RECOVERY OF WORKING MEMORY FOLLOWING PEDIATRIC TRAUMATIC BRAIN INJURY: A LONGITUDINAL ANALYSIS

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

Stephanie A. Gorman

December, 2012

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ABSTRACT

The purpose of this dissertation was to investigate the developmental trajectories of verbal and visual-spatial WM in children following traumatic brain injury, and to determine how age at injury and injury severity affects growth. As part of a larger assessment, the sample included 42 children with severe head injury, 13 children with complicated mild-moderate head injury, and 47 children with orthopedic injury. Longitudinal data was collected at 2, 6, 12 and 24 months post-injury. A multivariate approach to individual growth curve modeling was utilized and the data was centered at 12 months post-injury. Results indicated that at 12 months post-injury, children in all three injury groups with varying age at injury did not differ significantly on verbal or visual-spatial working memory performance. The injury groups did not differ on working memory performance when age at injury was held constant. A significant rate of change (slope) by age at injury by injury group interaction for verbal working memory (and a similar pattern for visual-spatial working memory) revealed that children injured at a younger age with more severe injuries demonstrated the slowest working memory growth, but that as age at injury increased, older children with severe injuries exhibited faster growth. A significant positive relation was found between level of performance on verbal and visual-spatial working memory tasks at 12 months post-injury, but not for rate of growth. This study lends further support to an early vulnerability hypothesis, which suggests that children brain-injured at a younger age are more vulnerable to cognitive deficits.

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Recovery of Working Memory Following Pediatric Traumatic Brain Injury: A Longitudinal Analysis

Traumatic brain injury (TBI) is one of the most common causes of acquired disability in children, and significantly impacts the development of numerous cognitive skills. It has been estimated that between the years 1995 and 2001, 475,000 Caucasian and African American children between the ages of 0 and 14 years sustained a TBI (Langlois, Rutland-Brown, & Thomas, 2005). Other estimates suggest that 250 per 100,000 children sustain a TBI each year (Kraus, 1995). TBI can negatively impact the development of a variety of cognitive skills; in particular, working memory (WM) (Conklin, Salorio, & Slomine, 2008; Ewing-Cobbs, Prasad, Landry, Kramer, & DeLeon, 2004; Gorman, Barnes, Swank, Prasad, & Ewing-Cobbs, 2012; Levin et al., 2002; Levin et al., 2004; Roncadin, Guger, Archibald, Barnes, & Dennis, 2004). Because WM has been implicated in the acquisition of academic skills such as reading, reading comprehension, and certain aspects of mathematics (reviews in Raghubar, Barnes, & Hecht, 2010; Swanson & Alexander, 1997; Swanson & Ashbaker, 2000; Swanson & Berninger, 1995; Swanson & Jerman, 2006; Swanson, Zheng, & Jerman, 2009), it is possible that deficits in WM resulting from TBI can lead to poorer academic functioning and social cognition (Dennis, Agostino, Roncadin & Levin, 2009). Thus, it is important to understand the developmental course of growth of WM following TBI, as well as how injury-related variables such as age at injury and injury severity affect growth. However, relatively few studies have examined growth of WM following pediatric TBI using statistical approaches that model characteristics of change (Levin et al., 2004).

To address these gaps in the literature, the aim of the present study is to characterize the growth pattern of verbal and visual-spatial domains of WM following head injury using

age at injury and injury severity as predictors in a sample of children with complicated mild-moderate, and severe TBI as compared to a sample of children with orthopedic injuries not involving the head or face.

Working Memory

Working memory (WM) can be conceptualized as the mental workspace in which task-relevant information is monitored, processed, and maintained in order to respond to immediate environmental demands (Baddeley & Logie, 1999). According to the multicomponent model of Baddeley (1996), WM consists of a central executive (responsible for selective attention, divided attention, switching of attention, and retrieval of information from long term memory), a phonological loop (a temporary storage system that briefly maintains acoustic information unless refreshed by rehearsal), and a visuo-spatial sketchpad, (analogous to the phonological loop, except that it maintains visual information). More recently, the episodic buffer was added to Baddeley's model (Baddeley, 2002), which is proposed to temporarily maintain and manipulate integrated information from the phonological loop, visuo-spatial sketchpad and long-term memory. It is suggested that the episodic buffer is controlled by the central executive (Baddeley, 2002).

Working Memory Development. Diamond (2002) found that the development of the maintenance component of WM begins as early as 7 months of age. Diamond utilized a search task in which a desirable object was initially placed in one of two wells, and in subsequent trials the location of the object was switched. Children younger than 7 months continued to search for the object in the initial well, while a much longer delay was required to elicit the same mistake in children between 7 and 12 months of age. This suggested that with increasing age, children were able to store information in memory for a longer duration.

The development of the three components of the Baddeley (1996) WM model was investigated by Gathercole, Pickering, Ambridge, and Wearing (2004), in children ages 4 through 15. The authors used the Working Memory Test Battery for Children (Pickering & Gathercole, 2001). Three of the tasks utilized were verbal maintenance tasks associated with the phonological loop, three tasks were visual maintenance tasks associated with the visuo-spatial sketchpad, and three tasks were complex memory tasks involving both maintenance and manipulation of verbal material, associated with both the central executive and the phonological loop. The authors found that all three components (the central executive, phonological loop and visuo-spatial sketchpad) were established by 6 years of age, and the maintenance capacity of each component increased linearly between age 4 through adolescence. Linear increases in the complex memory tasks involving both maintenance and manipulation were observed beginning at age 6.

The development of maintenance and manipulation components of verbal and visual-spatial memory spans were directly compared by Isaacs and Vargha-Khadem (1989) in a cross-sectional study, using the Digit Span subtest of the WISC-R (Wechsler, 1982) to measure verbal memory span, and Corsi Blocks (Corsi, 1972) to measure visual-spatial span. Forward and Backward tasks of Digit Span and Corsi Blocks were examined, with the Forward measures assessing maintenance and the Backwards measures assessing both maintenance and manipulation. The sample included 288 children between the ages of 7 and 15, with an equal number of children at each age level. The authors found a significant effect of age for each measure, with Digit Span Forward and Backward increasing gradually between the ages of 7 and 15. Blocks Forward had the most significant increase between the ages of 9 and 10, while Blocks Backward increased most significantly between the ages of 7

and 8. A significant effect of task type was also found, with subjects performing better on the verbal memory span task across all age groups. There was not a significant interaction between task type (verbal or visual-spatial) and age, suggesting that developmental increases in memory span were similar for both verbal and visual-spatial material. Interestingly, the effect of the order of presentation (Forward or Backward) was only significant for Digit Span, with better performance on Digit Span Forward. This suggests that the order of information may be extracted in a fundamentally different manner from spatial memory than from verbal memory (Gathercole, 1998). This might also suggest that maintaining spatial locations in short-term memory draws more heavily on central executive processes because there is not a well-practiced rehearsal mechanism for spatial information, as there appears to be for verbal information (Baddeley, 1996). Thus, visual-spatial short term memory and visual-spatial WM might draw on similar processes, making it more difficult to detect differences in performance as compared to differences detected between verbal short term and verbal WM measures (Miyake, Friedman, Rettinger, Shah, & Hegarty, 2001).

The age and task main effect findings of Isaacs and Vargha-Khadem (1989) were extended by Nichelli, Bulgheroni, and Riva (2001). Nichelli et al. (2001) administered Digit Span and Corsi Block tasks to a sample of children ranging in age from 5 years, 4 months to 13 years, 6 months, a wider age range than the sample of Isaacs and Vargha-Khadem (1989). Nichelli et al. (2001) found a slow, constant improvement in performance on the two measures, with Digit Span having an advantage of 1.5 verbal span items over visual span items. The authors attribute the superior performance on the verbal span measure to the use of different processing channels and learned knowledge. That is, verbal memory strategies

may be more frequently used in school, resulting in superior performance on the verbal memory span task.

