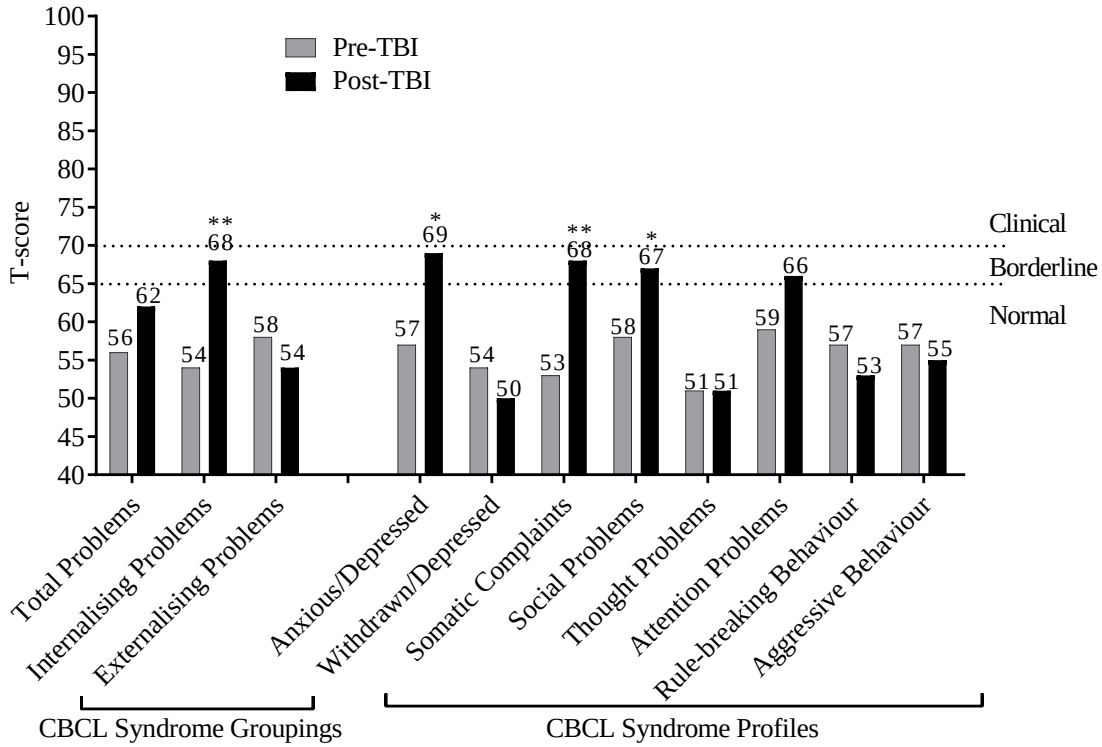

Figure 25. Katlego's Child Behavioural Checklist (CBCL) syndrome profiles before and after the traumatic brain injury (TBI). T-scores between 65 and 70 are in the borderline range, while scores equal to or greater than 70 are in the clinical range (Achenbach & Ruffle, 2000). *a change with 95% confidence; **a change with 99% confidence.

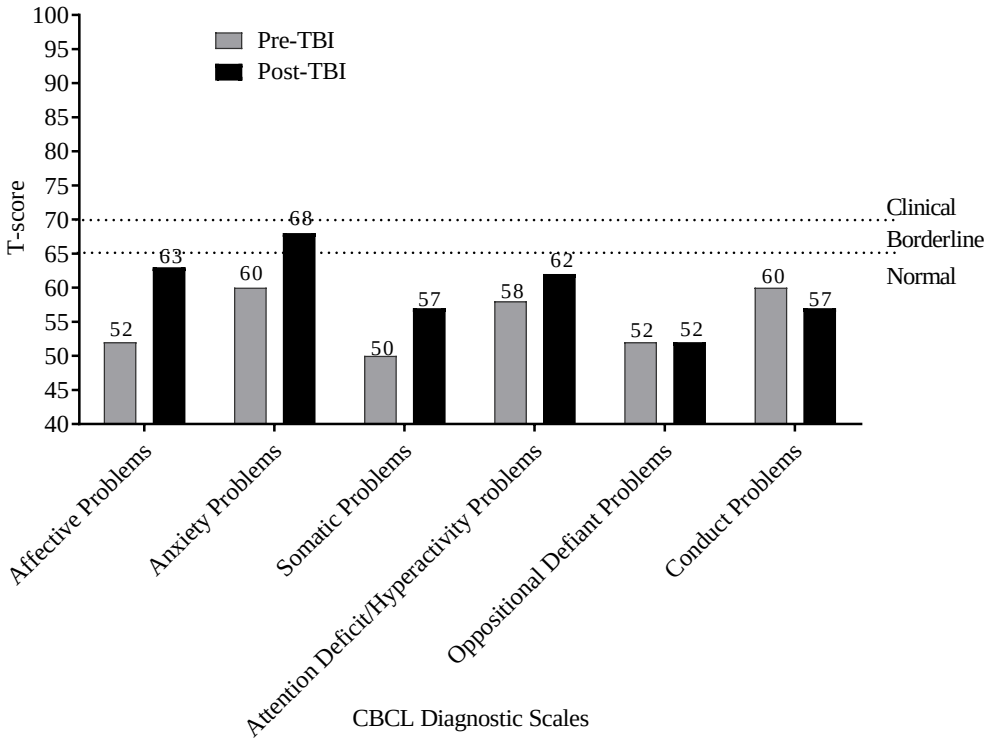

Figure 26. Katlego's Child Behavioural Checklist (CBCL) diagnostic scales before and after the traumatic brain injury (TBI). T-scores between 65 and 70 are in the borderline range, while scores equal to or greater than 70 are in the clinical range (Achenbach & Ruffle, 2000).

MRI Results

Katlego's 6-month post-TBI MRI scan showed evidence of encephalomalacia in the left frontal deep white matter (See Figures N10 – N12 in Appendix N). This was associated with slight ex vacuo dilatation of the left frontal horn of the lateral ventricle and prominent adjacent perivascular spaces.

Summary of Outcomes

Katlego presented with severe attentional, executive, and behavioural deficits that impacted his performance across all cognitive domains. Specifically, Katlego had difficulty in attention and concentration, selective attention, working memory, impulse control, problem-solving, cognitive flexibility, and rule adherence. Katlego fell into the clinical range for most BRIEF indices both before and after the TBI, suggesting premorbid executive and behaviour problems. His MRI showed white matter abnormalities affecting the left frontal lobe. A graphical summary of the potential factors influencing Katlego's outcomes can be found in Appendix O (Figure O5).

Discussion

Overall Findings

During the 6-month recruitment window, five patients with pTBI were enrolled and completed the study. These participants presented with 6-month post-TBI outcomes that ranged from mild neuropsychological deficits and an MRI scan with no visible abnormalities to severe neuropsychological deficits and evidence of multifocal pathology on imaging. Further descriptive investigation revealed several factors that might have interacted with the TBI to influence participant outcomes. Of concern was the relatively high occurrence of adverse developmental, socioeconomic, and/or neuropsychological histories.

Outcome heterogeneity was described as a "hallmark" of TBI as patients present with an assortment of neuroanatomical, physical, and cognitive impairments (Allen, Leany, et al., 2010; Covington & Duff, 2021). In agreement, there was considerable variability in the 6-month post-TBI outcomes. Briefly, Alice presented with severe behavioural, attentional, and executive deficits that influenced her performance across all cognitive domains and made standardised neuropsychological assessment difficult and MRI unmanageable. Ethan had some mild to moderate executive difficulties, which might have been pre-existing, no behavioural changes, no caregiver concerns, and a normal MRI scan. Mia had severe deficits across all measured cognitive domains, drastic behavioural changes, high caregiver burden, and extensive pathology on imaging. Thando presented with some neuropsychological

deficits in certain domains (sustained attention, audioverbal memory, and working memory), while others remained relatively intact, but his MRI showed widespread subcortical white matter abnormalities. Lastly, Katlego had significant attentional and executive deficits, which was likely an exacerbation of premorbid ADHD, and encephalomalacia affecting his frontal lobe on MRI. Participants' premorbid characteristics varied greatly, which would have further contributed to the heterogeneity of post-TBI outcomes.

Neuroimaging Outcomes

Structural MRI scans were completed on four of the participants at 6-months post-TBI. Ethan's scan had no visible abnormalities. In contrast, pathology was noted on Mia, Thando, and Katlego's scans. Children are more susceptible to TAI due to physiological and biomechanical characteristics (Pinto et al., 2012) and in agreement, TAI pathology was the most frequent feature on imaging.

Severe TAI most commonly causes lesions in the grey and white matter junctions or the white matter tracts of the corpus callosum, internal capsule, thalamus, basal ganglia, cerebellum, and/or brainstem (Hamdeh et al., 2017; Mendoza et al., 2018). Three participants showed lesions in the areas associated with TAI. Specifically, Mia had encephalomalacia in the corpus callosum, the external capsule extending into the corona radiata, and the deep white matter of the postcentral gyrus. Thando displayed white matter abnormalities in the corpus callosum, thalamus, midbrain, and cerebellum. Katlego's pathology was visible in the left frontal lobe deep white matter.

The traditional histopathological grading of TAI proposed by Adams et al. (1989) classifies three grades of ascending TAI severity. Briefly, grade 1 injuries have evidence of microscopic axonal injury in the cerebral hemispheres, corpus callosum, brain stem and cerebellum; grade 2 injuries include an additional focal macroscopic lesion within the corpus callosum; and grade 3 injuries have an added macroscopic lesion in the brainstem (Adams et al., 1989). More recent MRI-based research implicated lesions in the corpus callosum, thalamus, basal ganglia, and brainstem with a greater risk of poor outcomes (Cicuendez et al., 2019; Moen et al., 2014). Overall, Mia's 6-month post-TBI neuropsychological outcomes were understandable given the extensive TAI pathology noted on her imaging, while Thando's outcome was better than expected given the widespread subcortical lesions seen in his scan.

In addition to the TAI, Mia had bilateral frontal lobe encephalomalacia presumably from the contusions observed on the initial hospital scans. Alice also sustained bifrontal contusions, which were visible on her acute hospital imaging, and therefore might have had

similar encephalomalacia on her 6-month post-TBI scan, had the scan been conducted. The frontal lobe is especially vulnerable to pTBI contusions given its location behind the frontal bone and above the sharp bony protrusions of the skull base (Bigler, 2001).

Neuropsychological Outcomes

Examining the trends across participants indicated that attention and executive functions were the most frequently disrupted domains, with all participants showing some deficits in these areas. Memory, processing speed, and behavioural measures were affected in some, but not all participants.

Attention

Research has consistently described attention deficits following pTBI (Babikian et al., 2015; Mathias & Wheaton, 2007). All the participants had some difficulties with the Digit Span forward trial, suggesting that basic attention and concentration were susceptible to disruption following TBI in this cohort. Alice, Ethan, and Katlego additionally displayed selective attention difficulties on the TMT Visual Scanning task. Although sustained attention was not formally assessed, qualitatively, Alice, Mia, Thando, and Katlego struggled to maintain their attention.

Alice, Mia, and Thando additionally had post-TBI CBCL Attention Problems syndrome profile scores in the clinical range, while Katlego's score fell into the borderline range post-TBI, indicating real-world attention problems. Alice and Mia also had CBCL Attention Deficit/Hyperactivity Problems diagnostic scale scores in the clinical range post-TBI, and Alice was diagnosed with ADHD after the TBI in line with the established elevated secondary ADHD risk post-TBI (Narad et al., 2018). Surprisingly, Katlego's pre-TBI Attention Problems and Attention Deficit/Hyperactivity Problems scores were in the normal range, which was at odds with his premorbid ADHD diagnosis.

Memory

The study assessed both audioverbal (RAVLT) and visuospatial memory (Dot Locations). Alice and Mia scored poorly on both audioverbal and visuospatial tasks, Thando struggled with the audioverbal task but did well in the visuospatial task, Katlego had good audioverbal delayed recall scores but struggled with the visuospatial task, and Ethan performed well in both domains. Intact attention faculties are a prerequisite for almost all cognitive processes (Burgoyne & Engle, 2020). The memory tests were particularly vulnerable to the effects of poor attention. Alice, Mia, and Katlego struggled to maintain their attention on the stimuli and, therefore, it was difficult to ascertain the true memory performance of these participants.

Thando had pronounced difficulties with his RAVLT spontaneous recall but did well on the recognition trial suggesting that it was his memory retrieval, rather than memory encoding that was deficient. Patients with pTBI have been shown to have encoding and/or retrieval difficulties at varying levels (Lajiness-O'Neill et al., 2010).

Processing Speed

Processing speed is dependent on white matter integrity (Penke et al., 2010; Turken et al., 2008) and is, thus, susceptible to disruption following TBI (Felmingham et al., 2004; Rabinowitz et al., 2018). Alice, Mia, and Katlego scored poorly on the processing speed tasks. However, Alice and Katlego's performances were confounded by their attention and executive deficits and therefore not adequately representative of their processing speed. Mia had profound processing speed deficits both qualitatively and on assessment. Ethan had some evidence of mild processing speed deficits on Coding and TMT, but his Symbol Search scores were in the average range. Thando had no noticeable processing speed deficits. Therefore, despite three of the four scanned participants (Mia, Thando, and Katlego) showing TAI pathology on their 6-month MRIs, only one participant (Mia) had strong evidence of slowed processing speed.

Executive Functions

Working memory, sequencing, cognitive flexibility, problem-solving, impulsivity, and rule-adherence were some of the executive functions evaluated in the neuropsychological assessment, while the BRIEF added the caregivers' assessment of several executive functions. Executive functions are frequently disrupted following pTBI (Babikian & Asarnow, 2009) and, in agreement, all participants showed deficits in at least one aspect of executive functioning.

All participants scored in the borderline or extremely low ranges for the Working Memory Index. This was mostly due to the performances on the Letter-number Sequencing subtest, where all but Ethan scored in the extremely low range. One thing to note was that three participants (Alice, Mia, and Katlego) struggled with sequencing the alphabet, which confounded the Letter-number Sequencing subtest. The South African schooling system faces several challenges (Letseka, 2014; Reddy, 2014), which has resulted in low literacy rates among learners (Howie et al., 2007) and might explain the participants' alphabet difficulties. The participants did better on the backward trial of the Digit Span Task, with scores in the average (Thando), low average (Alice and Ethan), and borderline (Mia and Katlego) ranges but it was still evident that most of the cohort had working memory difficulties. In support,

Alice, Mia, and Katlego also had BRIEF Working Memory profile scores in the clinical range post-TBI.

Cognitive flexibility deficits are frequently noted post-pTBI (Beauchamp et al., 2011; Catroppa & Anderson, 2009; Treble-Barna et al., 2017) and all participants scored poorly on the TMT Number-Letter Switching condition. Although this trial was often confounded by factors including a slow and careful approach, working memory lapses, impulsivity, selective attention deficits, and alphabet difficulties, there was still evidence that Alice, Ethan, and Katlego struggled with the cognitive flexibility component. Mia did not complete the TMT but would likely have had difficulties. The BRIEF Shift syndrome profile is a measure of cognitive flexibility and Alice, Mia, Thando, and Katlego had post-TBI Shift scores in the clinical range indicating everyday difficulties. Ethan had pre-TBI, but not post-TBI, Shift scores in the clinical range which was at odds with his TMT test performance.

Only Ethan and Thando were able to complete most of the Towers task constructions at close to an age-appropriate level without making rule-breaks, indicating that they could problem-solve at a reasonable level and adhere to a ruleset. Alice and Katlego had severe difficulties on the Towers test with impulsivity and rule-adherence, both of which are commonly reported deficits post-TBI (Babikian et al., 2015; Babikian & Asarnow, 2009; Tuerk et al., 2020). Although Mia did not complete the Towers task it was clear that she also had difficulties with impulsivity and rule-adherence on other tasks. The impulsivity problems were mirrored on the BRIEF parent reports, where Alice, Mia, and Katlego had Inhibit profile scores in the clinical range post-TBI. Alice and Mia also had post-TBI CBCL Rule-breaking Behaviour scores in the clinical range, indicating problems with rule-adherence at home.

There were discordances between Thando and Katlego's measures of rule-breaking on the CBCL and Towers. Specifically, Thando made no rule violations on the Towers task, but his caregivers reported CBCL Rule-Breaking behaviours in the clinical range. In contrast, Katlego was unable to adhere to the Tower test's ruleset but had a CBCL Rule-Breaking profile score in the normal range. These findings suggest that either the rule-breaking behaviour was context dependant or the caregivers' reporting of these behaviours was biased or inaccurate.

Behaviour

Alice and Mia had dramatic differences between their pre- and post-TBI BRIEF and CBCL scores. These changes were noted across almost all measures suggesting widespread post-TBI behavioural difficulties. In support, both Alice and Mia's caregivers described

behavioural changes as their main post-TBI concerns. Interestingly, the CBCL Anxious/Depressed and Withdrawn/Depressed syndrome profiles and the Anxiety Problems diagnostic scale were the only unchanged post-TBI measures for both Alice and Mia, indicating that the anxiety and depression-related measures were less affected by the TBI.

Katlego's mother reported that Katlego's behaviour had worsened following the TBI. However, there were few clinically statistically significant changes measured on the CBCL and BRIEF. Katlego had several pre-TBI BRIEF measures in the clinical range and therefore there might have been ceiling effects on these indices. In support, Katlego's mother described his pre-TBI behaviour as being bad, but now even worse post-TBI. Consideration must therefore be given as to how to accurately measure behavioural changes in those with pre-existing difficulties.

The behaviour profiles of the other participants were relatively unchanged by the TBI. Therefore, there was only a subset of patients who developed clear behavioural deficits post-TBI, which was in agreement with a systematic review that indicated that 50% of patients with pTBI are at risk of developing behavioural problems (Li & Liu, 2013). A limitation was that behaviours were retrospectively reported by caregivers and were therefore possibly influenced by recall bias as well as emotional factors related to the TBI (Brooks et al., 2014; Sheikh et al., 2016). Obtaining accurate pre-injury behavioural profiles is a common limitation of studies investigating post-TBI changes (Emery et al., 2016).

Predictive Factors

Although the sample size was too small to draw conclusions between potential predictive factors and post-TBI outcomes, the study was able to highlight trends and factors that might require deeper investigation in follow-up studies.

Injury Mechanism

In agreement with previous literature (Dewan et al., 2016; Schrieff et al., 2013), the majority of pTBIs (4/5) were as a result of PVAs. All participants were injured in the evening or on the weekend similarly in accordance with findings documenting the heightened pTBI risk outside of school hours (Dewan et al., 2016). Interestingly, the participants were all injured between the 28th and the 3rd of the month, indicating a potential spike in pTBI cases toward the end of the month and the start of the next. While there is no available evidence directly explaining this pattern, this timeframe coincides with the week following the

traditional South African "payday"[21]. Payday is associated with increased alcohol consumption in South Africa (Desai et al., 2020) and drunk driving is a considerable factor in South African MVA deaths (Meel, 2007). Therefore, the period following payday might result in increased risks of MVAs and thus pTBIs. However, a larger sample size would be required to fully assess this pattern. Of additional concern was that two of the PVAs were "hit-and-runs", where the accident was unwitnessed, and the driver immediately fled the scene. This is problematic for many reasons, most importantly that it might delay the initiation of medical care.

Initial Injury Severity

The initial GCS and coma duration are used as indicators of TBI severity but have been inconsistently correlated with TBI outcomes (Babikian & Asarnow, 2009; Donders & Janke, 2008; Fay et al., 2009; Krasny-Pacini et al., 2017; Strong et al., 2010; Trivedi et al., 2007). Ethan had the highest GCS on admission and the best post-TBI outcomes, while Mia had the lowest GCS and worst outcomes, in agreement with the suggested relationship between initial GCS and TBI outcomes. Coma duration differed greatly between participants (range: 8 to 89 days) but did not seem to correlate with outcomes on an individual level. For example, although Mia had the longest period of reduced GCS and the worst 6-month post-TBI outcomes, Ethan had the second-longest duration and the best outcomes. However, the study was underpowered to provide a thorough assessment of the relationship between GCS or coma duration and post-TBI outcomes.

Physiological Brain Monitoring

Of the three participants that underwent physiological brain monitoring, Mia was the only participant with prolonged episodes of ICP over 20mm Hg and $PbtO_2$ less than 20mm Hg. She also had the worst 6-month post-TBI outcomes, in line with research implicating elevated ICP and depressed $PbtO_2$ with adverse TBI outcomes (Badri et al., 2012; Schrieff-Elson et al., 2015; Slawik et al., 2009).

Post-acute MRI Findings

Larger, more diffuse, and bilateral pathology is generally associated with worse post-pTBI outcomes (Puffer et al., 2019; Wong et al., 2011). In agreement, Ethan had no visible pathology on his 6-month post-TBI MRI scan and had the best outcomes. The other

[21] In South Africa there is a precedent that most employees receiving monthly salaries get paid on or near the 25th of each month.

participants had differing MRI presentations that could have contributed to the specific pattern of deficits post-TBI.

TAI, which was the most common pathology on the participants' 6-month post-TBI scans, is most often associated with attention, processing speed, and executive deficits (Catharine et al., 2019; Grassi et al., 2021; Kourtidou et al., 2013). Attention and executive deficits were the most frequent cognitive difficulties in this cohort, however, only Mia had strong evidence of slowed processing speed.

A further exception was Thando, who had TAI lesions in the corpus callosum, basal ganglia, midbrain, and cerebellum but surprisingly performed relatively well on the processing speed and executive function tests. Previous literature suggests that TAI lesions in the corpus callosum, basal ganglia/thalamus, and midbrain are associated with the worst cognitive outcomes (Catharine et al., 2019; Cicuendez et al., 2019). Therefore, his performance was unexpected given his MRI pathology. Although, one cannot rule out further deficits as time progresses or subtle deficits given his high premorbid baseline.

