THE IMPACT OF PEDIATRIC TRAUMATIC BRAIN INJURY ON WRITTEN EXPRESSION: A DIFFUSION TENSOR IMAGING STUDY UTILIZING TRACT-BASED SPATIAL STATISTICS

A Dissertation

Presented to

The Faculty of the Department

of Psychology

University of Houston

In Partial Fulfillment

Of the Requirements for the Degree of

Doctor of Philosophy

By

Lindsey M. Harik

July 24th, 2015

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Abstract

The aim of this study was to determine if cerebral white matter integrity is predictive of Written Expression (WE) performance in children, and if the relation between white matter integrity and WE performance differs between children with traumatic brain injury (TBI) and children with orthopedic injury (OI). White matter integrity was approximated via diffusion tensor imaging (DTI) using tract-based spatial statistics. The current study utilized two DTI metrics, fractional anisotropy (FA) and mean diffusivity (MD), to assess integrity of white matter tracts. White matter tract integrity values were used to predict WE performance in the TBI group and the OI comparison group. General linear modeling (GLM) and multiple mediation analyses were used to predict performance on measures of WE at twelve months post-injury from white matter integrity at three months post-injury. Measures of WE included Thematic Maturity, Writing Fluency, and Spelling. Children with OI demonstrated significantly stronger performance on Writing Fluency and Spelling than children with TBI but there was no significant difference between groups on TMI performance. Children with TBI showed significantly decreased white matter integrity three months post-injury as compared to children with OI. Writing Fluency and TMI performance were fully mediated by FA values of the anterior thalamic radiation and corticospinal tract and Writing Fluency performance was also predicted by group differences in cingulum bundle microstructure. Taken together, these findings suggest that TBI negatively impacts the microstructural integrity of specific pathways that support WE performance and that these microstructural alterations account for post-traumatic changes in the content and fluency of production of written narratives. These findings are relevant for further understanding the role of white matter in academic performance and the impact of TBI on the developing brain.

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Introduction

Traumatic brain injury (TBI) contributes to approximately one third of injury related deaths in the U.S. (Centers for Disease Control and Prevention [CDC], 2000) and over half a million injuries are experienced by children ages 14 and younger annually (Faul, Xu, Wald & Coronado, 2010). Following a moderate to severe TBI, children may exhibit a wide range of neuropsychological changes that adversely impact their ability to meet expected milestones, particularly in academic areas. These changes include alterations in motor performance (Gagnon, Forget, Sullivan & Friedman, 1998; Kuhtz-Buschbeck et al., 2003), executive functioning (Levin & Hanten, 2005; Anderson & Catroppa, 2005), academic performance (Ewing-Cobbs, Fletcher, Levin, Iovino & Miner, 1998; Ewing-Cobbs et al., 2006), language skills (Ewing-Cobbs et al., 1987; Ewing-Cobbs & Barnes, 2002), working memory (Conklin, Salorio & Slomine, 2008), attention (Catroppa & Anderson, 2003; Catroppa, Anderson, Morse, Haritou & Rosenfield, 2007) and behavior (Ganesalingam, Sanson, Anderson & Yeates, 2007; Taylor et al., 2002; Schwartz et al., 2003). These changes often contribute to academic difficulties, which have been identified among the most disruptive consequences of TBI in children (Jaffe et al., 1993).

In the following sections, an overview of the impact of pediatric TBI on cognitive and academic development will be provided and the role of DTI in studying TBI and brain areas and pathways related to WE will be reviewed. Our rationale and hypotheses will be outlined, as will the methods by which this study was executed. Finally, the results of this study will be described as they relate to our current understanding of pediatric TBI and the role of white matter in WE. Given that WE critically important for current academic and vocational

success, there is a relative paucity of research in this area as compared to reading and mathematical abilities. Indeed, writing difficulties have been dubbed the "forgotten learning disability" (Katusic, Colligan, Weaver, & Barbaresi, 2009). Because WE is related to multiple brain areas and is reliant on cognitive efficiency, it is highly susceptible to disruption following TBI. This study will help to contribute to the current understanding of the impact of TBI on WE and will highlight the importance of understanding the mechanisms by which WE is executed.

Epidemiology and Pathophysiology of Childhood TBI

Epidemiology

Estimates of incidence rates for traumatic TBI in children vary between 70:100,000 and 799:100,000, or one million annually in the U.S. (Langlois et al., 2004). Finding an accurate incidence figure for traumatic TBI in children is a challenge for several reasons. Lack of hospitalizations following mild TBI, lack of standardized definitions of injury (and injury severity), inconsistent rating scales, varied collection methods and other factors have made this an increasingly difficult task (Yeates, Ris, Taylor & Pennington, 2010). In 2006 the CDC compiled epidemiological data from several sites across the U.S. and found that nearly half a million (473,947) emergency department visits for TBI are made annually by children aged 0 to 14 years, 35,136 of which require hospitalization. Common causes of traumatic TBI in children listed by the CDC are falls (50.2% of cases), being hit by or against an object (24.8%), motor vehicle collisions (6.8%), assault (2.9%) and injuries of an unknown or unlisted origin (15.3%).

Pathophysiology

TBI leads to several pathological consequences at varying time points. Acutely, neuronal transmission is disrupted by alternations in ions, chemicals, and neurotransmitters. Immediately after the brain receives the mechanical force of the injury, a swift and severe influx of glutamate, calcium, and sodium, and an efflux of glutamate occurs that then leads to disruption of lipid membranes. The initial ionic flux and depolarization then leads to alterations in gating of ion channels, causing a wide spread dampening of neuronal activity (Giza & Hovda, 2014). The brain then goes into hyper drive in an effort to balance these initial changes, causing an overall energy shortage that has been linked to deficits in learning during this period of posttraumatic reaction (Yoshino, Hovda, Kawamata, Katayama, & Becker; 1991).

These acute effects may lead to a cascade of secondary effects that further disrupt cellular functioning (e.g. cerebral edema, hypoxia, ischemic events, alteration in blood flow) and late effects (e.g. hydrocephalus, seizure disorders). Specifically, over time axons exhibit reduced plasmic transport with sustained axonal swelling and disconnection. This traumatic axonal injury in many cases eventually leads to Wallerian degeneration and deafferentation (Povlishock, 1992). Children are at an increased risk of posttraumatic brain swelling and hypoxic-ischemic insults. Perhaps most pertinent to recovery of cognitive function is the fact that TBI effects are often both diffuse and multifocal (Adelson & Kochanek, 1998). Physiological differences in children, as compared to adults, such as greater head-to-body ratio, less myelination, and greater relative proportion of water content and cerebral blood volume make this pattern of injury especially relevant in school-aged children (Giza, Mink, & Madikians, 2007). Quantitative neuroimaging studies in children with TBI have revealed reductions in white and grey matter volume in the corpus collosum and frontotemporal

regions (Ewing-Cobbs et al., 2008; Wilde et al., 2005). Focal injuries in pediatric TBI occur most frequently in the frontal and temporal poles due to their location near rough edges of the skull.

A Model of Written Expression Following Pediatric Traumatic Brain Injury

Among the academic skills affected by TBI is written expression (WE), or, the ability to express oneself through writing. Written expression is the product of the following processes executed in concert: handwriting, spelling, transcription, verbal comprehension, working memory, processing speed and written discourse. Any deficit in one or more of the skills that results in impaired written expression is sufficient to identify a written expression deficit. Despite the importance of mastering WE for continued academic and occupational success (Wallach & Butler, 1994), little research has been conducted to understand the underpinnings of WE difficulties in children. This is especially true for children with TBI.

In typically developing children, Berninger and colleagues demonstrated that difficulties in WE could be traced back to earlier developed, simpler skills such as handwriting and spelling. Variability in these low-level skills could be similarly traced to related neuropsychological skills (Berninger, Mizokawa & Bragg, 1991) across grade levels. However, handwriting and spelling skills predicted different components of WE among children of different ages. For children who are earlier on in the process of learning to write, compositional length and quality are more strongly related to spelling skills. Compositional length and fluency were related to handwriting skills for children across elementary grade levels (Graham, Berninger, Abbott, Abbott, & Whitaker, 1997). These findings informed the development of the Simple View of Writing (see Figure 1), which posits that WE is

comprised primarily of transcription skills and executive functions, and incorporates the role of working memory in order to facilitate text generation, execute idea generation and revise written work (Berninger, Abbott, Abbott, Graham & Richards, 2002).

However, this model does not specifically address automatization of learned skills, a factor that has been critically important for understanding deficits in reading (Wolf & Bowers, 1999; Barnes, Dennis & Wilkinson, 1999), math (Fuchs et al., 2008; Geary, Brown & Samaranayake, 1991) and writing (McCutchen, 2011). In beginning writers especially, automaticity of low-level skills is important for recruiting working memory, which then allocates cognitive resources to executing higher-level skills (Berninger et al.,1992). The Simple View of Writing emphasizes the importance of working memory as the mechanism by which a complex cascade of skill execution can be accomplished. Because there are known deficits in working memory following TBI (Gorman, Barnes, Swank, Prasad, & Ewing-Cobbs, 2011; Levin et al., 2004), this model may be particularly applicable to children with TBI.

Impact of Pediatric Traumatic Brain Injury on Written Expression

Among the academic skills affected by TBI is written expression (WE). Despite the importance of mastering WE for continued academic success (Wallach & Butler, 1994), little research has been conducted to understand the neural underpinnings of WE difficulties in children. This is especially true for children with TBI. The aim of the current study is to further understand the contribution of alterations in particular white matter tracts in order to further understand the mechanism by which WE is disrupted following TBI.

Developmental course and severity of injury must be considered when conceptualizing the impact of TBI on WE. Often at the time of injury, children are still actively developing those skills upon which WE is dependent, potentially making them more vulnerable to disruption than earlier established skills (see Barnes, Dennis and Wilkinson, 1999 as an example with reading). Age effects have been observed consistently in motor skills following TBI, including fine motor and graphomotor skills, such that younger as opposed to older children show more detrimental changes in fine motor skills following TBI as compared to children older at the time of injury (Thompson et al., 1994). Similar age effects on impact of TBI on cognition have been observed also with verbal working memory (Levin et al., 2004), processing speed (Crowe, Catroppa, Babl, Rosenfeld & Anderson, 2012), and attentional skills (Ewing-Cobbs et al., 1998; Catroppa and Anderson, 2005). Additionally, severity of injury has demonstrated a dose-response effect on academic and cognitive performance, including WE (Catroppa, Godfrey, Rosenfeld, Hearps & Anderson, 2012; Ewing-Cobbs et al., 1997; Ewing-Cobbs et al., 2006, Yorkston, Jaffe, Liao & Polissar, 1999).