Neural Substrates of Working Memory. Numerous studies have investigated the underlying neural substrates of WM, with most studies determining that the frontal lobes are most strongly associated with WM (Huttenlocher, 1990; Loose, Kaufmann, Auer, & Lange, 2003; Mellers et al., 1995; Mrzlijak, Uylings, van Eden, & Judas, 1990). Several of these studies are discussed briefly below (for an extensive review see Collette & Van der Linden, 2002).

In one of the first studies to investigate the neural substrates of verbal WM using functional imaging (positron emission tomography), Petrides, Alivisatos, Meyer, and Evans (1993) found strong activation of the dorsolateral prefrontal cortex (DLPFC) bilaterally during two experimental conditions requiring both maintenance and manipulation of a sequence of numbers. A similar experiment was conducted by Petrides, Alivisatos, Evans, and Meyer (1993) using non-verbal material and the authors found strong activation of the mid DLPFC, anterior cingulate and posterior parietal cortex.

Another study implicating DLPFC in WM was conducted using functional magnetic resonance imaging (fMRI) in adult participants (Cohen et al., 1997). Participants were shown sequences of 14 consonants on a computer screen, and were later asked to press a button when shown previously occurring target items. The authors found sustained activation of DLPFC during performance of the task even following delays of 20 seconds. In an effort to confirm that this pattern of activation was the result of processes specific to WM, a follow-up study was conducted (Barch et al., 1997) in which the authors independently manipulated tasks with memory-demanding conditions, and other tasks that were difficult but did not rely

on memory processes. Barch et al. (1997) found that DLPFC was activated in memory-demanding conditions only, lending support to the previous finding that DLPFC underlies WM processes.

In a study by Crone, Wendelken, Donohue, van Leijenhorst, and Bunge (2006), the authors utilized event-related fMRI to determine brain regions associated with developmental improvements in maintenance and manipulation in a WM task. The WM task required participants to name three objects that appeared on a screen, then mentally rehearse the names of these objects either in the same, or in the reverse order in which the objects were presented. Participants were then shown a probe object and asked to indicate whether the object had appeared first, second or third in the forward or backward sequence. The authors examined the following age groups: 8-12, 13-17 and 18-25 years. The authors found that increased activity of the right and superior bilateral parietal cortex DLPFC (areas that are not sufficiently developed in the youngest age group) was associated with the ability to successfully manipulate information within memory. These findings were confirmed by a more recent study (Jolles, Kleibeuker, Rombouts & Crone, 2011) which also found that increased activation of the right DLPFC was associated with improved performance on a verbal WM task requiring maintenance and manipulation.

Effects of TBI on WM and WM Neural Substrates

Neuropathology of TBI and Frontal Lobe Vulnerability. There are two major classes of TBI: penetrating head injury and closed head injury. Because the sample included in this study consisted of children with closed head injuries, this discussion will focus on the neuropathology of closed head injury in children. With closed head injury, the brain is not penetrated, but is shaken and twisted within the skull cavity as a result of high-velocity

acceleration/deceleration forces. This can result in multiple injury sites (both coup and countercoup injuries) and traumatic axonal injury that results from rotational forces that cause white matter to stretch and tear. Compression and deformation of the skull can lead to contusion. Areas that are particularly vulnerable to contusion are discussed in detail below. Traumatic axonal injury is particularly common in the junctions between gray and white matter, the basal ganglia, hypothalamus, cerebellum and brain stem, corpus callosum, and frontal and temporal poles (Amacher, 1988; Gale, Johnson, Bigler, & Blatter, 1995; Pang, 1985). Secondary injuries resulting from closed head injury include elevated levels of glutamate and aspartate, which can disrupt cell function and result in cell death (Novack, Dillon, & Jackson, 1996), hematoma, cerebral edema, and increased intracranial pressure. These secondary injuries are associated with poorer outcome (Quattrocchi, Prasad, Willits, & Wagner, 1991).

The frontal lobes are the brain region most vulnerable to injury in TBI (Bigler, 1990), making WM particularly vulnerable to disruption. This is likely due to the fact that the frontal lobes are the largest of the four cerebral lobes, and this region is near bony protruberances of the skull (Graham, Gennarelli, & McIntosh, 2002). That is, the frontal bone curves over the anterior frontal lobe, essentially cupping this region of the brain (Bigler, 2007). TBI can lead to impact between the frontal lobe and anterior cranial fossa resulting in deformation and cortical contusion and disruption of white matter pathways of the frontal lobes (Oni et al., 2010). Several studies have used neuroimaging techniques to compare frontal lobe regions in children following TBI, with comparison children. These studies are discussed below.

Wilde et al. (2005) utilized MRI volumetric analyses to investigate brain volume differences between children who had sustained TBI, and a comparison group of children. The authors looked not only at whole brain volume, but also at prefrontal, temporal and posterior brain regions. Sixteen children with moderate to severe head injury and sixteen comparison children were examined. Volumetric analyses revealed significantly reduced whole brain, ventromedial frontal, superior medial frontal, lateral frontal and temporal lobe volume in the children with TBI. The authors also found a significant group difference in gray and white matter in the superior medial and ventromedial prefrontal regions, white matter in the lateral frontal region and gray matter, white matter and cerebrospinal fluid in the temporal region (Wilde et al., 2005). Additionally, the authors examined the effects of diffuse and focal brain injury to the frontotemporal region. They found that gray matter loss of the frontal region was primarily attributable to focal injury, and white matter loss in both frontal and temporal regions was related to diffuse and focal injury. These findings suggest that frontotemporal regions are particularly vulnerable to disruption resulting from TBI.

A more recent study by Oni et al. (2010) used diffusion tensor imaging (DTI) to compare white matter integrity in 46 children with moderate to severe TBI, 3 months post-injury, with 47 children with extracranial orthopedic injuries. Fractional anisotropy (which measures the restriction of diffusion of water in white matter), apparent diffusion coefficient (denotes speed of water diffusion in all directions) and radial diffusivity (denotes the direction and speed of diffusion perpendicular to the axon) were compared between the two groups (Oni et al., 2010). Results revealed reduced frontal lobe fractional anisotropy, increased apparent diffusion coefficient and increased radial diffusivity in the children with TBI, reflecting white matter damage. These findings are consistent with the adult literature

and may reflect damage caused by traumatic axonal injury (Buki & Povlishock, 2006; Povlishock & Katz, 2005).

Effects of TBI on Working Memory. Numerous studies have demonstrated that pediatric TBI has a detrimental effect on WM. Many of these studies have focused on verbal WM (Hanten, Levin, & Song, 1999; Mandalis, Kinsella, Ong, & Anderson, 2007), with Digit Span (Conklin et al., 2008) and N-back tasks (Levin et al., 2002; Levin et al., 2004) frequently used to measure maintenance and manipulation in verbal WM. Furthermore, studies that have considered severity of injury generally find that more severe injuries are related to greater deficits in WM (Levin et al., 2002; Levin et al., 2004; Roncadin et al., 2004). Studies that have examined the effect of age at injury on cognitive outcomes have found poorer outcomes for children injured at a younger age in areas such as attention, expressive language, and reading (Anderson & Moore, 1995; Anderson, Morse, Catroppa, Haritou, & Rosenfeld, 2004; Barnes, Dennis, & Wilkinson, 1999; Ewing-Cobbs et al., 1998; Taylor & Alden, 1997). However, the research on the effect of age at injury on WM is not entirely consistent. Roncadin et al., (2004) found that a younger age at injury predicted poorer item maintenance and load in moderately injured children on a verbal WM task. However, Gorman et al., (2012) found that age at injury was a significant predictor of a visual-spatial WM task with both maintenance and manipulation components, but not of an analogous verbal WM task. Thus, further investigation of the effects of age at injury on WM, in particular growth of WM, is necessary. Furthermore, very few studies have examined both verbal and visual-spatial WM, and few studies have utilized a longitudinal (rather than a cross-sectional) design.

