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White matter integrity and cognition in young Traumatic Brain Injury patients:
 a diffusion tensor imaging study

Master thesis in aspiration for the degree of Master of Science in Psychology,
option Theoretical and Experimental Psychology

Louise Puttevils
01010789

Promotor: Guy Vingerhoets
Co-promotor: Karen Caeyenberghs
Mentor: Helena Verhelst
Acknowledgements

This master thesis is the final realization before obtaining my master’s degree in Theoretical and Experimental Psychology. It has been a hell of a ride, by all means. It hasn’t always been easy, but on the way I have learned a lot of valuable skills and obtained interesting knowledge that I will carry with me in the future.

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Traumatic Brain Injury (TBI) is a leading cause of disability in young children and adolescents, and often involves the occurrence of diffuse axonal injury (DAI). DAI can lead to neurological impairment, and this affects higher cognitive functions such as cognitive control, attention and memory. Previous studies have already revealed a link between certain white matter structures and performance on cognitive tests. The current study aims to investigate whether there is a link between attention and working memory, and the Superior Longitudinal Fasciculus (SLF) and cingulum as white matter tracts of interest in adolescents with chronic TBI. Compared to other neuroimaging techniques, Diffusion Tensor Imaging (DTI) is a more suitable tool to detect DAI and to predict functional outcome. DTI parameters (fractional anisotropy and mean diffusivity) were calculated and subsequently correlated with performance on neuropsychological tests (spatial span and flanker task). The data acquired in nine adolescents who sustained moderate-to-severe TBI revealed no significant relationship between working memory and white matter bundles, and the correlation with attention turned out to be non-significant as well. These results are not consistent with previous findings, that found that the decreased structural connectivity and integrity of the SLF and cingulum in TBI patients have a significant impact on certain aspects of cognition. Our findings could be explained by issues such as methodological choices and biological confounds.

**Keywords:** Traumatic Brain Injury, Diffuse Axonal Injury, Attention, Working Memory, Diffusion Tensor Imaging, Superior Longitudinal Fasciculus, Cingulum
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<th>Full Form</th>
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<td>TBI</td>
<td>Traumatic Brain Injury</td>
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<tr>
<td>DAI</td>
<td>Diffuse Axonal Injury</td>
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<tr>
<td>GCS</td>
<td>Glasgow Coma Scale</td>
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<td>LOC</td>
<td>Loss of Consciousness</td>
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<td>PTA</td>
<td>Post-Traumatic Amnesia</td>
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<td>WM</td>
<td>Working Memory</td>
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<tr>
<td>CT</td>
<td>Computed Tomography</td>
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<td>MRI</td>
<td>Magnetic Resonance Imaging</td>
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<td>DWI</td>
<td>Diffusion Weighted Imaging</td>
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<tr>
<td>DTI</td>
<td>Diffusion Tensor Imaging</td>
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<tr>
<td>ADC</td>
<td>Apparent Diffusion Coefficient</td>
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<td>FA</td>
<td>Fractional Anisotropy</td>
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<td>MD</td>
<td>Mean Diffusivity</td>
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<tr>
<td>SLF</td>
<td>Superior Longitudinal Fasciculus</td>
</tr>
<tr>
<td>CANTAB</td>
<td>Cambridge Neuropsychological Test Automated Battery</td>
</tr>
<tr>
<td>SSP</td>
<td>Spatial Span</td>
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<tr>
<td>TR</td>
<td>Repetition Time</td>
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<tr>
<td>TE</td>
<td>Echo Time</td>
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<tr>
<td>FOV</td>
<td>Field of View</td>
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<td>ROI</td>
<td>Region of Interest</td>
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Introduction

Traumatic Brain Injury (TBI) can be defined as “an alteration in brain function, or other evidence of brain pathology, caused by an external force” (Menon, Schwab, Wright, & Maas, 2010, p. 1637). External forces (due to a traffic accident, fall, sports injury, …) may include direct impact of the head with another object, indirect forces from acceleration/deceleration, or a blast injury (Blyth & Bazarian, 2010). TBI is a major cause of death and disability, especially in children and young adults (Kraus & McArthur, 1996; Bruns & Hauser, 2003). In industrialized countries, the incidence is approximately 1/2000, and TBI is most common in young children between zero and four years old, older adolescents between 15 and 19 years old, and adults aged 65 and older (Faul, Xu, Wald, & Coronado, 2010). Falls are responsible for half of the incidences of TBI among children between 0 and 14 years old, followed by motor vehicle accidents, collisions and assaults (Faul et al., 2010).

Neuropathology of TBI

Different lesion types can occur after sustaining TBI, and these types of brain damage can co-occur. A first distinction can be made between primary and secondary brain damage. Primary brain damage is the degree of damage which is measured at the moment of the impact (skull fracture and bleeding). The damage that evolves over time after the trauma, is called secondary brain damage (e.g. swelling and increased intracranial pressure; Baethmann et al., 1998). These processes have their origin at the start of the injury, but have a delayed clinical manifestation.

Another way to differentiate between different types of TBI includes the location of the brain damage (Povlishock & Katz, 2005): in focal brain damage, the lesion is manifested locally, and this includes incidents such as (superficial) brain contusions, skull fractures, and intracranial hematomas. In addition to focal damage, closed head injuries frequently cause diffuse brain injuries or damage to several other areas of the brain. Diffuse (also known as multifocal) brain injury on the other hand is more spread out, and may result in diffuse axonal injuries and diffuse brain swelling (Graham, Adams, Nicoll, Maxwell, & Gennarelli, 1995). Diffuse axonal injury (DAI) is caused by rotational acceleration (the head suddenly accelerates and the stationary brain is struck by the accelerated cranium at the site of the blow)/deceleration (rapidly moving skull is abruptly stopped (e.g., an auto accident), while the brain continues forward and impacts directly below the site where the skull stops) forces that arise at the time of the injury (Gentry, 1994). DAI is defined by microscopic
lesions that occur throughout regions that contain white matter such as corpus callosum, upper brain stem and internal capsule (Levin et al., 1997).

**Diagnosis and classification of TBI**

There are different ways to classify the severity of TBI (see Figure 1). In most TBI research, TBI is classified according to single indicators such as the Glasgow Coma Scale (GCS, Teasdale & Jennett, 1974), Loss of consciousness (LOC) and Post Traumatic Amnesia (PTA). The GCS exists of three subscales (eye opening, motor response and verbal response) and is commonly used to define the severity of a TBI within 48 hours after the injury has taken place. The score on the GCS is used to distinguish between mild (GCS 13-15), moderate (GCS 9-12) and severe (GCS 3-8) TBI. Loss of consciousness (LOC) and post traumatic amnesia (PTA) are more recent classification methods to define TBI. Based on the LOC criteria, one can make an alternative discrimination between mild (the patient has been unconscious for 30 minutes or less), moderate (more than 30 minutes but less than 24 hours) and severe (more than 24 hours) TBI. PTA can be defined as “a period of mental confusion immediately following head trauma during which disorientation as to place, time and person is present, and in addition the inability to retain (new) experiences” and is the interval between injury and the return of continuous recall (Rujis, Keyser, & Gabreels, 1994). For mild TBI, the PTA lasts 0-1 days, up to seven days for moderate TBI and one speaks of severe TBI if the PTA lasts for longer than seven days.