Because skills related to WE are in a rapid stage of development during childhood, the impact of TBI in children and adolescents may vary at different developmental stages. Written expression serves as an appropriate model to illustrate the detrimental nature of these cognitive changes because it draws on a wide range of cognitive skills including orthographic fluency, spelling, planning, and processing speed as well as proficiency in other related academic realms.

Several studies have found WE to be disproportionately affected following TBI when compared to other language or academic measures (Ewing-Cobbs, Levin, Eisenberg &

Fletcher, 1987; Taylor et al., 2002). In the few studies that have directly measured the quantity and quality of writing samples in children with TBI, these children consistently write less than their non-injured peers, and what they do write is of lower quality (Yorkston, Jaffe, Polissar, Liao, & Fay, 1997; Yorkston, Jaffe, Liao, & Polissar, 1999). WE may be especially vulnerable to disruption following TBI because of the negative impact on several neuropsychological skills related to transcription, fluency and executive functioning (Yorkston, Jaffe, Polissar, Liao & Fay, 1997). Harik and colleagues examined neuropsychological predictors of WE in school-aged children with TBI in relation to an orthopedic comparison group (Harik et al., 2015). The TBI group showed reduced quality of WE, as well as significant reductions in transcription, fluency and executive skills. Although groups differed on nearly all cognitive and academic measures, only the speed with which children were able to write (as measured by speeded letter and sentence writing tasks) significantly mediated the relation between TBI and quality of WE. In light of these findings, the Simple View of Writing was refined for this study to explicitly highlight the impact of changes in fluency on the production of written text after pediatric TBI. The current model (depicted in Figure 2) emphasizes the role of skill automatization and orthographic fluency that is necessary for effectively executing higher order skills such as WE.

Diffusion Tensor Imaging and Pediatric Traumatic Brain Injury

Previously, imaging techniques such as computerized tomography scans and standard magnetic resonance imaging (MRI) allowed researchers to link focal insults to changes in cognitive functioning. However, these methods are limited in capturing traumatic axonal

injury (Mori & Zhang, 2006), a particularly harmful consequence of pediatric TBI (Levin, 2003). Diffusion tensor imaging (DTI) is a structural imaging technique used to measure diffusion of water molecules in the brain. Diffusion within tissue is neither random nor free; water molecules move along paths, reflecting structure within the brain. Depending on the characteristics of the surrounding tissue, water molecules move more quickly in some directions as compared to others. Specifically, water molecule diffusion is more rapid when moving parallel to the direction to tissue fibers. The utility of using DTI to study healthy and unhealthy brain tissue rests on the assumption that water molecules diffuse more quickly along tissue with higher structural integrity, meaning the fibers are densely packed and arranged consistently in one direction (Mori & Zhang, 2006). By measuring the speed and direction of water molecules as they transfer along axonal myelin sheaths, an estimate of white matter integrity can be made. DTI provides information that allows inferences to be made regarding the integrity of tissue in the brain and is particularly useful for capturing white matter integrity due to structural properties. From this, relations between white matter integrity and cognition have been established (Mosely, Bammer, & Illes, 2002).

DTI may be particularly useful in studying pediatric populations due to its utility in measuring normal white matter development (Eluvathingal, Hasan, Kramer, Fletcher & Ewing-Cobbs, 2007). Several trends have been documented during typical white matter development including increased fiber organization and myelination as measured by DTI (Neil, Miller, Mukherjee & Huppi, 2002). DTI is also particularly useful in studying the impact of TBI on brain tissue due to its ability to reveal changes in white matter properties that are thought to reflect shearing and tearing of axonal fibers and the subsequent cascade of white matter tissue integrity changes over time that are seen in TBI. Studies of TBI in

children have linked white matter integrity to levels of cognition (Wilde et al., 2010; Treble et al., 2013; Ewing-Cobbs et al., 2008), which have allowed the impact of TBI on white matter to be further understood.

The diffusion of water along axons may be quantified in terms of anisotropy, or the degree of restriction of movement of molecules in all directions. Fractional anisotropy (FA) is a metric ranging from 0 to 1 that measures overall directionality of diffusion, where 0 represents free diffusion in any direction and 1 represents the most restricted diffusion in one direction (Pierpaoli & Basser, 1996). FA is affected by several factors including myelin thickness, the direction of water molecules moving in multiple directions, and the density of white matter fiber tracts. Higher FA values indicate greater congruence of orientation of axonal fibers and greater fiber density that allow for more rapid and efficient diffusion of water molecules through the pathway. This characteristic is thought to translate to greater white matter integrity (Pfefferbaum et al., 2000b), which has been linked to increased cognitive performance (Durston & Casey, 2006). Conversely, lower FA values are thought to be indicative of poorer white matter integrity, which has been linked to decreases in cognitive performance (Klingberg et al., 2000; Rovaris et al., 2002).

In addition to FA, mean diffusivity (MD) is often used as a measure of white matter integrity. MD is the overall average measure of the speed of diffusion (mm^2/second) of water in any direction and is thought to reflect white matter integrity (Alexander, Lee, Lazar & Field, 2007). Lower MD values indicate increased white matter integrity; tissue with lower MD typically has increased fiber density, axonal diameter and myelination (Mukherjee & McKinstry, 2006). Following pediatric TBI, increased MD values have been associated with slower reaction time (Wilde et al., 2010) and decreased verbal and visual memory skills

(Bigler et al., 2012). Overall, higher MD values are observed in TBI groups when compared to orthopedic controls in most brain areas though exceptions have been noted (Wilde et al., 2012). Increased MD values have been correlated with lower GCS scores when FA values were uncorrelated with severity of injury (Wilde et al., 2010). However, there is evidence that FA may be more sensitive to white matter disruption underlying cognitive changes following TBI than MD (Ewing-Cobbs et al., 2008; Levin et al., 2008b).

Radial and axial diffusivity are two components of MD and represent the amount of diffusion occurring perpendicular or parallel to the direction of primary diffusivity, respectively (Song et al., 2002). Although related, these metrics appear to represent dissociable processes related to pathology in the brain. In the realm of TBI and other pathological disease processes, it has been demonstrated that axial diffusivity represents the integrity of axonal fibers whereas radial diffusivity reflects the integrity of myelin (Budde, Xie, Cross, & Song, 2009; Concha, Gross, Wheatley & Beaulieu, 2006). As a result, differences in axial diffusivity and radial diffusivity levels between acute and chronic stages of neuronal insult have been observed. In the acute phase of injury, axial diffusivity levels decrease significantly, reflecting disorganization of water molecule diffusion resultant from disruption in axonal composition. Chronically, when demyelination is thought to occur following injury, radial diffusivity levels elevate significantly, indicating greater levels of water molecule movement occurring incongruently with the primary direction of diffusivity (Concha et al., 2006) reflecting decreased tissue integrity (Song et al., 2002).

Tract-Based Spatial Statistics

Tract based spatial statistics (TBSS) is a method for making statistical comparisons of DTI metrics. Unlike other voxelwise statistical approaches for DTI metrics of white matter, TBSS co-registers multi-subject FA maps and projects single-subject data onto a common skeleton of voxels. The result is a group mean FA skeleton which represents the centers of all fiber bundles common to each subject with each subject's FA data added to the mean FA skeleton (Smith et al., 2006). This technique permits global comparisons between groups at the level of the individual voxels to reveal changes throughout the entire brain (Yuan et al., 2007). Notable benefits of utilizing TBSS to analyze DTI data include the embedded correction for making multiple corrections and increased assurance for capturing white matter pathways exclusively, rather than accidental inclusion of grey matter that can occur with other methodologies (Smith et al., 2006).

Studies that have utilized TBSS to analyze neuroimaging data following TBI have established links between white matter alteration (Wilde et al., 2012) and cognitive changes (Leunissen et al., 2013; Adamson et al., 2013; Irimia et al., 2012; Palacios et al., 2011), and to some extent have found that location of white matter damage predicts cognitive function (Kinnunen et al., 2010). Group differences in white matter integrity have been established between individuals with and without TBI across studies and in several cases white matter metrics have been correlated with cognitive performance for individuals with TBI but not for those in uninjured comparison groups (Adamson et al., 2013; Kinnunen et al., 2010).

Neuroimaging of Written Expression

Functional MRI studies have identified several brain areas that are associated with skills related to WE. The most commonly identified areas involved in studies measuring

activation during writing-related tasks are the left superior parietal cortex, left premotor area, left orbitofrontal area, left fusiform gyrus and right cerebellum (Rapp & Dufor, 2011; Richards et al., 2009; James & Gauthier, 2006, James & Engelhardt, 2012; Matsuo et al., 2000; Sugihara, Kaminaga & Sugishita, 2006; Menon & Desmond, 2001; Katanoda, Yoshikawa & Sugishita, 2001; Planton, Jucla, Roux & Demonet, 2013). These cortical areas are tied to several skills that have been linked to WE, including fine motor planning (Richards et al., 2009), letter/icon writing (James & Gauthier, 2006; James & Engelhardt, 2012; Sugihara, Kaminaga & Sugishita, 2006), copying (Matsuo et al., 2000), writing to dictation (Menon & Desmond, 2001; Matsuo et al., 2000) and written object naming (Katanoda, Yoshikawa & Sugishita, 2001).

As previously noted, children who sustain TBI commonly experience impairments in motor, language and executive skills. Given the varied components of WE, we are interested in the relation between the pathways that are involved in WE-related skills, either directly or indirectly by connecting relevant brain areas, and WE skills. This study aims to further our understanding of the neural underpinnings of WE following TBI by examining white matter integrity in the context of WE performance in children with and without TBI.

White Matter Pathways of Interest

WE is a complex skill that involves simultaneous execution of multiple cognitive skills and recruitment of several brain areas. Cognitive skills include low-level transcriptional skills that are dependent on the motor system, and higher-level executive skills such as organization and planning that rely on fluid communication between frontal and posterior areas. Due to the developmental nature of skills involved in WE, it is critical

that execution of skills at each foundational step of the process be automatized and fluent in order to distribute cognitive resources to more demanding skills. White matter integrity is thought to subserve such functions, by facilitating fluent and efficient communication along neural networks. In healthy and in non-typical populations, white matter integrity is positively correlated with increases in fluency, and similarly, reductions in white matter integrity are correlated with reduced fluency (Theilman et al., 2013; Vannorsdall, Waldstein, Kraut, Pearlson, & Schretlen, 2009; Baird, Colvin, VanHorn, Inati, and Gazzaniga, 2005). The following white matter tracts were selected based on their potential involvement in facilitating skills thought to be related to written expression such as transcription, fluency and executive skills (Harik et al., 2015).