Thando did, however, have deficits in sustained attention and audioverbal memory. The thalamus plays an important function in attentional control and the ability to sustain attention (Schmitt et al., 2017; Yu et al., 2018) and therefore Thando's attentional fluctuations could be related to his thalamic lesions. Thalamic injuries can also cause memory deficits (Pergola et al., 2013; Sweeney-Reed et al., 2016). The thalami maintain the lateral organization of the cortex, in that the left thalamus is more associated with audioverbal processing while the right is more involved with visuospatial information (Hebb & Ojemann, 2013; Schott et al., 2003). Thando had greater left thalamic pathology, which might explain his audioverbal, but not visuospatial, memory deficits.

Katlego's white matter abnormalities were located in the deep white matter of the frontal lobes, and, in accord with the functional roles of white matter and the frontal lobe (Cristofori et al., 2015; Lipszyc et al., 2014; Mendoza et al., 2018; Rossi et al., 2009), he had severe attention, executive, and behavioural deficits. Alice and Mia both had frontal contusions affecting the orbitofrontal area, which is an area specifically associated with emotional and behavioural regulation (Mendoza et al., 2018; Stuss, 2011). Unsurprisingly, both displayed striking behavioural changes following the TBI.

The structural MRI scans were able to identify macroscopic lesions but were unable to investigate the microscopic or functional damage associated with TAI (Grassi et al., 2021; Tang et al., 2012). In addition, the brain operates largely as a complex interconnected system and therefore the role of networks and the effect of diffuse injuries could not be commented

on. Additional advanced imaging modalities that can elucidate the microscopic or functional changes will improve the understanding of the relationships between pathology and neuropsychological presentations.

Developmental History

Katlego was born prematurely and with complications. Pre-eclampsia, premature birth, and potential perinatal hypoxic events (associated with underdeveloped lungs in premature babies) have all been associated with increased risk of developmental delays, ADHD, and neuropsychological difficulties later in life (Gumusoglu et al., 2020; Maher et al., 2020; Sucksdorff et al., 2015; Vieira & Linhares, 2011) and might have, in part, explained Katlego's developmental delays, poor academic history, and prior ADHD diagnosis. It was most likely that Katlego's post-TBI presentation is a result of the TBI worsening his premorbid difficulties. Ethan was also born prematurely but there was less evidence of developmental delays or premorbid academic problems.

A concerning finding was that two of the participants (Ethan and Mia) had suspected substance abuse exposure in utero. The reported methamphetamine use could not be confirmed or quantified, as both mothers were absent for reasons related to their substance abuse. In-utero substance exposure can have effects on developmental (Conradt et al., 2019; Ladhani et al., 2011; Wouldes et al., 2014), neuropsychological (Kwiatkowski et al., 2014; Sirnes et al., 2017), and structural brain (Roos et al., 2014; Sirnes et al., 2017) characteristics, which could be confounding to pTBI studies investigating these outcomes.

Methamphetamine use has been associated with increased occurrence of child neglect, household conflict, and physical and sexual violence resulting in an adverse environment for children (Watt et al., 2014). In agreement, both Ethan and Mia had difficult social histories. Parental substance abuse was also associated with increased incidences of child injury, as a result of decreased supervision, and therefore might also play a role in pTBI risk (Raitasalo & Holmila, 2017). However, to the best of our knowledge, there is no research comparing the relationship between parental substance abuse and pTBI risk.

Although the exact incidence is unknown, methamphetamine use was described as an epidemic and ubiquitous in certain communities in Cape Town, South Africa (Plüddemann et al., 2008, 2013; Watt et al., 2014). Although the sample size was small and therefore interpretations need to be cautious, 40% of the cohort had a suspected history of in-utero drug exposure. In contrast, only 4% of pregnant women from the USA reported using illegal substances according to the National Survey on Drug Use and Health (Wendell, 2013). Therefore, the developmental history, and specifically any prenatal exposures, needs to be

taken into consideration when comparing or combining South African participants with participants from other countries.

Neuropsychological History

Premorbid academic and intellectual functioning is a strong predictor of post-TBI neuropsychological performance (Liou et al., 2018; Moran et al., 2016) and therefore could be a mitigating factor to consider when interpreting post-TBI outcomes. Three of the participants (Alice, Ethan, and Katlego) had failed a school grade before the TBI, suggesting that a proportion of the cohort might have had premorbid neuropsychological difficulties. Thando and Mia were reportedly above average at school pre-TBI, and this appeared to be protective for Thando who performed better than expected on the neuropsychological assessment given the pathology on his 6-month post-TBI MRI scan.

Alice and Katlego had premorbid attention deficits, evidenced in caregiver histories and BRIEF and CBCL scores. Katlego was diagnosed with ADHD before the TBI, while Alice had not been reviewed by a medical professional for ADHD. ADHD is commonly under-reported in the general population (Ginsberg et al., 2014; Nussbaum, 2011). Both Katlego and Alice had significant attentional difficulties post-TBI, which was likely a result of the TBI exacerbating premorbid difficulties. ADHD was shown to increase health-risk behaviours and the occurrence of accidents (Liou et al., 2018) and therefore might increase pTBI risk and result in an over-representation of children with ADHD in pTBI cohorts. It would be difficult to ascertain whether ADHD was over-represented in the present cohort, given the low sample size and that there are no known South African ADHD incidence rates. The potential confounding nature of ADHD and the suggested over-representation in TBI cohorts creates a dilemma for TBI research. To exclude patients with premorbid ADHD would reduce the generalizability of findings and therefore future studies need to consider how to isolate the post-TBI neuropsychological deficits from premorbid difficulties.

Social History

Only Katlego and Thando were being cared for by their biological parents at the time of the TBI and only Katlego remained with his biological parents following the TBI as Thando was subsequently sent to live with his grandparents. The circumstances surrounding the loss of a biological parent were frequently traumatic and involved the death of a parent (Alice and Mia), illicit substance abuse (Ethan and Mia), and incarceration (Ethan). Recent census data indicated that only 34% of South African children live with both biological parents (Statistics South Africa, 2018). Suggested reasons for South African parental absence include poverty, labour migration, historic population control, and educational opportunities

(Amoateng & Heaton, 2007). In contrast, the US Census Bureau reported that 69% of children in the USA live with both biological parents (The Bureau of the Census for the Bureau of Labor Statistics, 2020). Traumatic primary caregiver changes can increase the risk of psychiatric or behavioural issues (Draper & Hancock, 2011; Otowa et al., 2014), which creates a potentially complicated premorbid emotional state and post-TBI recovery environment. In addition, the absence of biological parents in this study made it difficult to record developmental histories.

Children living with neither biological parent were shown to have a greater unintentional fatal injury risk (Tooley et al., 2006) and therefore might also have a greater TBI risk. However, no study has investigated this association. Decreased parental supervision has also been suggested as a significant component of pTBI susceptibility (Punchak et al., 2018). For example, parents were reported to be absent at the time of injury in 88% of pTBIs caused by PVAs in a Ugandan cohort (Punchak et al., 2018). Similarly, in the present study, only one of the four PVAs occurred when a caregiver was present.

Three of the participants had previous social trauma that included parental substance abuse, sexual assault, parent incarceration, and poverty. An adverse social history can increase the risk of neuropsychological, behavioural, and psychiatric difficulties in the absence of TBI (Draper & Hancock, 2011; Malarbi et al., 2017; Otowa et al., 2014) and therefore might negatively influence pTBI outcomes. There is a shortage of studies investigating the influence of prior trauma on pTBI outcomes but one such study found that children with greater pre-injury psychosocial adversity index[22] scores had a greater risk of developing post-TBI ADHD (Max et al., 2005). There might also be an interaction between previous trauma and the effects of the TBI as was seen in the case of Mia whose previous sexual assault and the loss of insight and behavioural control post-TBI appeared to result in inappropriate sexual behaviour.

The prevalence of adverse social histories could have been due to the difficult socio-economic circumstances in South Africa (Higgs, 2007) and/or that children in difficult social environments were over-represented in the cohort. A large prospective study of Ugandan children found that those who experienced more adverse family life events had a greater TBI risk (McKinlay et al., 2010), highlighting the vulnerability of children in unfavourable social environments.

[22] The psychosocial adversity index used in the study investigated six areas including parental criminality, not living with biological parents, and admission of the child into protective services due to family issues.

SES

A large portion of the South African population lives in low SES conditions, with a third of households living below the food poverty line (Statistics South Africa, 2015), and an unemployment rate of 35% (Statistics South Africa, 2021). Thando and Katlego's caregivers were both unemployed with inconsistent temporary employment. Thando's family had severe financial troubles that meant that none of their needs were reasonably met on the FRS and that Thando was sent to live with his grandmother after the TBI, which would limit his accessibility to follow-up monitoring and potential interventions if required. Low SES was associated with TBI risk (Amram et al., 2015; Bruns Jr. & Hauser, 2003), poor TBI outcomes (Brown, 2010; Moran et al., 2016; N. Ryan et al., 2014), and reduced access to rehabilitation (Cook et al., 2004) and therefore care needs to be taken when combining or comparing South African populations with first-world counterparts.

Limitations and Future Directions

One of the study aims was to identify barriers and considerations for the successful implementation of a large-scale, multi-site collaborative study investigating neuroimaging and neuropsychological pTBI outcomes in South Africa. The pilot study highlighted several factors worth considering.

Recruitment

The small sample size was the main limitation of the study. During the 6-month recruitment window, 13 eligible patients were identified but only five completed the study. Inability to contact caregivers (n=4), caregivers declining to participate (n=3), and caregivers lost to follow-up (n=1) were the reasons for non-inclusion. Caregivers were approached during the hospital stay or telephonically shortly after discharge and, in those that declined to participate, there appeared to be a hesitancy to agree to further hospital testing. Caregiver strain is common following prolonged child hospitalization (Commodari, 2010; Wray et al., 2011) and could have influenced participation willingness. An additional opportunity to provide consent at a follow-up hospital appointment might improve recruitment by providing caregivers with more time to recover from the acute emotional trauma and consider the study. The contact details provided on medical records were frequently inaccurate or changed with time, and therefore using follow-up appointments as additional recruitment opportunities may be beneficial.

MRI in Children

Advanced neuroimaging is becoming a crucial non-invasive tool in pTBI research (Ashwal et al., 2014). However, some considerations need to be overcome to successfully

conduct TBI imaging studies in paediatric patients. MRI sequences involve longer image acquisition times and are therefore more sensitive to movement artefacts, which can be problematic in a paediatric population. The likelihood of attention, hyperactivity, and behavioural deficits following pTBI (Babikian et al., 2015; Li & Liu, 2013) further complicate this issue. Children also experience greater anxiety and claustrophobia in the MRI machine due to the enclosed space and loud sound (Byars et al., 2002; Kotsoni et al., 2006). This could be further exacerbated in children with prior pTBI due to the increased risk of anxiety disorders, altered emotional regulation, and posttraumatic stress disorder (Iljazi et al., 2020; Li & Liu, 2013; Max et al., 2011).

Only three of the participants were able to complete the full one-hour MRI scan. Alice refused to cooperate with the MRI technicians, while Mia was scared of the MRI machine. Alice and Mia were the youngest and had the greatest executive and behavioural changes following the TBI. There were concerns before the start of the study that the potential pTBI-associated attention difficulties would increase the risk of movement artefacts and decrease the chance of successful MRI. Surprisingly, Katlego was able to complete the full MRI scan despite his severe attention difficulties, suggesting that, in this small cohort, behavioural regulation rather than purely attentional deficits, was the greater barrier to conducting lengthy MRI scans.

Without additional strategies to ensure that all participants can be scanned, the risk for future pTBI MRI research is that a subgroup of the cohort, potentially with the greatest behavioural and/or neuropsychological deficits, may be excluded from the research, which would reduce the generalizability of findings. Sedation is seen as a last-resort option due to the need for trained medical personnel and monitoring, the extra risk to participants, and the exclusion of functional studies such as fMRI. The study made use of a mock scanner and audio-visual media within the MRI, which have been found to reduce the need for sedation in paediatric MRI studies (Carter et al., 2010; Törnqvist et al., 2015). A child-friendly environment, noise reduction, behavioural training, customized play therapy, and practice MRI sessions have shown promise in improving MRI success rates (Barnea-Goraly et al., 2014; Bharti et al., 2016; Dong et al., 2019; Kozak et al., 2020; Rothman et al., 2016). However, these additional strategies are time and resource consuming and only required for a portion of the cohort. Therefore, it might be worthwhile to screen for participants that might be at high risk of an unsuccessful scan and then provide additional support to those participants.

Neuropsychological Assessment

A complication of the neuropsychological assessment was that certain gate-keeping cognitive domains, including attention and behavioural regulation, frequently confounded the scores of other domains. For example, most participants scored poorly on the memory tasks but this was seldom due to purely memory deficits. Future large cohort studies will need to be careful in how they identify and control for these confounding effects.

Tests that required a sound knowledge of the alphabet were problematic for this cohort and may need to be substituted for tests that do not disadvantage those who do not know their alphabet. In addition, several of the tests were too difficult for Mia to complete, which resulted in incomplete data. It might be advantageous to include tests with lower baselines to obtain more complete data from severely impaired participants.

A limitation was that not all the attention domains were formally assessed and therefore some could only be commented on qualitatively. Future studies should, if possible, include a more thorough examination of this key cognitive domain. The CBCL and BRIEF parent report results occasionally did not correlate with the findings of the neuropsychological assessment. Including a teacher assessment of functioning on the BRIEF and CBCL could provide a useful additional viewpoint.

Control Group

The study did not include a control group as the aim was to provide an in-depth investigation of the characteristics and potential influencing factors of South African children with pTBI to guide a future study. The participants' standardised scores were obtained from the neuropsychological tests' technical manuals, which are based on data from other countries, most commonly the USA. Unfortunately, there is currently no comprehensive normative neuropsychological data from South African paediatric populations. Comparisons with Western normative data can overestimate deficits of South African children due to cultural and sociodemographic differences (Aghvinian et al., 2021). Future studies should incorporate a local control group for more accurate estimations of deficits. However, care will need to be taken when selecting an appropriately matched control group given the prevalence of adverse premorbid developmental, social, and neuropsychological histories noted in this cohort. Furthermore, the significant cultural diversity and socioeconomic inequality within South Africa (Leibbrandt et al., 2012; Mclaughlin, 2007) means that there can be no universal South African control group and that each study would need to carefully match controls to the included participants.

Assessment Timing

Another limitation was that the neuropsychological assessments were conducted at 6-months post-injury. Patients usually experience a gradual improvement in cognitive functions in the first two years post-TBI (Anderson et al., 2012) and therefore a 6-month assessment might not have fully captured the participants' long-term outcomes. A 6-month assessment was deemed appropriate given the time frame and scope of this pilot study. Neuropsychological assessments conducted in the post-acute phase (4 to 5 months post-TBI) were found to be highly predictive of cognitive performance at chronic timepoints (Moran et al., 2016) and therefore still provide a reasonable indication of the participants' outcomes. Similarly, evidence indicates that pathology can evolve over years following pTBI (Lindsey et al., 2019) and therefore a limitation was that the MRIs were conducted at 6-months post-TBI given the time constraints of the study.

Conclusion

The study provided an in-depth investigation into the premorbid factors and neuropsychological and neuroimaging outcomes following pTBI in a South African cohort. A standout feature of the study was the heterogeneity of outcomes. The neuropsychological presentations ranged from relatively mild to severely debilitating, while the neuroimaging outcomes varied from no visible abnormalities to multifocal cortical and subcortical pathology.

No single factor stood out as the strongest predictor of outcomes, highlighting the importance of collecting comprehensive multifactorial participant data when aiming to investigate TBI outcome predictors. Although the study was limited in size, it emphasized the vulnerability of South African children given the prevalence of adverse developmental, social, economic, and neuropsychological histories and the known role these factors can have in pTBI outcomes. Care will also need to be taken when selecting an appropriate control group and potentially combining South African participants with other cohorts in future collaborative studies.

A further aim was to identify barriers and considerations for research in a paediatric South African population that has largely been excluded from TBI research. Additional strategies will be required to improve recruitment and increase the rate of successful imaging, while changes may need to be made to the neuropsychology assessment to optimize the validity of neuropsychological test scores in this population. In conclusion, the findings of this study will help to improve the likelihood of the much-needed large-scale neuropsychological and neuroimaging research in this at-risk and understudied population.

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Appendices

Appendix A.

Typical Imaging Profiles of Traumatic Brain Injury Pathologies.

Pathology	Typical imaging presentations
Epidural haematoma	Lentiform-shaped blood collections between the inner layer of the skull and the outer layer of the dura that do not cross cranial sutures (Kim & Gean, 2011). Epidural haematomas often lie under the coup site and are frequently associated with skull fractures (Zimmerman & Bilaniuk, 1982). Acute blood collections are hyperdense (white) on CT imaging but will vary in appearance based on the age of injury and the sequence in the case of MRI.
Subdural haematoma	Crescent-shaped blood collections between the dura mater and the arachnoid mater (Kim & Gean, 2011). Subdural haematomas can occur at both the coup and contrecoup sites but are more commonly seen at the contrecoup site. Subdural haematomas can cross suture lines but not the midline. Acute blood collections are hyperdense (white) on CT imaging but will vary in appearance based on the age of injury and the sequence in the case of MRI.

Pathology	Typical imaging presentations
Subarachnoid haemorrhage	Subarachnoid haemorrhages present as areas of high attenuation in the sulci of the cortical convexity, the sylvian fissures, or the basal cisterns on non-contrast CT scans (Kim & Gean, 2011). Acute blood collections will vary in appearance based on the age of injury and the sequence in the case of MRI.
Cerebral contusions	Contusions occur at both the coup and contrecoup sites but are often more severe at the contrecoup areas. Contusions present as focal areas of petechial haemorrhage located peripherally in the grey matter that may involve surrounding oedema (Kim & Gean, 2011). Contusions often grow in the days following the initial imaging indicating the evolution of the contusion (Beaumont & Gennarelli, 2006). Specifically, repeat imaging studies show the transformation of contusions from contusions surrounded by vasogenic oedema, to an organized haematoma with less associated oedema, to the final stage of encephalomalacia and volume loss (Currie et al., 2016). Frequently located on the inferior aspects of the frontal and temporal lobes following TBI (Kim & Gean, 2011).
Cerebral swelling caused by hyperaemia	Cerebral swelling caused by hyperaemia can cause loss of sulcal markings, basilar cistern compression, and ventricular margin flattening on imaging (Kim & Gean, 2011).
Cytotoxic oedema	Cytotoxic oedema presents as a loss of grey-white matter differentiation on imaging (Kim & Gean, 2011).
Vasogenic oedema	Vasogenic oedema can be viewed as areas of low attenuation on CT scans (Kim & Gean, 2011).
Traumatic axonal injury / Diffuse axonal injury	Multiple small focal lesions (haemorrhagic and/or non-haemorrhagic) at the grey-white matter junctions, corpus callosum, subcortical white matter, and/or brainstem (Kim & Gean, 2011). Can present with normal

Pathology	Typical imaging presentations
	CT imaging in 50 - 80% of cases. Lesions are evident as areas of high intensity on MRI T2 and FLAIR sequences (Kim & Gean, 2011).
Encephalomalacia	Encephalomalacia presents as areas of low attenuation on CT scans, hypointensity on MRI T1-weighted images, and high intensity on MRI T2 and FLAIR sequences (Kim & Gean, 2011).

Note. CT: Computerized Tomography; MRI: Magnetic Resonance Imaging; TBI: Traumatic brain injury.

Appendix B.

Demographic Questionnaire and Asset Index

GENERAL INFORMATION

Full name (Parent):	
Telephone:	Work: ( ) Home: ( ) Cell:
How would you describe your ethnicity/race?	1. Black 2. Coloured 3. White 4. Asian 5. Other(specify):
Home Language:	
Full name (Child):	
Gender:	M F
Date of Birth:	
Grade:	

HOUSEHOLD INCOME: (Please circle appropriate number)

Household income per year:	1. R0 2. R1 – R5 000 3. R5001 – R25 000 4. R25 000 – R100 000 5. R100 001+

PARENTAL EDUCATION: (Please circle appropriate number)

	Biological mother	Biological father	Guardian
Highest level of education reached? Mark one response for each person as follows:			
1. 0 years (No Grades / Standards) = No formal education (never went to school)	1.	1.	1.
2. 1-6 years (Grades 1-6 / Sub A-Std 4) = Less than primary education (didn't complete primary school)	2.	2.	2.
3. 7 years (Grade 7 / Std 5) = Primary education (completed primary school)	3.	3.	3.
4. 8-11 years (Grades 8-11 / Stds 6-9) = Some secondary education (didn't complete high school)	4.	4.	4.
5. 12 years (Grade 12 / Std 10) = Secondary education (completed senior school)	5.	5.	5.
6. 13+ years = Tertiary education (completed university / technikon / college)	6.	6.	6.
7. Don't know	7.	7.	7.

PARENTAL EMPLOYMENT: (Please circle appropriate number)

Hollingstead categories:	Biological mother	Biological father	Guardian
1. Higher executives, major professionals, owners of large businesses)	1.	1.	1.
2. Business managers of medium sized businesses, lesser professions (e.g. nurses, opticians, pharmacists, social workers, teachers)	2.	2.	2.
3. Administrative personnel, managers, minor professionals, owners / proprietors of small businesses (e.g. bakery, car dealership, engraving business, plumbing business, florist, decorator, actor, reporter, travel agent)	3.	3.	3.
4. Clerical and sales, technicians, small businesses (e.g. bank teller, bookkeeper, clerk, draftsperson, timekeeper, secretary)	4.	4.	4.
5. Skilled manual – usually having had training (e.g. baker, barber, chef, electrician, fireman, machinist, mechanic, painter, welder, police, plumber, electrician)	5.	5.	5.
6. Semi-skilled (e.g. hospital aide, painter, bartender, bus driver, cook, garage guard, checker, waiter, machine operator)	6.	6.	6.
7. Unskilled (e.g. attendant, janitor, construction helper, unspecified labour, porter, unemployed)	7.	7.	7.
8. Homemaker	8.	8.	8.
9. Student, disabled, no occupation	9.	9.	9.

MATERIAL AND FINANCIAL RESOURCES (ASSET INDEX): (Please circle appropriate number)

Which of the following items, in working order, does your household have?