<table>
<thead>
<tr>
<th>Severity of Traumatic Brain Injury</th>
<th>GCS</th>
<th>PTA</th>
<th>LOC</th>
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<tr>
<td>Mild</td>
<td>13-15</td>
<td>&lt;1 day</td>
<td>0-30 mins</td>
</tr>
<tr>
<td>Moderate</td>
<td>9-12</td>
<td>&gt;1 to &lt; 7 days</td>
<td>&gt;30 mins to &lt; 24 hrs</td>
</tr>
<tr>
<td>Severe</td>
<td>&lt; 9</td>
<td>&gt; 7 days</td>
<td>&gt; 24 hrs</td>
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*Fig. 1.* Classification of TBI based on the Glasgow Coma Scale (GCS), Post-Traumatic Amnesia (PTA) and Loss of Consciousness (LOC).
The Mayo Classification system for TBI severity (Malec et al., 2007) makes use of a combination of the GCS, PTA, and LOC. According to this system, TBI patients can be categorized into three levels of injury severity: Moderate-Severe (Definite) TBI, Mild (Probable) TBI, and Symptomatic (Possible) TBI. The criteria for each category can be found in Figure 3. One advantage of the Mayo Classification system over single indicator systems is that it can classify a larger number of cases with reasonable accuracy (Malec et al., 2007). It also makes use of a positive classification method, which implies that as soon as one or more of the TBI criteria apply (as stated in Figure 2), an individual can already be classified as (A) Moderate-Severe TBI, (B) Mild (Probable) TBI or (C) Symptomatic (Possible) TBI, according to outcome severity.

![Fig. 2. The Mayo TBI Severity Classification System (Malec et al., 2007).](image)
Consequences of TBI

Different types of TBI severity can result in a variety of cognitive, neurological, emotional and behavioural changes, and there is a lot of variability in outcome across individuals. Most progress is made during the first six months following the trauma, and most of the recovery is made between the first and the second year after injury (Babikian & Asarnow, 2009; Babikian, Merkley, Savage, Giza, & Levin, 2015). Both acute critical care variables and premorbid psychosocial variables can predict the degree of recovery during the first years post-injury (Woodwarth et al., 1999; Green et al., 2008).

Even several years after post-injury, patients still experience impairment on a lot of different ‘high-level’ domains, such as intelligence, memory, attention, executive function, learning, language, (psycho)motor skills, and social judgment (Langlois, Rutland-Brown, & Wald, 2006; McAllister, 2011; Babikian et al., 2015). Other deficits can be located on the behavioural level, such as poor impulse control, anxiety, irritability, agitation, confusion, loss of spontaneity, frustration, stress, denial, and affective disturbances (e.g. Trenchard, Rust, & Bunton, 2013). Cognitive impairment is one of the most frequent consequences of TBI, and they persist to exist even several years after sustaining TBI (Chen & D’Esposito, 2010; Whitnall, McMillan, Murray, & Teasdale, 2006). The information of these cognitive functions is spread out across several spatially divergent brain regions. Since DAI damages long-distance white matter tracts that connect several regions, cognitive functions will be impaired (Mesulam, 1998). Disruption in large-scale intrinsic connectivity networks can be an indicator for damage on the functional level, which often leads to cognitive impairment (Sharp, Scott, & Leech, 2014). Because TBI has an influence on a widespread variety of domains, some cognitive functions are more vulnerable than others to develop impairments due to DAI. Working memory and attention are two of the most frequent domains that are affected by TBI (McAllister et al., 1999; Levin et al., 2002; Levin et al., 2007; Wassenberg, Max & Lindgren, 2004). Although these cognitive domains have often been studied as independent cognitive constructs, more recent studies have shown that these two concepts are strongly related, and that attention is a critical component for WM capacity, and WM is a valid predictor of attentional control (Kane, Bleckley, Conway, & Engle, 2001).

**Working Memory.** Memory impairment is not only one of the most frequent complaints, but also among the most severe deficits following TBI (e.g. McAllister, Flashman, McDonald, & Saykin, 2006; Sanchez-Carrion et al., 2008). One of the components of explicit memory that can be damaged in TBI patients, is working memory (WM). WM can
be defined as a limited capacity system that accounts for the temporary maintenance and processing of task-relevant information that is necessary for reasoning, language comprehension, memory updating and learning (Baddeley, 1992). According to the model of Baddeley & Hitch (1974), WM consists of three components: the central executive, the phonological loop and the visuo-spatial sketchpad (separate systems for verbal and spatial information). The central executive acts as a supervisor and coordinates its two slave systems (phonological loop & visuo-spatial sketchpad). The phonological loop is one of the slave systems of WM that processes and stores verbal information, and consists of two subcomponents: a phonological store (holds speech-based information for a few seconds) and an articulatory control process (related to inner speech, this process registers and maintains verbal material in the phonological store). The visuo-spatial sketchpad on the other hand temporarily holds and manipulates spatial and visual information, and it is also involved in navigation processes. In a more recent version, Baddeley (2000) added a fourth component to the model: the episodic buffer (Figure 3). This component acts as another slave system that integrates the processed information of the other slave systems. The episodic buffer is probably linked to long-term memory as well as to semantic meaning. If we look at the number of information units that can be stored in WM, there is some evidence for the fact that the maximum span contains about seven units (Miller, 1956).

![Fig. 3. The updated version of the working memory model (Baddeley, 2000).](image)

WM is a complex system and is associated with multiple brain regions (Gazzaley, Rissman, & D'Esposito, 2004). Critical regions for WM typically include prefrontal cortex, anterior cingulate cortex, and medial frontal and parietal regions (Christodoulou et al., 2001;
Newsome et al., 2007; Scheibel et al., 2007; Perlstein et al., 2004). The different WM components are localised in different brain regions. The left temporoparietal region is involved in the phonological loop (Vallar, DeBetta, & Silveri, 1997; Baddeley, 2003), while the visuospatial sketchpad can be divided into a ventral (from occipital to temporal cortex) and a dorsal stream (from occipital to parietal cortex; Müller & Knight, 2006). The dorsolateral prefrontal cortex is involved in the central executive (D’Esposito et al., 1995).