Anterior Thalamic Radiation

The anterior thalamic radiation projects anteriorly from the anterior and dorsomedial thalamic nuclei to the dorsolateral prefrontal cortex (Coenen, Panksepp, Hurwitz, Urbach, & Madler, 2012). The anterior thalamic radiation is thought to play a role in executive functioning (Mamah et al., 2010), working memory (Duering et al., 2014), error monitoring (Fjell, Westlye, Amlien, & Walhovd, 2012), memory (Van der Werf, Jolles, Witter, & Uylings, 2010), and emotion and motivation systems (Panksepp, 1998). DTI metrics of the anterior thalamic radiation have been correlated with symptoms of neurological and psychiatric disease including Alzheimer's disease, Tourette's syndrome, and major depression (Lagopoulos et al., 2013) and white matter integrity of the anterior thalamic radiation has been linked with reduced writing abilities in children diagnosed with and without dysgraphia (Richards et al., 2015; Richards et al., 2009).

Cingulum Bundle

The cingulum bundle projects from the cingulate gyrus to prefrontal and entorhinal cortices and is involved in several cognitive functions including cognitive control (Wilde et al., 2010), set shifting (O'Sullivan, Barrick, Morris, Clark, & Markus, 2005), and memory (Wu et al., 2010). The cingulum bundle is susceptible to damage as a result of TBI (Merkley, Larson, Bigler, Good & Perlstein, 2013). Increased MD in the cingulum bundle has been shown to correlate with higher injury severity (Wilde et al., 2010). In a study measuring cingulum bundle white matter integrity following pediatric TBI, faster reaction times on measures of cognitive control were correlated with increased FA and decreased MD (Wilde et al., 2010). Cingulum bundle functioning is relevant for assessing WE following TBI because of its implication in higher order functioning, such as cognitive control, which is thought to facilitate monitoring of performance and feedback, two common areas of intervention for WE problems (Graham, Harris & Mason, 2005). Notably, the cingulum bundle has been described as a "back up system" to the prefrontal cortex during times of cognitive overload, instances that are common following TBI (Cazalis et al., 2011). Damage to the cingulum bundle is thought to explain many classic TBI-related symptoms including executive dysfunction, problems with memory and changes in emotional processing (Levin, 1995; Wilde et al., 2010).

Corticospinal Tract

The corticospinal tract is a descending cortical tract that has origins in the primary motor area, premotor area, supplementary motor area, frontal lobes, primary sensory area, primary somatosensory cortex, posterior parietal cortex and parietal operculum (Lemon, 2008; Dum & Strick, 1991). Axons within the corticospinal tract descend through centrum semiovale, corona radiata, internal capsule, pons, medulla, and finally to the spinal cord (Al

Masri, 2011). The corticospinal tract is the most important neural tract for motor functioning and is often damaged as a result of TBI (Ward et al., 2006; Jang, 2011). Resultantly, motor weakness and incoordination are common impairments following TBI (Jang et al., 2009). Although WE is often described as a higher-order cognitive skill, it is also dependent on motor functioning in order to execute low level transcription skills which have been shown to predict quality of WE (Graham, Weintraub, & Berninger, 2001). There is also evidence for the corticospinal tract's involvement in cognitive functioning, including semantic verbal fluency (Spalletta, Piras, Fagioli, Caltagirone & Piras, 2014; Canu et al., 2013).

Inferior Fronto-occipital Fasciculus

The inferior fronto-occipital fasciculus is a direct pathway connecting ventral occipital, posterior temporal and orbitofrontal areas (Ashtari, 2012). It is comprised of a dorsal component which connects the frontal and superior parietal and posterior-middle occipital gyri and a ventral component that connects the frontal lobe and inferior occipital and posterior-temporal lobes (Martino, Bragna, Robles, Vergani & Duffau, 2010). It is thought to be involved in reading (Catani & Mesulam, 2008), attention (Doricchi et al., 2008), visual processing (Fox et al., 2008), and semantic knowledge (Duffau et al., 2005). The inferior fronto-occipital fasciculus is vulnerable to damage following pediatric TBI (Yuan et al., 2007). FA values in the left inferior fronto-occipital fasciculus have been linked to decreased verbal memory. FA, but not MD, was related to visual memory as well (Bigler et al., 2010).

Inferior Longitudinal Fasciculus

The inferior longitudinal fasciculus projects to lateral and medial anterior temporal regions from the occipital cortex and is thought to mediate fast transfer of visual signals to

anterior temporal regions and projections from the amygdala to visual areas (Ortibus et al., 2012). Damage to the inferior longitudinal fasciculus following TBI has been documented in multiple studies (Yaun et al., 2007; Singh, Jeong, Hwang, Sungkarat & Gruen, 2010) and is thought to share significant anatomical (Wahl et al., 2010) and functional (Ashtari, 2012) overlap with the inferior fronto-occipital fasciculus. Significant changes in FA values of the inferior longitudinal fasciculus have been shown in children one year post TBI (Yaun et al., 2007). Reductions in FA of the inferior longitudinal fasciculus following TBI have been linked with decreased memory performance in young adults with severe TBI (Bigler et al., 2010).

Superior Longitudinal Fasciculus

The superior longitudinal fasciculus connects the frontal lobes with posterior brain locations. It is thought to originate in the superior parietal lobule and pass through the superior frontal gyrus, and to terminate in the supplementary motor area and dorsal premotor area (Jang & Hong, 2012). It is anatomically linked with the arcuate fasciculus and heavily implicated in language function and dysfunction (Dick & Tremblay, 2012) White matter metrics including FA and radial diffusivity in the superior longitudinal fasciculus following pediatric TBI are correlated with injury severity (Yuan et al., 2007), executive dysfunction (Wozniak et al., 2007), and inhibition and switching in the left superior longitudinal fasciculus (Kurowski et al., 2009).

Uncinate Fasciculus

The uncinate fasciculus connects orbitofrontal and anterior temporal lobes and is involved in emotional regulation and is susceptible to damage as a result of TBI due to its frontotemporal location (Bigler et al., 2010). Damage to the uncinate fasciculus resulting

from TBI has been shown to predict behavioral dysregulation in children (Johnson et al., 2011). In addition to behavioral regulation, there is some evidence to suggest that damage to the uncinate fasciculus negatively impacts initial learning (Geary, Kraus, Pliskin & Little, 2010) and long-term storage for verbal information (Bigler et al., 2010). Damage to the left uncinate fasciculus has been linked to semantic impairment in verbal language use (Liegeois et al., 2013).

As discussed above, the identified white matter pathways are involved in many cognitive processes, several of which are directly related to WE-related skills such as motor, language and executive functioning. WE is a complex construct. It is somewhat paradoxically described as a higher-order skill, however, it is dependent on low-level transcription skills for successful execution (Berninger et al., 1992; Limpo & Alves, 2013). This is best-understood as a "bottleneck" wherein successful execution of a complex skill is dependent on facile and automatic low-level skill execution so that cognitive resources can be delegated to more challenging tasks such as planning, reflecting, editing and organizing. When low-level skills are not automatic, a bottleneck causes decreased execution of more developmentally complex skills, reflecting a deficit or delay in earlier, simpler processes (Barnes, Dennis & Wilkinson, 1999). For these reasons, combined with susceptibility to damage following TBI or damage to areas to which they project, we expect those tracts that have the involvement in motor, language and executive functioning to have predictive ability of WE performance.

Aims of the Current Study

While the exploration of white matter integrity in cognition following TBI is still relatively new, several findings have been established. Overall white matter integrity, as estimated by metrics such as FA and MD, is related to cognition such that more coherent white matter pathways are correlated with higher cognitive performance (Vannorsdall, Waldstein, Kraut, Pearlson & Schretlen, 2009; Baird, Colvin, VanHorn, Inati & Gazzaniga, 2005; Theilmann et al., 2012). DTI metrics have been shown to be related to severity of injury and have been noted to predict functional outcome over initial clinical presentation or lesion characteristics (Sidaros et al., 2008). However, findings regarding FA and MD values are not always convergent; these DTI metrics are reflective of different pathological processes and thus predict different outcomes, many of which are time dependent (Kinnunen et al., 2010). White matter integrity can be informative regarding specific cognitive functions, as well. In many instances, the location of white matter damage is related to the cognitive skill that is impacted, though this relationship remains elusive particularly for complex functions that involve multiple brain areas (Kinnunen et al., 2010).

The manner in which TBI negatively impacts WE through disruption of white matter pathways is largely unknown. To address this gap in the literature, we examined the relation of several white matter tracts to WE performance. WE was measured by performance on three writing skills: story construction, spelling and writing fluency. DTI metrics for white matter pathways, including FA, MD, and radial and axial diffusivity were used to approximate white matter integrity. Performance on WE measures was predicted by the integrity of seven pathways identified for their role in coordinating, connecting and transmitting messages between brain areas believed to subserve WE.

In this study, we evaluated whether white matter integrity assessed at three months post-injury is a predictive biomarker for WE performance at twelve months post-injury as a compliment to a previous study in which cognitive and academic predictors of WE were identified in children with TBI. When compared to children with orthopedic injuries (OI), children with TBI showed reduced performance on nearly all WE-related skills, including orthographic fluency, spelling, story construction, processing speed and working memory. While each of these skills was significantly correlated with WE performance, the relation between TBI and WE was mediated only by orthographic fluency (Harik et al., 2015). In the current study, comparison between a TBI group and an OI comparison group was included to control for injury-related effects such as stress associated with injury and hospitalization. Inclusion of an OI comparison group may also control for pre-morbid characteristics that, in some cases, have shown an increased risk for injury, such as ADHD (DiScala, Lescohier, Barthel & Li, 1998).

The following hypotheses were examined:

1) The TBI group will show reduced performance on WE measures as compared to the OI group. 2) FA will be lower and MD will be higher for each pathway in the TBI group as compared with the OI group, reflecting widespread left hemisphere white matter damage. 3a) Based on previous literature exploring the role of specific cognitive skills on WE, we expect that performance in each WE measure will be predicted by DTI metrics for specific left hemisphere white matter tracts: Thematic maturity performance is expected to be significantly related to anterior thalamic radiation, cingulum bundle, corticospinal tract, inferior fronto-occipital fasciculus, superior longitudinal fasciculus, and uncinate fasciculus and DTI metrics; Writing Fluency performance is expected to be significantly related to

anterior thalamic radiation, cingulum bundle and corticospinal tract DTI metrics; and Spelling performance is expected to be significantly related to corticospinal tract, inferior longitudinal fasciculus and superior longitudinal fasciculus DTI metrics.

3b) We expect that groups will differ on the relation of DTI metrics and WE performance such that there will be a significant interaction between group and DTI metrics when using DTI metrics to predict WE performance.

Method

Participants

Data on participants were collected originally in compliance with the IRB of the University of Texas – Health Science Center at Houston (UT-HSCH) regulations and were part of a National Institutes of Health grant (NIH NS ROI 046308). During that research, informed written consent was obtained from the child's guardian. Oral assent was obtained from children ages 6 to 7 years, and written assent was obtained from children 8 years and older. Approval for the current archival study was obtained from the University of Houston (UH) Committee for the Protection of Human Subjects (CPHS) that is part of their Institutional Review Board (IRB).