The effects of TBI on both verbal and visual-spatial WM were investigated by Gorman et al. (2012), utilizing measures of verbal and visual-spatial WM with parallel processing requirements. The effect of age at injury was also examined, and was previously discussed. The performance of 73 children who had sustained TBI was compared with that of 30 children with orthopedic injuries and 40 children without injury. Children in the TBI group were examined between 2 and 12 years post-injury. Children with TBI performed more poorly than children in both comparison groups, and there was not a significant effect of the type of material (i.e. verbal or visual-spatial). The results suggested that both verbal and visual-spatial WM were significantly impacted by TBI to a similar extent. That is, TBI did not have a greater impact on one modality of WM. However, it is not known whether verbal and visual-spatial WM exhibit a similar pattern of growth following injury.

One study that examined verbal WM longitudinally using growth curves was conducted by Levin et al. (2004). The authors administered an N-back task at 1, 3, 6, 12, and 24 months post-injury. The percentage correct score on the N-back task was compared over time in children with mild, moderate and severe injuries. WM performance of participants in all three injury severity groups improved over the first year post-injury. However, continued improvement through the second year post-injury was only demonstrated in children with mild and moderate injuries, while the performance of children with severe injuries actually declined between 12 and 24 months post-injury. That is, children with severe injuries obtained a lower percent correct score at 24 months than they obtained at 12 months. The authors attributed this finding to decreased frontal lobe gray matter volume in severely injured children (Berryhill et al., 1995) or to disruption of white matter development as measured by volumetric and diffusion tensor imaging (Ewing-Cobbs et al., 2008; Levin et

al., 2000; Levin et al., 2008; Wilde et al., 2005). The findings of this study are discussed in further detail below, but first a discussion of multilevel modeling and growth curves is necessary to comprehend the advantages of such an approach.

Growth Curve Modeling

Growth curve modeling is a type of multilevel model in which longitudinal data are analyzed and changes in an outcome over time are modeled using potential growth patterns (Field & Miles, 2010). Multilevel modeling is a statistical approach to analyzing hierarchical data. Hierarchical data contain variables that are clustered, or nested within another variable (Field & Miles, 2010). The hierarchy of this type of data is that time points (Level 1 variables) are nested within people (Level 2 variables). Essentially, it is a way of analyzing repeated measures data with a hierarchical structure (Field & Miles, 2010) that also allows for random effects. With four time points, as is the case in the current study, three random effects can be considered- intercept, slope, and curvature (type of growth pattern, e.g. linear, quadratic or cubic).

The current study investigated the growth pattern of WM in children following head injury. Children were examined at four time points following injury, and WM data at each time point was collected. In this case, the data taken at each time point was nested within each child. This suggested that the data collected at the four time points was likely to be more similar within children than between children. Thus, the data were not independent and within subject variance was likely to be smaller than between subject variance. This violated the assumption of independence of observations of a traditional analysis of variance, and, while a repeated measures analysis of variance might be able to accommodate a lack of independence when a polynomial trend is used, it assumes a spherical variance-covariance

matrix and it deletes cases listwise when data are missing, making typical analysis of variance not the optimal approach when working with hierarchical data. Some advantages of multilevel modeling are that it does not assume independence of observations and includes a hierarchical data structure, and does not require listwise deletion of missing data. In the aforementioned example, each time point was nested within the child and was considered a Level 1 variable, while the participant was considered a Level 2 variable (hence the hierarchical structure).

Multilevel modeling is essentially an extension of a regular regression model, but in a multilevel model, estimated parameters are not assumed to be fixed. This is yet another advantage of the multilevel model approach because it may not always be feasible to assume that coefficients are fixed for all subjects and all clusters. Consider the implications of including random intercepts and slope in the aforementioned example. Allowing the intercept to vary for each time point, depending on the child the data is collected from, allowed for the consideration of the contextual effect of each child (e.g. of being "Jimmy" versus being "Susie"). Allowing the slope (which is the change in WM performance per one unit change in time) parameter of the exact time since injury (in days) to vary allowed the researcher to consider whether there was a different relation between time since injury and WM. Thus, there was no assumption of homogeneity of regression slopes. Growth curve modeling also allows for a multivariate component, permitting the examination of multiple outcome variables. This allowed for the consideration of verbal and visual-spatial WM in the current dataset.

Growth curve modeling is but one approach to measuring change. Several approaches to measuring change were discussed by Francis, Fletcher, Stuebing, Davidson, and

Thompson (1991). The authors discussed the disadvantages of both measuring change by calculating a difference score, and using more traditional approaches such as analysis of variance using polynomial trend analysis, and the advantages of using individual growth curves. Some of the primary problems with using a difference score calculation to measure change are: it does not consider the rate of change between the two time points, the inverse relationship between the reliability of the difference score and the correlation can only be interpreted reasonably when individuals do not change at different rates (not likely to be the case), and measurement error creates a tendency for the observed correlation to underestimate the real parameter of interest, (i.e. the population correlation between true initial status and true change) (Willett, 1988). Thus, Francis et al. (1991) do not recommend using difference scores as a way to measure change.

Within the field of psychology, many researchers tend to analyze group mean differences, without considering change as a characteristic of the individual (Francis et al., 1991). Such analyses include mixed model ANOVA, the MANOVA approach to repeated measures, ANCOVA, residualized change analysis, and analysis of covariance with reliability correction (ANCOVARC) (Francis et al., 1991). A polynomial trend analysis can be used with ANOVA or MANOVA, which allows change to be viewed as a continuous process. However, this approach is limited by the fact that all subjects within the sample must have data at each measurement time point, and the spacing between time points must be the same for all subjects. Furthermore, this type of analysis considers within-group differences in intraindividual change as error, and is unable to incorporate continuous predictors of growth (Francis et al., 1991).

Finally, Francis et al. (1991) discuss the advantages of an individual growth model approach to measuring change. First, this approach is flexible and considers individual change and the correlates of change. Because parameters of each growth curve describe individual change, subject characteristics correlating with change relate systematically to the parameters of the model. Furthermore, Level 1 and Level 2 equations incorporated in the model allow the researcher to consider questions about both individual and group change (Francis et al., 1991). Growth curve analysis is also well-suited to work with more than two time points (which is the case in the current study), which allows the researcher to estimate how reliably change has been measured, improving the estimated correlation between subject characteristics and true change (Willett, 1988). Finally, one of the foremost advantages to utilizing an individual growth approach is that there need not be data at each time point for each subject. As long as there is enough data to estimate the specified Level 1 parameters, then an individual growth trajectory can be created from the data points that are available. This is particularly relevant to post-injury data analyses, in which it is not always possible to obtain data at each specified time point for all subjects.

Using Growth Curves and Multilevel Modeling to Assess Change Post-TBI in Children

Growth curve modeling has been used to look at level of performance and rate of growth in several academic and cognitive skills including academic achievement (Ewing-Cobbs et al., 2004), visual-spatial and motor skills (Thompson et al., 1994), word fluency (Levin, Song, Ewing-Cobbs, Chapman, & Mendelsohn, 2001), declarative memory (Yeates et al., 2002) and WM (Levin et al., 2004). Several of these studies found that younger children with more severe injuries demonstrated a slower rate of growth over time relative to younger children with milder injuries and older children with severe injuries (Ewing-Cobbs

et al., 2004; Levin et al., 2001; Thompson et al., 1994). However, Yeates et al. (2002) found a faster rate of growth between baseline and 6 months post-injury in children with severe injuries, with no age at injury interactions. Children with more severe injuries also tended to have lower levels of performance (Ewing-Cobbs et al., 2004; Yeates et al., 2002), with discrepancies greater in children injured at an older age with regards to arithmetic (Ewing-Cobbs et al., 2004). Ewing-Cobbs et al. (2004) also found a negative relation between arithmetic level of performance and rate of growth, suggesting that children with lower levels of performance exhibited greater rates of growth.