Items	Yes	No
1. A refrigerator or freezer	1.	1.
2. A vacuum cleaner or polisher	2.	2.
3. A television	3.	3.
4. A hi-fi or music centre (radio excluded)	4.	4.
5. A microwave oven	5.	5.
6. A washing machine	6.	6.
7. A videocassette recorder or DVD player	7.	7.

Which of the following do you have in your home?

Items	Yes	No
1. Running water	1.	1.
2. A domestic servant	2.	2.
3. At least one car	3.	3.
4. A flush toilet	4.	4.
5. A built-in kitchen sink	5.	5.
6. An electric stove or hotplate	6.	6.
7. A working telephone	7.	7.

Do you personally do any of the following?

Items	Yes	No
1. Shop at supermarkets	1.	1.
2. Use any financial services such as a bank account, ATM card or credit card	2.	2.
3. Have an account or credit card at a retail store	3.	3.

Appendix C.
The Family Resource Scale

This scale is designed for you to tell us if your family has adequate resources (time, money, energy, and so on) to meet the needs of your family.

Most of the items below are the needs of all families, but some items may not apply to your family (such as item 10 or item 17). If the need does not apply to your family, fill in the circle under Does Not Apply.

For each item, please fill in the circle for the response that **best describes** how well each of the following needs is being met **at this time in your family**. For example, if you always have food for at least two meals a day, you would mark as follows:

	Does Not Apply	Not at All	A Little	Sometimes	Often	Almost Always
1. Food for two meals a day		①	②	③	④	●

For each item, please fill in the circle for the response that **best describes** how well each of the following needs is being met **at this time in your family**.

	Does Not Apply	Not at All	A Little	Sometimes	Often	Almost Always
1. Food for two meals a day		①	②	③	④	⑤
2. House or apartment		①	②	③	④	⑤
3. Money to buy necessities		①	②	③	④	⑤
4. Enough clothes for your family		①	②	③	④	⑤
5. Heat for your house or apartment		①	②	③	④	⑤
6. Indoor plumbing/water		①	②	③	④	⑤

	Does Not Apply	Not at All	A Little	Sometimes	Often	Almost Always
7. Money to pay monthly bills		①	②	③	④	⑤
8. Good job for yourself or spouse/partner	NA ○	①	②	③	④	⑤
9. Medical care for your family		①	②	③	④	⑤
10. Public assistance (SSI, TANF, Medicaid, etc.)	NA ○	①	②	③	④	⑤

	Does Not Apply	Not at All	A Little	Sometimes	Often	Almost Always
11. Dependable transportation (own car or provided by others)		①	②	③	④	⑤
12. Time to get enough sleep/rest		①	②	③	④	⑤
13. Furniture for your home or apartment		①	②	③	④	⑤
14. Time to be by yourself		①	②	③	④	⑤
15. Time for the family to be together		①	②	③	④	⑤
16. Time to be with your child(ren)		①	②	③	④	⑤
17. Time to be with spouse/partner or close friend	NA ○	①	②	③	④	⑤
18. Telephone or access to a phone		①	②	③	④	⑤
19. Babysitting for your child(ren)	NA ○	①	②	③	④	⑤
20. Child care/daycare for your child(ren)	NA ○	①	②	③	④	⑤
21. Money to buy recommended equipment/supplies for the child(ren)	NA ○	①	②	③	④	⑤
22. Dental care for your family		①	②	③	④	⑤

	Does Not Apply	Not at All	A Little	Sometimes	Often	Almost Always
23. Someone to talk to		①	②	③	④	⑤
24. Time to socialize		①	②	③	④	⑤
25. Time to keep in shape and look nice		①	②	③	④	⑤
26. Toys or activities for your child(ren)		①	②	③	④	⑤
27. Money to buy things for yourself		①	②	③	④	⑤

	Does Not Apply	Not at All	A Little	Sometimes	Often	Almost Always
28. Money for family entertainment		①	②	③	④	⑤
29. Money to save		①	②	③	④	⑤
30. Travel/vacation		①	②	③	④	⑤

Appendix D.

The Six Subscales and Associated Needs of the Family Resource Scale (Brannan et al., 2006; Dunst & Leet, 1985)

Subscale	Needs
Basic needs	Food for two meals a day, money to buy necessities, money to pay bills, enough clothes, money for children's toys.
Housing/Utilities	House or apartment, furniture for the home, heat for apartment/house, indoor plumbing, dependable transportation, telephone, or access to a telephone.
Benefits	Good job, public assistance (i.e., grant/social welfare), medical care, dental care.
Social needs/Self-care	Time to get enough sleep, time to be by self, time for family, time for children, time for spouse/friend, someone to talk to, time to socialize, time to keep in shape.
Childcare	Babysitting, childcare.
Extra resources	Money for special equipment, money to buy things for self, money to save, money for family entertainment, money to travel or vacation.

Appendix E.

The Developmental Questionnaire

Child's Name: _____

Date of Birth: _____ Age: _____

PREGNANCY AND BIRTH

Were there any complications during the *pregnancy*?

Did you take any medicine during pregnancy? Prescribed or over the counter?

Did you smoke cigarettes while you were pregnant? If so, how many?

Did you drink when you were pregnant? If so, how much?

Anything else, like dagga? Any drugs?

Was the birth on time? *If early or late, find out why*

Was it a natural birth or via C-section/Caesarean? Was labour induced?

Were there any complications during the birth?

Were there any early *separations* from you? (When and for how long)

Have there been any *emotionally difficult* experiences for your child?

ADDITIONAL QUESTION RELATED TO SCHOOLING

What *type* of school does your child attend? (mainstream / special needs)

Name of History-Taker: _____

Date: _____

Signed: _____

Appendix F.

Family Burden of Injury Self-Report Questionnaire (Burgess et al., 1999)

What is your relationship to the child? (circle 1)

Mother Father Step-Mother Step-Father Guardian Other

Explain: _____

Please rate how much stress each of the following issues has caused for you since the child's injury using the following scale:

0 NOT AT ALL STRESSFUL	1 A BIT STRESSFUL	2 FAIRLY STRESSFUL	3 QUITE STRESSFUL	4 EXTREMELY STRESSFUL	NA Not Applicable

Statement	**Stress Rating**					
1. Concerns about how your child reacts or relates to you or your spouse/partner Are these concerns related to the injury? Y N	0	1	2	3	4	NA
2. Disciplining or managing your child's behaviour Are these concerns related to the injury? Y N	0	1	2	3	4	NA
3. The behaviour of your other children Are these concerns related to the injury? Y N	0	1	2	3	4	NA
4. Disciplining or managing your other children's behaviour Are these concerns related to the injury? Y N	0	1	2	3	4	NA
5. Concerns about how your other children are reacting to or accepting _____'s injury or any consequences of the injury	0	1	2	3	4	NA
6. Concerns about your child's recovery from the injury, or any possible problems related to the injury in the future	0	1	2	3	4	NA
7. Consequences of the injury affecting the day to day life in your family	0	1	2	3	4	NA
8. You or your spouse missing work or other commitments because of the injury or any consequences of the injury	0	1	2	3	4	NA

Please continue to rate how much stress each of the following issues has caused for you since the injury using the following scale:

0	1	2	3	4	NA
NOT AT ALL STRESSFUL	A BIT STRESSFUL	FAIRLY STRESSFUL	QUITE STRESSFUL	EXTREMELY STRESSFUL	Not Applicable

Statement	**Stress Rating**					
9. Taking care of your other children Are these concerns related to the injury? Y N	0	1	2	3	4	NA
10. Taking care of daily chores, such as shopping or household tasks Are these concerns related to the injury? Y N	0	1	2	3	4	NA
11. Difficulties handling or accepting feelings about the injury	0	1	2	3	4	NA
12. Achieving your long-term goals Are these concerns related to the injury? Y N	0	1	2	3	4	NA
13. Achieving your spouse's long-term goals Are these concerns related to the injury? Y N	0	1	2	3	4	NA
14. Achieving your injured child's long-term goals Are these concerns related to the injury? Y N	0	1	2	3	4	NA
15. Achieving your other children's long-term goals Are these concerns related to the injury? Y N	0	1	2	3	4	NA
16. Concerns about how your injured child is accepted by his/her peers Are these concerns related to the injury? Y N	0	1	2	3	4	NA
17. Concerns about your spouse's/partner's reaction to your child's injury or any consequences of the injury	0	1	2	3	4	NA
18. Disagreements between you and your spouse/ partner about how to take care of family problems Are these concerns related to the injury? Y N	0	1	2	3	4	NA

Please continue to rate how much stress each of the following issues has caused for you since the injury using the following scale:

0 NOT AT ALL STRESSFUL	1 A BIT STRESSFUL	2 FAIRLY STRESSFUL	3 QUITE STRESSFUL	4 EXTREMELY STRESSFUL	NA Not Applicable

Statement	**Stress Rating**					
19. Talking about your child's injury with your spouse/partner	0	1	2	3	4	NA
20. The reactions of others (outside your family) to your child's injury	0	1	2	3	4	NA
21. Disagreements with others about how to best care for your family Are these concerns related to the injury? Y N	0	1	2	3	4	NA
22. Disagreements with others about how to discipline your children, or the kinds of things you allow them to do/not do Are these concerns related to the injury? Y N	0	1	2	3	4	NA
23. Talking about your child's injury with others	0	1	2	3	4	NA
24. Finding time for your own activities Are these concerns related to the injury? Y N	0	1	2	3	4	NA
25. Finding time to be with your spouse/partner and to do things together Are these concerns related to the injury? Y N	0	1	2	3	4	NA
26. Finding time to do things with your other children Are these concerns related to the injury? Y N	0	1	2	3	4	NA

Appendix G.

The Clinical Measures and Descriptions of the Behaviour Rating Inventory of Executive Function Parent Report (Gioia et al., 2000)

Clinical indices and scales	Description
Behavioural Regulation Index	The child's ability to cognitively shift and regulate their emotions and behaviour via adequate inhibitory control.
Inhibit	The child's inhibitory control: the ability to inhibit or resist acting on an impulse.
Shift	The child's capability to alternate attention, to change the mindset from one topic to another and to switch between aspects of problem solving, activities or situations as the circumstances change.
Emotional Control	The child's ability to appropriately modulate their emotional reactions to a given situation.
Metacognition Index	The child's ability to initiate, organize, plan, and sustain future-orientated problem-solving in their working memory.
Initiate	The child's ability to start an activity or task and generate ideas or problem-solving strategies.
Working Memory	The child's ability to hold relevant information in mind to complete a task.
Plan/Organize	The child's ability to manage demands of present and future tasks by anticipating future situations, setting goals and pre-emptively developing the appropriate steps to complete the task.
Organization of Materials	The child's ability to organize work, play and storage spaces in an orderly fashion.
Monitor	The child's ability to consistently check their work and progress toward achieving a goal or completing a task.

Appendix H.

Description of the Created Composite Variables

Composite variable	Component variables included	Cronbach's Alpha
Attention	Digit Span Forwards TMT Visual Scanning	0.408
Audioverbal memory	RAVLT Learning RAVLT Short delay RAVLT Long delay RAVLT Recognition	0.936
Visuospatial memory	Dot Locations Learning Dot Locations Short delay Dot Locations Long delay	0.985
Processing Speed	Coding Symbol Search	0.846
Executive Functions	Digit Span Backwards Letter-Number Sequencing TMT Number-Letter Switching Tower Achievement Tower Rule violations per Item	0.837

Note. RAVLT: Rey Audioverbal Learning Test; TMT: Trail Making Test.

Appendix I.

University of Cape Town Human Research Ethics Committee Ethical Approval Letter

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

Room E52-24 Old Main Building
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13 March 2018

HREC REF: 764/2017

Prof A Figaji
Department of Surgery
Division of Neurosurgery
Red Cross Children's Hospital

Dear Prof Figaji

PROJECT TITLE: AN EXPLORATORY STUDY OF INTERHEMISPHERIC TRANSFER TIME, ADVANCED NEUROIMAGING AND NEUROPSYCHOLOGICAL OUTCOMES OF MODERATE TO SEVERE TRAUMATIC BRAIN INJURY IN A SOUTH AFRICAN PAEDIATRIC COHORT

Thank you for submitting for your considered response to the Faculty of Health Sciences Human Research Ethics Committee dated 02 March 2018.

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 March 2019.

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

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.

Yours sincerely

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

This serves to confirm that the University of Cape Town Human Research Ethics Committee complies to the Ethics Standards for Clinical Research with a new drug in patients, based on the Medical

Appendix J.

University of Cape Town Department of Psychology Ethical Approval Letter

UNIVERSITY OF CAPE TOWN

Department of Psychology

University of Cape Town Rondebosch 7701 South Africa
Telephone (021) 650 3417
Fax No. (021) 650 4104

11 October 2017

Sarah McFie
Department of Psychology
University of Cape Town
Rondebosch 7701

Dear Sarah

I am pleased to inform you that ethical clearance has been given by an Ethics Review Committee of the Faculty of Humanities for your study, An exploratory study of interhemispheric transfer time, advance neuroimaging and neuropsychological outcomes of severe traumatic brain injury in a South African Paediatric cohort. The reference number is PSY2017 -049.

I wish you all the best for your study.

Yours sincerely

Lauren Wild (PhD)
Associate Professor
Chair: Ethics Review Committee

Appendix K.

Consent Form

Informed consent to participate in research and authorization for collection, use, and disclosure of neuroimaging, electrophysiological, cognitive performance, and other personal data

Dear Parents or Caregivers

Your child is being asked to take part in a University of Cape Town research study, where we are trying to understand the possible changes in how the brain looks and how children think after head injury and why some children don't recover well. If you and your child would like to participate, your child will be asked to undergo a brain scan, complete an assessment where electrical activity in the brain is measured and do a series of paper-and-pencil cognitive tests, while you will be asked to complete some questionnaires.

This form provides you with information about the study and seeks your permission for researchers to approach your child to ask them whether they would like to participate in the study. Furthermore, the form asks your permission to collect, use and disclose your child's brain-imaging, electrophysiological and 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 child's participation is entirely voluntary. Before you decide whether or not your child can take part, read the information below and ask questions about anything you do not understand. By not participating in this study your child will not be penalized or lose any benefits to which he/she would otherwise be entitled.

1. Title of research study

An exploratory study of interhemispheric transfer time, advanced neuroimaging, and neuropsychological outcomes of moderate to severe traumatic brain injury in a South African paediatric cohort.

2. Principal Investigator and researchers

Professor Anthony Figaji
Paediatric Neurosurgery Unit
Red Cross War Memorial Children's Hospital
Tel: 021 658 5340
Email: anthony.figaji@uct.ac.za

Dr Leigh Schrieff
Department of Psychology
University of Cape Town
Tel: 021 650 3708
Email: leigh.e.elson@gmail.com

Dr Sarah Mc Fie
Department of Psychology
University of Cape Town
Tel: 084 707 0850
Email: sarah.mcfie@gmail.com

3. Source of funding or other material support

National Research Foundation.

4. What is the purpose of this research study?

The purpose of this research study is to better understand the possible changes in brain structure (how the brain looks) and cognitive functioning (thinking, reasoning and remembering) in children who have experienced a head injury.

5. Must my child and I participate?

No, not at all. This study is completely optional and there are no negative consequences if you don't want your child to participate. 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. Your child will not receive better medical treatment because they are participants in the study. Also, if you first decide to participate but then change your mind, you can just let us know that you are withdrawing your child and you don't even need to provide a reason. If this happens, you and your child will not be penalised in any way.

6. What will be done if your child takes part in this research study?

In this study, your child will undergo a brain scan, complete a task that measures electrical activity in the brain and do a series of paper-and-pencil cognitive tests. The brain scan will give us information of how the structures of the brain are recovering following the head injury. The electrical activity task will help us understand how the brain is functioning. The cognitive tests will measure functions such as attention, memory, thinking, problem solving, and reasoning. You will also be asked to complete some questionnaires about your child and other background information.

Your child will be asked to complete two testing sessions, the first at three months after the head injury and the second at six months after the head injury. You will be required to bring

your child to Red Cross War Memorial Children's Hospital for the first testing session. Your child will complete the electrical activity task at this testing session.

Then, six months after your child's head injury, you will be asked to bring your child back to the Red Cross War Memorial Children's Hospital, where your child will repeat the electrical task and complete cognitive testing. You will also be asked to bring your child to the Cape Universities Body Imaging Centre at Groote Schuur hospital, where the brain scan will take place. You will be remunerated for the travel costs.

Either the principal investigators or a trained member of their research team will individually conduct each testing session. You or another caregiver may be present at the testing session.

Within two weeks of the final testing session, you will be given information on your child's cognitive test outcomes and brain scan. You may choose to get the information over the phone or in person at the Red Cross War Memorial Children's Hospital. You will be remunerated for the travel costs to the hospital. You will also be informed in detail about the design of the study and the research questions we hope to answer and you will have the opportunity to ask questions and thus learn more about psychological research.

If you have any questions now or at any time during the study, you may contact the Principal Investigator or researchers listed in item 2 of this form.

7. If you choose to allow your child to participate in this study, how long will he/she be expected to participate in the research?

There will be two testing sessions in the study. The first testing session will take place three months after the date of your child's head injury. The second testing session will take place six months after the date of your child's head injury. Your child's participation will end after the second session. However, if at any time during the study you or your child finds any of the procedures uncomfortable, you are free to discontinue participation without penalty.

8. How many children are expected to participate in the research?

Ten children are expected to take part in the study.

9. What are the possible discomforts and risks?

There are minimal risks associated with participation in this study. The brain scan and electrical activity tasks do not involve injections and are not painful for your child. However, your child may feel some discomfort being placed in the brain-scanner because of the small space and loud noise. The researcher will allow your child to try a "mock (pretend) scan" to feel what it is like to be in the brain scanning machine before the actual scan. Your child will be taken out of the scanner if he/she feels discomfort.

If anything unexpected or abnormal is found on the brain scan, you will be immediately referred to Professor Figaji, head of the Paediatric Neurosurgery Unit at Red Cross War Memorial Children's Hospital.

The research staff will watch your child for signs of being upset, such as whining, crying, or struggling. If your child becomes upset we will stop the session for a short break of 5 to 10 minutes. If he or she remains upset, we will stop the sessions for that day.

Your child may experience a little tiredness during testing. If he/she becomes tired during any of the procedures, we will take a break. Your child will be allowed to take breaks whenever requested. You may find out that some of your child's thinking and memory abilities are worse than you expected, and this may cause some sadness or distress. If this happens, we will talk with you and give a referral for care.

Although the risks associated with the study are minimal, the study is covered by an insurance policy taken out by the University of Cape Town. If your child suffers a bodily injury because your child is taking part in the study, the insurer will pay for all reasonable medical costs required to treat your child's bodily injury, according to the South African Good Clinical Practice Guidelines (2006). The insurer will pay without you having to prove that the study was responsible for your child's bodily injury.

If you wish to discuss the information above or any discomforts you or your child may experience, you may ask questions now or call the Principal Investigators or researchers listed in item 2 of this form.

10. What are the possible benefits to you and your child?

You and your child may or may not personally benefit from participating in this study. The treatment your child receives will not be affected by this study. However, your child partaking in the assessments may provide you with a deeper understanding of the functioning of your child.

11. What are the possible benefits to others?

The information from this study may help improve our understanding of head injuries in children, particularly with regard to the effects of head injury on the structures and functions of the brain, such as the ability to memorize, think, reason, and pay attention. The information we obtain might benefit the future diagnosis and treatment of head injury.

12. If you choose to take part in this research study, will it cost you anything?

Participating in this study will not cost you anything.

13. Will you receive compensation for taking part in this research study?

No, but we will cover the cost of transport to the testing sessions.

14. Can you withdraw your child from this study?

You are free to withdraw your consent and to stop participating in this research study at any time. If you do withdraw your consent, there will be no penalty.

15. 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. 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.

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

In general, presenting the results of research 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.

The data collected as part of the titled study may be used to compliment other research in the field of paediatric head injuries. Research ethics approval will be obtained from the University of Cape Town's Human Research Ethics Committee before any future use of data collected in the current study.

17. Who has approved this study?

This study has received ethical approval from the University of Cape Town's Human Research Ethics Committee. If you have any ethical concerns, or any questions about your child's rights or welfare as a study participant, please contact the University of Cape Town's Faculty of Health Sciences Human Research Ethics Committee:
Tel: 021 406 6492
E-mail: sumaya.ariefdien@uct.ac.za

18. Signatures

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. 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 and Authorizing Date

_____ _____

Name of Child Age

Authorization for _____ (your child's name) to participate in the study.

Relationship to child participating in the study: mother / father / legal guardian

_____

As a representative of this study, I have explained to the parent/guardian of the participant the purpose, the procedures, the possible benefits, and the risks of this research study; and how the participant's performance and other data will be collected, used, and shared with others:

_____ _____

Signature of Person Obtaining Consent and Authorization Date

Informed consent for the use of your child's data collected in the study "An exploratory study of interhemispheric transfer time, advanced neuroimaging and neuropsychological outcomes of moderate to severe traumatic brain injury in a South African paediatric cohort"

As you have agreed to have your child take part in the study titled "An exploratory study of interhemispheric transfer time, advanced neuroimaging and neuropsychological outcomes of moderate to severe traumatic brain injury in a South African paediatric cohort", it is possible that some of the information collected might be copied into a "limited data set" and shared for research purposes. If so, the limited data set will only include information that does not directly identify your child – their identity will remain confidential. Data will be labelled using participant numbers rather than names, so that they cannot be used to directly identify any particular individual. A separate and private log will be used to relate participant names to numbers in the event that a participant needs to be contacted or contacts the Principle Investigator.

The data collected as part of the titled study may be used to complement other research in the field of paediatric head injuries, as it provides researchers at UCT with a very specific and unique data set. Data from this current study may, for example, be compared to, or collated with, data collected in future related research projects. Research ethics approval will be obtained from the University of Cape Town's Human Research Ethics Committee before any future use of data collected in the current study.

The researchers involved in this study will only keep the data for a maximum of five years. Once this time has elapsed, all data pertaining to individual participants stored on the computers will be permanently deleted, and all hard copies of this data will be shredded.