Even several years post-injury, WM was still impaired in children who had sustained a severe TBI compared to mild traumatic brain injury (Levin et al., 2002). The more time elapsed since the occurrence of the injury and the older the individual is at the moment of injury both have a negative impact on WM (Dunning, Westgate, & Adlam, 2016). Individuals with TBI have impaired performance on dual task paradigms that involve the intervention of a central executive, and this effect was more noticeable in individuals with severe TBI (McDowell, Whyte, & D’Esposito, 1997; Leclerq et al., 2000; Perlstein et al., 2004; Phillips, Parry, Mandalis, & Lah, 2015). A lot of studies have been focusing on the verbal component of WM, but very few studies investigated the visuo-spatial component of WM (Dunning et al., 2016).

**Attention deficits in TBI.** TBI is not only associated with memory disorders, another cognitive function that is often impaired after TBI, is attention (Ponsford & Kinsella, 1992; Mathias & Wheaton, 2007). Attentional networks are widespread throughout the whole brain, including the parietal, frontal, temporal and cingulate cortices in addition to the midbrain (Posner and Petersen, 1990; Petersen & Posner, 2012). Attention can be categorized into different types. Sustained attention is the ability to direct and focus cognitive activity over time without getting distracted. In one of the TBI studies that made use of the Continuous Performance Test (Rosvold, Mirsky, Sarason, Bransome, & Beck, 1956), children with TBI had a significant lower performance compared to children with mild to moderate TBI six months post injury (Kaufman, Fletcher, & Levin, 1993). Children with moderate to severe TBI also showed larger reaction times and less accurate responses compared to healthy controls (Anderson & Pentland, 1998). Selective attention is the ability to focus on one task and meanwhile filtering out unwanted information relevant to our goals, and this is often a part of controlled processing (Desimone & Duncan, 1995). Studies have shown that children with moderate to severe TBI performed significantly worse than a control group on a selective attention task (Anderson & Pentland, 1998; Park, Allen, Barney, Ringdahl, & Mayfield, 2009), while other longitudinal studies show long-lasting impairments caused by the TBI.
(Anderson & Pentland, 1998; Verger et al., 2000). When you shift your focus of attention between several different tasks, one can speak of alternating attention. Children with severe TBI show impaired performance on alternating attention tasks compared to children with mild to moderate TBI (Catroppa, Anderson & Stargatt, 1999). A significant difference in performance on a shifting attention task was also found between children with moderate to severe TBI compared to a control group (Park et al., 2009). Divided attention is known as the ability to simultaneously focus on more than one source of information at the same time. In studies where children had to attend two different stimuli at the same time, performance was significantly impaired according to the severity of the injury (Anderson, Fenwick, Manly, & Robertson, 1998; Catroppa, Anderson, Morse, Haritou, & Rosenfeld, 2007). The two types of attention that seem to be most sensitive to show impairment after the occurrence of TBI are sustained and divided attention (Ginstfeldt & Emanuelson, 2010), but deficits in processing speed, selective attention, attentional control and attention span are also frequently affected following TBI (Mathias & Wheaton, 2007).

Cognitive impairment is one of the main consequences following DAI. To investigate the relationship between white matter integrity and behavioural outcome into more detail, a variety of neuroimaging techniques can be used to obtain more information about the severity of the injury in specific white matter tracts, and subsequently link these results to measures on the cognitive level.

**Structural Imaging of TBI**

**Standard neuroimaging of TBI.** In the acute stage following a head injury, standard neuroimaging techniques are carried out to identify the location and size of possible brain damage and to determine operability. A Computed Tomography (CT) scan is routinely the first imaging method to be performed (Coles, 2007; Toyama et al. 2005), since it is highly accurate to detect skull fractures and intercranial haemorrhage. A large advantage of this technique is that it allows rapid assessment of brain pathology and it can even be used with unstable and critically injured patients. However, CT scans are not very sensitive to detect abnormalities and pathological changes in regions that are commonly injured following TBI (Coles, 2007). Magnetic Resonance Imaging (MRI) is superior to CT in detecting diffuse axonal injury (Coles, 2007), although it is not suited to use with severely injured patients due to its sensitivity to motion artefacts. In MRI, a small number of tissue protons is able to absorb and emit radio wave energy within a magnetic field, by aligning and displacing the tissue protons from the main magnetic field with the use of radiofrequency gradients. It is a
non-invasive imaging method that holds different imaging modes to investigate the neurological damage, including T1-weighted imaging (demonstrates differences in the magnetization time of diverse tissues; useful for visualisation of normal anatomy) and T2-weighted imaging (demonstrates different dephasing times of diverse tissues; useful for visualization of pathology). Even though these MRI techniques are able to pick up white matter damage, techniques such as Diffusion Weighted Imaging (DWI) are more suitable to detect subtle markers of diffuse axonal injury.

**Diffusion Weighted Imaging.** DWI, as well as its extension into Diffusion Tensor Imaging (DTI), is a neuroimaging technique based on MRI that measures the random Brownian motion of water molecules within a voxel of tissue. Brownian motion or molecular diffusion can be described as the random movement of microscopic particles suspended in a liquid or gas, propelled by thermal energy. If there are few to no physical constraints, the water molecules are able to spread out equally and randomly in all directions, the diffusion is isotropic (e.g. cerebrospinal fluid regions). Diffusion is anisotropic if water molecules are constrained by physical boundaries (e.g. axon walls and myelin sheaths enclosing the axons) and have a dominant orientation (e.g. white matter fibre bundles such as the corpus callosum; Deprez, Billiet, Sunaert, & Leemans, 2013; Rosenbloom, Sullivan, & Pfefferbaum, 2003, see Figure 4). The relative amount of water in white matter is about 70 percent, while cerebrospinal fluid consists of about 99 percent water (Rosenbloom et al., 2003). In DWI, there is a diffusion gradient to measure the movement of the water molecules in the direction of this gradient. This is quantified by the apparent diffusion coefficient (ADC), the magnitude of diffusion derived from the DWI image and a reference image (also referred to as “b=0” image).