To date, there is only one study that has utilized a growth curve approach to WM (Levin et al., 2004). The statistical analyses utilized in that study will now be discussed in detail. Using a linear mixed model approach to model growth, intercept and slope were set as Level 1 random effects and curvature (degree of acceleration/deceleration of growth) was fixed. Time since injury was centered at 12 months post-injury. Injury severity was included as a Level 2 predictor. Memory load, research center and the two-way interaction of these two variables were included as covariates. Results revealed that WM performance increased in all three severity groups (mild, moderate and severe) over the first 3 months post-injury. However, as previously stated, continued improvement was only observed from 12-24 months post-injury in the mild and moderate injury groups. Severely injured patients tended to decline during this same period. At 12 months post-injury slope did not differ by severity groups, while curvature differed significantly. The mild group showed slight acceleration, while the severe group demonstrated significant deceleration. The present study seeks to extend these findings.

Rationale for the Present Study

Many studies demonstrate that WM is negatively impacted by pediatric TBI, with evidence suggesting that both verbal and visual-spatial WM are impacted similarly (Gorman et al., 2012). However, very few of these studies have looked at growth of WM longitudinally to examine recovery post-injury, and only one has taken an individual growth modeling approach (Levin et al., 2004), which has numerous advantages. The results of Levin et al. (2004) suggested that longitudinal growth patterns differ depending on injury severity, but to date, no study has replicated or extended the results of Levin et al. (2004), and no study has considered how age at injury might affect the developmental trajectory of WM. Gaining a better understanding of the recovery of WM following TBI is of value not only empirically, but also clinically. First, it has been suggested that degenerative brain changes may underlie differences in WM growth in children with injuries of varying severities (Levin et al., 2004). This study may provide further support for this idea, spurring future research to investigate growth of WM and neuroimaging data simultaneously to more directly examine this possibility, as well as to consider how degenerative brain changes in children injured at different ages might affect growth of WM. In terms of real-world significance, because WM is related to successfully completing multi-step instructions (frequently given by parents and teachers), and has been implicated in academic achievement in reading (Baddeley, Eldridge, & Lewis, 1981; Christopher et al., 2012) and mathematics (Bull & Scerif, 2001; Raghubar et al., 2010; Swanson, 1999; Swanson & Jerman, 2006), then understanding the developmental trajectory of WM in children with TBI of varying severities and varying age at injury can aid clinicians in helping parents and teachers in setting realistic expectations for children following head injury, as well as identifying children who may be

at risk for late academic difficulties in the years following a TBI (Levin et al., 2004). Furthermore, academic support could be provided to minimize the impact of WM difficulties on learning.

The aims of the current study were 1) to use individual growth curve modeling to evaluate the pattern of WM growth in children with complicated mild-moderate and severe head injury, as compared with a sample of children with orthopedic injuries, using a multivariate approach to examine both verbal and visual-spatial WM, and 2) to determine whether the growth pattern was affected by age at injury and injury severity. With regards to fixed effects group differences, I hypothesized that (1a) children injured at a younger age with severe injuries would demonstrate the poorest level of performance in both verbal and visual-spatial WM at 12 months post-injury (reflected by a significant three-way intercept by age at injury by injury group interaction); (1b) if a significant three-way interaction was not found, it was hypothesized that there would be a significant two-way intercept by injury group interaction, with children with more severe injuries having a poorer level of performance, while controlling for age at injury. In addition, I hypothesized that (2a) children injured at a younger age with severe injuries would demonstrate the slowest rate of growth in both verbal and visual-spatial WM at 12 months post-injury (reflected by a significant three-way slope by age at injury by injury group interaction); (2b) if a significant three-way interaction was not found, I hypothesized that there would be a significant two-way slope by injury group interaction, with children with more severe injuries demonstrating a slower rate of growth, while controlling for age at injury. For the pattern of change, I hypothesized that (3) the growth patterns of children with more severe injuries would demonstrate curvature that decelerated over time (reflecting initial improvements in performance, followed by a

performance decline), while controlling for age at injury (reflected by a significant two-way curvature by injury group interaction). With regards to random effects, I hypothesized that (4) there would be a positive relation between intercepts (level of performance) of verbal and visual-spatial WM, such that individuals with better performance on verbal WM would perform better on the visual-spatial measure; (5) that there would be a positive relation between slopes (rate of growth) between the two WM measures, suggesting that individuals with greater rates of growth on the verbal measure would have greater rates of growth on the visual-spatial measure, and (6) that there would be a negative relation between slope and intercept, suggesting that as level of performance improved, rate of growth would slow.

Methods

Participants

Participants included 42 children who sustained severe TBI, 13 children who sustained complicated mild-moderate injuries, and 47 comparison children with orthopedic injuries. Participants were evaluated longitudinally at approximately 2, 6, 12 and 24 months post-injury. Children were recruited from a prospective cohort injured from 2004-2007. Inclusionary criteria for children in the TBI groups were: 1) TBI resulting from acceleration-deceleration or blunt impact injuries caused by vehicular accidents, falls, or impact with a blunt object, 2) moderate and severe TBI, defined as the lowest post-resuscitation GCS score of 3-12, and complicated mild TBI defined as the lowest post-resuscitation GCS score of 13-15, with neuroimaging evidence of parenchymal injury, 3) skeletal or body Abbreviated Injury Score ≤ 2 in children with complicated mild-moderate TBI to minimize any confounding influence of severe orthopedic injury on accurate assessment of GCS scores and outcome, and 4) bilingual or primarily English-speaking.

Exclusionary criteria for the TBI groups were: 1) children with a prior history of TBI or repeated TBI after enrollment, 2) children with injury mechanisms occurring with low frequency that have differing outcomes than acceleration/deceleration injuries (e.g., penetrating brain injuries), 3) children of illegal immigrants and families residing outside the catchment area due to difficulty maintaining enrollment, and 4) children with major developmental or psychiatric disorders, including mental retardation and pervasive developmental disorders. Exclusionary criteria were determined with a brief questionnaire administered to parents. Exclusionary criteria 3 and 4 were also applied to the orthopedic comparison group, as was the additional criterion of no previous head or facial injuries.

Children in both the complicated mild-moderate and severe TBI groups were recruited from the Level 1 Pediatric Trauma Center at Children's Memorial Hermann Hospital in Houston, Texas. After determining that the child met the inclusion criteria, informed written consent was obtained from the child's guardian. In accordance with guidelines established by the Institutional Review Board at the University of Texas Health Science Center at Houston, oral assent was obtained from children 6 years of age, written assent was obtained from children ages 7-11, and written adolescent consent was obtained for participants ages 12-18. From the overall cohort, 460 individuals were screened following admission to the hospital. Of those individuals, 363 did not meet the inclusion criteria. Of the remaining 97 patients with TBI that were eligible for the study, 17 were not contacted prior to discharge and 18 did not want to participate, resulting in 62 children with TBI. Of these 62 children, 7 could only be evaluated at 2 or fewer time points post-injury and were not included in the final sample for analyses. Thus, a total of 55 children were included for the

analyses in this study, 42 with severe injuries and 13 with complicated mild-moderate injuries.

The comparison group was composed of 47 children who sustained orthopedic injuries with no head or facial injuries, as indicated by a normal MRI 2 months post-injury. These children were recruited from the Level 1 Pediatric Trauma Center at Children's Memorial Hermann Hospital in Houston, Texas between 2004 and 2007. Six hundred twenty five individuals were screened in the emergency room, and 372 did not meet the inclusion criteria. Of the 253 eligible children, 113 elected not to participate and 83 were not contacted prior to discharge. Ten children were unable to complete a minimum of three evaluations, and thus, were not included in the analyses for this study, resulting in 47 comparison children with orthopedic injuries. Informed consent for comparison groups was obtained in the same manner as the TBI groups.