All information collected will be stored in locked filing cabinets and on computers with security passwords, in a secure computer lab at the University of Cape Town. 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 child's research records will not be released without your permission unless required by law or a court order.

Please note that the storage of data is optional, and that your child can take part in the main study without your consenting to future storage of data.

Can you withdraw your child's data from future use?

You may withdraw your consent to your child's participation and the intended future storage periods of five years after the data have been collected at any stage during the course of the study, without any penalty to you or your child.

If you have a complaint or complaints about your child's rights and welfare as a research participant, please contact the University of Cape Town, Faculty of Health Sciences Human Research Ethics Committee.
Tel: 021 406 6492
E-mail: sumaya.ariefdien@uct.ac.za

Dissemination of research findings

It is the aim that these future reports be published in an academic journal in order to widen the knowledge base of paediatric head injuries.

Signatures

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 agree for your child's data to be stored as part of the current study for future use. You hereby authorize the collection, use and sharing of your performance and other data. By signing this form, you are not waiving any of your legal rights.

_____ _____
Signature of Person Consenting and Authorizing Date

Relationship to child participating in the study: parent / legal guardian

_____

Name of Participant ("Study Participant" – the child)

_____

Authorization for _____ (child's name) data to be stored for future use.

As a representative of this study, I have explained to the participant's (child's) parents or caregivers how the participant's performance and other data will be collected, stored for possible use in future studies.

_____ _____
Signature of Person Obtaining Consent and Authorization Date

Appendix L.

Assent Form

Assent form for participants

Principal Investigator: Professor Anthony Figaji
Researchers: Dr Leigh Schrieff-Elson and Dr Sarah Mc Fie

Dear (name)

Hi there! We are doing a project at the University of Cape Town that is looking at how head injuries affect the brain and how you think. We have already spoken to your parents and they have said that we can ask you if you would like to be involved in the project.

What is this project about?

The project is going to help me to understand how a head injury might change how you can think. We also want to try find out why some children get better quickly and others take a long time to get better. If we can learn about this, we may be able to help the children that take a long time to get better after a head injury.

Why am I being asked to participate?

You are being asked to help us in this project because you had a head injury. We are asking all the children that come to this hospital with a head injury to be in the project.

What do I have to do in this part of the project?

If you want to be part of the project, we will ask you to come to the hospital and play a computer game while we stick little metal buttons onto your head to see how your brain works. A few months later we will ask you to play the same computer game with us again. We will also ask you to go inside a big machine that takes photos of your brain. This won't hurt at all!

We will also ask you to play some games and do some puzzles with us. Afterwards, we will ask you some questions about yourself, your feelings and your thoughts and some problems you might be having. Nobody else will be told your answers to the questions.

Will it hurt?

Not at all! The metal buttons may feel cold or ticklish against your head but they won't hurt at all. The big machine can be noisy and you may feel a little scared inside of it, but we will let you go into the machine so you can see what it is like before we take the photos. Your mom, dad or any family member can stay with you the whole time. During the games and puzzles, you can also stop if you are feeling tired and need to take a break.

Do I have to be in this part of the project?

Not at all. You only have to be in the project if you want to. If you don't want to, or if at first you want to but then feel like you don't want to anymore, that's okay. You just need to tell me and we can stop at any time. You won't get into any trouble and we won't be upset if you want to stop.

What must I do if I want to participate?

So if you want do the project, we need you to write your name on the next page saying you are okay with doing a computer task with little metal buttons stuck on your head, going into a big machine that takes photos of your brain and playing some games and puzzles with us.

Do you have any questions?

If you think of any questions later, you can always tell your mom and dad, and they can contact:

Professor Anthony Figaji
Paediatric Neurosurgery Unit
Red Cross War Memorial Children's Hospital
Tel: 021 6585340
Email: anthony.figaji@uct.ac.za

Or

Dr Leigh Schrieff-Elson
Department of Psychology
University of Cape Town
Tel: 021 650 3708
Email: leigh.e.elson@gmail.com

Or

Dr Sarah Mc Fie
Department of Psychology
University of Cape Town
Tel: 084 7070 850

Email: sarah.mcfie@gmail.com

Assent for Participation in the Study:

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

_____ _____

Signature of Child / Participant Date

_____

Printed Name of Child / Participant

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

Assent form for data usage

Dear (name)

Thank you for agreeing to help us with our project. We need to ask you if you would mind if we keep the answers that you give in this project, so that they may help us again later on.

We won't keep your name with your answers, so no one else will know that they are your answers. We will keep all of your answers safe and locked away and only a few people will get to see them.

It's also okay if you don't want us to keep your answers. You can just let us know and you won't get into any trouble and we won't be upset with you.

Assent for storage of data:

I agree to let the researchers keep my answers so that they can use them later on.

_____ _____

Signature of Child / Participant Date

_____

Printed Name of Child / Participant

Appendix M.

Detailed Participant Data

Table M1

The Medical Details of Each Participant's Traumatic Brain Injury (TBI).

	Alice	Ethan	Mia	Thando	Katlego
Date of TBI	01/06/2018	30/06/2018	28/07/2018	02/08/2018	03/09/2018
Time	Unknown	17:00	13:00	19:00	18:40
Day of the week	Friday	Saturday	Saturday	Thursday	Monday
Cause of TBI	MVA (head-on collision)	PVA (hit and run)	PVA	PVA (hit and run)	PVA
Accident witnessed	Yes	No	Yes	No	Yes
Activity at time of TBI	Travelling in a taxi with her grandmother	Playing on/near the road	Going to the shops with her grandmother	Playing on/near the road	Going to the shops with a friend
GCS at scene	3	Not reported	3	7	3
Post-traumatic seizure	No	Yes (at the scene)	No	No	No
GCS on admission	6T	10	3	7T	8T
Lowest reported GCS	3	6T	3	7	3

	Alice	Ethan	Mia	Thando	Katlego
Classification of TBI	Severe	Severe	Severe	Severe	Severe
Pupil response	Pupils were small and reactive but sluggish	Pupils were equal and reactive	Pupils were pinpoint and unreactive	Pupils were equal and reactive	Left pupil was dilated and unreactive
Physiological brain monitoring	Yes	No	Yes	No	Yes
Neurosurgical intervention	Monitors placed	None	Monitors placed	None	Monitors placed
Initial imaging findings	CTB 02/06/2018: A right, mildly depressed comminuted frontal fracture, bilateral frontal haemorrhagic contusions with generalized cerebral oedema, and petechial haemorrhages at the bifrontal grey-white matter junctions.	CTB 30/06/2018: Generalised cerebral oedema and a subarachnoid haemorrhage in the lateral ventricles and basal cisterns.	CTB 28/07/2018: Comminuted frontal bone fractures, bifrontal haemorrhagic contusions, generalised brain swelling, subarachnoid blood seen in the ambient cisterns, the fourth ventricle, left parietal region, and posterior horns of the lateral ventricles, subdural blood lining the tentorium cerebelli and the falx cerebri.	CTB 03/08/2018: Generalized cerebral oedema and a sliver of subdural blood along the tentorium cerebelli.	CTB 03/10/2018: Haemorrhagic contusions at the grey/white matter interface of the left frontal lobe, a subdural haemorrhage in the left hemisphere, a subdural haematoma in the interhemispheric fissure, a minimal subarachnoid haemorrhage in the interpeduncular fossa with hyperdensity in the prepontine cistern and craniocervical junction, mild

	Alice	Ethan	Mia	Thando	Katlego
					rightward midline shift at the third ventricle.
Notable follow-up imaging	n/a	CTB 02/07/2018: Worsening of the previously noted cerebral oedema.	MRI 13/08/2018: Multifocal areas of T1 hyper-intensity in the subcortical white matter and the grey-white matter interface of both frontal and temporal lobes, anterior limb of the left internal capsule, the posterior body and splenium of the corpus callosum, the left parafalcine occipital lobe, and bilateral brachim pontis.	CTB 14/08/2018: An ill-defined area of hypo-attenuation within the left basal ganglia and to a lesser extent in the left centrum semi-ovale.	n/a
Additional neurological difficulties	None reported	Monoparesis in his upper right limb	Globally increased tone, fixed dilated pupils, right hemiparesis, left facial palsy, and ataxic dysarthria.	Left-sided hemiparesis and decreased tone, and diplopia.	None reported

	Alice	Ethan	Mia	Thando	Katlego
Other injuries	Extensive bilateral facial fractures and bilateral orbital injury, which resulted in right eye proptosis.	Multiple haematomas and abrasions.	Multiple facial fractures, mild left proptosis, and a fractured femur	Pneumomediastinum, a fractured right jaw (mandibular condyle) and left periorbital abrasions with associated swelling and conjunctival infection.	Left tibia/fibula fracture, abrasions to the left side of his head and abdomen, periorbital haematoma, left orbital fractures, and left eye proptosis
Nosocomial infection	Yes (Rhinovirus/Staphylococcus aureus)	No	Yes (Staphylococcus aureus)	No	No
Recovery course description	Steady neurological recovery	Gradual neurological recovery with a relatively prolonged period of restlessness and reduced consciousness.	Slow neurological recovery with a prolonged period of reduced consciousness and significant neurological difficulties.	Gradual neurological recovery but developed a delayed onset left hemiparesis.	Fast neurological recovery
Days until GCS = 15	14	17	89	12	8
Days in RXH	19	9	32	14	9
Days in pICU	7	1	15	1	5
Days at GSH rehabilitation unit	29	45	61	22	0

	Alice	Ethan	Mia	Thando	Katlego
Total days in hospital (RXH and GSH)	48	54	93	36	9
Discharged to	Home	Home	Intermediate care facility	Home	Home

Note. MVA: Motor vehicle accident; PVA: Pedestrian vehicle accident; GCS: Glasgow Coma Scale; CTB: Computerized tomography brain scan; MRI: Magnetic resonance imaging; RXH: The Red Cross War Memorial Children's Hospital; pICU: Paediatric intensive care unit; GSH: Groote Schuur Hospital.

Table M2

The Intracranial Pressure (ICP) and Partial Pressure of Brain Tissue Oxygenation ($Pbto_2$) Monitoring Data of the Monitored Participants

	Alice	Mia	Katlego
Monitoring duration (h)	94	158	102
Highest ICP (mm Hg)	22	39	20
Episodes ICP >20mm Hg	2	38	0
Episodes ICP >25mm Hg	0	9	0
Median ICP over first 24h (mm Hg)	15 (IQR: 4)	16 (IQR: 7)	9 (IQR: 4)
Median ICP (mm Hg)	12 (IQR: 6)	15 (IQR: 10)	9 (IQR: 5)
Lowest $PbtO_2$ (mm Hg)	20	13	27.6
Episodes $PbtO_2$ <10mm Hg	0	0	0.0
Episodes $PbtO_2$ <20mm Hg	0	4	0.0
Median $PbtO_2$ over first 24h (mm Hg)	34 (IQR: 8.3)	30.4 (IQR: 8.2)	46.4 (IQR: 22.2)
Median $PbtO_2$ (mm Hg)	35 (IQR: 3.5)	37 (IQR: 8.7)	41.4 (IQR: 8.6)

Note. Each episode denotes one hour of monitoring time. H: hours; IQR: Interquartile range.

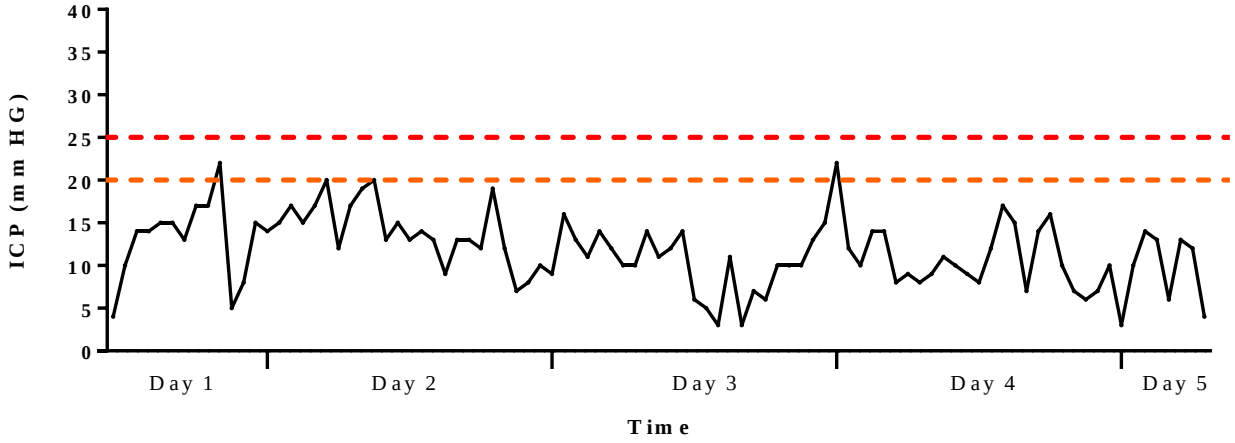

Figure M1. Alice's intracranial pressure (ICP) levels recorded over 94 hours of monitoring. ICP levels over 20mm Hg have been associated with unfavourable outcomes following TBI, while levels over 25mm Hg further increase this risk (Bratton et al., 2007).

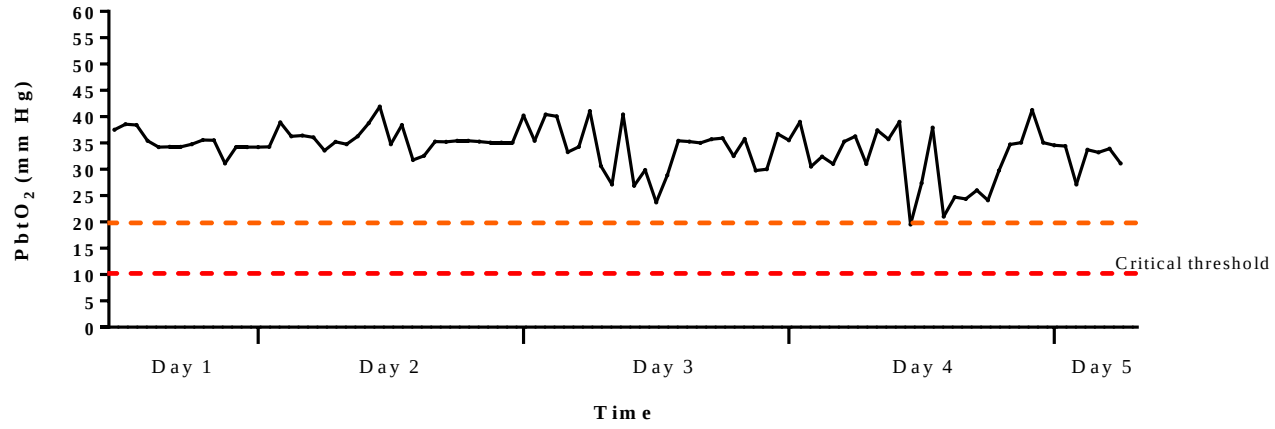

Figure M2. Alice's partial pressure of brain tissue oxygen ($PbtO_2$) levels recorded over 94 hours of monitoring. $PbtO_2$ levels below 20mm Hg have been associated with increased risk of poor outcomes, while 10mm Hg was described as the critical threshold, under which ischemia is more likely to occur (Maloney-Wilensky et al., 2009).

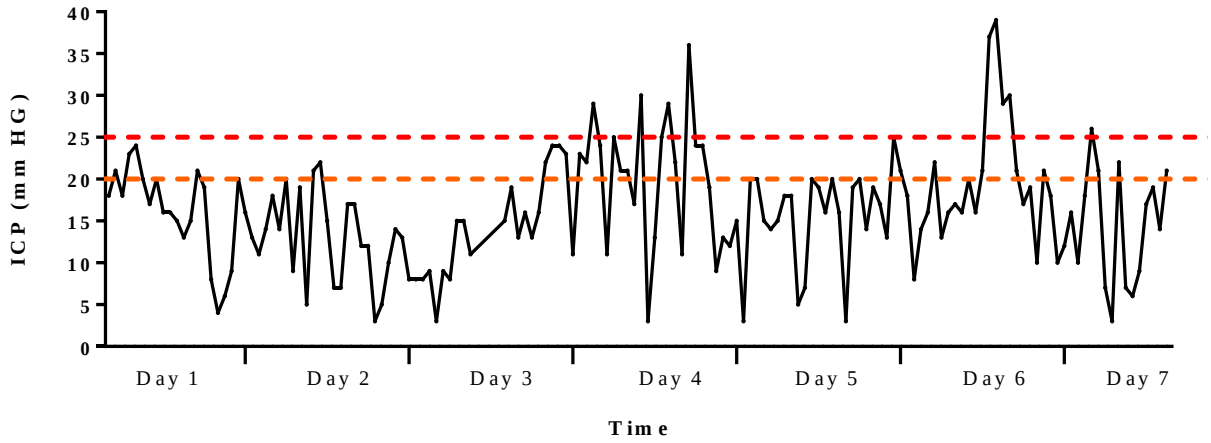

Figure M3. Mia's intracranial pressure (ICP) levels recorded over 158 hours of monitoring ICP over 20mm Hg has been associated with unfavourable outcomes following TBI, while levels over 25mm Hg further increase this risk (Bratton et al., 2007).

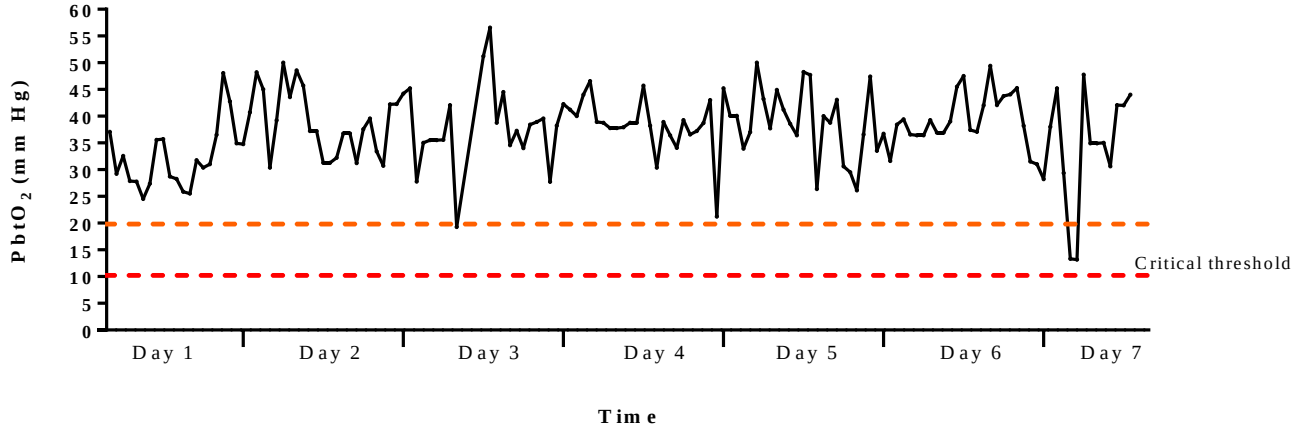

Figure M4. Mia's partial pressure of brain tissue oxygen ($PbtO_2$) levels recorded over 158 hours of monitoring. $PbtO_2$ below 20mm Hg has been associated with an increased risk of poor outcomes, while 10mm Hg was described as the critical threshold, under which ischemia is more likely to occur (Maloney-Wilensky et al., 2009).

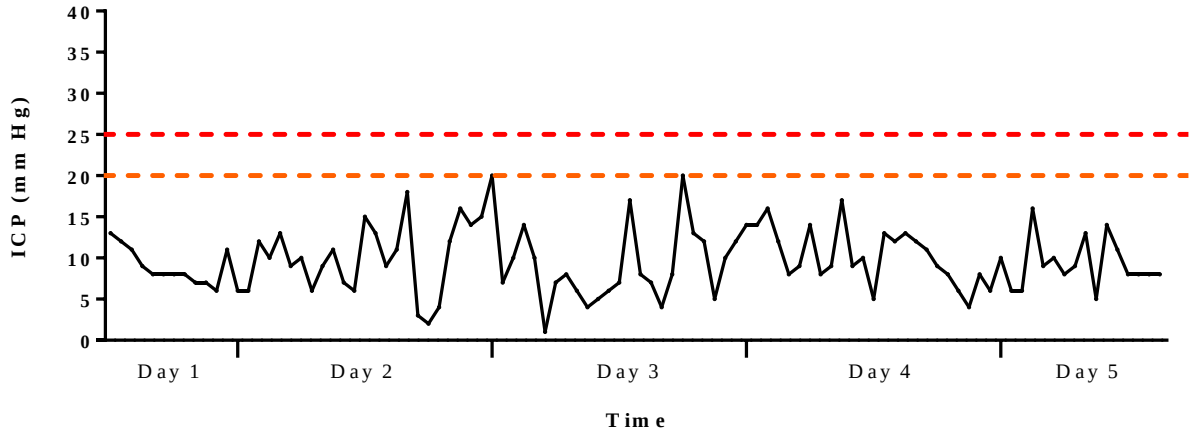

Figure M5. Katlego's intracranial pressure (ICP) levels recorded over 102 hours of monitoring. ICP levels over 20mm Hg have been associated with unfavourable outcomes following TBI, while levels over 25mm Hg further increase this risk (Bratton et al., 2007).