**Fig. 4.** Example of isotropic (a) and anisotropic (b) diffusion (Deprez et al., 2013).
Although DWI is a useful technique to visualize diffusion contrast, it is unable to measure anisotropy and primary fibre orientation in a direct way (Deprez et al., 2013). DTI (Basser, Mattiello, & LeBihan, 1994) is a non-invasive neuroimaging technique derived from DWI that is used to measure the diffusion of water molecules to make inferences concerning white-matter tracts connecting different brain regions (Basser, Pajevic, Pierpaoli, Duda, & Aldroubi, 2000; Alexander, Lee, Lazar, & Field, 2007). DTI needs at least six DWI images (next to the “b = 0” image; the minimum number required for tensor calculation), each obtained with a different orientation of the diffusion gradients. Diffusion Tensor Imaging is more suited than other neuroimaging techniques to examine DAI that is caused by TBI, due to its degree of sensitivity to changes in the microstructure of white matter (Neil, Miller, Mukherjee, & Huppi, 2002). Whereas conventional magnetic resonance imaging (MRI) is useful to reveal focal brain damage, it is less susceptible to detect diffuse axonal injury (Azouvi, 2000; Goetz et al., 2004). The study of Huisman et al. (2004) revealed that changes in white matter, as measured by DTI, show a significant correlation with acute scores on the Glasgow Coma Scale and scores on the Rankin Scale at discharge, which is used to determine the degree of disability in the daily activities (Rankin, 1957). The authors concluded that DTI might be an important biomarker for the severity of tissue injury and a predictor for outcome.

In order to determine the magnitude and directionality of water diffusion along white matter tracts as characterized by the diffusion tensor and its derived diffusion parameters. In the current study, we made use of two DTI based measures, fractional anisotropy and mean diffusivity (Le Bihan et al., 2001).

**DTI based measures.**

**Fractional anisotropy.** One way to detect TBI on neuronal level is through common metrics such as Fractional Anisotropy (Nakayama et al., 2006; Xu, Rasmussen, Lagopoulos, & Haberg, 2007). Fractional anisotropy (FA; Figure 5) is a diffusion anisotropy measure and reflects the extent to which the diffusion process is anisotropic and the water molecules have a dominant orientation (ratio of the diffusion in the principal direction of axons to diffusion in the perpendicular directions; Wozniak et al., 2007). While FA is highly sensitive to microstructural changes, it is less specific to the type of change (e.g. radial or axial; Alexander et al., 2011), so multiple diffusion tensor measures should be used in order to define the tissue microstructure. FA values vary between 0 (isotropic diffusion) and 1 (anisotropic diffusion) (Le Bihan et al., 2001). Water molecules located in fiber tracts are more likely to be anisotropic (diffusion occurs only along a single axis), as they are restricted
in their movement, while water molecules located in the rest of the brain have less limited motion and hence demonstrate more isotropy (unrestricted in all directions).

Fig. 5. Fractional anisotropy (Nagy et al., 2005)

**Mean diffusivity.** Mean Diffusivity (MD), also known as ADC, is a measure of the average diffusivity (of water molecules) within tissue using DWI. MD represents the average amount of water diffusion in a given region, and is considered to be influenced by the integrity and size of the axon. Higher MD values are a possible indicator of increased diffusion rates (Bennett, Madden, Vaidya, Howard, & Howard Jr., 2010; Soares, Marques, Alves, & Sousa, 2013).

**DTI studies in TBI.** Studies involving DTI can reveal a spectrum of injuries following TBI (Hulkower, Poliak, Rosenbaum, Zimmerman, & Lipton, 2013). A common finding is that brain regions typically associated with TBI have reduced FA values, such as in the genu of the corpus callosum in patients with chronic cognitive impairment after TBI (Salmond et al., 2006; Kraus et al., 2007). This indicates that brain injury might likely be the cause of cognitive deficits (Lo, Shifteh, Gold, Bello, & Lipton, 2009; Ewing-Cobbs et al., 2008), even though sometimes no lesion has been found with conventional MRI (Nakayama et al., 2006). Due to variability in study outcomes, the relationship between FA values (indicator of white matter integrity) and cognitive functioning remains unclear (Nakayama et al., 2006; Salmond et al., 2006). Corpus callosum, cingulum, inferior longitudinal fasciculus, and superior longitudinal fasciculus are some of the neuroanatomical regions that show an abnormal FA value after the occurrence of TBI (Hulkower et al., 2013; Caeyenberghs et al.,
Kraus et al. (2007) found significantly reduced FA values in all the regions of interest (analysis included corpus callosum, cingulum, cortico-spinal tract and superior longitudinal fasciculus) in adults with moderate to severe TBI, and the larger the white matter pathology, the larger the cognitive deficits were. However, in a study of Bazarian et al. (2007), the researchers found significantly higher values of FA in TBI patients in a more acute stage compared to controls. The most common locations of abnormal MD values in TBI patients are corpus callosum, cingulum bundle, fronto-occipital fasciculus, superior longitudinal fasciculus and inferior longitudinal fasciculus (Hulkower et al., 2013, Wu et al., 2010).

One neuroanatomical region that is often affected by TBI, is the cingulum (Palacios et al., 2013; Hulkower et al., 2013). The cingulum is a bundle of white matter tracts that connects the cingulated gyrus to the entorhinal cortex, whereby components of the limbic system can communicate with one another. In addition, the cingulum can also be described as a white matter structure consisting of short and long association tracts, that runs within the cingulate gyrus all surrounding the corpus callosum, and it connects the medial frontal and parietal lobes as well (Catani, Howard, Pajevic, & Jones, 2002). A part of the cingulate cortex called the anterior cingulate cortex is involved in cognitive control (Barch, Braver, Sabb, & Noll, 2000), and disruption of this area (rostral cingulum) is correlated with mild cognitive impairment (Metzler-Baddeley et al., 2012). Also the cingulum itself has been investigated on the effects of TBI, and several lesion studies have shown that the cingulum is a part of an important neural network that is responsible for cognitive abilities, and TBI has an impact on the functioning of this network (Wilde et al., 2010, Kim et al., 2008; Levine et al., 2008). Decreased FA and increased MD values of the cingulum have been correlated with impaired performance on the flanker task (Wilde et al., 2010). Bonnelle and colleagues (2011) revealed that smaller FA values reflected attention impairment in the right cingulum. Furthermore, FA and MD values have also been linked to the left cingulum in TBI patients (Wu et al., 2010).

Another region that is often damaged after the occurrence of TBI (Hulkower et al., 2013), is the Superior Longitudinal Fasciculus (SLF; Xiong et al., 2014). The SLF is a bundle of white matter fibres underlying the dorsolateral prefrontal cortex (Kollias, 2009, Thiebaut de Schotten et al, 2011). Vestergaard et al. (2011) reported that better spatial WM performance is associated with increased FA values in left fronto-parietal connections, and this significant effect was only found in regions of interest (ROI) that included SLF fibres. Furthermore, Burzynska and colleagues (2011) revealed that the SLF is associated with WM, and that white matter integrity of this fibre bundle reflects better performance on WM tasks.
A global decrease in FA is linked to performance on WM tasks, and positive correlations have been found between the SLF and WM performance (Palacios et al., 2011). But not merely memory processes are involved in the SLF, attention processes as well are influenced by this region (Klarborg et al., 2013).