Demographic information for the three injury groups is presented in Table 1. Chi-square revealed that groups did not differ significantly at the .05 level of alpha on ethnicity, $\chi^2(8, N = 102) = 4.04$, $p = .85$, or sex $\chi^2(2, N = 102) = 3.57$, $p = .17$. All injury groups were male majority, which is expected because males have a higher rate of injuries than females. The ethnic composition tends to parallel that of the recruitment area.

Descriptive statistics and injury-related statistics are presented in Table 2. One-way analysis of variance (ANOVA) revealed that group differences in age at injury were not significant, $F(2, 99) = 1.16$, $p = .32$. Because this is a prospective longitudinal study, age at injury is similar to age at test. Group differences in socioeconomic status (SES), (as measured by the Hollingshead Family Factor Index) were not significant $F(2, 99) = 1.95$, $p = .15$. However, because significant correlations were found between SES and the outcome

measures, and there was a trend for lower SES in the groups with TBI, it was included as a covariate in analyses.

The relation between SES and the outcome measures may be the result of fewer family and educational resources of families with lower SES, which may moderate poorer cognitive outcomes (Taylor et al., 2002; Yeates et al., 2004). Including SES as a covariate affected outcome mean scores by raising the means of the two TBI groups (whose mean SES scores were below the grand mean of SES), and lowering the means of the orthopedic group (whose mean SES score was above that of the grand mean of SES), thus controlling for possible moderating effects of SES.

IQ was determined using the Wechsler Abbreviated Scale of Intelligence (WASI) (Wechsler, 1999). One-way ANOVA revealed a significant difference in IQ scores between the groups, $F(2, 99) = 7.44$, $p < .01$, with contrasts revealing significant differences between the orthopedic comparison and severe TBI groups. IQ differences between TBI and comparison groups are commonly reported in the pediatric TBI literature (Jaffe et al., 1992). However, IQ was not covaried because it does not meet the requirements for a covariate when applied to an acquired injury (Dennis et al., 2009). Namely, IQ differences are not unrelated to group membership, and reflect the effects of the injury itself. Adjusting for IQ would be tantamount to adjusting for the effects of the injury, an inappropriate use of ANCOVA. Statistics for age at injury in months are presented in Table 2 for each group, and statistics for head injury severity are presented for the TBI groups. There were no significant correlations between age at injury and GCS or days of impaired consciousness, suggesting that age at injury was not related to injury severity.

Table 1

Percentage of Ethnicities and Genders in Each Injury Group

	Orthopedic Comparison (n = 47)	Complicated Mild-moderate TBI (n = 13)	Severe TBI (n = 42)
Ethnicity			
Caucasian	42.6	61.5	40.4
African American	21.2	7.7	16.7
Hispanic	29.8	23.1	33.3
Asian	4.3	0	4.8
Other/Mixed	2.1	7.7	4.8
Sex			
Male	57.4	61.5	76.2
Female	42.6	38.5	23.8

Table 2

Means and Standard Deviations of Demographic and Injury-Related Variables

Demographic Variables	Comparison (n = 47) Mean (SD) Range	Complicated Mild-moderate TBI (n = 13) Mean (SD) Range	Severe TBI (n = 42) Means (SD) Range
SES	43.15 (13.77)	35.1 (12.01)	39.32 (14.76)
	20-66	13-55.5	13-64.5
IQ	109.19 (12.72)	108.69 (16.29)	98.24 (14.58)
	83-140	84-138	69-131
Age at Injury (months)	122.81 (34.71)	135.54 (38.46)	132.90 (36.34)
	72-187	72-180	72-191
Lowest GCS Score	--	12.46 (1.39)	6.10 (3.74)
		9-15	3-8
Impaired Consciousness	--	0.42 (0.64)	8.76 (9.89)
(days)		0-2	0-33

Note. * $p < .01$

Measures

Category Listening Span Task (CLS). The CLS assesses verbal WM. It was developed by De Beni, Palladino, Pazzaglia, and Cornoldi (1998), based on Daneman and Carpenter (1980) and adapted and translated into English for this study. The CLS is composed of five levels of one, two, three, four, or five strings of three words, with the number of word strings corresponding to a particular WM span. Each level consists of four trials, for a total of 20 possible trials. The child is asked to recall the last word in each string, in order, at the end of

the trial. Additionally, the child must tap the table at the end of each string if an animal name is said. For example, in a two-span trial, the examiner might say "pill, dog, water" then say the next word string "chin, wool, rice." A correctly performed trial at a span of two would be to tap the table at the end of the first string of words, and recall "water" and "rice" in that order. A ceiling was established when both trials at a level were incorrect. The basal was established as the lowest level at which both trials were correct. The total number of correctly answered trials, including the number of trials below the basal level, were included in analyses.

Visuospatial Span (VSS; Cornoldi et al., 2001). Because the VSS was created with the same processing demands as the CLS, it allows for a more direct comparison of verbal and visual-spatial WM than often occurs in studies comparing these two modalities of WM. The experimenter touches three contiguous positions in a four by four matrix of small square blocks. VSS is composed of five levels of one, two, three, four or five string series or memory spans, with four trials per level for a total of 20 trials. The number of strings corresponds to a particular WM span. The child recalls the location of the last block touched in each string, in order, at the end of each trial and is asked to tap the table after each string if the positions are in a linear pattern (horizontal, vertical or diagonal). The same basal and ceiling rules from the CLS were applied to the VSS. The total number of correctly answered trials, including those below the basal level, were included in analyses.

WM Measure Correlations. Correlations between scores obtained on the verbal and visual-spatial WM measure were run at each time point to determine whether the two were significantly correlated over time. Significant correlations were found between the two measures at each time point (2 months, $r = .63$, $p < .01$, 6 months, $r = .74$, $p < .01$, 12 months,

$r = .70$, $p < .01$ and 24 months, $r = .65$, $p < .01$) suggesting a significant relation between the two measures over time.

Currently there are no estimates of reliability of the two WM measures utilized in this study. To estimate the stability of the two measures over time, correlations between scores obtained at each time point were calculated for the verbal and the visual-spatial WM measures. The correlations (see Tables 3 and 4) between each time point were significant ($p < .0001$) for both WM measures suggesting stable measurements over time. However, it should be noted that the correlations are higher for the verbal WM measure, suggesting greater stability over time for the CLS measure, relative to the VSS measure.

Table 3

Correlations of CLS Measure Across Evaluations

	CLS 2 months	CLS 6 months	CLS 12 months	CLS 24 months
CLS 2 months	1.00	0.78*	0.75*	0.70*
CLS 6 months	--	1.00	0.86*	0.78*
CLS 12 months	--	--	1.00	0.80*
CLS 24 months	--	--	--	1.00

Note. * $p < .0001$

Table 4

Correlations of VSS Measure Across Evaluations

	VSS 2 months	VSS 6 months	VSS 12 months	VSS 24 months
VSS 2 months	1.00	0.76*	0.69*	0.65*
VSS 6 months	--	1.00	0.71*	0.59*
VSS 12 months	--	--	1.00	0.71*
VSS 24 months	--	--	--	1.00

Note. * $p < .0001$

Procedure

To identify children who met the study inclusion criteria, the study project coordinator reviewed daily admissions to Memorial Hermann Hospital through electronic medical records. Parents of all children who appeared eligible to participate were asked by the research nurse or other staff member of Memorial Hermann Hospital if they were willing to discuss the research study with the study project coordinator. If parent assented, the project coordinator met with the family in the hospital to review the study. If parents and children were interested in participating, additional screening (to determine prior history of head injury, history of learning or developmental disabilities) was performed. If the child was eligible following screening, copies of the consent form were provided. Parents were then contacted via telephone following their child's discharge to schedule an appointment to review consent further and to discuss the study in further detail. If child assent and parental consent were provided, an initial appointment was scheduled.