Participants included children who sustained a TBI (n=36) or orthopedic injury (OI; n=30). Participants were recruited from the Level 1 Pediatric Trauma Center at Children's Memorial Hermann Hospital/University of Texas Health Science Center as a part of a prospective, longitudinal study. Inclusion criteria for all participants were age at injury between 6 and 15 years, hospitalization for their injury, and proficiency in English. All participants received an MRI scan at approximately three months post-injury and were

evaluated with cognitive and academic measures at approximately one year post-injury. Injury severity was rated for each participant using the Injury Severity Scale (ISS), a method for describing and rating patients with multiple injuries (Baker, O'Neill, Haddon, & Long, 1974). For children with TBI, the severity of head injury was rated using the GCS motor score (ranging from one to six with higher scores indicating better motoric response). The GCS motor score appears to be as good a predictor of injury severity as the total GCS score in children with TBI (Acker et al., 2014). Given the difficulty in reliably assessing eye and verbal responses in children following TBI, the worst GCS motor score, in this case, the lowest post-resuscitation score was used. The GCS motor score (ranging from one to six with higher scores indicating better motoric response) appears to be as good a predictor of injury severity as the total GCS score in children with TBI (Acker et al., 2014). Inclusion criteria for the TBI group were: 1) TBI resulting from acceleration-deceleration or blunt impact injuries caused by vehicular collisions, falls, or impact with a blunt object, 2) complicated-mild, moderate or severe TBI, 3) skeletal or body ISS scores ≤ 2 in children with complicated-mild or moderate TBI to minimize any confounding influence of severe orthopedic injury on accurate assessment of Glasgow Coma Scale (GCS; Teasdale & Jennett, 1974) scores and outcome, and 4) DTI data available at three months post-injury and behavioral data available at one year post-injury. Inclusion criteria for the OI group were: 1) skeletal or body ISS score ≤ 4, 2) injury resulting from acceleration-deceleration or blunt impact injuries caused by vehicular collisions, falls, or impact with a blunt object, 3) DTI data available at three months post-injury and behavioral data available at one year post-injury.

Exclusion criteria for both groups were: 1) children of nonresidents and families who reside outside the catchment area (125 mile radius) due to difficulty maintaining enrollment, 2) children with major developmental or psychiatric disorders that would complicate assessment of outcome and 3) previous head injury. This was determined with a brief questionnaire administered to parents.

Imaging

All MRIs were performed on a Philips 3T scanner with SENSE (Sensitivity Encoding) technology using an eight-channel phase array head coil. After conventional scout, T1, and T2-weighted images were collected, followed by a DTI sequence. The DTI sequence consisted of a single-shot spin-echo diffusion sensitized echo-planar imaging sequence with the following parameters: 21 non-collinear equally distributed diffusion encoding directions (e.g., Icosa21; Hasan & Narayana, 2003); repetition time/echo time = 6100/84 ms; b = 0, and 1000 s/mm2; field-of-view = 240 x 240 mm2; matrix = 256 x 256; slice thickness = 3.0 mm; in-plane pixel dimensions (x,y) = 0.94,0.94; SENSE acceleration factor = 2; a total scan time of approximately 7 minutes.

Processing

Tract-Based Spatial Statistics (TBSS) is an approach to evaluating significant differences in integrity of white matter pathways in the brain. The use of neuroanatomical atlases included with the FSL software allows parsing and summarization of white matter integrity metrics that can be exported to statistical packages for use in predictive linear models. It is worth noting that this method shares some similarities and terminology with tractography, but is a separate approach to analyzing microstructural integrity in white matter

pathways. Most notably, TBSS relies on clear registration of brains to generate usable models. However, in its favor as a tool, TBSS provides data that is independent of tracking algorithms, vagaries of partial voluming, and evaluation of varying volume pathways which may result in DTI metrics which are difficult to interpret without significant volume information (Smith et al., 2006).

Voxelwise analysis of FA and MD data was carried out using TBSS (Smith et al., 2006), part of FSL (Smith et al., 2004). First, raw diffusion data was processed to correct for eddy currents and motion (e.g. FSL's eddy current correction (ECC) tool). Next, FA images were created by fitting a tensor model to the ECC data using DTIFIT from FSL's Diffusion Toolbox, generating spatial maps of FA values for each individual subject. All participants' FA data was then aligned onto the MNI152 standard-space template using the nonlinear registration tool FMRIB Nonlinear Image Registration Tool (Anderson, 2007). Next, a mean FA skeleton, which represents the centers of all white matter tracts common to all subjects included in the analyses, was created. Each subject's aligned FA data (thresholded at FA values >0.15) was then projected onto this skeleton. Probabalistic tracts derived from the Johns Hopkins University white-matter tractography atlas were overlaid onto each subject's skeletonized FA values. Binary masks were derived from each white matter tract of interest included with the Johns Hopkins University atlas. The intersection of each subject's skeletonized FA values and binary mask for each white matter tract of interest were used to record the mean value of each tract in each subject using FSL-based command-line utilities. Subsequently, the same process was used to generate MD, axial diffusivity and radial diffusivity values for each tract (Hua et al., 2008). These values were exported to Statistical Analysis System version 9.3 for further analysis.

Written Expression Measures

The Test of Written Language-I (TOWL; Hammill & Larsen, 1978) is a norm-referenced, comprehensive, diagnostic test of WE. In the Story Construction subtest, students are asked to write a brief story based on an illustration that is presented to them. The student's story is evaluated relative to the quality of its composition and given a standard score via the Thematic Maturity Index (TMI). Passages with higher thematic maturity ratings incorporate higher order processes such as plot development, variegated use of vocabulary and overall continuity. The TMI is shown to have moderate test-retest reliability (.77 coefficient), inter-rater reliability (76% agreement amongst raters), and standard error (1.4), and with acceptable content and criterion validity (Hammill & Larsen, 1978). Spelling was assessed using the Woodcock-Johnson Tests of Academic Achievement-III (WJ-III) Spelling subtest, for which children are required to write letters and words that are dictated to them orally (Woodcock, McGrew, & Mather, 2001). Writing fluency was measured using the WJ-III Writing Fluency subtest. The child writes simple sentences using three target words and a visual prompt, with the aim of writing as many sentences as possible for seven minutes (Woodcock, McGrew, & Mather, 2001). Good to excellent internal consistency, inter-rater and test-retest reliability have been established for these subtests. These subtests have also shown strong predictive and external validity (Woodcock, McGrew, & Mather, 2001).

Procedures

Participants had been previously examined individually at the University of Texas Health Science Center at Houston in a quiet testing room approximately one year post-injury. Evaluations were conducted by a trained research assistant. The aforementioned tests were part of a larger battery including cognitive and academic assessments, which took approximately four hours for administration. The tests presented here took approximately forty-five minutes to administer. All participants were provided with the same directions.

Statistical Analysis

The goal of the following analyses was to understand the impact of changes in white matter integrity after TBI on several measures of WE. Prior to conducting the statistical analyses, visual inspection and screening of the data was used to ensure accuracy and to identify outliers and other abnormal data points (Van den Broek, Cunningham, Eeckles, & Herbst, 2005). Age at injury was included as a covariate in the general linear models (GLM). The rate of atypical (bilateral or right-hemisphere) language lateralization in left-handers is approximated at 15-30% and in 4-6% of right-handers (Pujol, Deus, Losilla, & Capdevilam 1999). Six participants in the current sample are left-handers. White matter metrics of the corticospinal tract was compared in left- and right-handers and no significant differences were found and so left-hemisphere data was used for all participants. Twelve month behavioral data was used and analyses were conducted with SAS, 9.3. All analyses were exploratory.

Hypothesis 1: The TBI group will show reduced performance on WE measures as compared to the OI group.

GLM was used to determine if WE outcomes scores in the OI group were significantly different from those in the TBI group. Group membership was the independent variable and TMI, Writing Fluency and Spelling scores were the dependent variables. Each dependent variable was analyzed separately culminating in three separate GLM procedures. An age at injury X group interaction term was included to determine if the effect of age-was the same for the TBI and OI groups in relation to WE scores. Nonsignificant interactions were trimmed from each model.

Hypothesis 2a: FA values from DTI analyses will be lower for each pathway in the TBI group as compared with the OI group.

GLM was used to determine if FA values for the TBI group were less than those in the OI group, with group membership as the independent variable and mean FA values for each pathway as the dependent variable. The omnibus F-test was examined to determine overall group differences in FA values. Analyses for each pathway were conducted separately. An age at injury X group interaction term was included to determine if the effect of age is the same for the TBI and OI groups in relation to FA values. Nonsignificant interactions were trimmed from each model.

Hypothesis 2b: MD values from DTI analyses will be higher for each pathway in the TBI group as compared to the OI group.

GLM was used to determine if MD values in the TBI group were significantly higher than those in the OI group, with group membership as the independent variable and mean MD values for each pathway as the dependent variable. The omnibus F-test was examined to

determine overall group differences in MD values. Analyses for each pathway were conducted separately. An age at injury X group interaction term was included to determine if the effect of age was the same for the TBI and OI groups in relation to MD values. Nonsignificant interactions were trimmed from the model. As MD values were significantly different between groups, post hoc analyses were run to explore how radial and axial diffusivity values, components of MD, differed between groups.

Hypothesis 3a: DTI metrics for white matter pathways will significantly predict performance on WE measures. Specifically, the TMI will be significantly related to corticospinal tract, superior longitudinal fasciculus, anterior thalamic projection, inferior fronto-occipital fasciculus, uncinate fasciculus and cingulum bundle DTI metrics; Writing Fluency performance will be significantly related to corticospinal tract, anterior thalamic projection and cingulum bundle DTI metrics; and Spelling performance will be significantly related to corticospinal tract, superior longitudinal fasciculus and inferior longitudinal fasciculus DTI metrics.

Hypothesis 3b: Groups will differ on the relation of DTI metrics and WE performance.

For hypotheses 3a and 3b, GLM was used to predict WE performance from mean FA and MD values (FA was run first). Mean FA/MD for the entire sample for each pathway was the independent variable, TMI, Writing Fluency and Spelling scores were the dependent variables and age at injury was included as a covariate. Each pathway was analyzed independently. Group was entered as a main effect and a group x FA/MD interaction term was included to determine if groups differed on the relation of FA/MD and WE performance.

Results

Participant Demographics and Group Comparisons

The children selected for participation in the current study were participants in a larger prospective longitudinal study examining the impact of TBI on academic outcomes. The sample for the original study included 102 children, 55 children with TBI and 47 children with OI. In both groups, ages ranged between 6 and 15 years. Of these 102 original participants, 7 were removed due to lack of imaging at the three month time point. Of the remaining 95 participants, 74 of them received the DTI sequence. Of those 74, eight were missing cognitive data, leaving the final sample to be analyzed at 66 participants, 36 with TBI and 30 with OI. When comparing the group of participants for the current study to those included in the original sample, two-tailed t-test and chi square analyses revealed no significant differences between groups on demographic or injury variables. All p-values associated with t-tests and chi square analyses were greater than 0.36.