Current Study

Previous studies have revealed that attention and working memory are cognitive functions that are often affected in TBI patients, as has been revealed by DWI measures. In the past, studies have been focusing brain-behaviour relationships in healthy participants (e.g. Burzynska et al., 2011), in adults (e.g. Bonnelle et al., 2011), and in adolescents with mild TBI (e.g. Wu et al., 2010) or adolescents with moderate-severe TBI in a subacute stage (e.g. Wilde et al., 2010). But to the best of our knowledge, no research has been done in adolescents with moderate-to-severe TBI in a chronic stage (>1 year post-injury). In the current study, we investigated the degree to which diffusion rates measures of the cingulum and SLF can be linked to individual differences in attention and WM performance, within adolescents suffering from moderate to severe chronic TBI. Since both the cingulum and the SLF have been shown to be susceptible to DAI, we hypothesized that FA and MD values in these white matter regions would account for variability in performance on attention and WM tasks. We expected to find a positive correlation between FA values and attention and WM tests, and a negative correlation between MD values and these neuropsychological tests. Furthermore, we predicted to find stronger correlations between cingulum and attention, and also between SLF and WM, since these regions have shown to have a stronger link with a specific cognitive function (Wilde et al., 2010; Burzynska et al., 2011).

Method

Participants

Nine adolescents (seven boys and two girls) that were diagnosed with DAI as a result of TBI (mean age = 16.23; SD = 0.95; range = 14.5-17.5) were selected to participate in the current study, and they were recruited by contacting two rehabilitation centres, a specialized rehabilitation centre for children and youth (Pulderbos), and the child rehabilitation centre of Ghent University Hospital. All patients were earlier dismissed from these rehabilitation centres before they were contacted to participate in the current study. At the time that the current study was carried out, the children no longer participated in motor rehabilitation or
retraining programs. All adolescents had to be classified with moderate to severe TBI as measured by the Mayo Classification system (Malec et al., 2007) in order to be allowed to participate in the current study. In addition, all participants had to be assessed at least one and maximum five years post-injury, when neurological recovery was stabilized. Exclusion criteria were as follows: younger than 10 years old at the age of injury, contraindications to take a MRI scan (e.g. braces), and large focal injuries as mentioned in the medical records. This study was approved by the local Ethics Committee of Ghent University Hospital and was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki. All participants and their parents gave their written informed consent. Demographic characteristics of participants are shown in Table 1.

<table>
<thead>
<tr>
<th>TBI patient No.</th>
<th>Gender</th>
<th>Age</th>
<th>Time since injury</th>
<th>Age at time of injury</th>
<th>IQ</th>
</tr>
</thead>
<tbody>
<tr>
<td>TBI 1</td>
<td>M</td>
<td>16.38</td>
<td>3.83</td>
<td>12.55</td>
<td>124</td>
</tr>
<tr>
<td>TBI 2</td>
<td>M</td>
<td>16.7</td>
<td>3.15</td>
<td>13.55</td>
<td>90</td>
</tr>
<tr>
<td>TBI 3</td>
<td>M</td>
<td>17.54</td>
<td>2.24</td>
<td>15.3</td>
<td>117</td>
</tr>
<tr>
<td>TBI 4</td>
<td>M</td>
<td>15.57</td>
<td>3.15</td>
<td>12.42</td>
<td>104</td>
</tr>
<tr>
<td>TBI 5</td>
<td>F</td>
<td>16.67</td>
<td>4.55</td>
<td>12.13</td>
<td>113</td>
</tr>
<tr>
<td>TBI 6</td>
<td>F</td>
<td>14.47</td>
<td>1.29</td>
<td>13.18</td>
<td>98</td>
</tr>
<tr>
<td>TBI 7</td>
<td>M</td>
<td>15.54</td>
<td>1.67</td>
<td>13.87</td>
<td>95</td>
</tr>
<tr>
<td>TBI 8</td>
<td>M</td>
<td>17.26</td>
<td>1.35</td>
<td>15.91</td>
<td>122</td>
</tr>
<tr>
<td>TBI 9</td>
<td>M</td>
<td>15.99</td>
<td>2.79</td>
<td>13.2</td>
<td>76</td>
</tr>
</tbody>
</table>

Gender codes: M = male, F = female; IQ = Intelligence Quotient as measured by the WISC III (Wechsler, 1991).

**Tasks and procedure**

First, all participants were asked to sign an informed consent, in which they stated that they were informed about the content of the study. Prior to the scanning procedure, participants had to take neuropsychological tests that measured both working memory and attention. After completing these tests, participants were scanned at the University Hospital of Ghent (UZ Gent) with a clinical Siemens Trio 3T scanner.

**Neuropsychological Assessment.** Subjects completed a series of tests that were developed to measure executive function, attention and working memory. Tests included
some subtests of the CANTAB (Stockings of Cambridge, Intra-Extra Dimensional Set and Spatial Span), Continuous Performance Test (Conners, Epstein, Angold, & Klaric, 2003), some subtests of the WISC-III (Digit Span and Coding), and the Flanker task (Eriksen & Eriksen, 1974). Participants and their parents were also asked to complete the Behavioural Rating Inventory of Executive Function (Gioia, Isquith, Guy, & Kenworthy, 2000), a questionnaire to assess the impairment of executive functioning. The Spatial Span and Flanker Task were included in the current study (see Table 2).