Participants were examined individually in an outpatient setting at the University of Texas Health Sciences Center at Houston, in a quiet testing room. Evaluation was conducted by a trained research assistant. All research assistants were trained by a senior research assistant who was experienced in administering and scoring all tests due to involvement in previous head injury research projects utilizing the same test measures. Children were given a large battery assessing cognitive abilities. All participants were provided the same directions. The duration of the total battery was approximately 4 hours. Breaks were provided per the child's request. The CLS and VSS tasks were administered towards the middle of the battery, but were not administered successively to provide variation in task requirements. A total of four evaluations took place at approximately 2, 6, 12, and 24 months post-injury.

Statistical Analyses

First, in order to determine the appropriate polynomial trend in the model, WM scores were plotted as a function of time since injury for each child using SAS statistical software. The curvature of the plot was visualized, which determined whether the data fit a linear, quadratic, or cubic trend.

Next, it was determined whether a general linear mixed model approach was appropriate for the dataset. In order to do this, a model was run including time since injury as a predictor, using SAS statistical software, and residuals were plotted to determine whether the distribution was symmetric and unimodal, indicating that a linear approach was appropriate. An unconditional means model does not include level 2 predictors, and can be specified in hierarchical linear model notation as follows:

$$Level\ 1:$$
$$WM_{ti} = b_{visual0} + b_{verbal0} + b_{visual1} * T_{visual} + b_{verbal1} * T_{verbal} + b_{visual2} * T_{visual}^2 + b_{verbal2} * T_{verbal}^2 + e_{ti}$$
$$Level\ 2:\ b_{visual0} = \gamma_{visual00} + u_{visual0i}$$
$$b_{verbal0} = \gamma_{verbal00} + u_{verbal0i}$$
$$b_{visual1} = \gamma_{visual10} + u_{visual1i}$$
$$b_{verbal1} = \gamma_{verbal10} + u_{verbal1i}$$
$$b_{visual2} = \gamma_{visual20} + u_{visual2i}$$
$$b_{verbal2} = \gamma_{verbal20} + u_{verbal2i}$$

Where WM refers to the predicted WM score, t refers to the time point at which the individual was evaluated (e.g. 2 months post injury etc.), i refers to the individual participant, b_{0i} refers to the intercept for individual i, b_1 is the slope of time since injury for individual i (with $visual$ and $verbal$ denoting for which modality of WM it is estimating), T is the exact number of days since injury for individual i at time point t (as the exact number of days since injury will vary by subject at each time point), $b_2$is the slope of the quadratic component (curvature) of time since injury, and T^2 is the quadratic component (curvature) of time. In keeping with the previous literature (Levin et al., 2004), time since injury was centered at 12 months, which is thought to represent a point in time at which cognitive changes are thought to be more enduring, as most spontaneous recovery has resolved (Anderson, Catroppa, Morse, Haritou, & Rosenfeld, 2000; Chadwick, Rutter, Brown, Shaffer, & Traub, 1981; Chadwick, Rutter, Shaffer, & Shrout, 1981; Ewing-Cobbs, Levin, Eisenberg, & Fletcher, 1987; Fay et al., 1994; Jaffe, Polissar, Fay, & Liao, 1995; Klonoff, Low, & Clark, 1977; Knights et al., 1991; Yeates et al., 2002). Error associated with individual i at time point t is denoted e_{ti}, γ_{00}refers to the overall mean, u_{0i} is the error associated with individual i, γ_{10}, refers to the overall slope of time since injury and u_{1i} is the error associated with individual i,

γ_{20}refers to the overall slope of the quadratic component of time since injury and u_{2i} is the error associated with individual i.

Next, individual growth curve modeling was performed, adding age at injury and severity of injury as Level 2 predictors, and including SES as a time invariant covariate. The age at injury by injury group interaction was included to evaluate hypotheses pertaining to three-way interactions. The model included a multivariate component to examine both visual-spatial and verbal WM within the same model. In order to determine which of the Level 1 predictors should be included as random effects, the Akaike Information Criterion (AIC) values of models including the intercept, slope of linear time and slope of quadratic time (curvature) as random, and then as fixed were compared. The model including all three Level 1 predictors (for both verbal and visual-spatial WM) as random effects was specified as follows:

$Level\ 1$:

$$WM_{ti} = b_{visual0} + b_{verbal0} + b_{visual1} * T_{visual} + b_{verbal1} * T_{verbal} + b_{visual2} * T_{visual}^2 + b_{verbal2} * T_{verbal}^2 + e_{ti}$$

$Level\ 2$:

$$b_{visual0} = \gamma_{visual00} + \gamma_{visual01} * S_i + \gamma_{visual02} * A_i + \gamma_{visual03} * S_i * A_i + \gamma_{visual04} * SES_i + u_{visual01}$$

$$b_{verbal0} = \gamma_{verbal00} + \gamma_{verbal01} * S_i + \gamma_{verbal02} * A_i + \gamma_{verbal03} * S_i * A_i + \gamma_{verbal04} * SES_i + u_{verbal01}$$

$$b_{visual1} = \gamma_{visual10} + \gamma_{visual11} * S_i + \gamma_{visual12} * A_1 + \gamma_{visual13} * S_i * A_i + \gamma_{visual14} * SES_i + u_{visual1i}$$

$$b_{verbal1} = \gamma_{verbal10} + \gamma_{verbal11} * S_i + \gamma_{verbal12} * A_1 + \gamma_{verbal13} * S_i * A_i + \gamma_{verbal14} * SES_i + u_{verbal1i}$$

$$b_{visual2} = \gamma_{visual20} + \gamma_{visual21} * S_i + \gamma_{visual22} * A_i + \gamma_{visual23} * S_i * A_i + \gamma_{visual24} * SES_i + u_{visual2i}$$

$$b_{verbal2} = \gamma_{verbal20} + \gamma_{verbal21} * S_i + \gamma_{verbal22} * A_i + \gamma_{verbal23} * S_i * A_i + \gamma_{verbal24} * SES_i + u_{verbal2i}$$

Statistical Assumptions

$e_{ti} \sim N(0, \sigma^2)$

$$\begin{matrix} u_{01} \\ u_{1i} \sim N \\ u_{2i} \end{matrix} \begin{matrix} 0 \\ 0 \\ 0 \end{matrix} \begin{matrix} \tau_{00} & \tau_{01} & \tau_{02} \\ \tau_{10} & \tau_{11} & \tau_{12} \\ \tau_{20} & \tau_{21} & \tau_{22} \end{matrix}$$

The same notation from the aforementioned model still applies to this model, but now, a Level 2 predictor, two time invariant covariates and an interaction term have been added. In this model, S_i refers to severity of injury for each individual, A_i refers to age at injury for each individual and SES_i refers to socioeconomic status for each individual. Intercepts for severity, age at injury, the severity group by age at injury interaction, and SES are designated γ_{01}, γ_{02}, $\gamma_{03}$and γ_{04}respectively (and include $visual$ or $verbal$ in front of them to denote which modality of WM they represent), while slopes for injury severity, age at injury, the injury severity group by age at injury interaction, and SES are designated γ_{11}, γ_{12}, γ_{13}, and γ_{14}. Residual error in slopes is designated u_{1i}. In keeping with Levin et al., (2004), time since injury was centered at 1 year. The aforementioned model assumes a quadratic curvature. The intercept of the quadratic component is denoted γ_{20}, and γ_{21}, γ_{22}, γ_{23}, and γ_{24}refer to the respective slopes (severity, age at injury, severity group by age at injury and SES) for the quadratic component while u_{2i} refers to residual error in the slope. With regards to statistical assumptions, σ^2 refers to within subject variance, τ_{00} refers to intercept variance, τ_{11}refers to slope of linear time variance, τ_{22} refers to slope of quadratic time variance, τ_{01}refers to covariance between intercept and slope of linear time, τ_{02} refers to covariance between intercept and slope of quadratic time, and τ_{12} refers to covariance between slope of linear time and slope of quadratic time.