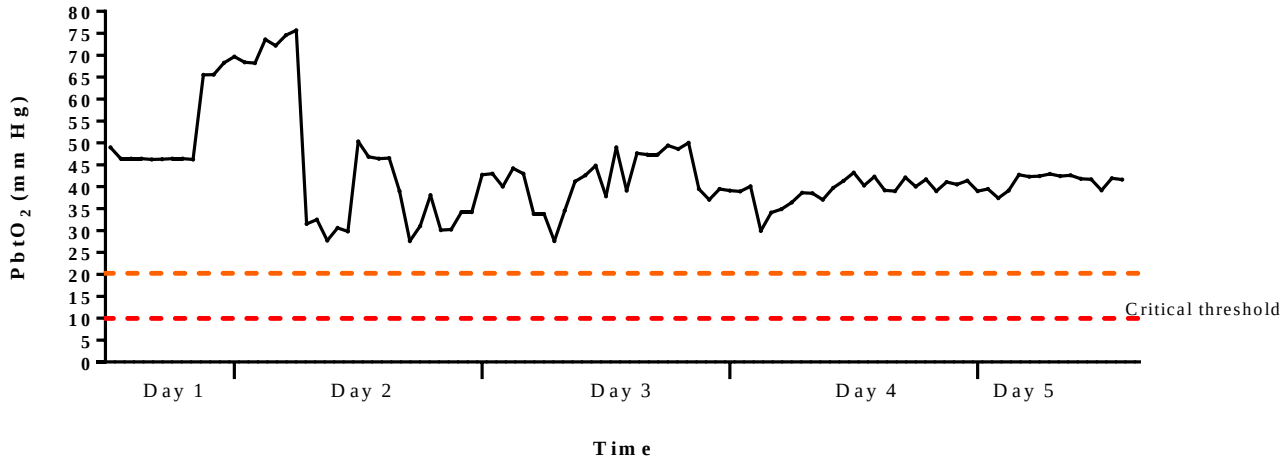

Figure M6. Katlego's partial pressure of brain tissue oxygen ($PbtO_2$) levels recorded over 102 hours of monitoring. $PbtO_2$ levels below 20mm Hg have been associated with increased risk of poor outcomes, while 10mm Hg was described as the critical threshold, under which ischemia is more likely to occur (Maloney-Wilensky et al., 2009).

Table M3

The Developmental History Details of each Participant

	Alice	Ethan	Mia	Thando	Katlego
Source of developmental history	Aunt and grandmother	Aunt	Grandmother	Mother	Mother
Pregnancy					
Complications	None	None	None	None	Pre-eclampsia
Medication use	None	None	None	None	Antihypertensives
Smoking	No	Unknown	Yes	No	No
Alcohol consumption	No	Unknown	No	No	No
Substance abuse	No	Suspected (methamphetamine)	Suspected (methamphetamine and nyaope)	No	No
Birth and newborn period					
Natural or C-section	Natural	C-section	Natural	Natural	C-section
Birth complications	None	Premature birth (twins)	None	None	Premature birth (delivered at 7 months)
Newborn complications	None	Ethan had a low birth weight (unknown weight) and required incubation. His twin	None	None	Low birth weight (800g), underdeveloped

	Alice	Ethan	Mia	Thando	Katlego
		was born with an atrial septal defect.			lungs, and an atrial septal defect.
Early childhood					
Childhood illnesses	No notable illnesses	No notable illnesses	No notable illnesses	No notable illnesses	No notable illnesses
Developmental milestone achievement	Exact milestones are unknown but reported to be faster than other children.	Exact milestones are unknown but reported to be like his siblings.	Exact milestones are unknown but reported to be like other children.	Exact milestones are unknown but similar to other children.	A delayed developmental milestone achievement in comparison to siblings and other children.
Separations from the primary caregiver	Alice's mother passed away when she was six years old. Her father was absent from birth.	Ethan's father was jailed, and his mother abandoned the family in 2014 when Ethan was eight years old.	Mia alternated between living with her mother and grandmother until she was four years old. Thereafter she stayed with her grandmother permanently.	Thando was sent to live with his grandmother for approximately 18 months between the ages of two and four.	None reported

Note. C-section: Caesarean section.

Table M4

The Socioeconomic Information for each Participant

	Alice	Ethan	Mia	Thando	Katlego
Primary Caregiver	Maternal grandmother	Maternal aunt	Paternal grandmother	Biological parents	Biological parents
Living with	Grandmother, step-grandfather, and step-grandfather's grandson (aged 7 years)	Aunt, uncle and four siblings (aged 14, 13, 10, and 8 years)	Grandparents and younger brother (aged 6 years)	Parents, uncle and younger sister (aged 1 year old).	Parents and sisters (aged 19, 8, and 6 years)
Previous trauma	Mother was killed in a car accident. Father absent from birth.	Father was jailed in 2014. Mother abused substances and left the family after Ethan's father was jailed.	Parents abused substances and her mother overdosed and died. Mia was sexually assaulted.	None reported	None reported
Caregiver education	Some secondary education (8 - 11 years)	Some secondary education (8 - 11 years)	Primary education (7 years)	Some secondary education (8 - 11 years)	Completed secondary education (12 years)
Caregiver employment	Skilled manual	Skilled manual	Skilled manual	Unskilled	Unskilled
Current employment status	Retired	Employed	Employed	Inconsistently employed	Inconsistently employed
Annual household income	R25 000 - R100 000	R25 000 - R100 000	R25 000 - R100 000	R0	R1 - R5 000
Asset Index	11 (Medium)	11 (Medium)	14 (High)	9 (Medium)	10 (Medium)
Family Resource Scale total	18.1	25.2	19.0	7.8	19.3

	Alice	Ethan	Mia	Thando	Katlego
Basic needs	4	4.6	3.2	1.6	4.2
Housing/Utility	4	4.5	4.5	1	4.4
Benefits	2.5	4.5	3.5	1	4.3
Social needs/Selfcare	4.4	4	4.0	2	2.3
Childcare	1	5	2.0	1	2
Extra Resources	2.2	2.6	1.8	1.2	2.2

Note. Higher Family Resource Scale (FRS) scores indicate greater access to resources. The maximum attainable score for each FRS subscale is 5, with scores of 1 or 2 indicating that a need is not being met (Sexton & Rush, 2012).

Table M5

The Academic History and Functioning of each Participant

	Alice	Ethan	Mia	Thando	Katlego
Pre-TBI					
Attended creche	Yes (from four years old)	No	Yes (from four years old)	No	Yes (from 18 months)
School type	Mainstream public	Mainstream public	Mainstream public	Mainstream public	Mainstream public
School language	English	English	English	isiXhosa	English
Grade at time of TBI	Grade 3	Grade 5	Grade 2	Grade 4	Grade 3
Term at time of TBI	Second term	Second term holiday	Third term	Third term holiday	Third term holiday
Previously failed grades	Yes (grade 2)	Yes (grade 1)	No	No	Yes (grade 1)
Parent's description of functioning	Above average in maths and languages (obtained 6's and 7's) and average in her other subjects (achieving 4's and 5's). Had problems with attention.	Ethan performed at an average level at school, obtaining 5's and 6's for all his subjects. He was reportedly disruptive in class and was waiting to see the school psychologist.	Mia was an excellent student before the TBI. She received 7's for all her subjects	Thando was an above-average student who achieved 6's and 7's for all his subjects. He was particularly strong in languages and mathematics.	Katlego struggled at school from grade R. He obtained 3's and 4's for his subjects. He was placed in the LSEN unit at his school.
Learning difficulties reported by caregivers	Attention problems (not diagnosed)	Behavioural problems	None	None	Attention problems (diagnosed with ADHD)

	Alice	Ethan	Mia	Thando	Katlego
Post-TBI					
School	Mainstream public	Mainstream public	Special needs	Mainstream public	Mainstream public
Progressed to the next grade in 2019	Yes	Yes	No	Yes	Yes
Parent's description of post-TBI	Alice's grades dropped following the TBI and she was only just passing her subjects.	Ethan was doing relatively well at school and had passed grade 5.	Mia had severe difficulties following the TBI and required special needs schooling.	Thando did not do as well at school following the TBI but was still passing his subjects. He achieved grades of 3 and 4 for his subjects at the end of grade 4 and progressed to grade 5.	Katlego did worse at school following the TBI. He achieved now obtaining 1's and 2's for all his subjects in the first term of grade 4.

Note. South African academic levels of achievement (grades): level 1: "Not achieved", 0 – 29%; level 2: "Elementary achievement", 30 – 39%; level 3: "Moderate achievement", 40 – 49%; level 4: "Adequate achievement", 50 – 59%; level 5: "Substantial achievement", 60 – 69%; level 6: "Meritorious achievement", 70 – 79%; level 7: "Outstanding achievement"; 80 – 100%. LSEN: Learners with Special Educational Needs; ADHD: Attention Deficit with Hyperactivity Disorder.

Table M6

The Caregivers' Concerns and Family Burden of Injury (FBI) Scores for each Participant

	Alice	Ethan	Mia	Thando	Katlego
Caregivers' main concerns	Behaviour	No concerns	Behaviour	Academic functioning and memory.	Behaviour and academic functioning.
Details of caregivers' concerns	Alice was socially inappropriate, disinhibited, emotionally labile, hyperactive and acted like a much younger child.	Ethan was initially temperamental but by the 6-month assessment, he had returned to his pre-TBI baseline.	Mia needed constant supervision and was child-like, disinhibited and socially inappropriate.	Thando was doing worse at school and would forget the tasks he was asked to do or what people tell him.	Katlego was not coping with his schoolwork and was impulsive, distractible, and childlike.
FBI total	54	1	44	40	26
Number of items scored ≤3 / total items	13/26	0/26	10/26	5/26	5/26
Child total	18	1	12	11	8
Number of items scored ≤3 / total items	5/5	0/5	3/5	2/5	2/5
Spouse total	3	0	2	6	4
Number of items scored ≤3 / total items	0/4	0/4	0/4	0/4	1/4
Others total	7	0	0	3	6

	Alice	Ethan	Mia	Thando	Katlego
Number of items scored ≤3 / total items	1/4	0/4	0/4	0/4	0/4
Siblings total	7	0	8	4	0
Number of items scored ≤3 / total items	1/5	0/5	1/5	0/5	0/5
Family Routines/planning total	19	0	22	16	8
Number of items scored ≤3 / total items	5/8	0/8	6/8	3/8	2/8

Note. Higher scores indicate a greater burden. Scores of three or more on an item of the FBI indicate a substantial burden. TBI: Traumatic brain injury.

Table M7

The Neuropsychological Test Results for each Participant

Domain and test	Alice	Ethan	Mia	Thando	Katlego
Attention and concentration					
Digit Span: Forward Span[a]	6 (low average)	4 (Borderline)	4 (Borderline)	5 (Borderline)	4 (Borderline)
TMT: Visual Scanning[a]	9 (Average)	6 (Low average)	1 (Extremely low)	1 (Extremely low)	4 (Borderline)
TMT: Visual Scanning Errors[b]	23 (Low average)	100 (Average)	100 (Average)	100 (Average)	1 (Extremely low)
Audioverbal memory					
RAVLT: Learning[a]	1 (Extremely low)	9 (Average)	1 (Extremely low)	5 (Borderline)	4 (Borderline)
RAVLT: Short Delay[a]	1 (Extremely low)	11 (Average)	1 (Extremely low)	1 (Extremely low)	9 (Average)
RAVLT: Long Delay[a]	1 (Extremely low)	11 (Average)	1 (Extremely low)	5 (Borderline)	10 (Average)
RAVLT: Recognition[a]	1 (Extremely low)*	12 (High average)	3 (Extremely low)	10 (Average)	10 (Average)
Visuospatial memory					
Dot Locations: Learning[a]	1 (Extremely low)	10 (Average)	6 (Low average)*	13 (High average)	6 (Low average)
Dot Locations: Short Delay[a]	4 (Borderline)	12 (High average)	7 (Low average)*	13 (High average)	5 (Borderline)
Dot Locations: Long Delay[a]	5 (Borderline)	13 (High average)	7 (Low average)*	14 (High average)	7 (Low average)
Processing speed					

Domain and test	Alice	Ethan	Mia	Thando	Katlego
Processing Speed Index[c]	73 (Borderline)	83 (Low average)	50 (Extremely low)	103 (Average)	75 (Borderline)
Coding[a]	7 (Low average)	6 (Low average)	1 (Extremely low)	9 (Average)	5 (Borderline)
Symbol Search[a]	3 (Extremely low)	8 (Average)	1 (Extremely low)	12 (High average)	6 (Low average)
Executive functions					
Working Memory Index[c]	65 (Extremely low)	74 (Borderline)	56 (Extremely low)	71 (Borderline)	59 (Extremely low)
Digit Span: Backwards Span[a]	7 (Low average)	7 (Low average)	4 (Borderline)	10 (Average)	5 (Borderline)
Letter-Number Sequencing[a]	2 (Extremely low)	6 (Low average)	3 (Extremely low)	3 (Extremely low)	3 (Extremely low)
TMT: Number Sequencing[a]	11 (Average)	7 (Low average)	1 (Extremely low)	3 (Extremely low)	1 (Extremely low)
TMT: Number Sequencing Errors[b]	100 (Average)	100 (Average)	5 (Borderline)	100 (Average)	1 (Extremely low)
TMT: Letter Sequencing[a]	1 (Extremely low)	5 (Borderline)	DNC	2 (Extremely low)	1 (Extremely low)
TMT: Letter Sequencing Errors[b]	1 (Extremely low)	100 (Average)	DNC	100 (Average)	1 (Extremely low)
TMT: Number-Letter Switching[a]	2 (Extremely low)	1 (Extremely low)	DNC	5 (Borderline)	1 (Extremely low)
TMT: Number-Letter Switching Errors[b]	8 (Borderline)	17 (Low average)	DNC	100 (Average)	3 (Extremely low)
TMT: Motor Speed[a]	5 (Borderline)	10 (Average)	DNC	1 (Extremely low)	6 (Low average)
TMT: Motor Speed Errors[b]	100 (Average)	100 (Average)	DNC	100 (Average)	100 (Average)

Domain and test	Alice	Ethan	Mia	Thando	Katlego
Tower: Achievement Score[a]	3 (Extremely low)	7 (Low average)	DNC	11 (Average)	1 (Extremely low)
Tower: Time Per Move[a]	1 (Extremely low)	12 (High average)	DNC	13 (High average)	5 (Borderline)
Tower: Move Accuracy Ratio[a]	13 (High average)	8 (Average)	DNC	4 (Borderline)	8 (Average)
Tower: Total Rule Violations[b]	<1 (Extremely low)	10 (Average)	DNC	100 (Average)	6 (Low average)
Tower: Rule Violations Per Item[a]	1 (Extremely low)	8 (Average)	DNC	11 (Average)	1 (Extremely low)

Note. Scores are represented as [a]scaled scores, [b]percentiles, or [c]standard scores. RAVLT: Rey Auditory Verbal Learning Test; TMT: Trail Making Test; DNC: Did not complete. *Score invalidated by the participant.

Table M8

The Behaviour Rating Inventory of Executive Function (BRIEF) T-Scores Measuring Participants' Executive Functions and Behaviour Before and After Their Traumatic Brain Injury (TBI) and the Resultant Reliable Change Indices (RCI) to Indicate Significant Change Between Pre- and Post-TBI Scores

	Alice			Ethan			Mia			Thando			Katlego		
BRIEF parent report	Pre-TBI	Post-TBI	RCI	Pre-TBI	Post-TBI	RCI	Pre-TBI	Post-TBI	RCI	Pre-TBI	Post-TBI	RCI	Pre-TBI	Post-TBI	RCI
Global executive composite	63	**77**	***	53	51	ND	38	**81**	***	63	60	*	**80**	**80**	ND
BRI	**67**	**79**	***	62	57	*	39	**83**	***	**69**	64	*	**82**	**80**	ND
MI	60	**74**	***	48	48	ND	38	**78**	***	58	57	ND	**75**	**77**	ND
Inhibit	**67**	**77**	**	53	50	ND	42	**89**	***	**71**	64	*	**82**	**78**	ND
Shift	62	**83**	***	**67**	59	*	41	**80**	***	**74**	**67**	*	**81**	**88**	*
Emotional Control	64	**69**	*	64	59	*	38	**69**	***	58	56	ND	**71**	**67**	ND
Initiate	55	**71**	**	47	47	ND	43	**74**	***	63	56	*	**75**	**81**	ND
Working Memory	57	**74**	***	47	49	ND	44	**77**	***	58	58	ND	**67**	**72**	*
Plan/Organize	**67**	**78**	**	49	49	ND	40	**78**	***	58	61	ND	**80**	**77**	ND
Organization of materials	57	63	*	49	49	ND	34	**66**	***	52	49	ND	64	61	ND
Monitor	52	**67**	**	51	45	*	35	**72**	***	50	53	ND	**66**	**66**	ND
Negativity Scale	0	1		0	1		1	6		3	1		4	6	

	Alice			Ethan			Mia			Thando			Katlego		
BRIEF parent report	Pre-TBI	Post-TBI	RCI	Pre-TBI	Post-TBI	RCI	Pre-TBI	Post-TBI	RCI	Pre-TBI	Post-TBI	RCI	Pre-TBI	Post-TBI	RCI
Inconsistency Scale	5	0		2	4		0	0		7	4		4	4	

Note. T scores equal to or greater than 65 are considered to be in the clinical range (Gioia et al., 2000) and are shown in bold. *a change with 68% confidence, **a change with 95% confidence; ***a change with 99% confidence, ND: no difference.

Table M9

Child Behavioural Checklist (CBCL) T-Scores Measuring Participants' Behaviour Before and After Their Traumatic Brain Injury (TBI) and the Resultant Reliable Change Indices (RCI) to Indicate Significant Change Between Pre- and Post-TBI Scores

	Alice			Ethan			Mia			Thando			Katlego		
CBCL	Pre-TBI	Post-TBI	RCI	Pre-TBI	Post-TBI	RCI	Pre-TBI	Post-TBI	RCI	Pre-TBI	Post-TBI	RCI	Pre-TBI	Post-TBI	RCI
Anxious/Depressed	57	60	ND	51	50	ND	60	51	*	62	59	ND	57	69	**
Withdrawn/Depressed	56	64	*	57	57	ND	64	64	ND	66	66	ND	54	50	ND
Somatic Complaints	50	72	***	54	54	ND	53	96	***	53	84	***	53	68	***
Social Problems	62	77	***	58	63	*	50	75	***	65	69	ND	58	67	**
Thought Problems	58	71	**	55	50	ND	50	84	***	51	64	**	51	51	ND
Attention Problems	64	77	***	55	53	ND	50	100	***	64	71	*	59	66	*
Rule Breaking Behaviour	68	79	***	63	60	ND	52	82	***	71	73	ND	57	53	ND
Aggressive Behaviour	69	85	***	58	61	ND	50	85	***	70	69	ND	57	55	ND
Internalizing Problems	54	68	***	54	50	ND	61	75	***	63	72	**	54	68	***
Externalizing Problems	71	81	**	61	61	ND	41	83	***	72	72	ND	58	54	ND
Total Problems	66	77	***	58	56	ND	46	82	***	70	74	*	56	62	*
Affective Problems	60	73	**	51	50	ND	52	78	***	70	73	ND	52	63	*
Anxiety Problems	59	59	ND	53	50	ND	51	59	*	65	55	*	60	68	*

	Alice			Ethan			Mia			Thando			Katlego		
CBCL	Pre-TBI	Post-TBI	RCI	Pre-TBI	Post-TBI	RCI	Pre-TBI	Post-TBI	RCI	Pre-TBI	Post-TBI	RCI	Pre-TBI	Post-TBI	RCI
Somatic Problems	50	77	***	56	56	ND	56	97	***	50	90	***	50	57	*
Attention Deficit/Hyperactivity Problems	66	73	*	57	52	*	50	80	***	62	66	*	58	62	*
Oppositional Defiant Problems	67	77	*	62	58	ND	50	80	***	62	58	ND	52	52	ND
Conduct Problems	71	86	***	66	66	ND	50	80	***	75	74	ND	60	57	ND

Note. T-scores between 65 and 70 are considered to be in the borderline range, while scores equal to or greater than 70 are designated to be in the clinical range (Achenbach & Ruffle, 2000) and are highlighted in bold. *a change with 68% confidence, **a change with 95% confidence; ***a change with 99% confidence, ND: no difference.

Appendix N.

Select Images From Participant Magnetic Resonance Imaging Scans.

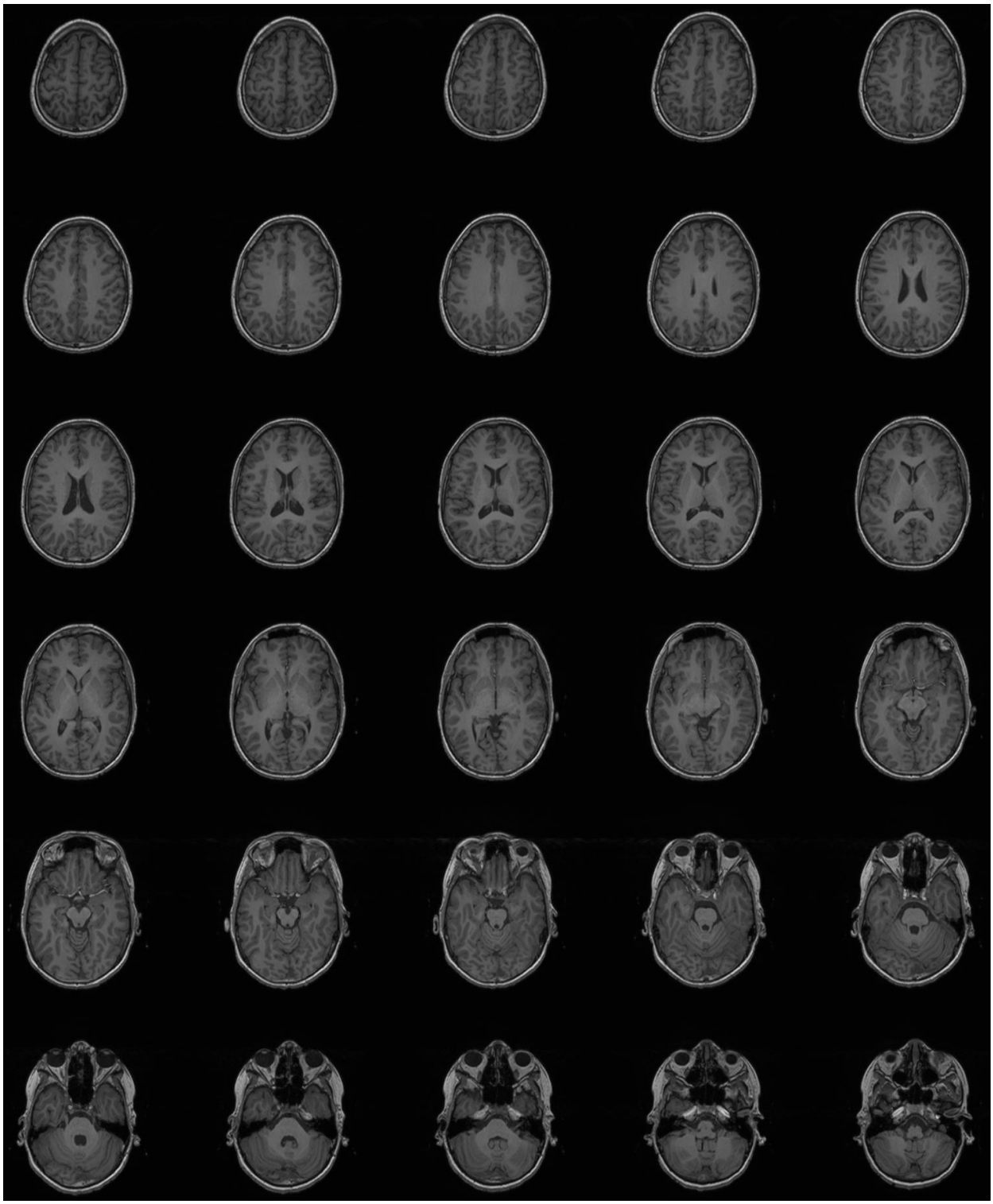

Figure N1. Serial images of Ethan's 6-month post-TBI T1-weighted magnetic resonance imaging axial scan.