**Working memory task.** The neuropsychological test that was used in this study to measure visuo-spatial working memory, is the spatial span (SSP, see Figure 6). This is a cognitive test that is included in the CAMbridge Neuropsychological Test Automated Battery, rather known as CANTAB (Sahakian & Owen, 1992). The SSP was performed on a touch-screen tablet supplied by the University of Cambridge, and had a duration of 5 minutes. Several white squares were shown to the participants, and during each trial, some squares briefly changed colour in a variable sequence. After a tone was presented, participants had to recall the same sequence of squares as had been displayed before by touching the boxes which changed colour in the same order that they were presented. The test started with two squares that changed colour, and the length of the sequence increased as the task proceeded. It could go up to a maximum sequence of nine squares at the end of the test, but the task finished earlier when participants made errors for three sequences in a row of the same length. Different sequences and colours were used throughout the whole test. In the current study, a reversed version of the SSP was used as well. The same stimuli were shown to the participants, but now they had to recall and tap the sequence of squares they had just seen before in the reverse order. The dependent variables of the test that were measured were span length (the longest sequence that has been recalled successfully), errors, number of attempts and latency. For the analysis and correlation with white matter tracts, maximal span length of the SSP (normal and reverse version) was used as variable of interest.
Attention task. To test selective mechanisms of attention, the current study made use of an Eriksen Flanker task (Eriksen & Eriksen, 1974) created with PEBL software (Mueller & Piper, 2014). In this test, a row of five arrows is presented on each trial, and participants get the instruction to respond to the central arrow by pressing the right or left shift key on the keyboard (See Figure 7). Each trial started with a central fixation cross that stayed on the screen for 500 ms. Subsequently, the stimulus (row of arrows) would appear on the screen. Once the arrows were presented, participants had to determine the direction of the central arrow and they were given a limited timeframe of 800 ms to respond. A response was given by pressing one of the response buttons (right and left control key on the keyboard) as quickly and accurate as possible. After a response was given (or no response was given within 800 ms), a blank screen appeared with a fixed inter trial interval of 1000 ms. Participants performed a short practice of 12 trials before the actual experiment started. Feedback was given after each trial (accuracy and reaction time in milliseconds). The experiment consisted of 120 trials, and feedback was no longer given after the practice block. There are three conditions in the experiment: a congruent, an incongruent and a neutral condition. In the congruent condition, the middle arrow points in the same direction as the other arrows, while the middle arrow points in the opposite direction as the other arrows in the incongruent condition. In the neutral condition, only one arrow is presented, surrounded by dashes. Within congruent trials, the distracter items are the same as the target stimulus, whereas in incongruent trials, the distracter items are different from the target stimulus, so that two possible response tendencies become active and conflict occurs (Botvinick, Barch, Carter, &
Because of the occurrence of conflict, larger reaction times and more errors are usually measured on incongruent trials. Conflict cost (reaction time difference between congruent and incongruent trials) was taken into account as variable of interest.

**Fig. 7.** Illustration of an incongruent trial of the Eriksen Flanker Task ((Eriksen & Eriksen, 1974).

**MRI data acquisition.** MR examination was performed on a Siemens 3T Magnetom Trio MRI scanner (Siemens, Erlangen, Germany) with a 32-channel head coil. A DTI SE-EPI (diffusion weighted single shot spin-echo echoplanar imaging) sequence ([TR] = 10800 ms, [TE] = 83 ms, voxel size = $2.5 \times 2.5 \times 2.5$ mm, slice thickness = 2.5 mm, [FOV] = 240 × 240 mm, 60 contiguous sagittal slices covering the entire brain and brainstem) was acquired. A diffusion gradient was applied along 64 noncollinear directions with a b-value of 1200 s/mm². Additionally, one set of images with no diffusion weighting (b = 0 s/mm²) was acquired. Moreover, a high resolution T1-weighted image was acquired for anatomical detail using a 3D magnetization prepared rapid acquisition gradient echo (MPRAGE; [TR] = 2250 ms, [TE] = 4.18 ms, voxel size = $1 \times 1 \times 1$ mm, slice thickness = 1 mm, [FOV] = 256 × 240 mm, 176 contiguous sagittal slices).

**DTI preprocessing.** The DTI data were analyzed and processed in ExploreDTI (Leemans, Jeurissen, Sijbers, & Jones, 2009). First, the raw data quality was visually inspected (investigation of a loop through the separate raw diffusion-weighted images to
identify and exclude gross image distortions, inspection of orthogonal, axial and sagittal views, inspection of residuals and outliers). Subsequently geometrical distortions, induced by subject motion and eddy currents (originated from rapid switching of magnetic gradients), and Echo Planar Imaging (EPI) and susceptibility distortions were corrected (Leemans, and Jones, 2009). Next, the diffusion tensors and the diffusion parameters were calculated using a non-linear regression procedure (Mori et al., 2008), and finally the DTI data were transformed to standardised anatomical space (Montreal Neurological Institute space). FA and MD were selected for further analysis as proxy markers of white matter microstructural organization (Table 2). A region of interest (ROI) analysis is useful when a research question wants to investigate specific white matter fibre bundles, and since the current study is interested in the relationship between cognitive functions and specific white matter tracts, a ROI analysis was carried out. ROIs can be drawn around a particular white matter structure, either by manual delineation or by automatic segmentation or parcellation (Van Hecke, Emsell, & Sunaert, 2016). The SLF and cingulum were chosen as the white matter tracts of interest, and were delineated in an automated fashion by transforming atlas labels from the ICBM Mori Atlas (Mori et al., 2008) to each subject, and subsequently the DTI measures were calculated.

**Statistical analysis.** To investigate whether there is a relationship between neuropsychological measures on the one hand and white matter integrity on the other hand, a Spearman correlation analysis was performed to examine the relationship between mean FA and MD of right and left cingulum/SLF bundles and results on the behavioural tests. Statistical analyses were carried out using SPSS version 23 (IBM SPSS Statistics, IBM Corp, New York, NY). Bonferroni corrections for multiple comparisons were made (hence \( p < 0.00625 \) was considered significant following correction for DTI metrics regarding the four ROIs).

**Results**

On average, participants could recall a sequence of 7.22 items on the SSP forward and 7 items on the reverse version. On the flanker task, there was an average difference of 59.68 ms between congruent and incongruent trials (conflict cost). The results from the diffusion parameters can be found in Table 2. The calculated correlations between behavioural performance and DTI based measures are described below (for a clear overview, see Table 3).
Table 2. Group results for DTI metrics (Fractional Anisotropy and Mean Diffusivity), mean ± standard error for each ROI.

<table>
<thead>
<tr>
<th>Anatomical Region</th>
<th>FA</th>
<th>MD (×10⁻³ mm²/s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Right SLF</td>
<td>0.26 ± 0.05</td>
<td>0.85 ± 0.10</td>
</tr>
<tr>
<td>Left SLF</td>
<td>0.22 ± 0.04</td>
<td>0.89 ± 0.11</td>
</tr>
<tr>
<td>Right Cingulum</td>
<td>0.23 ± 0.07</td>
<td>0.88 ± 0.11</td>
</tr>
<tr>
<td>Left Cingulum</td>
<td>0.2 ± 0.07</td>
<td>0.89 ± 0.11</td>
</tr>
</tbody>
</table>

Relationship Between DTI Measures And Behavioural Outcome

Fractional Anisotropy. If we look at the correlations between SSP (forward), there are no significant findings for both right SLF (r = -0.165, p = 0.671) and left SLF (r = -0.294, p = 0.443), as well as for right (r = 0.101, p = 0.796) and left (r = -0.009, p = 0.981) cingulum. For the reverse version of the SSP, no significant relationship was found for right (r = 0.173, p = 0.657) and left (r = 0.000, p = 1) SLF, and the correlation with right (r = 0.035, p = 0.930) and left (r = -0.173, p = 0.657) cingulum turned out to be non-significant as well. Finally, if we take a look at the correlations of the white matter tracts with the flanker task, we found no significant correlations for right (r =0.25, p = 0.516) and left (r = 0.2, p = 0.606) SLF, as for right (r = 0.233, p = 0.546) and left (r = 0.033, p = 0.932) cingulum. Overall, there seems to be no stronger correlation between SLF-WM and cingulum-attention compared to other correlations.