Each hypothesis was tested by examining different parameters of the aforementioned model. In this section, each hypothesis is restated, followed by the parameter that was

examined to determine whether the hypothesis was supported. It was hypothesized that: (1a) children injured at a younger age with severe injuries would demonstrate the poorest performance in both verbal and visual-spatial WM at 12 months post-injury (reflected by a significant three-way intercept by age at injury by injury group interaction)- this was tested by examining $\gamma_{verbal01} * A_i * S_i$ and $\gamma_{visual01} * A_i * S_i$; (1b) if the three way interaction was not significant the significance of $\gamma_{verbal01} * S_i$ and $\gamma_{visual01} * S_i$was examined to determine whether children with more severe injuries performed more poorly at 12 months post-injury, while controlling for age at injury; (2a) children injured at a younger age with severe injuries would demonstrate the slowest rate of growth in both verbal and visual-spatial WM at 12 months post-injury (reflected by a significant three-way slope by age at injury by injury group interaction)- this was tested by examining $\gamma_{verbal11} * A_i * S_i$ and $\gamma_{visual11} * A_i * S_i$; (2b) if the three-way interaction was not significant, the significance of $\gamma_{verbal11} * S_i$ and $\gamma_{visual11} * S_i$ was examined to determine whether children with more severe injuries demonstrated the slowest rate of growth, when controlling for age at injury; (3) children with more severe injuries would demonstrate a curvature that decelerated over time (reflecting initial improvements in performance, followed by a performance decline not exhibited by children with less severe injuries). This was tested by examining $\gamma_{verbal21} * S_i$ and $\gamma_{visual21} * S_i$ (4) there would be a positive relation between intercepts (performance) of verbal and visual-spatial WM, reflecting that individuals with better performance on verbal WM performed better on the visual-spatial measure- the significance of the random coefficient $\tau_{verbal0visual0}$was examined; (5) there would be a positive relation between slopes (rate of growth) between the two WM measures, suggesting that individuals with greater rates of growth on the verbal measure also had greater rates of growth on the visual-

spatial measure- $\tau_{verbal1visual1}$ was examined and (6) there would be a negative relation between slope and intercept, suggesting that as performance improved, rate of growth slowed- $\tau_{verbal0verbal1} and\ \tau_{visual0visual1}$ were examined.

Adjusted Means and Power Estimates

Adjusted means were calculated for level of performance on the verbal and visual-spatial WM measures at each time point for each injury group. Adjusted means presented in Table 5 were calculated at the average age at injury and average SES. The unadjusted root mean square error and R^2 values are also presented. The unadjusted values present an estimate of effect size in the original standard deviations units, facilitating interpretation.

Table 5

SES and Age at Injury Adjusted Means, Root Mean Square Errors and R^2 Values for each Measure

	Orthopedic (n = 47)	Complicated Mild-Moderate (n = 13)	Severe (n = 42)
	Least Squares Mean (RMSE)* R^2**	Least Squares Mean (RMSE)* R^2**	Least Squares Mean (RMSE)* R^2**
Category Listening Span			
2 Months Post-injury	9.25 (3.92) 0.04	8.21 (3.92) 0.04	7.11 (3.92) 0.04
6 Months Post-injury	11.19 (4.06) 0.02	10.07 (4.06) 0.02	9.36 (4.06) 0.02
12 Months Post-injury	12.71 (4.33) 0.05	11.06 (4.33) 0.05	9.94 (4.33) 0.05
24 Months Post-injury	12.94 (4.07) 0.04	10.56 (4.07) 0.04	10.96 (4.07) 0.04
Visuospatial Span			
2 Months Post-injury	10.21 (4.44) 0.005	10.78 (4.44) 0.005	9.61 (4.44) 0.005
6 Months Post-injury	12.13 (4.60) 0.02	12.73 (4.60) 0.02	10.79 (4.60) 0.02
12 Months Post-injury	13.51 (3.95) 0.09	15.03 (3.95) 0.09	11.28 (3.95) 0.09
24 Months Post-injury	13.78 (3.92) 0.03	14.10 (3.92) 0.03	12.25 (3.92) 0.03

Note. * denotes unadjusted root mean square error, ** denotes unadjusted R^2

Power was estimated by specifying a full model including age at injury and SES as continuous predictors and severity as a classification variable, and a restricted model including only severity as a class variable. The value of Lambda was then calculated as

follows: $\frac{Change\ in\ R^2 values\ between\ full\ and\ restricted\ model}{1-R^2} * (Full\ Model\ Degrees\ of\ Freedom + 1)$. The average change (over all four time points) in R^2 values between the full and restricted models resulted in a value of 0.0357 (verbal) and 0.0347 (visual), while the average (across all four time points) of the R^2 value of the full model was 0.48 (verbal) and 0.46 (visual). This resulted in a power estimate of 0.62 for the verbal WM measure and 0.59 for the visual-spatial WM measure (Cohen, 1988). These values represent a lower bound estimate of power because power is greater in a longitudinal repeated measure analysis due to correlations between time points. The power estimates above do not account for such correlations.

Results

Polynomial Trend of the Data

Working memory scores for the verbal measure (CLS) and the visual-spatial measure (VSS) were plotted as a function of time since injury using SAS statistical software. Separate plots were created for each level of injury (where 0 = orthopedic comparison, 1 = complicated mild/moderate injury, and 2 = severe injury), resulting in a total of six plots. This was performed to determine the appropriate form of the data (linear, quadratic or cubic). A linear trend would be indicated if there appeared to be no change in the direction of the slopes over time, while a quadratic trend would be indicated if there appeared to be one change in the slopes over time, and a cubic trend would be indicated if there appeared to be two changes in the slopes over time. Visual inspection of the overall trend in all six graphs showed that a quadratic trend best approximated the curvature of the growth curves, as WM scores appeared to increase from the two to six month evaluations and from the six to twelve month evaluations, but not between the 12 and 24 month evaluations. Refer to Figures 1-3 for plots of WM scores over time for each measure, by injury group.

Appropriateness of a General Linear Mixed Model

An unconditional means model was run including time since injury as a level 1 predictor, as well as the squared component of time since injury to account for the apparent quadratic curvilinearity of the data that was indicated by the previously discussed plots. Residuals of this model were then plotted to determine whether the distribution was symmetric and unimodal, which would have indicated whether a general linear mixed model was appropriate. The histogram in Figure 4 shows the distribution of residuals of the unconditional model. Visual inspection revealed a distribution that was symmetric and unimodal, suggesting that a general linear mixed model was appropriate.