Table 1 contains demographic characteristics and statistical comparison of the TBI and OI groups. Two-tailed t-tests and chi square analyses revealed that the TBI and OI groups differed significantly on age at injury and age at assessment, with the TBI group being older at both time points ($p=.02$ in both cases). Groups did not differ significantly on gender, ethnicity, or socioeconomic status as measured by years of maternal education.

Injury information, statistical comparisons of injury characteristics and Cohen's *d* effect sizes (Cohen's *d*) are provided in Table 2. The injury to testing time interval was comparable across groups for the WE outcomes. However, participants in the TBI group had a significantly longer interval between injury and MRI scanning. Groups differed significantly on the overall severity of their injuries; ISS scores were significantly lower in

the orthopedic than TBI group, indicating less severe injuries. This is likely because TBI is included in the ISS calculation. Groups differed significantly on mechanism of injury. Over half of all children with TBI had injuries sustained in a motor vehicle collision, followed by auto-pedestrian collisions, and falls. The leading mechanism of injury for children in the OI group was falls, followed by auto-pedestrian collisions and 'other' causes which included sports and play injuries. The least common mechanism of injury in the OI group was motor vehicle collision.

For the TBI group, the sample included children with complicated-mild (n=3), moderate (n=9) or severe (n=23) injuries. The distribution of GCS scores amongst the TBI group is provided in Table 2. In the TBI group, 19 children had a lowest motor GCS score of one or two, six had scores of three and four, and 10 had scores of five and six.

TBSS Screening

The current sample included 66 children; however, three were removed after screening the TBSS data. In one participant, the presence of residual subdural hematoma caused poor alignment of FA and MD masks onto this participant's skeleton maps. Misalignment errors caused us to remove the two remaining cases that had poor registration of the skeleton on their FA and MD maps, respectively. An intent-to-treat comparison including two-tailed t-tests and chi square analyses revealed that the original sample of 66 children did not differ significantly on any of the demographic and injury comparisons as compared to the final sample of 63 children.

Hypothesis 1: The TBI group will show reduced performance on WE measures as compared to the OI group.

To determine if children in the TBI group would show reduced WE performance as compared to the OI group, a general linear model procedure was followed using GLM with group as the independent variable and age at injury as the covariate as shown in Table 3a. TMI, Spelling, and Writing Fluency were the dependent variables using age-corrected standardized scores. The group X age interaction was not significant and was trimmed from each of the models. Group means and Cohen's *d* for group comparisons, in addition to main effects of group and age, are presented in Table 3a. The correlation of injury severity and WE performance for the TBI group only was explored, as well. For results of the same analyses run with raw scores in place of standardized scores, refer to Tables 7a and 7b in the Appendix.

Children in both groups performed in the average range across measures. In spite of this qualitative similarity, children with TBI performed significantly more poorly on Spelling ($F(1, 60) = 4.30$, $p = .04$) and Writing Fluency ($F(1, 61) = 4.46$, $p = .04$), but not TMI ($F(1, 54) = 1.52$, $p = .22$) as compared to children with OI, providing partial support for hypothesis 1. Cohen's *d* for the effect of group was moderate for Writing Fluency (0.53) and Spelling (0.53), and small for TMI (0.33). Of note, children who were between the ages of six and seven were removed from TMI analyses as standardized scores are not available in this age range. Age at injury was a significant predictor of WE performance for Spelling ($F(1, 60) = 6.07$, $p = .02$) and TMI ($F(1, 54) = 5.89$, $p = .02$) with children who were older at the time of injury performing better on Spelling and children who were younger at the time of injury performing better on TMI.

Table 3b shows the correlation of age at injury and injury severity (TBI group only) with age-corrected standardized scores from each of the measures. The TBI group only

showed a moderate correlation between age at injury and Spelling performance with children who were younger at the time of injury performing more poorly than children who were older at the time of injury. There was a moderate effect between age at injury and TMI performance (p=.07) for children with TBI suggesting that children who were older at the time of injury tended to perform more poorly on this measure. The OI group did not show significant correlations between age at injury and any of the WE measures. Injury severity (measured by duration of impaired consciousness as it is a continuous variable) for the TBI group showed significant, negative correlation with TMI and Writing Fluency performance but not Spelling performance. Shorter duration of impaired consciousness was related to stronger TMI and Writing Fluency performance and injury severity was unrelated to Spelling performance.

Hypothesis 2a: FA values from DTI analyses will be lower for all pathways in the TBI group as compared to the OI group.

To determine if FA values were lower in each of the white matter pathways in the TBI group as compared to the OI group, a one way GLM with group as the between subjects factor was performed for each tract with age at injury as a covariate, as shown in Table 4. The group X age interaction was not significant and was trimmed from each of the models. Table 4 contains least square mean FA values by group adjusted for age, as well as main effects of group and age with Cohen's *d* for the effect of group. The main effect of group on anterior thalamic radiation, cingulum bundle, corticospinal tract, inferior fronto-occipital fasciculus, inferior longitudinal fasciculus, superior longitudinal fasciculus, and uncinate fasciculus FA values from the left hemisphere was significant, providing full support for hypothesis 2a. The main effect for age at injury was also significant for each tract. Results

were in the hypothesized direction suggesting that children in the TBI group had, on average, lower FA values as compared to children in the OI group with moderate to large Cohen's *d*. The effect of age on mean FA values was significant across all tracts with younger age at injury associated with lower FA values.

Hypothesis 2b: MD values from DTI analyses will be higher for each pathway in the TBI group as compared to the OI group.

To determine if MD values were higher in each of the white matter pathways in the TBI group compared to the OI group, a one way GLM with group as the between subjects factor was performed for each tract with age at injury as a covariate. The group X age interaction was not significant and was trimmed from each of the models. Table 4 shows the comparison of groups on mean MD values for each of the white matter tracts with Cohen's *d* based on this group comparison.

The main effects of group and age on left hemisphere anterior thalamic radiation, cingulum bundle, corticospinal tract, inferior fronto-occipital fasciculus, inferior longitudinal fasciculus, superior longitudinal fasciculus, and uncinate fasciculus MD values were significant, providing full support for hypothesis 2b. Children with TBI showed higher MD values, on average, than children in the OI group with moderate to large Cohen's d. Age significantly predicted mean MD values for all tracts with younger children having higher MD values than older children.

Post hoc analyses were run to further explore group differences on MD values. MD is comprised of radial and axial diffusivity, which represent the amount of diffusion occurring perpendicular or parallel to the direction of primary diffusivity, respectively. As shown in Table 5, GLM models were run with group as the between subjects factor and mean

radial diffusivity values for each of the pathways as the dependent variable. Because these analyses were conducted post hoc, a level of $p<.004$ was set to correct for the 14 additional comparisons. Age at injury was included as a covariate. This process was repeated for mean axial diffusivity.

Age at injury X group interaction was not significant for any of the pathways and trimmed from each of the models suggesting no differential relation between age and white matter integrity between groups. The main effects of group and age on mean radial diffusivity values were significant for all tracts at the $p<.004$ level. This indicates that radial diffusivity differed significantly for each white matter tract between groups with radial diffusivity values being consistently higher in the TBI group. Additionally, age at injury was significant for each tract such that individuals who were older at time of injury had increased white matter integrity evidence by lower radial diffusivity values as compared to children who were younger at time of injury regardless of group.

When comparing mean axial diffusivity between groups, the age at injury X group interaction term was not significant and trimmed from each of the models suggesting no differential relation between age and white matter integrity between groups. The main effect of group on mean axial diffusivity was not significant for any of the tracts at the $p<.004$ level. The main effect of age at injury was significant for several tracts including the cingulum bundle, the inferior fronto-occipital fasciculus, the inferior longitudinal fasciculus, and the superior longitudinal fasciculus but not the anterior thalamic radiation, corticospinal tract, and uncinate fasciculus. In contrast to radial diffusivity values, older age at injury was correlated with decreased white matter integrity evidenced by reduced axial diffusivity

values as compared to children who were younger at the time of injury independent of group membership.

Hypothesis 3a: DTI metrics for left hemisphere white matter pathways will significantly predict performance on WE measures. Specifically, the TMI will be significantly related to corticospinal tract, superior longitudinal fasciculus, anterior thalamic projection, inferior fronto-occipital fasciculus, uncinate fasciculus and cingulum bundle DTI metrics; Writing Fluency performance will be significantly related to corticospinal tract, anterior thalamic projection and cingulum bundle DTI metrics; and Spelling performance will be significantly related to corticospinal tract, superior longitudinal fasciculus and inferior longitudinal fasciculus DTI metrics.

Hypothesis 3b: Groups will differ on the relation of DTI metrics and WE performance.

Prediction of WE outcomes using fractional anisotropy

To determine if DTI metrics significantly predicted performance on WE measures, GLMs were run with mean FA for the entire sample for each of the specified pathways as the independent variables, and age-corrected standardized scores from TMI, Writing Fluency and Spelling subtests as the dependent variables, as shown in Tables 6a, 6b, and 6c. Each pathway was run separately. Age at injury was included as a covariate. To test hypothesis 3b, group was added as a main effect and a group x FA interaction term was included to determine if groups differed on the relation of FA values and WE performance. Each of these analyses was repeated with MD values in place of FA. This culminated in 26 separate GLM procedures. Table 6 includes the effect of each tract on DTI metrics as well as the effect of age on DTI metrics, in addition to Cohen's *d* of the effect of tract on metrics. For results of the same analyses run with raw scores in place of standardized scores, refer to Table 8 in the Appendix.

As shown in Table 6a, for TMI scores, no significant interaction between group and FA values was found so this term was trimmed from each of the models. For mean FA, TMI

performance was significantly predicted by the anterior thalamic radiation, corticospinal tract, inferior fronto-occipital fasciculus and uncinate fasciculus with moderate to large Cohen's *d*. TMI performance was not predicted by mean FA values in the CB or SLF; however Cohen's *d* indicated moderate effects. Age at injury was a significant covariate for each of the tracts in predicting TMI performance.

As shown in Table 6b, for Writing Fluency scores, no significant interaction between group and FA values was found so this term was trimmed from each of the models. For mean FA, performance on Writing Fluency was significantly predicted by the anterior thalamic radiation, cingulum bundle, and corticospinal tract. Age at injury was not a significant covariate in any of the models.

As shown in Table 6c, for Spelling scores, no significant interaction between group and FA values was found so this term was trimmed from each of the models. Mean FA did not predict Spelling performance for any tract. Age at injury was not a significant covariate for any of the models.