Mean Diffusivity. There is no significant relationship between SSP (forward), and both right SLF (r = 0.376, p = 0.318) and left SLF (r = 0.376, p = 0.318), and the same holds for right (r = 0.000, p = 1) and left (r = -0.11, p = 0.778) cingulum. For the reverse version of the SSP, no significant correlation was found for right (r = -0.138, p = 0.723) and left (r = -0.276, p = 0.472) SLF, nor with right (r = -0.38, p = 0.314) and left (r = 0.035, p = 0.93) cingulum turned out to be non-significant as well. Subsequently, when we examine the correlations of the white matter tracts with the flanker task, no significant relationship was found for conflict cost and right (r =-0.283, p = 0.46) and left (r = -0.417, p = 0.265) SLF, as for right (r = -0.517, p = 0.154) and left (r = -0.083, p = 0.831) cingulum. All correlations between cognitive outcome and MD values taken into account, correlations between SLF-WM and cingulum-attention did not seem larger on average compared to other correlations.
Table 3. Results of the correlation analyses between DTI metrics (Fractional Anisotropy and Mean Diffusivity) and behavioural tests (SSP, SSP reverse and Flanker task).

<table>
<thead>
<tr>
<th>ROI</th>
<th>Fractional Anisotropy</th>
<th>Mean Diffusivity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SSP</td>
<td>SSP reverse</td>
</tr>
<tr>
<td>Right SLF</td>
<td>-0.17</td>
<td>0.17</td>
</tr>
<tr>
<td></td>
<td>(p = 0.671)</td>
<td>(p = 0.657)</td>
</tr>
<tr>
<td>Left SLF</td>
<td>-0.30</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>(p = 0.443)</td>
<td>(p = 1)</td>
</tr>
<tr>
<td>Right Cingulum</td>
<td>0.10</td>
<td>0.035</td>
</tr>
<tr>
<td></td>
<td>(p = 0.796)</td>
<td>(p = 0.93)</td>
</tr>
<tr>
<td>Left Cingulum</td>
<td>-0.01</td>
<td>-0.17</td>
</tr>
<tr>
<td></td>
<td>(p = 0.981)</td>
<td>(p = 0.657)</td>
</tr>
</tbody>
</table>

**Discussion**

The aim of the current study was to investigate the link between cognitive functions (attention and memory) and two specific white matter tracts, namely the cingulum and SLF, in adolescent individuals who suffer from moderate to severe TBI. In order to do so, participants completed neuropsychological tests that measured both WM and (sustained and selective) attention, and DWI images were acquired. Subsequently, diffusion parameters FA and MD were correlated with outcome on the neuropsychological tests to investigate whether there is a link between performance on the behavioural and neuronal level. We expected to find a positive correlation with FA and task performance, and a negative relation with MD outcome on both cognitive tasks. In addition, we hypothesized larger correlations between SLF-WM and cingulum-attention.

If we take a look at the correlations of both cingulum and SLF with the flanker task, it turned out that none of the compared brain-behaviour relationships are significant. Also, the link between attention and cingulum did not seem larger than other obtained correlations. These results are not in line with findings of previous studies. For example, Wilde et al. (2010) found a significant relationship between the FA and MD values of the left cingulum bundle and reaction time on the flanker task in children who sustained moderate-to-severe TBI. In another study, it was shown that performance on working memory tasks is associated...
with the cingulum (Wilde et al., 2011). Furthermore, Wu and colleagues (2010) revealed significant correlations between immediate recall and left cingulum bundles in adolescents with mild TBI. Also the right cingulum bundle is associated with attention (Takahashi et al., 2010), and reduced FA values are correlated with impairments of (sustained) attention in TBI patients (Bonnelle et al., 2011).

Correlations between performance on the forward and reverse version of the SSP, a measure of visuo-spatial WM, and diffusion parameters of two selected white matter bundles were calculated as well, and the outcome revealed no significant relationship between working memory and each ROI. On average, there did not seem to be a larger effect between SLF and WM. However, previous research has shown that these white matter tracts are related to higher cognitive functioning. In a study of Burzynska and colleagues (2011), higher FA values of the SLF were related to better WM performance in young controls. Palacios and colleagues (2011) found that FA values of the SLF correlated with WM measures. Furthermore, white matter microstructure of the right cingulum has been linked to outcome on a task that measures WM capacity (Takahashi et al., 2010).

Although most of the abovementioned studies investigated the relationship between cognitive outcome and microstructure of white matter bundles in TBI patients in similar ways to our study, there are still some differences with the current study which makes it not that easy to make straightforward comparisons. For example, while some studies examined TBI in adults (e.g. Palacios et al., 2011; Bonelle et al., 2011), our study focused on young adolescents (the youngest participant was 14 years old and all adolescents were younger than 18 years old). One should be careful to generalize these results to children/adolescents because of two reasons. First, the brain of adolescents is less mature and might be more vulnerable to the effects of DAI, and in addition injury at a young age can have an impact on the development of cognitive abilities and this could lead to cumulative impairment (Anderson & Moore, 1995). Second, an opposing argument might be that the paediatric brain is more plastic, and this plasticity might enable the brain to recover in a dramatic recovery of function after the occurrence of TBI (Ruijs et al., 1994). Another difference with other studies that investigate cognitive processes in TBI patients, is the time since injury. Some studies investigated subacute patients (up to three months post-injury, e.g. Wilde et al., 2010; Wu et al., 2010), while the population of the current study exists of adolescents in a chronic stage (>1 year post-injury). Participants tend to report more improvement as the time since injury increases (Brown et al., 2011), and higher FA values have been detected over time, indicating improvement of white matter integrity (Farbota et al., 2012).
Limitations and Future Directions