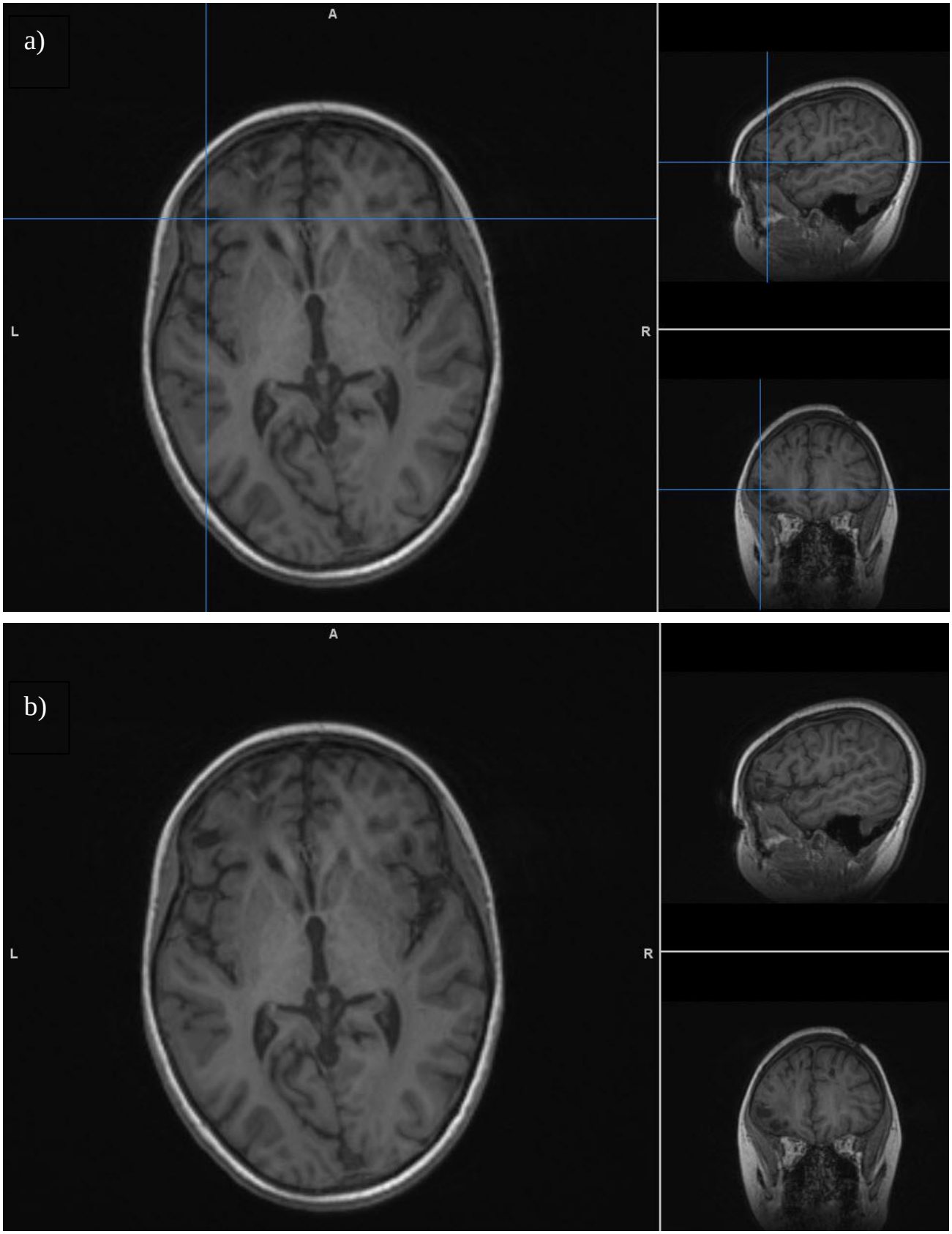

Figure N2. Mia's 6-month post-TBI T1-weighted magnetic resonance imaging axial scan (left images) with sagittal and coronal localisers (right images) and a) with and b) without crosshairs showing the level of the slice. The crosshairs point to an area of encephalomalacia in the left frontal lobe.

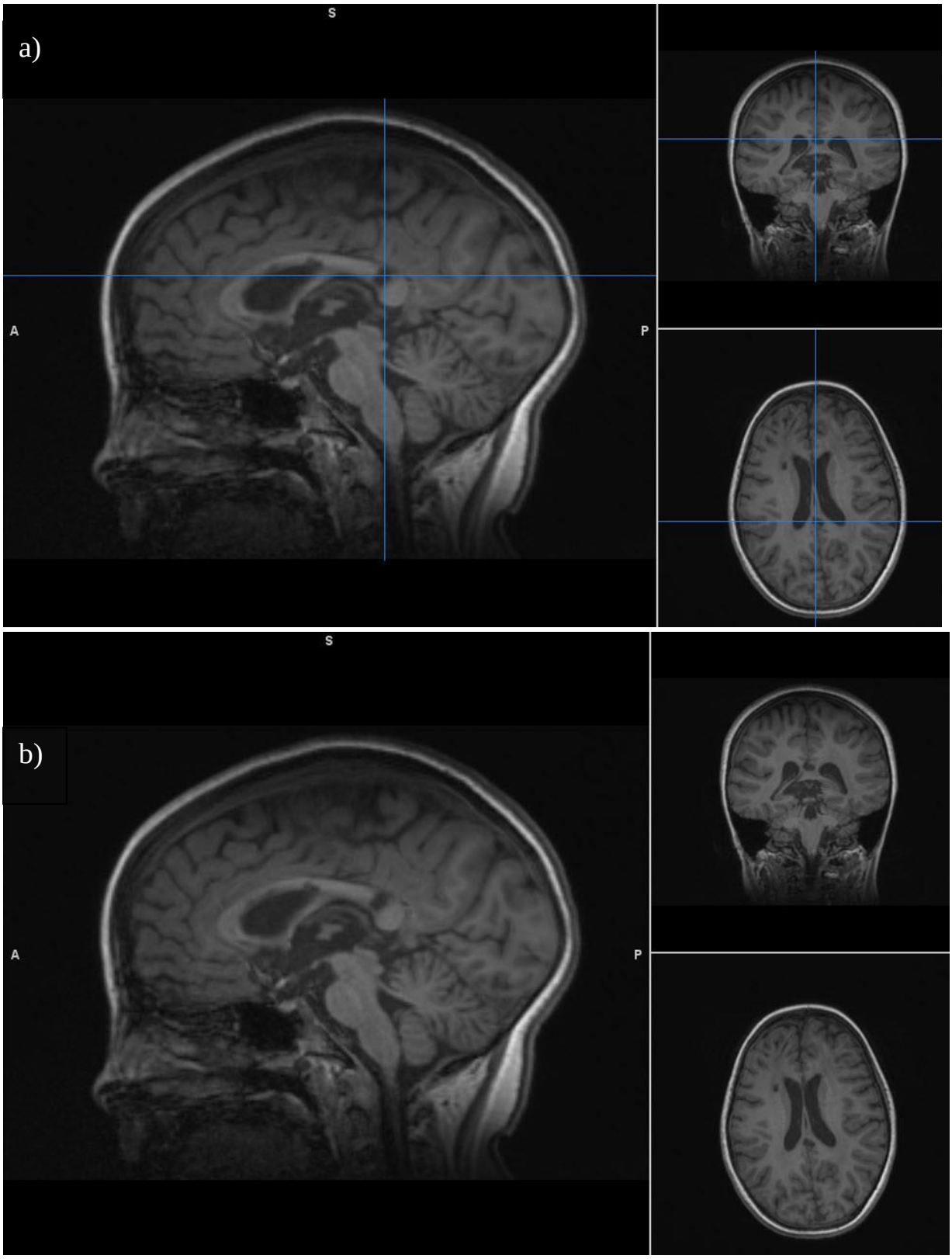

Figure N3. Mia's 6-month post-TBI T1-weighted magnetic resonance imaging sagittal scan (left images) with coronal and axial localisers (right images) and a) with and b) without crosshairs showing the level of the slice. Crosshairs point to an area of cystic encephalomalacia in the splenium of the corpus callosum. Additional areas of encephalomalacia can be seen anteriorly in the body and genu of the corpus callosum.

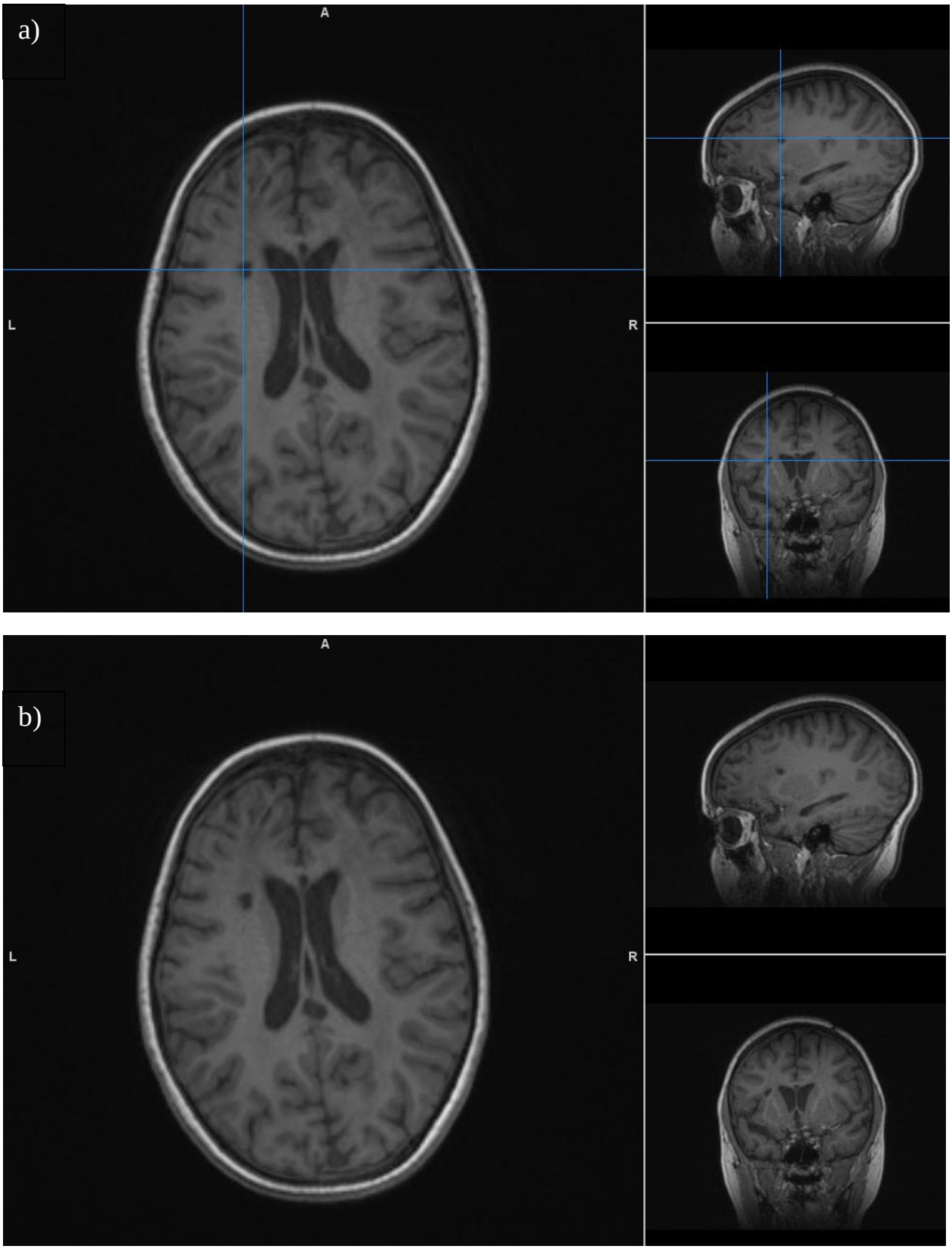

Figure N4. Mia's 6-month post-TBI T1-weighted magnetic resonance imaging axial scan (left images) with sagittal and coronal localisers (right images) and a) with and b) without crosshairs showing the level of the slice. The crosshairs point to an area of lacunar encephalomalacia in the left external capsule that extended into the left corona radiata. Areas of cystic encephalomalacia can also be seen in the corpus callosum.

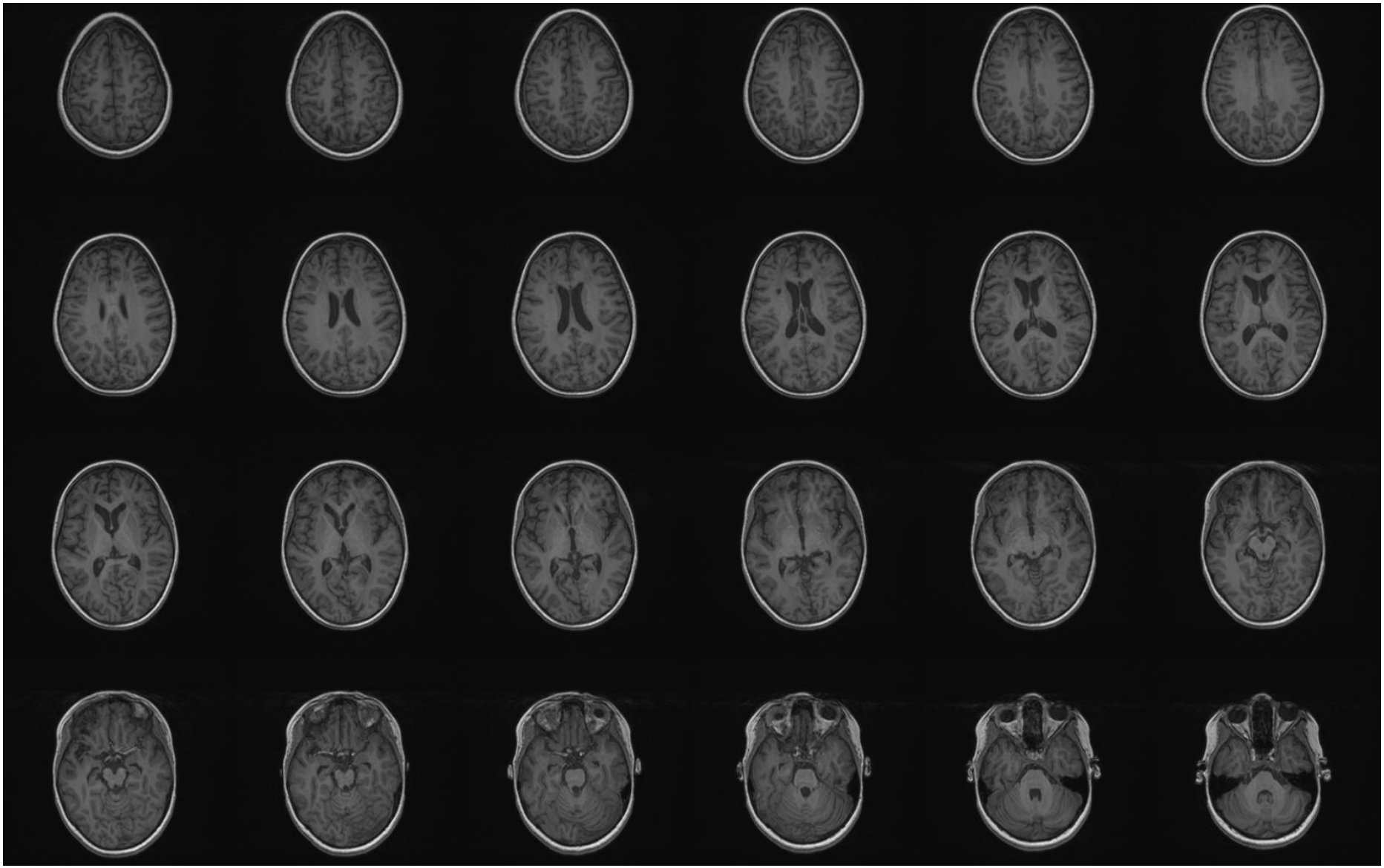

Figure N5. Serial images of Mia's 6-month post-TBI T1-weighted magnetic resonance imaging axial scan.

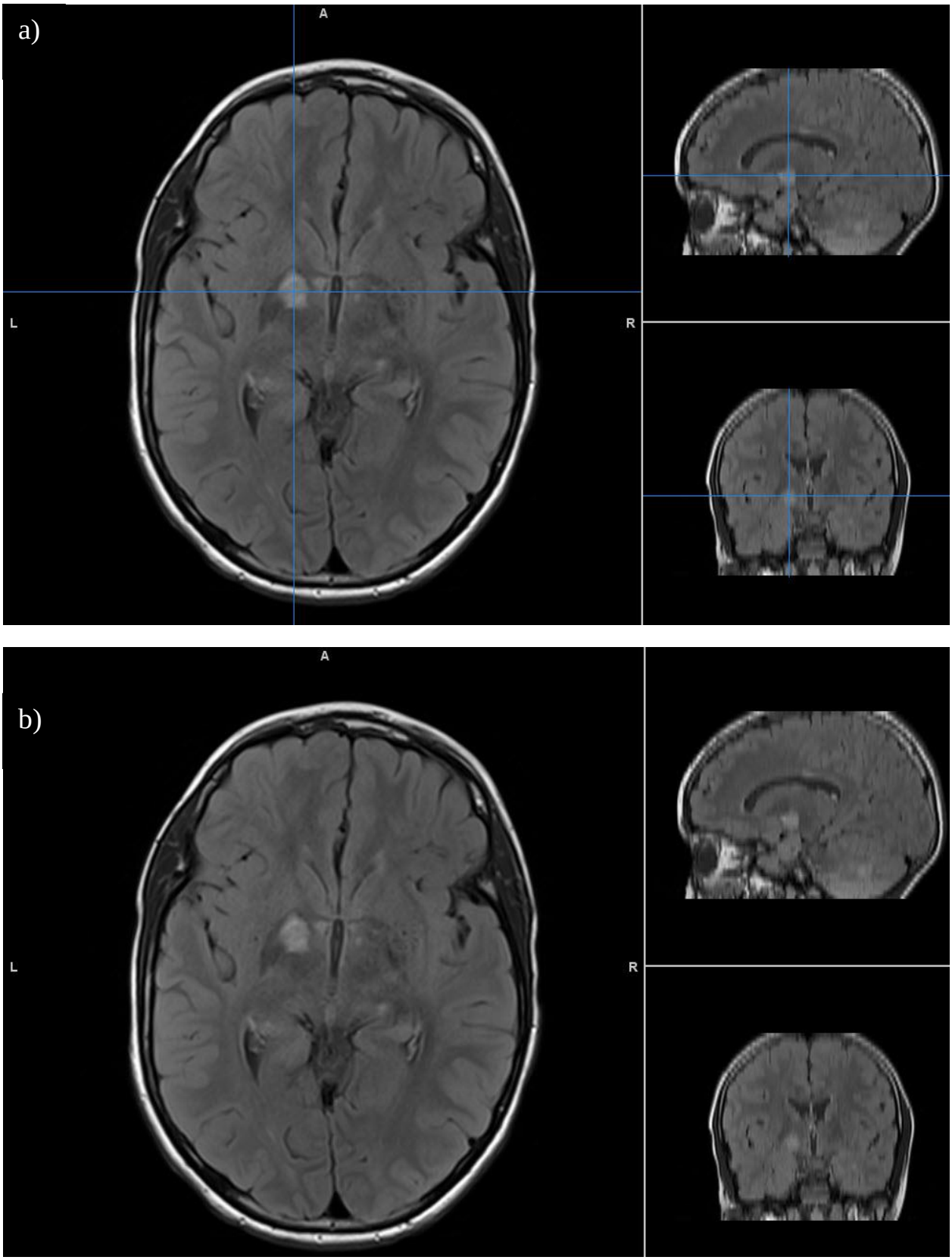

Figure N6. Thando's 6-month post-TBI fluid-attenuated inversion recovery (FLAIR) magnetic resonance imaging axial scan (left images) with coronal and sagittal localisers (right images) and a) with and b) without crosshairs showing the level of the slice. The crosshairs point to an area of FLAIR hyperintensity in the left thalamus. Hyperintensities can also be seen in the right thalamus.