Prediction of WE outcomes using diffusivity metrics

For TMI, there was no significant interaction between group and white matter tract mean MD and so this term was trimmed. TMI performance was significantly predicted by the anterior thalamic radiation and corticospinal tract but not the cingulum bundle, inferior fronto-occipital fasciculus, superior longitudinal fasciculus or uncinate fasciculus, suggesting that FA values may be more strongly related to thematic maturity performance than MD values. The effect of age at injury was a significant covariate for predicting TMI performance for each of the models (Table 6a).

For Writing Fluency, models showed significant interaction between group and MD from the anterior thalamic radiation (p=.01) and the cingulum bundle (p=.02). Performance on Writing Fluency was not predicted by mean MD values from the anterior thalamic radiation or cingulum bundle, however. Rather, performance on Writing Fluency was significantly predicted by group and the interaction of group with each of the tracts. The effect of age at injury for both tracts was nonsignificant. There was no significant interaction between group and the corticospinal tract MD values and so this term was trimmed. Writing Fluency performance was significantly predicted by mean MD values for the corticospinal tract (lower MD predicting stronger performance) and age at injury was not a significant covariate for this model (Table 6b).

There was no significant interaction between group and white matter tract MD values for any of the Spelling models and so this term was trimmed from each model. Performance on Spelling was not significantly predicted by mean MD values for any of the hypothesized tracts nor did age at injury predict MD values (Table 6c).

Post hoc MD x group interaction analyses

As a follow-up to findings of significant interactions between mean MD values and group in Writing Fluency models, post hoc analyses examined the ability of radial and axial diffusivity values of the anterior thalamic radiation and cingulum bundles to predict Writing Fluency performance. For the anterior thalamic radiation, the interaction of group and mean radial and axial diffusivity (run separately) did not reveal significant results assuming a post hoc p-value level of 0.0125 (.05/4 comparisons; radial diffusivity p-value = .06; axial diffusivity p-value = .04). For the cingulum bundle, neither interaction significantly predicted Writing Fluency performance (radial diffusivity p-value = .07; axial diffusivity p-

value = .75), however, radial diffusivity values trended toward prediction of lower Writing Fluency scores in the TBI group.

The above analyses provide partial support for hypotheses 3a and 3b; mean FA and mean MD values for several of the hypothesized tracts significantly predicted TMI and Writing Fluency performance, but not Spelling performance.

The interaction of group x MD was significant for Writing Fluency models including the anterior thalamic radiation and the cingulum bundle, suggesting that anterior thalamic radiation and cingulum bundle radial and axial diffusivity values have predictive ability of Writing Fluency that differs between groups.

DTI metrics mediate the relation of group and WE

As a follow-up to the originally planned analyses, mediation models were run to further understand the potential independent contributions of integrity of white matter tracts shown in the above analyses to be related to TBI and/or performance on WE measures. FA was selected as the index of white matter integrity because it has been shown to be more strongly related to cognitive outcomes than MD (Ewing-Cobbs et al., 2008; Levin et al., 2008). First, the individual pathways identified in Hypothesis 3a that showed significant predictions of WE performance were examined to see if they mediated the relation between group and WE. Any pathways showing significant mediation were then tested in a multiple mediation model. The independent variable was group, and the dependent variables were scores on the TMI and Writing Fluency tasks. Spelling was not predicted by any of the white matter tracts, thus the relation of TBI and Spelling performance was not explored in the mediation analyses.

A bootstrap regression approach was used to explore the unique contributions of specific white matter tracts as mediators between the relation of TBI and WE. Analyses were run using code provided by Preacher and Hayes (2008) with age-corrected standardized scores for WE measures. Two sets of analyses were run. In the first set, the dependent variable was TMI scores for the total sample, and for the second set Writing Fluency scores for the total sample was the dependent variable. FA values for white matter tracts shown in hypothesis 3 analyses that were related to each WE outcome were included as potential mediators. The independent variable was group membership, TBI or OI. Five thousand bootstrap samples with replacement were taken for each analysis to achieve a 95% confidence interval for the indirect effect. Age at injury was included as a covariate. Pathways that showed significant mediation of the relation of group to TMI and Writing Fluency scores were then tested in a multiple mediation model.

In Figure 3, mean FA values for the anterior thalamic radiation, corticospinal tract, inferior fronto-occipital fasciculus, and uncinate fasciculus were included as potential mediators between group and TMI performance. In Figure 4, mean FA values for the anterior thalamic radiation, cingulum bundle, and corticospinal tract were included as potential mediators between group and Writing Fluency performance. For TMI (Figure 3) and Writing Fluency (Figure 4) figures, the models show hypothesized mediators entered individually in the top half of the figures, and in the bottom half of the figures the results from entering the remaining significant mediators simultaneously are shown.

Figures 3 and 4 provide the results of multiple bootstrap regression analyses. These figures illustrate the total, direct and indirect effects of TBI on TMI and Writing Fluency performance for white matter tracts. In each figure, path *a* represents the effect of group on

each tract. Path *b* represents the effect of each tract on TMI and Writing Fluency performance. The total effect is denoted by *c* and refers to the effect of TBI on TMI and Writing Fluency performance without any mediators present, or, the simple relationship between TBI and TMI/ Writing Fluency performance. The direct effect is denoted by *c'* and refers to the effect of TBI on TMI and Writing Fluency performance when mediators are present (Preacher & Hayes, 2004). Finally, the indirect effect is denoted by *ab* and refers to the "amount of mediation" (Kenny, 2012), or, the amount of the relation between TBI and TMI/ Writing Fluency performance that can be accounted for by a particular mediator. The total effect can be subdivided into the direct and indirect effects. As illustrated in Figures 3 and 4, for a potential mediator to be significant, the 95% confidence interval (CI) must not contain zero.

First, analyses were conducted with TMI as the dependent variable with anterior thalamic radiation, corticospinal tract, inferior fronto-occipital fasciculus, and uncinate fasciculus mean FA values as potential mediators. Neither the total effect of group on TMI nor the direct effects were significant (anterior thalamic radiation p-value = .82; corticospinal tract p-value = .59; inferior fronto-occipital fasciculus p-value = .70; uncinate fasciculus p-value = .77) though there was a reduction in the direct effects of the model with mediators present. When mediators were entered individually (shown in the top half of Figure 3), the anterior thalamic radiation and corticospinal tract showed significant indirect effects suggesting that they mediated the relation of group to TMI scores. The inferior fronto-occipital and uncinate fasciculi did not show significant indirect effects. The anterior thalamic radiation and corticospinal tract were then entered simultaneously in the multiple mediation model. Again, direct effects were nonsignificant (p-value =.71) and neither tract

showed significant mediation (bottom half of Figure 3). Since the total and direct effects were not significant, these findings suggest suppression effects since the anterior thalamic radiation and corticospinal tract showed significant indirect mediation when entered as the sole mediators.

For Writing Fluency, potential mediators included the anterior thalamic radiation, cingulum bundle, and corticospinal tract. The total effect of group on Writing Fluency performance was significant, though direct effects were nonsignificant (anterior thalamic radiation p-value = .41; cingulum bundle p-value = .60; corticospinal tract p-value = .20). As shown in the top half of Figure 4, when run independently, each of the tracts had significant indirect effects, suggesting they totally mediated the relation of group and Writing Fluency scores. Each of the tracts was then run simultaneously in a multiple mediation model. The total effect of each independent model was significant, with nonsignificant direct effects (p-value = .57). In this format, none of the tracts proved to significantly mediate the relation between TBI and WE above and beyond the influence of the other (bottom half of Figure 4).

In sum, there is evidence that TBI has a causal, negative impact on WE performance through disruption of integrity of several white matter tracts. Decreases in white matter integrity in specific tracts selected through theoretically-derived hypotheses were related to decreased WE performance on measures of TMI and Writing Fluency. Furthermore, several white matter tracts demonstrated total mediation of the relation between TBI and TMI and Writing Fluency performance. While significant multicollinearity of white matter tracts does not allow for contributions of individual white matter tracts to be identified in a multiple mediation model, it is clear that the white matter integrity plays an important role in execution of WE in typically developing and brain-injured children and white matter

integrity in several tracts has a causal relation with measures of WE that involve cognitive efficiency and executive processes.

Discussion

The aim of this study was to determine if cerebral white matter integrity was predictive of WE performance in children, and if the relation between white matter integrity and WE performance differed between children with TBI and children with OI. Measures of WE included Thematic Maturity, Writing Fluency, and Spelling. White matter integrity was approximated via diffusion tensor imaging using tract-based spatial statistics. Children with OI demonstrated stronger performance on Writing Fluency and Spelling than children with TBI but there was no significant difference between groups on TMI performance. Children with TBI showed decreased white matter integrity three months post-injury as compared to children with OI on all tracts as measured by lower mean FA and higher MD values. Performance on TMI and Writing Fluency one year post-injury was predicted by several white matter tracts hypothesized a priori to support these abilities. The relation of both FA and MD to WE outcomes was similar across the TBI and OI groups. However, for Writing Fluency, MD values from several white matter tracts showed differential predictive ability between groups. Post hoc analyses revealed that lower axial and higher radial diffusivity values of the anterior thalamic radiation showed modest prediction of Writing Fluency performance. Higher radial diffusivity values of the cingulum bundle trended toward predicting reduced Writing Fluency for the TBI group. Finally, mediation analyses revealed that the effect of group on Writing Fluency and TMI performance was fully mediated by FA values of white matter tracts hypothesized to support skills in these areas. Group differences

in the integrity of the anterior thalamic radiation, and corticospinal tract were related to both TMI and Writing Fluency; the latter was also predicted by group differences in cingulum bundle microstructure. Taken together, these findings suggest that TBI negatively impacts the microstructural integrity of specific pathways that support WE performance and that these microstructural alterations account for post-traumatic changes in the content and fluency of production of written narratives. To our knowledge, this is the first study to establish the role of white matter integrity in WE following pediatric TBI. These findings are relevant, firstly, in further understanding the impact of TBI on white matter integrity in children and secondly, in understanding how alterations in white matter integrity relate to academic outcomes for children with TBI.

Children with TBI showed reduced WE performance

The TBI group performed more poorly as compared to children in the OI group on two of the three measures of WE included in this study: Writing Fluency, and Spelling. This is largely consistent with previous studies that have examined the impact of TBI on skills related to WE and on WE itself (Ewing-Cobbs, Levin, Eisenberg & Fletcher, 1987; Taylor et al., 2002; Yorkston, Jaffe, Polissar, Liao & Fay, 1997; Yorkston, Jaffe, Liao, & Polissar, 1999). Groups did not differ on TMI performance, a measure of the overall quality of a written composition. Given that successful WE is supported by executive skills such as those that are commonly impacted by TBI (e.g., organization, planning; Levin & Hanten, 2005) and evidence that discourse and verbal narratives of children with TBI are decreased in the absence of the written motoric component of story construction (Chapman et al., 2006; Ewing-Cobbs, Brookshire, Scott, & Fletcher, 1998), it is somewhat surprising that groups did not differ on TMI performance, a measure of written story construction. Although both

groups performed in the average range across all measures, compared to performance on measures of Writing Fluency and Spelling, TMI performance was comparatively lower than on the other measures for both groups. In the case of the OI group, TMI performance was the only mean score below the 50th percentile, suggesting that this measure may have been more challenging as compared to the other measures. Additionally, earlier studies have demonstrated that children with OI perform comparably to children with mild TBI on measures of cognitive performance suggesting that children with OI may perform lower than uninjured counterparts (Fay et al., 2010).