Despite its widespread use and its sensitivity to detect microstructural abnormalities in white matter, DTI also holds some disadvantages. One of the major confounds of DTI, is that it cannot measure more than one dominant fibre orientation in complex white matter configurations (Van Hecke et al., 2016), also known as ‘crossing fibres’ (different orientations relate to different fibre populations; Behrens, Berg, Jbabdi, Rushworth, & Woolrich, 2007). The amount of white matter voxels that contain crossing fibres is about 90% (Jeurissen, Leemans, Tournier, Jones, & Sijbers, 2013), and this has an impact on the DTI derived measures (Alexander, Hasan, Lazar, Tsuruda, & Parker, 2001). FA is very sensitive to the presence of crossing fibres in complex fibre configurations (Pierpaoli & Basser, 1996; Alexander et al., 2001). If there is no single dominant diffusion direction, they might average out and this will result in lower FA values (Van Hecke et al., 2016). This could be an explanation for the fact that we did not obtain any significant findings, especially because the SLF and cingulum are both complex white matter configurations (Behrens et al., 2007; Douaud et al., 2011). However, the opposite could also be the case in white matter structures that have been damaged: because of the degeneration of a specific fibre bundle, another neighbouring fibre bundle might become more dominant and this leads to a paradoxical increase in FA (Van Hecke et al., 2016). In a study that investigated mild cognitive impairment, patients showed increased FA values compared to controls (Douaud et al., 2011). Next to FA, MD can also be affected by the occurrence of crossing fibres (Van Hecke et al., 2016). Lower MD values have been found in complex white matter tissues compared to structures with a single dominant fibre orientation (Vos, Jones, Jeurissen, Viergever, & Leemans, 2012). These reduced values depend on a variety of factors such as relative contributions of different fibre bundles, microstructural properties, and acquisition settings (Vos et al., 2012). An increased variance in MD values in certain regions can be a result of a combination of single dominant fibre and crossing fibre configurations, which will lead to less statistical power to reveal differences in MD (Van Hecke et al., 2016).

Another possible explanation for the fact that the current study was not able to find any significant correlations, is that the ROIs were delineated in an automatic fashion. Registration tools are used to transform atlas labels of certain anatomical regions to each individual subject, and subsequently DTI measures are calculated for each ROI (Mori et al., 2008). Compared to manual delineation, automatic segmentation has some major advantages (less observer dependent, more reproducible) but it is not always the best method to use, since
it holds a risk of not exactly delineating the boundaries of white matter structures so the co-registration accuracy is less reliable (Verhoeven et al. 2010; Oishi et al. 2011).

A ROI analysis was used in this study, but this is not the only possible technique that can be used to analyse DTI datasets. Other analysis techniques include whole-brain analysis and more region-specific analyses such as tractography and voxel-based analysis (Van Hecke et al., 2016). ROI analysis might not always draw exactly around the white matter tract of interest and this could exclude some potential valuable information. Tractography (also known as fibre tracking) refers to the reconstruction of white matter pathways, based on local diffusion orientations from every voxel (Lazar, 2010). The tractography process starts at a seed point (a specific voxel) and continues by following the maximal amount of diffusion in a certain direction, and keeps tracking until a new voxel is reached (Van Hecke et al., 2016). Termination criteria depend on selection and exclusion ROIs, FA values, fibre length and curvature thresholds (Van Hecke et al., 2016). Compared to the conventional ROI based analysis, tractography is able to obtain more anatomically specific diffusion estimates (Deprez et al., 2013). However, this analysis technique also holds some disadvantages. The reconstructed tracts cannot be directly linked to the actual underlying microstructure, so tractography cannot prove the existence of an actual tract (Jbabdi & Johansen-Berg, 2011). Furthermore, high signal-to-noise ratio is required to be able to reduce the error accumulation that occurs during tract propagation (Lazar & Alexander, 2003), and tractography results are also more prone to be affected by the crossing fibres problem. Still, it is a valuable technique to reconstruct 3D virtual representations of white matter in vivo (Van Hecke et al., 2016) and can be more sensitive to changes than conventional ROI analysis (Kanaan et al., 2006).

Another limitation of the present study is its rather small sample size (n = 9), so an underlying effect might not have been detected. Although many studies face this problem, it is worth mentioning this shortcoming since these results are part of a larger study (in which the number of participants is at least twice as large as in the current study), therefore the current study should be regarded as preliminary. Another disadvantage is that this study did not include a control group, in contrast to most of the studies that investigate white matter abnormalities in DTI (Hulkower et al., 2013). Adding a control group might reveal some insights on the brain-behaviour relationships of healthy young controls. For example, if there would be a significant relationship between performance on the behavioural level and FA and MD values in the control group, than this might be an indication that the white matter structures of interest are more related to attention and working memory than the current study suggests, and this would also confirm previous findings. It would also be an opportunity to
gain more knowledge about the differences between healthy controls and TBI patients.

Future studies might consider to add an age-, education-, and gender-matched control group to the design to draw more solid conclusions on brain-behaviour relationships in young adolescents who sustained a moderate-to-severe TBI. Although rather time-consuming, using manual delineation of the white matter ROIs instead of automatic segmentation could also improve the methodological quality, so differences in DAI may reflect the amount of cognitive disability in a more conclusive way.

**Conclusion**

The present study investigated the link between cognitive outcome (working memory and attention) as measured by neuropsychological tests and the integrity of two white matter tracts (SLF and cingulum) as measured by DTI based parameters. More specifically, we expected to find a positive relationship between FA and task performance, and a negative relationship between MD values and task performance. We did not find any significant relationships, although previous research has shown that the ROIs of the current study are related to higher cognitive functioning. This might indicate that the current study lacked to find significant results due to biological confounds and methodological issues such as crossing fibres and automatic segmentation of the ROIs.
Nederlandstalige Samenvatting

Traumatisch hersenletsel is een belangrijke oorzaak van mentale en fysieke beperkingen bij jongeren, en gaat vaak samen met diffuse axonale schade. Deze schade kan leiden tot neurologische stoornissen, en dit beïnvloedt hogere cognitieve functies zoals cognitieve controle, aandacht en geheugen. Eerdere studies hebben al een verband aangetoond tussen specifieke witte stof structuren en prestaties op cognitieve tests. Het huidige onderzoek heeft als doel te onderzoeken of er een verband bestaat tussen aandacht en werkgeheugen enerzijds, en de Superior Longitudinal Fasciculus (SLF) en cingulum als witte stof bundels anderzijds bij jongeren met chronische TBI. In vergelijking met andere medische beeldvormingstechnieken, is Diffusion Tensor Imaging (DTI) meer geschikt om diffuse axonale schade te detecteren en gevolgen op cognitief vlak te voorspellen. DTI parameters (fractional anisotropy en mean diffusivity) werden berekend en vervolgens gecorreleerd met de prestaties op neuropsychologische tests (spatial span en flanker taak). De data verworven in negen adolescenten met matige tot ernstige TBI toonde geen significante relatie tussen het werkgeheugen en witte stof bundels, en ook de correlatie met aandacht bleek niet significant te zijn. Deze resultaten zijn niet in overeenstemming met eerdere bevindingen, die ontdekten dat de verminderde structurele connectiviteit en de integriteit van het SLF en cingulum in TBI patiënten wel een significante invloed heeft op bepaalde aspecten van cognitie. Onze bevindingen zouden onder meer kunnen verklaard worden door methodologische keuzes en biologische confounds.
References