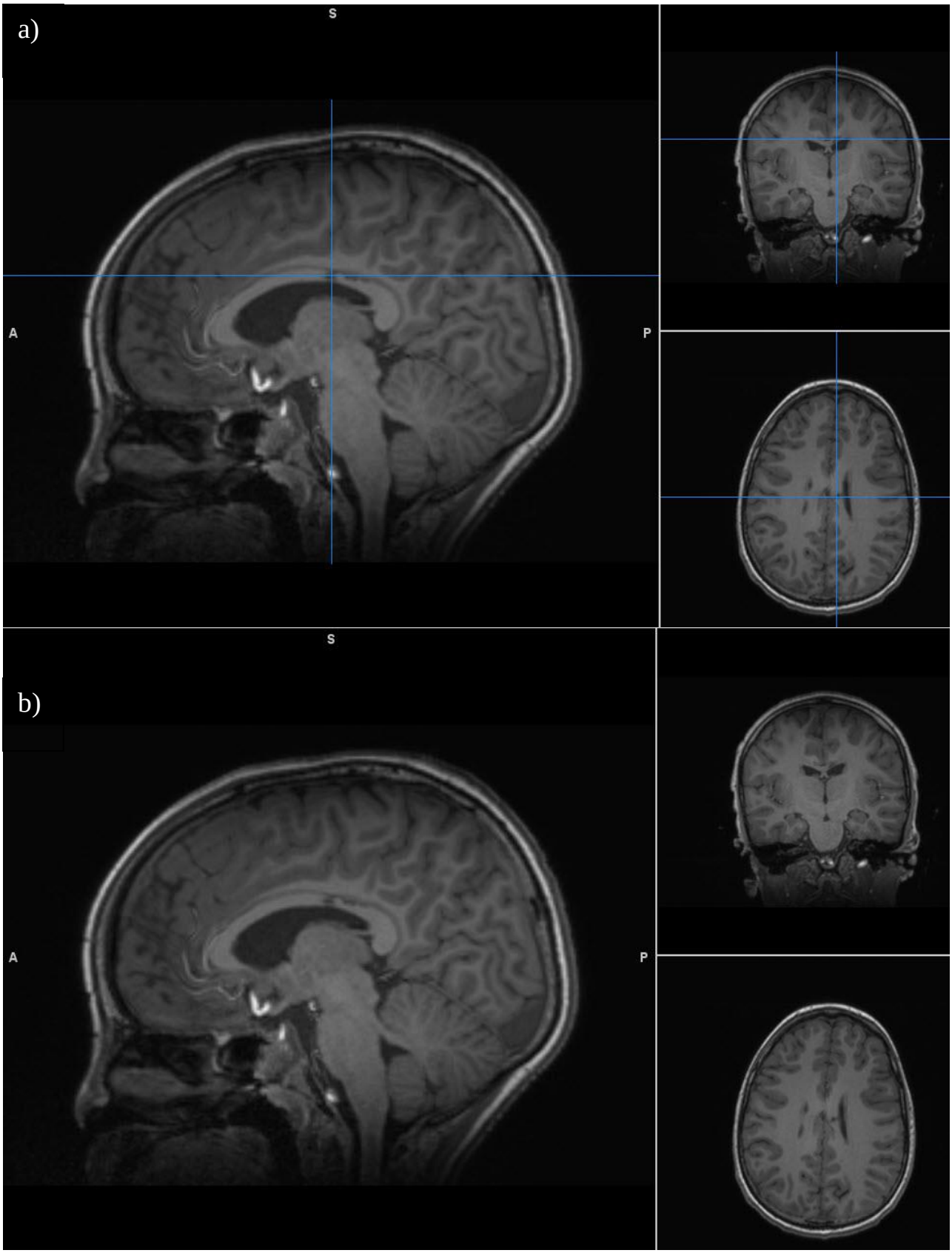

Figure N7. Thando's 6-month post-TBI T1-weighted magnetic resonance imaging sagittal scan (left images) with coronal and axial localisers (right images) and a) with and b) without crosshairs showing the level of the slice. The crosshairs point to areas of cystic encephalomalacia in the posterior aspect of the body and the isthmus of the corpus callosum.

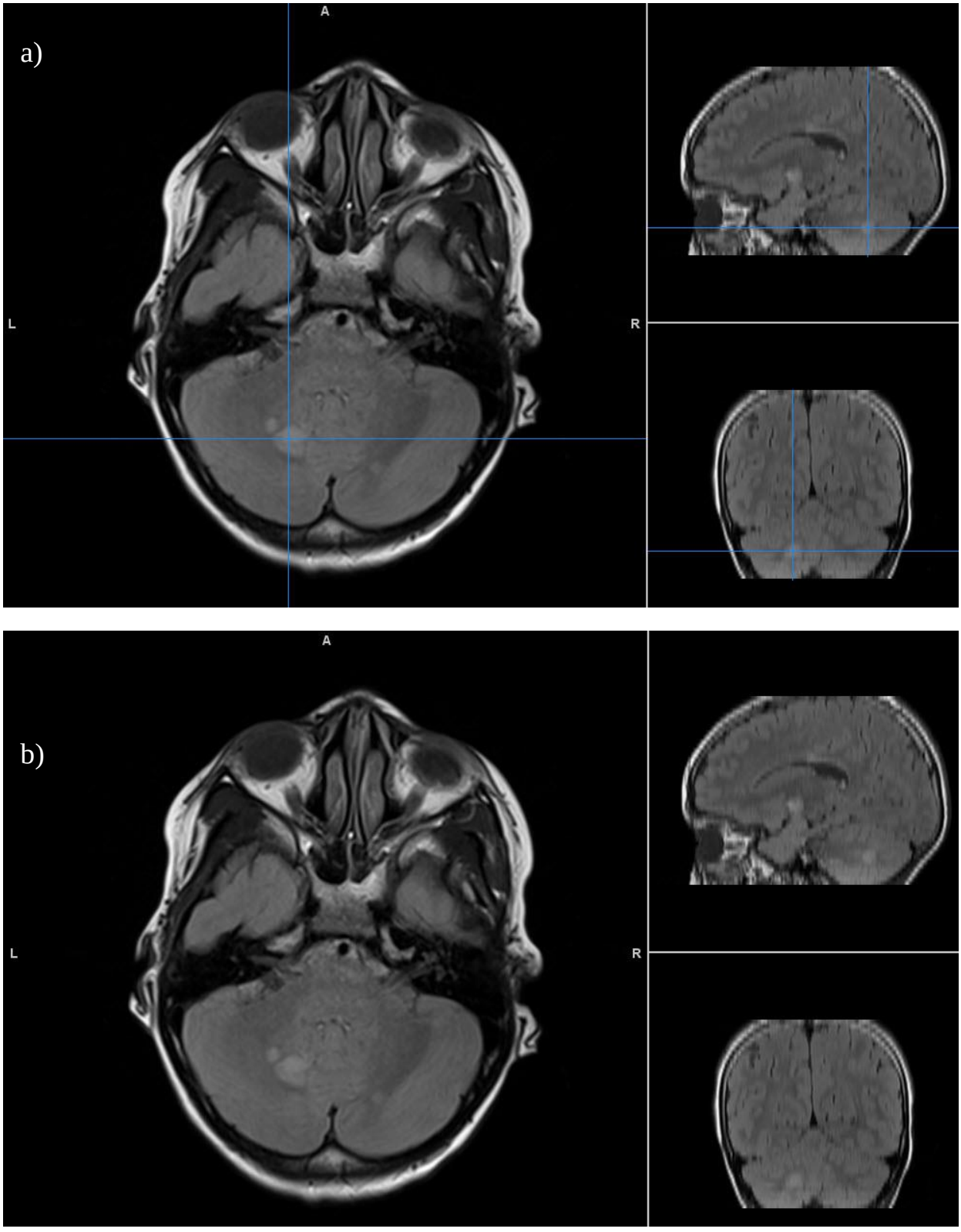

Figure N8. Thando's 6-month post-TBI fluid-attenuated inversion recovery (FLAIR) magnetic resonance imaging axial scan (left images) with coronal and sagittal localisers (right images) and a) with and b) without crosshairs showing the level of the slice. The crosshairs point to an area of FLAIR hyperintensity in the left hemisphere of the cerebellum.

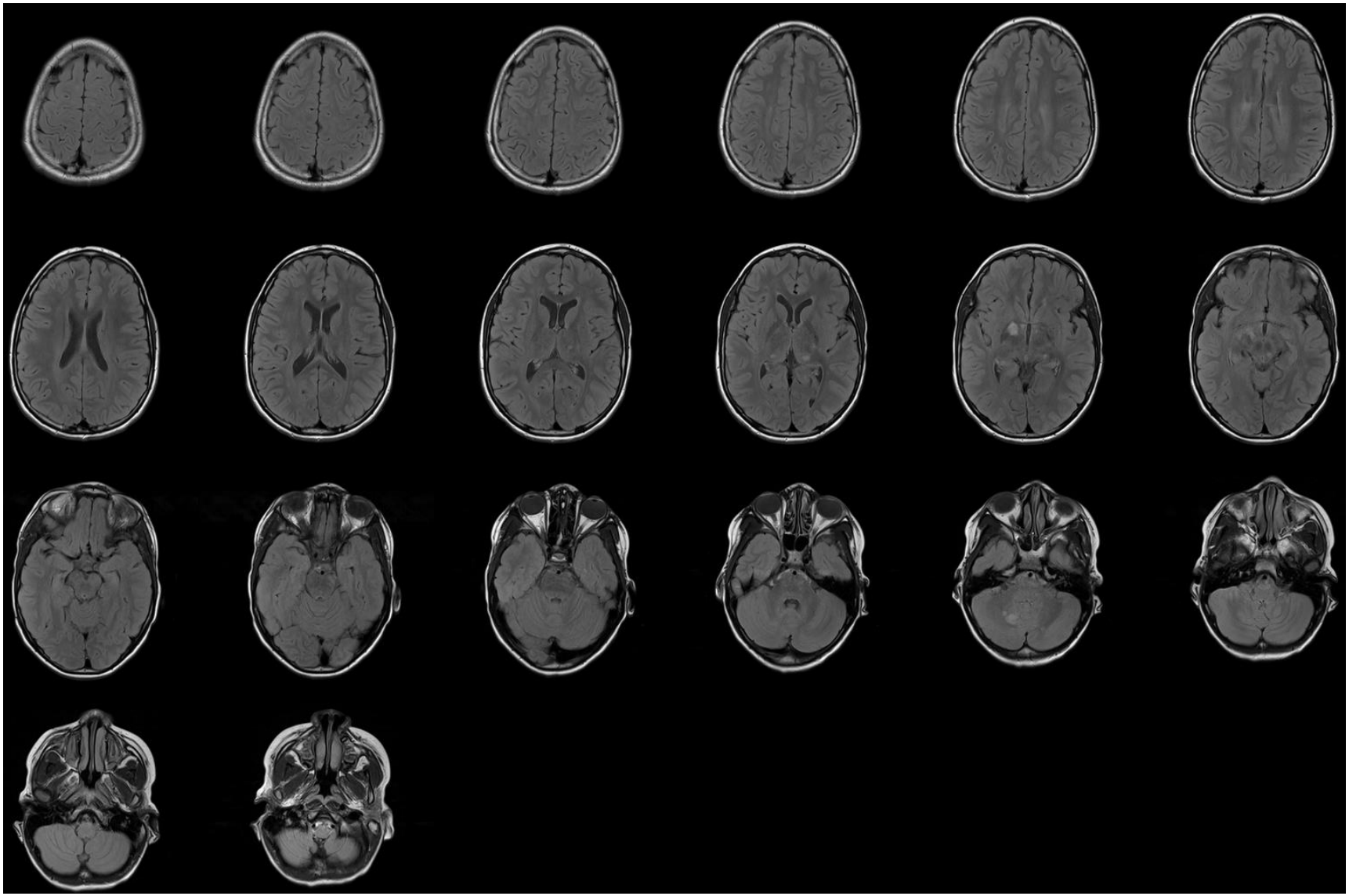

Figure N9. Serial images of Thando's 6-month post-TBI fluid-attenuated inversion recovery **(**FLAIR**)** magnetic resonance imaging axial scan.

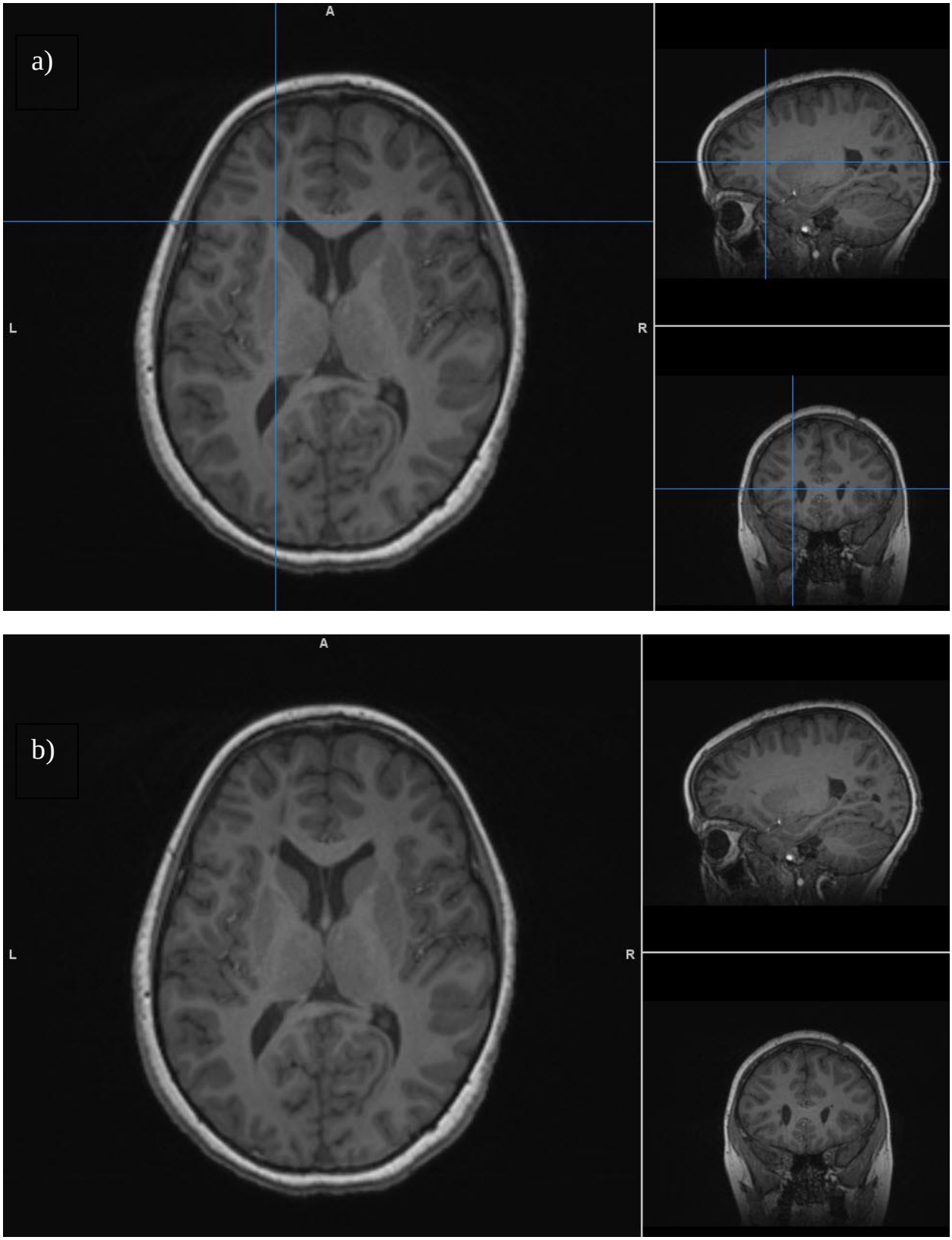

Figure N10. Katlego's 6-month post-TBI T1-weighted magnetic resonance imaging axial scan (left images) with coronal and sagittal localisers (right images) and a) with and b) without crosshairs showing the level of the slice. The crosshairs point to an area of encephalomalacia in the left frontal lobe. Additional encephalomalacia can be seen anterior to the crosshair point.

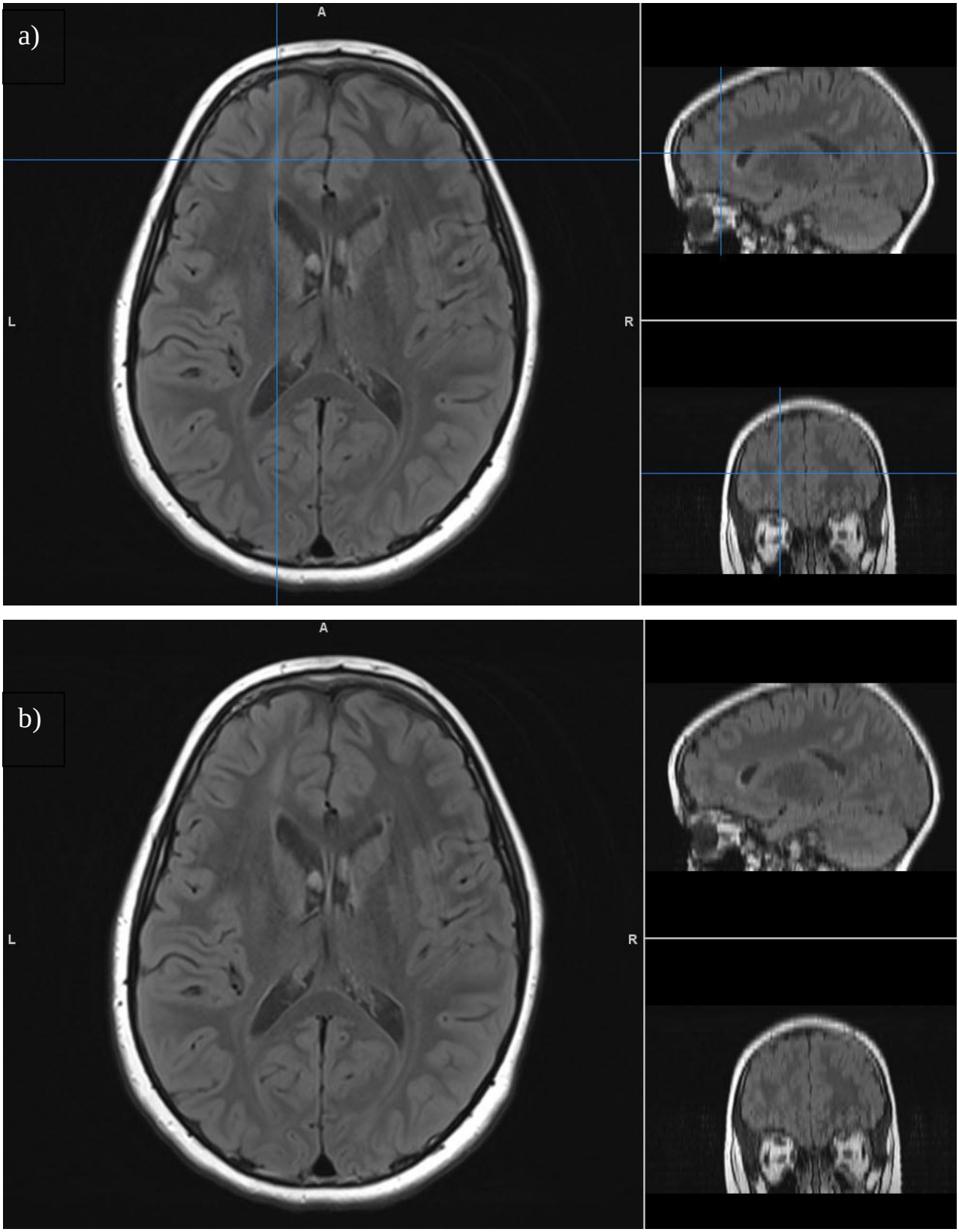

Figure N11. Katlego's fluid-attenuated inversion recovery (FLAIR) magnetic resonance imaging axial scan taken on 20/05/2019 (left image) with coronal and sagittal localisers (right images) and crosshairs showing the level of the slice. The crosshairs point to an area of encephalomalacia in the left frontal lobe.

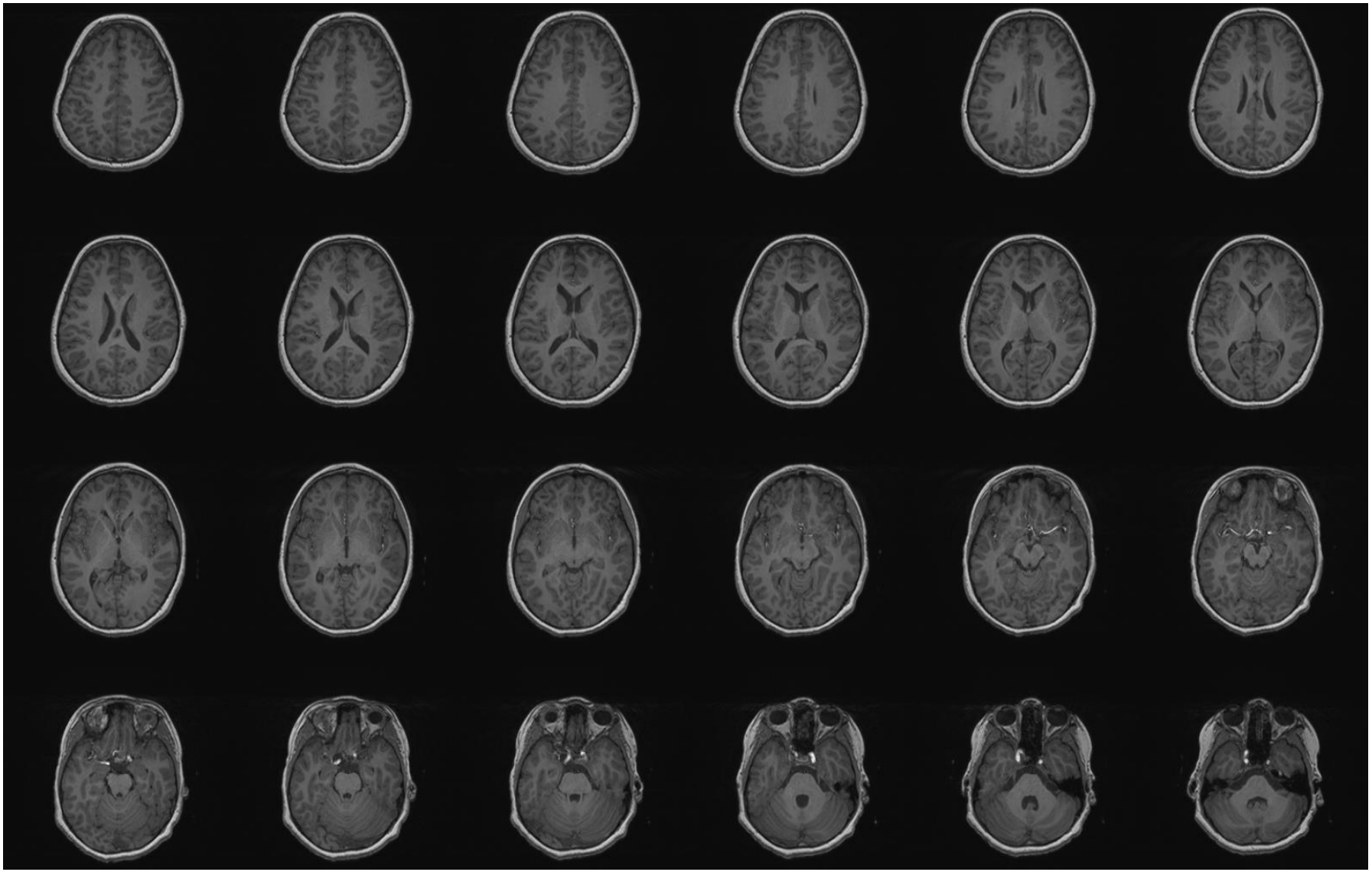

Figure N12. Serial images of Katlego**'s** 6-month post-TBI T1-weighted magnetic resonance imaging axial scan.