In a previous study that compared children with TBI and typically developing children on TMI scores and additional measures of the quality of the spontaneous writing sample one year post-injury, group differences were most striking on measures of completeness (use of naming, story structure, narrative development and total number of words) and efficiency (number of words written divided by time taken to write total sample; Yorkston, Jaffe, Liao, & Polissar, 1999). Completeness included standard TMI scoring criteria in addition to the number of words used. Overall, our findings are similar to those presented by Yorkston et al., showing a significant correlation of injury severity with TMI performance. In terms of group differences on TMI performance, our study found moderate, nonsignificant effects, unlike Yorkston et al., who showed significant group differences on this measure. The current study included an OI comparison group instead of a typically developing control group and so it is possible that the effect of orthopedic injury (e.g., broken arm) in our comparison group may explain the lack of differentiation between groups.

The Effect of Age at Injury and Severity of Injury on WE

The question of the impact of age at injury has been examined by studies that have considered the stage of development of academic skills at the time of injury (Ewing-Cobbs, Barnes, & Fletcher, 2003; Barnes, Dennis, & Wilkinson, 1999). That is, skills that are mastered, rapidly developing, or not yet learned may show different recovery patterns following TBI than well-established skills. A study of academic skill development following TBI that utilized growth trajectory models found that children who were younger at the time of injury showed slower changes in growth over time in arithmetic and reading decoding skills (Ewing-Cobbs et al., 2004). Furthermore, children who were older at the time of injury showed a more rapid recovery of word decoding skills. Conversely, reading comprehension performance was poorer in children who were older at the time of injury and younger children showed more rapid growth of reading comprehension scores than children who were older at the time of injury. A separate study of recovery of reading skills following TBI also found that children who were younger than six and a half years of age, presumably prior to mastering or actively learning word decoding skills, were at greater risk for word decoding difficulties than were their older counterparts (Barnes, Dennis, & Wilkinson, 1999). These data suggest that age at injury may be associated with greater vulnerability of word decoding skills in younger children and of comprehension in older children. The current study found that age at injury had a moderate effect in predicting performance on TMI and Spelling, and a small effect in predicting Writing Fluency performance. TMI was negatively correlated with age at injury, independent of TBI or OI group status. That is, children who were older at the time of testing performed more poorly on this measure than younger children independent of group status. In the case of Spelling, there was a significant positive correlation (younger age at injury predicted lower performance) between age at injury and

performance. Findings of vulnerability of spelling scores in the younger children and TMI scores in the older children parallel the findings in reading. Similar findings in the current study warrant consideration in the context of the rapid development hypothesis. Younger children may show disruption of more phonologically based skills underlying word decoding and spelling that develop relatively early. Older children may show selective disruption of later-developing skills such as reading comprehension and quality of written narratives. The pattern of older age predicting poorer TMI performance may suggest that skills related to other abilities such as inferencing, complex aspects of WE (i.e., development of discourse, summarizing, planning, and editing) are in the phase of rapid development in older children whereas skills such as phonological awareness and phonemic decoding are in rapid development for younger children, explaining poorer reading outcomes for young children.

The impact of injury severity on academic outcome has yielded largely consistent results, suggesting a dose-response relationship between injury severity and academic performance, with children sustaining severe injuries showing the most significant impairments in academic functioning compared to children who sustain mild or moderate injuries (Taylor, 2004). In the current study, severity of injury was significantly correlated with TMI and Writing Fluency performance such that children with more severe injuries performed more poorly on these measures. The results of the current study are consistent with this finding; injury severity predicted TMI and Writing Fluency performance.

Children with TBI show reduced white matter integrity

Our findings in the post-acute phase show significant reductions in mean FA and increases in MD across tracts in the TBI group, consistent with the course of FA and MD recovery in the post-acute phase following pediatric TBI (Ewing-Cobbs et al., 2006a, Wilde

et al., 2006). FA values have been shown to decrease significantly across tracts and brain regions in post-acute and chronic phases (several months up to several years post-injury; Roberts, Mathias, & Rose, 2014) up to two years post-injury (Wilde et al., 2012; Dinkel et al., 2013). In the case of MD, values decrease in the acute period (Roberts, Mathias, & Rose, 2014) and increase in the post-acute and chronic phases (Roberts, Mathias, & Rose, 2014; Dennis et al., 2015).

In terms of radial and axial diffusivity, in the current study children in the TBI group had significantly higher mean radial diffusivity as compared to the OI group for all tracts, and axial diffusivity did not differ significantly between groups for any tract. These findings are consistent with other studies examining the impact of TBI on white matter in children in the post-acute and chronic phases of recovery that show greater changes in radial diffusivity than in axial diffusivity in the chronic phase (Wilde et al., 2012; Johnson et al., 2011; Dennis et al., 2015). This pattern of change is suggestive of axonal disorganization coupled with chronic demyelination (Budde, Xie, Cross, & Song, 2009; Concha, Gross, Wheatley & Beaulieu, 2006).

White matter integrity predicts WE performance

In the current study, performance on measures of WE was predicted by integrity of white matter tracts that are involved in working memory, goal maintenance, and incorporation of somatosensory information into behavior, and that are anatomically linked with frontal brain areas including dorsolateral prefrontal and ventral medial cortices (Fuster, 1988) that support top-down cognition (Miller & Cohen, 2001). Thematic Maturity performance was significantly predicted by FA values from the anterior thalamic radiation, corticospinal tract, inferior fronto-occipital fasciculus and uncinate fasciculus and MD values

from the anterior thalamic radiation and corticospinal tract. Writing Fluency performance was significantly predicted by FA and MD values from the anterior thalamic radiation, cingulum bundle and corticospinal tract. Nonsignificant, small to moderate effects of FA and MD values on Spelling performance were observed for each of the hypothesized tracts. Trends toward significance for the inferior longitudinal (.08) and superior longitudinal fasciculi (.07) and moderate Cohen's *d* were demonstrated, however.

In order to further understand the potential unique effects of individual tracts on the relation of TBI and WE, mediation analyses were utilized. As shown in Figures 3 and 4, while direct effects were not significant for any of the models, the relation between group and Writing Fluency, and group and Thematic Maturity, was fully mediated by integrity of tracts related to working memory, cognitive efficiency, and motoric functioning with anterior projections in dorsolateral, medial, and ventral aspects of the prefrontal and frontal cortices (anterior thalamic radiation and the cingulum bundle), in addition to projections from the multiple primary and secondary motor areas (corticospinal tract). These findings confirm the assertion that WE is a complex, top-down skill that, in addition to temporal and parietal connections, relies on a neuroanatomical network involving projections to frontal and prefrontal cortices. This expands upon previous literature that has established the importance of temporal, parietal, and occipital structures and projections on aspects of writing including transcription and spelling (Richards et al., 2009; Purcell, Turkeltaub, Eden & Rapp, 2011).

Microstructural integrity of the anterior thalamic radiation was related to the fluency and production of written sentences and narratives. These findings complement previous studies that have found the anterior thalamic radiation to be related to academic and cognitive functions. White matter integrity of the anterior thalamic radiation is linked with stronger

writing abilities and children with a specific learning disability in writing (i.e., dysgraphia) have been shown to have reduced white matter integrity in this tract as compared to typically developing children (Richards et al., 2015). The anterior thalamic radiation is also involved in complex aspects of executive functioning such as error monitoring (Fjell, Westlye, Amlien, & Walhovd, 2012), which is consistent with its projections to dorsolateral prefrontal areas which are involved in maintenance and coordination of motoric and sensory information toward a goal-oriented behavior (Fuster, 1988). Amongst a variety of clinical populations, the anterior thalamic radiation is consistently related to two primary areas of cognitive functioning: working memory and processing speed or, in combination, as speeded set-shifting, commonly measured by Trails B (Duering et al., 2014; Pérez-Iglesias et al., 2010). Finally, increased integrity of the anterior thalamic radiation in childhood has been related to higher verbal abilities and has been linked with stronger intellectual development into young adulthood as compared to children with lower white matter integrity in this tract (Tamnes et al., 2010).

Integrity of the cingulum bundle was related to writing fluency. Our findings are consistent with previous studies of white matter across clinical and healthy populations that have demonstrated the importance of the cingulum bundle in speeded processing including reaction time (Wilde et al., 2010, Niogi et al., 2008), memory (Wu et al., 2010), and several executive skills, including set shifting (O'Sullivan, Barrick, Morris, Clark & Markus, 2005) and selective attention (Takei et al., 2009). The cingulum bundle has even been proposed as a "backup system" to the prefrontal cortex when it is overloaded by executive tasks, such as is the case for individuals with TBI (Cazalis et al., 2011). It has also been linked directly with writing abilities in children (Richards et al., 2015), with children with dysgraphia

showing lower FA values in the cingulum as compared to typically developing children. The corticospinal tract has historically been viewed as primarily a motor-related tract, with little evidence linking its involvement in cognitive functions. However, there is neuroanatomical and cognitive evidence to suggest that the corticospinal tract may be involved in more than motor functioning along. In one study, 71% of healthy children had corticospinal tract origins in pre-and post-central gyri, and 7% of children had corticospinal tract fibers originating purely in the post-central gyrus, highlighting the non-motor origins of the tract (Kumar et al., 2009). Indeed, the corticospinal tract has origins in several post-central gyrus areas including the primary somatosensory cortex, posterior parietal lobe, and parietal operculum (Lemon, 2008), several of which have been implicated in language skills including written language. Other studies have found that the corticospinal tract may subserve semantic fluency, a verbal and executive skill (Spalletta, Piras, Fagioli, Caltagirone & Piras, 2014; Canu et al., 2013). Taken together these findings are consistent with the current study in which the corticospinal tract was significantly mediated participant's abilities to produce meaningful written text, a skill reliant on verbal, executive and somatosensory functioning.

In sum, tracts identified by this study to play a significant role in the execution of WE have involvement in executive, language and motoric domains. WE is reliant on both low level and higher level skills that are executed fluently, which is highlighted by this study in the role of overall white matter integrity in WE performance and by the specific tracts that showed involvement in this skill. Several of the tracts that were hypothesized to play a role in WE did not show significant involvement. Specifically, neither mean FA nor MD values for the cingulum bundle and superior longitudinal fasciculus were related to TOWL

performance. Mean MD inferior fronto-occipital fasciculus and uncinate fasciculus values failed to show involvement in TOWL performance as well. Mean MD for the cingulum bundle did not predict Writing Fluency performance. In terms of the mediation models, although these tracts significantly predicted TOWL performance, mean FA of the inferior fronto-occipital fasciculus and uncinate fasciculus did not mediate the relation of group on TOWL performance.

Like other higher order cognitive skills, WE is reliant on distributed neural networks that function in concert via white matter pathways (Tsapkini & Hillis, 2013; Richards et al., 2015) and that involve structures that support sustained cognitive efficiency and distribution of attention for goal-directed behavior (Golestanirad, Das, Schweizer, & Graham, 2015). In the current study, white matter disruption was demonstrated through reduced FA and increased MD values that were shown to cause reductions in WE performance through several pathways providing connections to the dorsolateral prefrontal cortex, entorhinal cortex, and primary and secondary motor cortices. The networks that these connections support are involved in multiple cognitive processes related to WE including executing functioning (Mamah et al., 2010; Cazalis et al., 2011), memory (Van der Werf, Jolles, Witter, & Uylings, 2010, Wu et al., 2010), verbal fluency (Spallletta, Piras, Fagioli, Caltagirone, & Piras, 2014) and fine motor skills (Ward et al., 2006).

WE was initially considered a bottom-up process, including skills such as phonemic-orthographic translation, letter writing, and word writing (Berninger et al., 1992). These skills were thought to be housed in discrete brain areas, namely the left occipital temporal gyrus, supramarginal gyrus, precuneus, inferior frontal cortex (Purcell, Turkeltaub, Eden, & Rapp, 2011). More recently, WE has been proposed to rely primarily on top-down processes

located in prefrontal areas such as goal-directed behavior, working memory, integration of somatosensory information, and recruitment and allocation of attention (Miller & Cohen, 2001; Golestanirad, Das, Schweizer, & Graham; 2015). Additionally, these skills are executed via several white matter pathways identified by the current study as playing significant roles in WE and that make connections to the frontal and prefrontal cortices (Coenen, Panksepp, Hurwitz, Urbach, & Madler, 2012; Wilde et al., 2010; Lemon, 2008; Dum & Strick, 1991).

Berninger and colleagues highlighted the role of skills beyond simple mechanics of writing in their tripartite mode of WE (Figure 1). This model posits that WE is executed through transcription, text generation, and executive functioning (Berninger, Abbott, Abbott, Graham & Richards, 2002) via a network of 11 distinct brain areas including the cingulate, and parietal and temporal areas bilaterally primarily for transcription (Richards et al., 2009). Importantly, Berninger's model holds working memory as the central cognitive process through which WE is executed. This is quite relevant in the case of children with TBI, given the high incidence of impairments in working memory following pediatric traumatic brain injury (Gorman et al., 2011; Levin et al., 2002, Levin et al., 2005).

Researchers have examined the impact of TBI on the relation between white matter tract integrity and reading performance and have found that for children with TBI, lower mean FA of the cingulum bundle predicted lower reading fluency (Johnson et al., 2015). These findings are consistent with the current study and suggest that the cingulum bundle is involved in fluent communication in distributed neural networks to execute higher order skills such as learned academic abilities like reading and writing. Dissociation between reading and writing pathways is also demonstrated in Johnson et al., wherein untimed and

time reading performance following pediatric TBI was predicted by the superior longitudinal fasciculus. In the current study the superior longitudinal fasciculus was not significantly related to TMI performance.

This finding is echoed in the educational literature, wherein reading versus writing systems posses distinct neural pathways and networks (Richards et al., 2015). In a recent study, children identified as having dyslexia or dysgraphia have demonstrated "functional over-connectivity", suggesting less efficiency necessitating greater activation of reading and writing pathways. Children with dysgraphia showed greater activation of a written language connectome as compared to typically developing children or children with dyslexia. The identified written language connectome included the inferior fronto-occipital fasciculus and the left superior longitudinal fasciculus, the former of which significantly predicted WE performance in the current study (Richards et al., 2015). While the network of written language overlaps considerably in typically developing children as well as children with developmental and acquired (i.e., as a result of TBI) dysgraphia, the role of cognition appears to vary between the latter two clinical populations. Developmental dysgraphia is argued to be defined by impairments in the subword and word level of writing and independent of impairments in related cognitive processes such as idea generation (Richards et al., 2015). Conversely, in the TBI population, impairments in the quality of WE appear to be related to reductions in orthographic fluency (Harik et al., 2015) and the current study supports the neuroanotomical basis for these impairments. This contrast suggests that TBI disrupts the connectome underling cognitive skills related to writing fluency that thereby negatively impact one's ability to produce WE.

Summary of Findings

In sum, our data revealed that several white matter tracts contributed uniquely to specific WE tasks. These data suggest that WE is supported by white matter tracts involved in executive, verbal, and motoric skills and that these white matter tracts support fluent execution of these skills in concert. There is also evidence that age at injury predicts performance on WE outcomes with children who are younger at the time of injury performing more poorly on Spelling, an earlier developing skill, and children who are older at the time of injury performing more poorly on TMI, a more complex and later developing skill, lending support for the rapid development hypothesis. Building upon a previous study that examined the cognitive processes that contributed to WE following TBI and found that orthographic fluency was the strongest predictor of the quality of WE (Harik et al., 2015), these data provide further evidence for the role of fluency and cognitive efficiency in WE. The white matter tracts that were identified by this study as having an important role of WE execution have been shown to be related to a variety of executive functions that support efficiency including set-shifting and error monitoring. On a larger scale, these findings contribute to a growing body of literature that encourages scientists and clinicians to consider the impact of TBI on white matter integrity as it relates to cognition.

Future Research

The aim of this study was to understand the impact of TBI on WE and how white matter integrity is related to WE in this population. Individuals with TBI represent a heterogeneous group with individuals sustaining a wide range of severity of injuries that produce highly variable effects. The current study separated participants by presence of TBI or not. Further research in separating individuals with TBI based on severity of injury would allow for more precise understanding of the impact of TBI on WE, and how the function of

white matter integrity differentially relates to WE. This would be achieved through collecting large enough sample sizes within each category of injury severity to provide enough power for such analyses.

Our study examined white matter integrity at one time point along the recovery trajectory. As stated previously, the impact of TBI appears to have differential effects on white matter over time that produces variable changes in white matter metrics. We were able to capture the impact of TBI on seven white matter metrics at approximately three months post-injury. This information was used to predict performance on cognitive tasks at one year. Due to potential changes in white matter structure over time, examining the predictive ability of white matter integrity for cognitive outcomes and multiple times points would be an intriguing area of future research. Specifically, comparing axial and radial diffusivity values over time would provide a further understanding of pathology and recovery of white matter following pediatric TBI.

Finally, the current study highlights the need for continued research in the methodology of DTI. While great gains in understanding the role of white matter in cognition and neuropathology have been made, the need for refinement of this technique remains. Our study was able to identify the influence of specific white matter tracts on WE performance. However, findings were limited by multicollinearity of tracts, particularly when used in mediation analyses. It is possible that this finding is an artifact of our methodology that did not allow for division of white matter tracts based on variation of white matter metrics. In the case of the cingulum bundle, for example, heterogeneity of metrics such as radial diffusivity across regions has allowed researchers to parse out subdivisions of this prolific white matter tract and to appreciate the implications for neuropsychological

research that demonstrate the involvement of subdivisions of white mater tracts in distinct cognitive processes (Jones, Christiansen, Chapman, & Aggleton, 2013). Further research in this domain will enhance the accuracy of deductions from data such as those presented here.

Future studies in this realm will benefit from increased sample size with greater heterogeneity of severity of injury in TBI groups. Incorporation of a greater variety of WE measures would allow for greater generalization and validity of findings. Finally, implementation of neuroimaging techniques that allows for greater accuracy in identifying white matter tracts will allow for more specificity in identifying the role of particular white matter tracts in mediating WE.

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Table 1. Demographic Characteristics for Traumatic Brain and Orthopedic Injury Groups

Demographic Variable		Group		Statistic (df) (p)	ES
		TBI (*n*=35)	OI (*n*=28)		
Age at injury in months, M (SD)		137.5 (32.72)	117.4 (31.22)	t (61) =-2.49 (.024)	0.65
Age at assessment in months, M (SD)		150.4 (32.68)	130.6 (31.96)	t (61) =-2.42 (.021)	0.63
Males, *n* (%)		25 (71.46%)	15 (53.61%)	χ^2 (1)= 2.14 (.143)	0.18
Ethnicity				χ^2 (2)= 0.88 (.652)	0.12
Ethnic Categorization, *n (%)*	Caucasian/ Asian	16 (45.73%)	10 (35.73%)		
	African American	8 (22.82%)	9 (32.14%)		
	Hispanic/ Latino	11 (31.44%)	9 (32.13%)		
Maternal education in years				χ^2 (3)= 2.92 (.401)	0.33
Years of education, *n (%)*	≤8	6 (17.12%)	1 (3.57%)		
	High School	12 (34.42%)	11 (39.29%)		
	Bachelor's	11 (31.43%)	10 (35.71%)		
	Graduate	6 (17.13%)	6 (21.43%)		

Note. Based on independent-samples t-test and chi square analyses. M= mean, SD= standard deviation.

Table 2. Injury Characteristics for Brain Injury and Orthopedic Groups.

	Group			
Injury Variable	TBI (*n*=35)	OI (*n*=28)	**Statistic (df) (p)**	**ES**
Days since injury, M (SD)	393.0 (40.42)	401.4 (100.5)	t (61) =0.42(.684)	0.14
Days to DTI scan (days)	88.86 (38.59)	73.27 (22.81)	t (61) =2.02 (.054)	0.51
Injury Severity Score, M (SD)	22.3 (10.86)	6.3 (2.50)	t (61) =-8.54 (<.010)	2.75
Mechanism of injury, *n* (%)			χ^2 (6)=24.38 (<.011)	0.62
Motor vehicle collision	19 (54.30%)	2 (7.07%)		
Auto-pedestrian collision	7 (20.03%)	7 (25.04%)		
Fall	6 (17.12%)	11 (39.33%)		
Other	3 (8.55%)	8 (28.56%)		
Lowest total Glasgow Coma Score (GCS), *n*				
3-8	23			
9-12	9			
13-15	3			
Lowest motor GCS score, *n*				
1-2	19			
3-4	6			
5-6	10			
Days of Impaired Consciousness, M (SD)	4.6 (6.92)			
Severity Grouping, *n**				
Complicated-Mild	3			
Moderate	9			
Severe	23			

Note. Based on independent-samples t-test and chi square analyses. M= mean, SD= standard deviation.* Severity of brain injury determined by lowest motor GCS score and CT scan on admission.