Appendix O.

Graphical Representations of the Factors that Might Have Influenced Participant Outcomes.

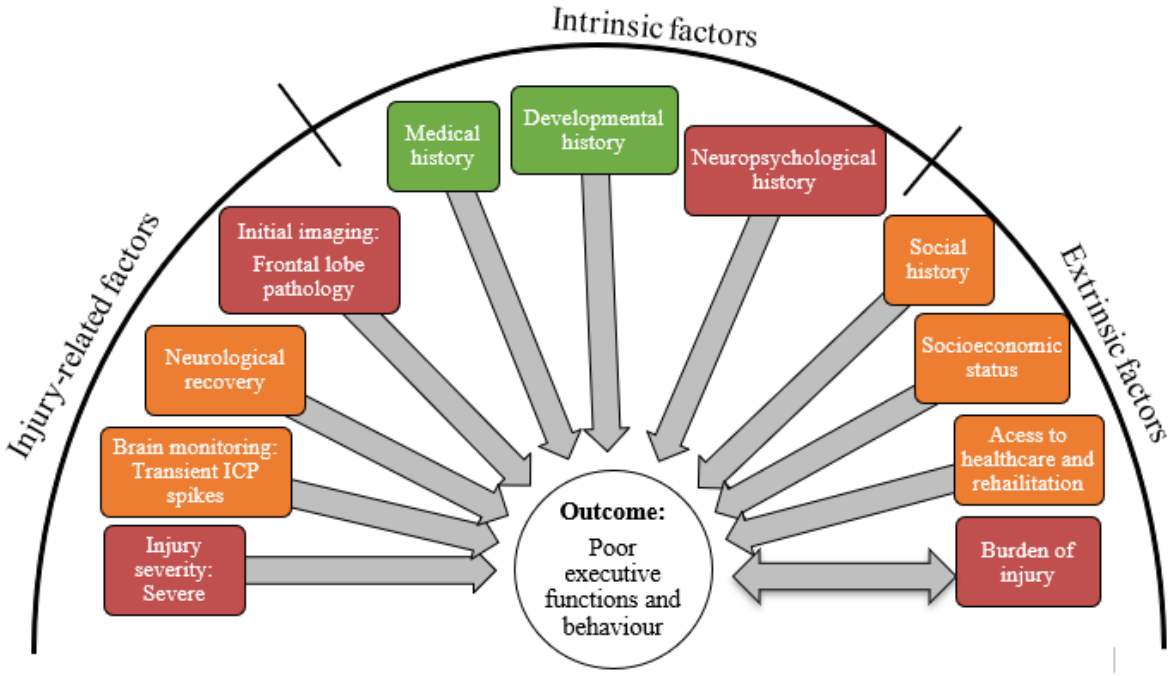

Figure O1. A summary of some of the potential factors influencing Alice's outcome following the traumatic brain injury (TBI). The colours of the text boxes indicate whether each influencing factor was suspected to be favourable or adverse to Alice's outcome, with green indicating a favourable factor, orange indicating a moderately unfavourable factor, and red indicating a severely unfavourable factor. In terms of injury-related factors, Alice sustained a severe TBI and her initial hospital imaging scans showed evidence of bifrontal contusions and traumatic axonal injuries (red). Alice had no prolonged elevated intracranial pressure (ICP) episodes or brain oxygenation deficits, but she did have some transient ICP spikes, which could have been moderately unfavourable to her recovery (orange). Alice had a gradual neurological recovery (orange). She had no significant prior medical conditions or developmental delays (green) but did have premorbid behavioural and attention difficulties (red). It appeared that these premorbid neuropsychological difficulties were significantly exacerbated by the TBI. In terms of extrinsic factors, Alice had a difficult social history with an absent father and the loss of her mother (orange). In terms of SES, Alice's family had a medium asset index and access to the resources to fulfil most of their basic needs. However, their location in a small town in the Eastern Cape and overall household income could limit their access to adequate healthcare facilities and rehabilitation (orange). The consequences of the TBI have placed a considerable burden on Alice's family, which in turn could negatively affect Alice (red).

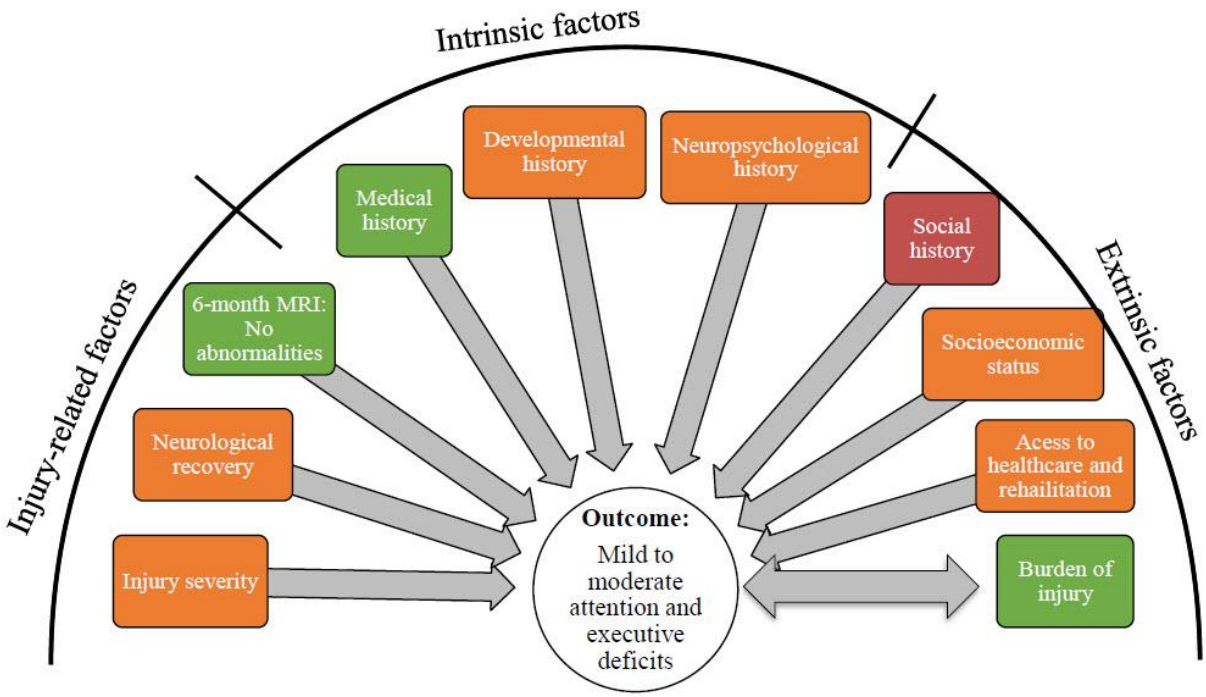

Figure O2. A summary of some of the potential factors influencing Ethan's outcome following the traumatic brain injury (TBI). The colours of the text boxes indicate whether each influencing factor was suspected to be favourable or adverse to Ethan's outcome, with green indicating a favourable factor, orange indicating a moderately unfavourable factor, and red indicating a severely unfavourable factor. In terms of the initial injury severity, Ethan sustained a severe TBI with no focal neurological deficits (orange). He had a prolonged period of restlessness but thereafter made a relatively good neurological recovery (orange). In support of this, his 6-month magnetic resonance imaging (MRI) showed no evidence of residual pathology (green). Ethan had no prior medical conditions (green). In terms of his developmental history, Ethan was potentially exposed to illicit substances in utero and was born prematurely (orange). There were also reports of some premorbid academic and behavioural issues (orange). Ethan had an unstable childhood social environment, which had previously affected his academic performance and might negatively influence his post-TBI recovery (red). Ethan's family had a moderate asset index and access to public health services, but extensive or private rehabilitation would be unaffordable (orange). Fortunately, Ethan's aunt reported few caregiver concerns and a low level of burden of injury following the TBI (green).

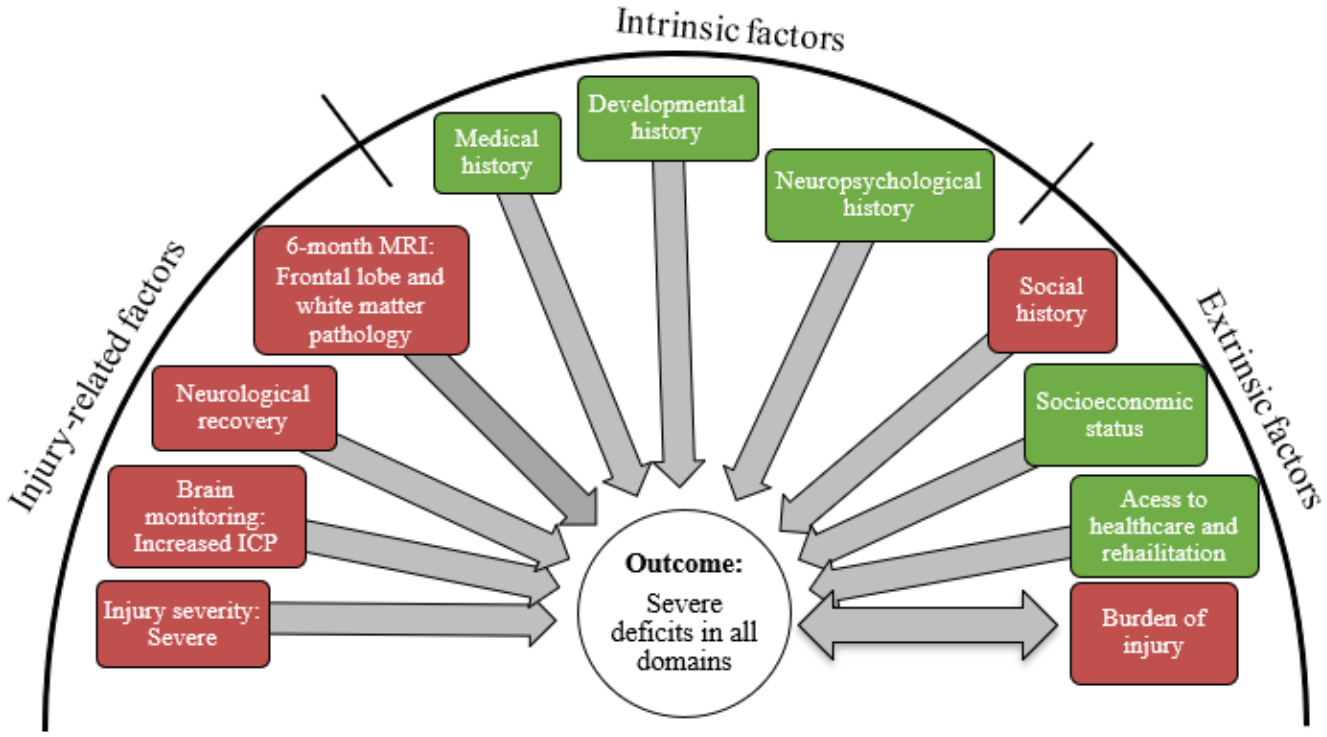

Figure O3. A summary of some of the potential factors influencing Mia's outcome following the traumatic brain injury (TBI). The colours of the text boxes indicate whether each influencing factor was suspected to be favourable or adverse to Mia's outcome, with green indicating a favourable factor, orange indicating a moderately unfavourable factor, and red indicating a severely unfavourable factor. In terms of initial injury severity, Mia had a severe TBI and a prolonged neurological recovery (red). Her primary injury appeared to be further complicated by secondary injuries, most notable episodes of increased intracranial pressure (ICP; red). The seriousness of her TBI pathology was supported by numerous abnormalities noted on her 6-month magnetic resonance imaging (MRI; red). Mia had no health concerns before the TBI (green). There were suggestions of possible prenatal drug exposure but her reported good pre-TBI baseline did not support the idea of the possible associated developmental delays (green). Mia had a good academic history (green). Although Mia's current living environment was quite stable, she had a traumatic social history (red). Mia's family currently have a relatively high socioeconomic status (green). In terms of rehabilitation, Mia spent two months in a hospital rehabilitation unit and was then discharged to an intermediate care facility where she received continued rehabilitation (green). Mia's TBI placed a high burden on her caregivers (red). Mia's grandmother complained of caregiver fatigue. Caregiver burnout can result in suboptimal care for children with pTBI, which may exacerbate Mia's difficulties.

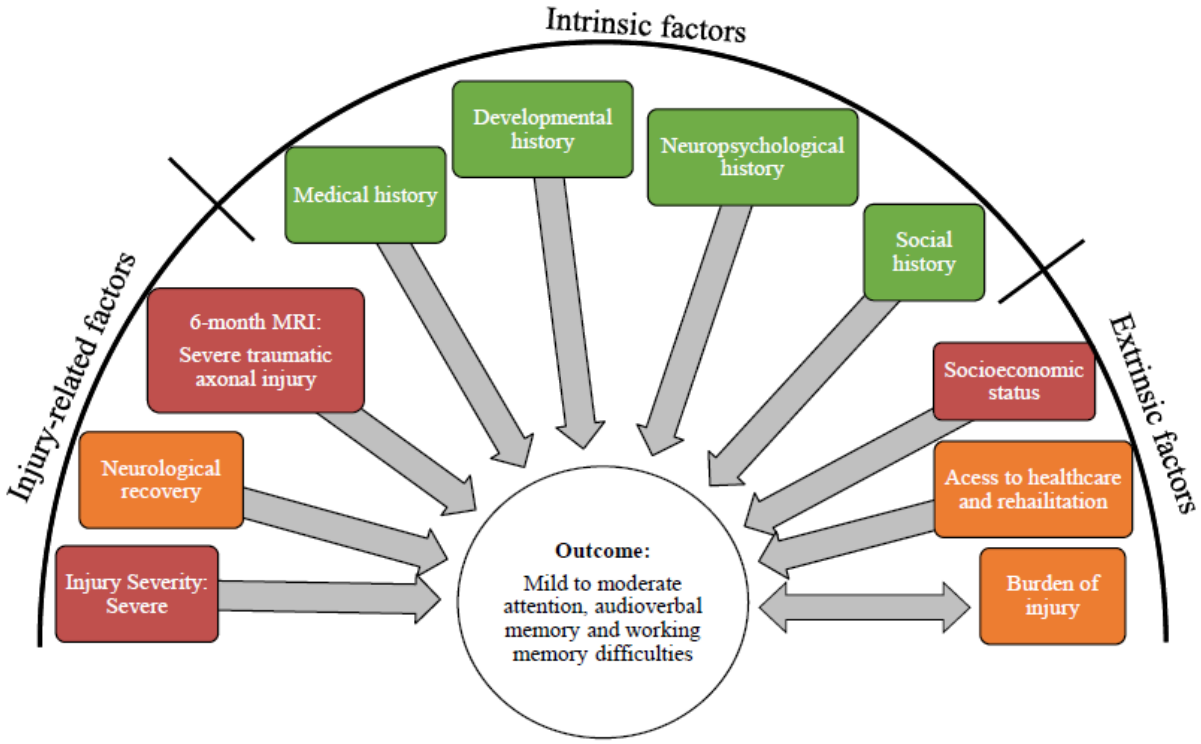

Figure O4. A summary of some of the potential factors influencing Thando's outcome following the traumatic brain injury (TBI). The colours of the text boxes indicate whether each influencing factor was suspected to be favourable or adverse to Thando's outcome, with green indicating a favourable factor, orange indicating a moderately unfavourable factor, and red indicating a severely unfavourable factor. Thando's strong neuropsychological history, normal developmental history, and stable social history were all likely to have improved the chances of a better neuropsychological outcome (all green). Injury-related factors that might have negatively influenced his TBI outcome include the initial severity of his injury (red), his gradual neurological recovery (orange), and the residual pathology noted on his 6-month post-TBI magnetic resonance imaging scan (red). Thando's parents reported severe financial struggles (red) that resulted in Thando being sent to live with his grandparents in the Eastern Cape following the TBI. This move would limit his accessibility to rehabilitation, follow-up monitoring and potential interventions if required (orange). Thando's TBI had placed a moderate burden on his caregivers (orange).

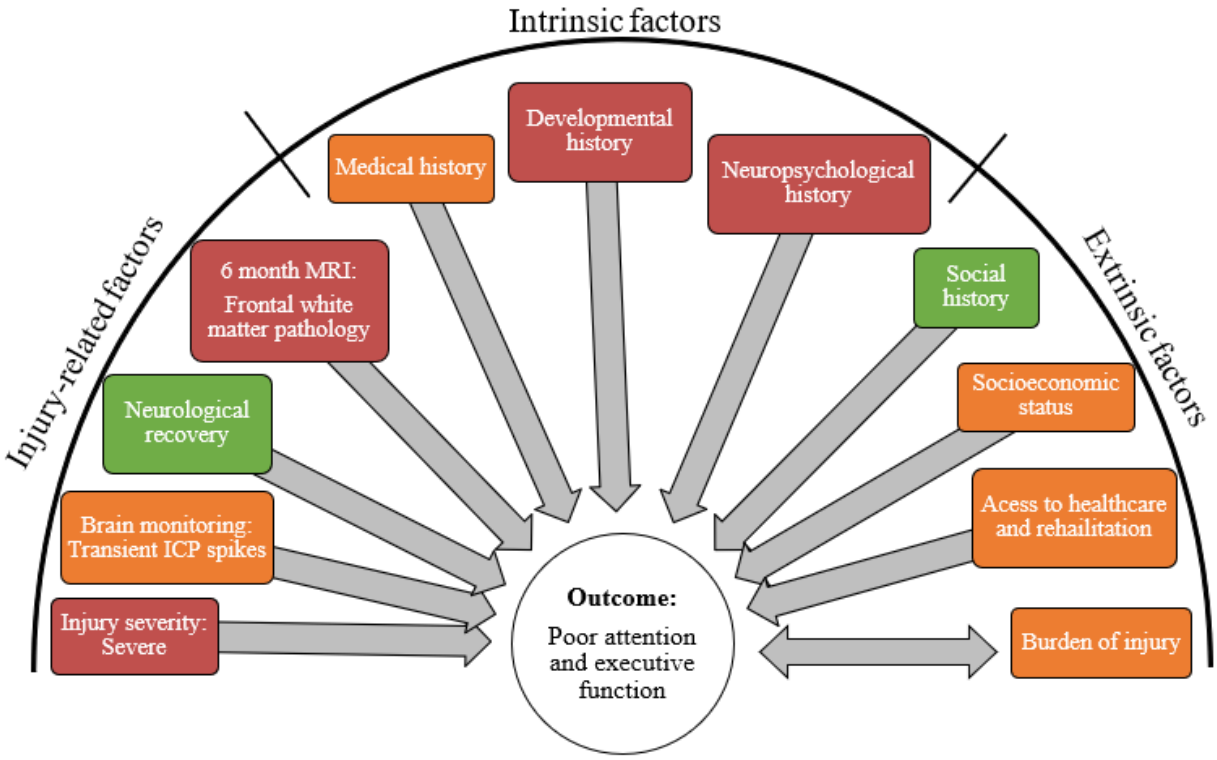

Figure O5. A summary of some of the potential factors influencing Katlego's outcome following the traumatic brain injury (TBI). The colours of the text boxes indicate whether each influencing factor was suspected to be favourable or adverse to Katlego's outcome, with green indicating a favourable factor, orange indicating a moderately unfavourable factor, and red indicating a severely unfavourable factor. Katlego had several adverse premorbid intrinsic factors that might have influenced his outcome. In terms of medical history, Katlego was born prematurely and with complications (orange). He had developmental delays and a prior ADHD diagnosis (red), and a poor neuropsychological history evidenced in his academic record (red). Although Katlego had a severe TBI with traumatic axonal injury and other pathologies noted on early imaging (red), he had a relatively fast neurological recovery (green). He had some transient spikes in intracranial pressure (ICP), but his brain monitoring data showed no strong evidence of persistently high ICP or low brain oxygenation (orange). The 6-month post-TBI MRI showed encephalomalacia in the deep white matter of the left frontal lobe (red). Although Katlego's family had a medium asset index, their income fluctuated due to his parents' temporary employment status (orange), which might also influence his access to treatment and rehabilitation (orange). On a positive note, Katlego had a stable social history with no significantly traumatic events and good family support (green). However, Katlego's mother did report a relatively high burden of injury and therefore she may experience caregiver fatigue in time, which may negatively affect the care given to Katlego in the future (orange).