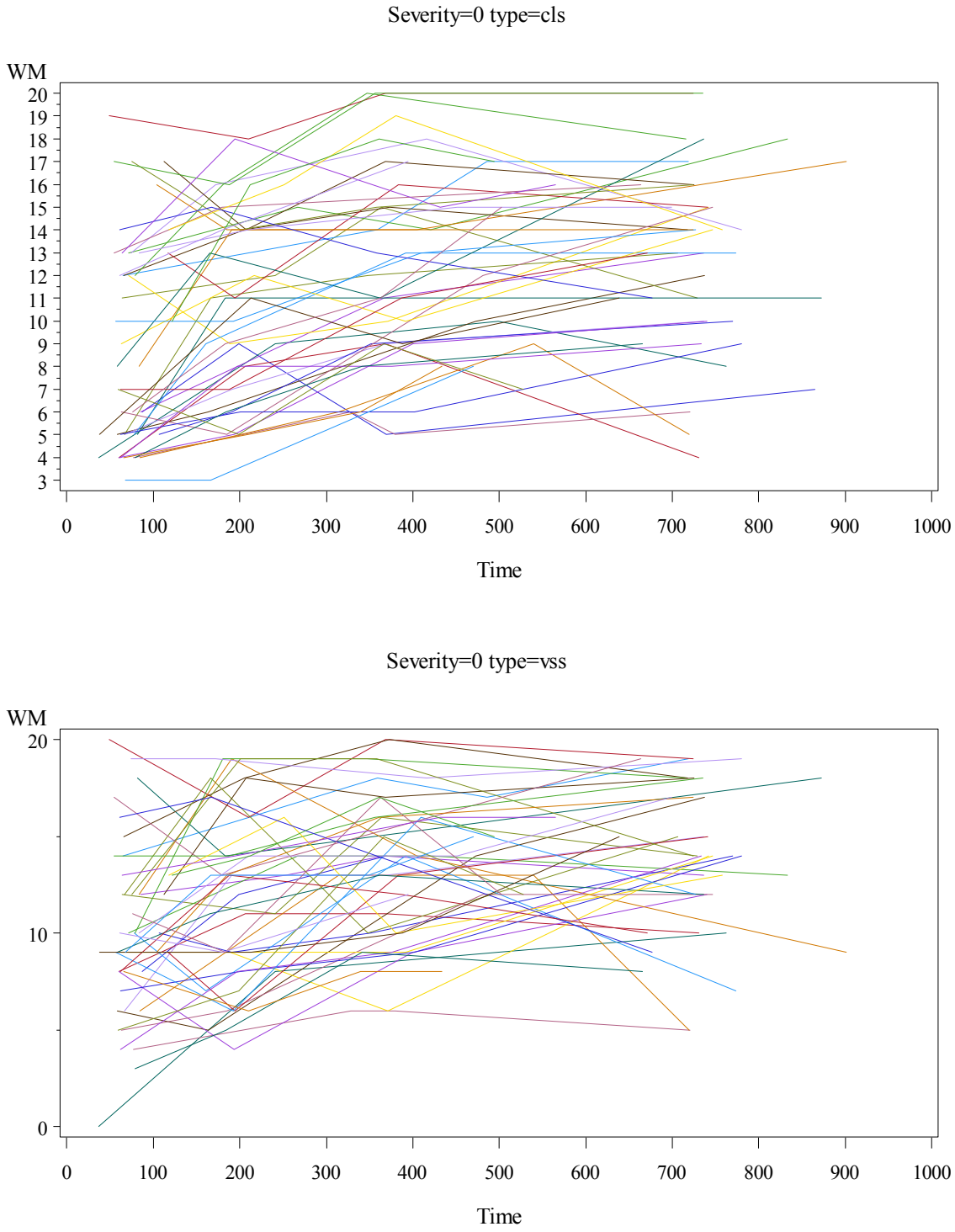
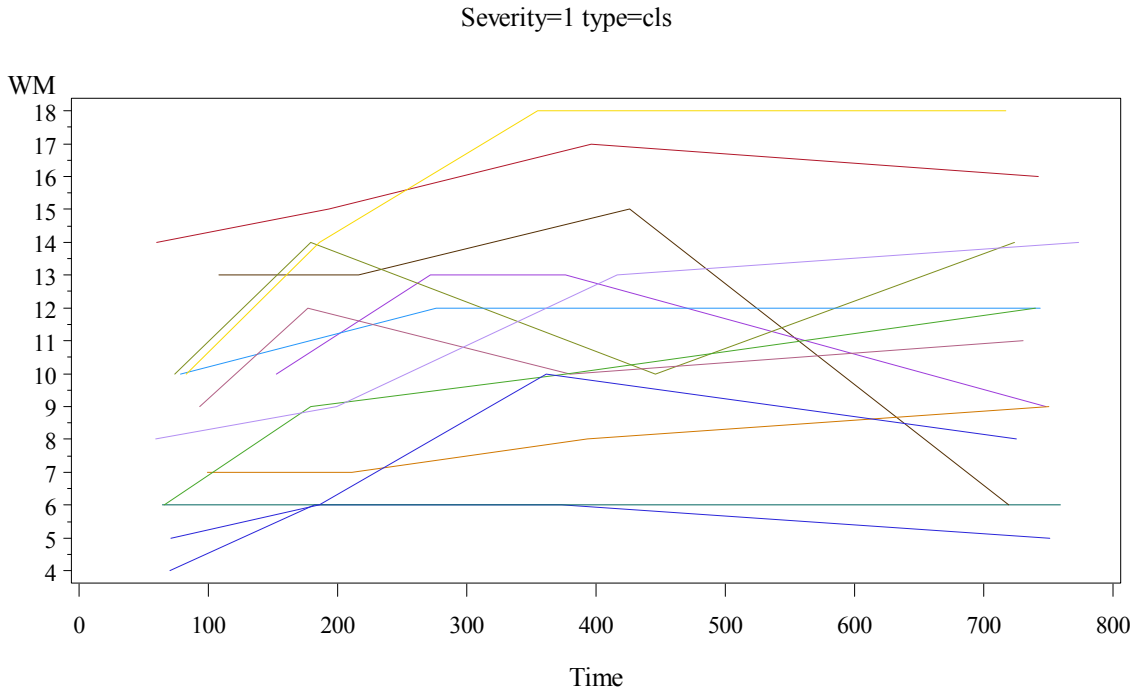


Figure 1. Plots of WM scores over time for children with orthopedic injuries



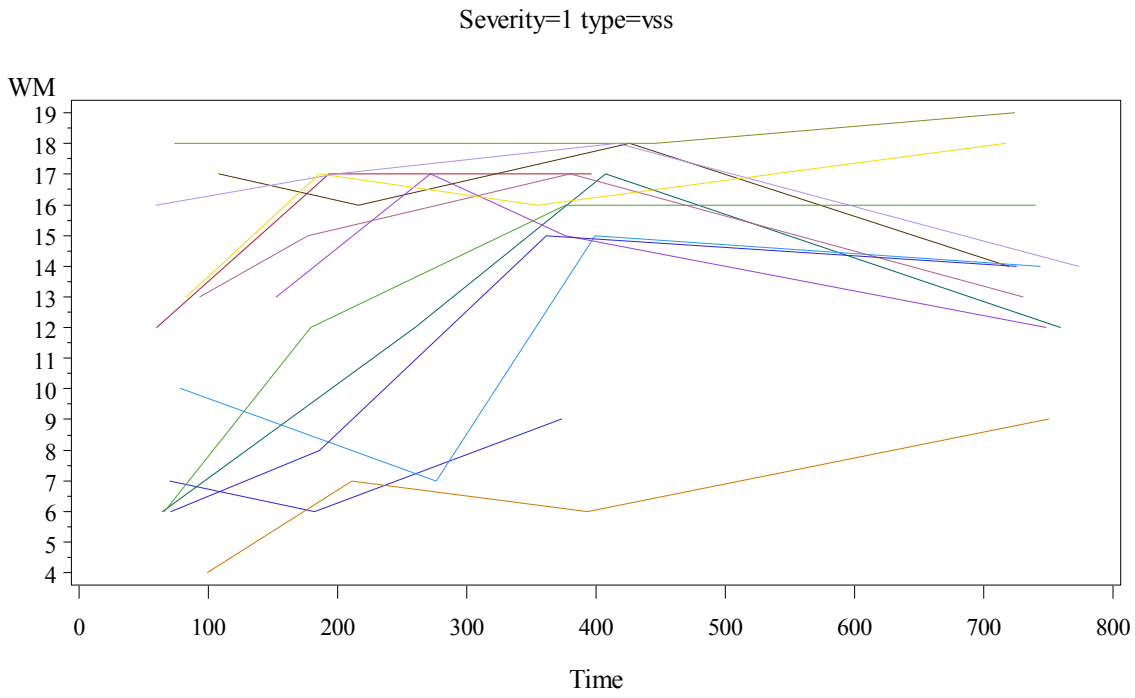
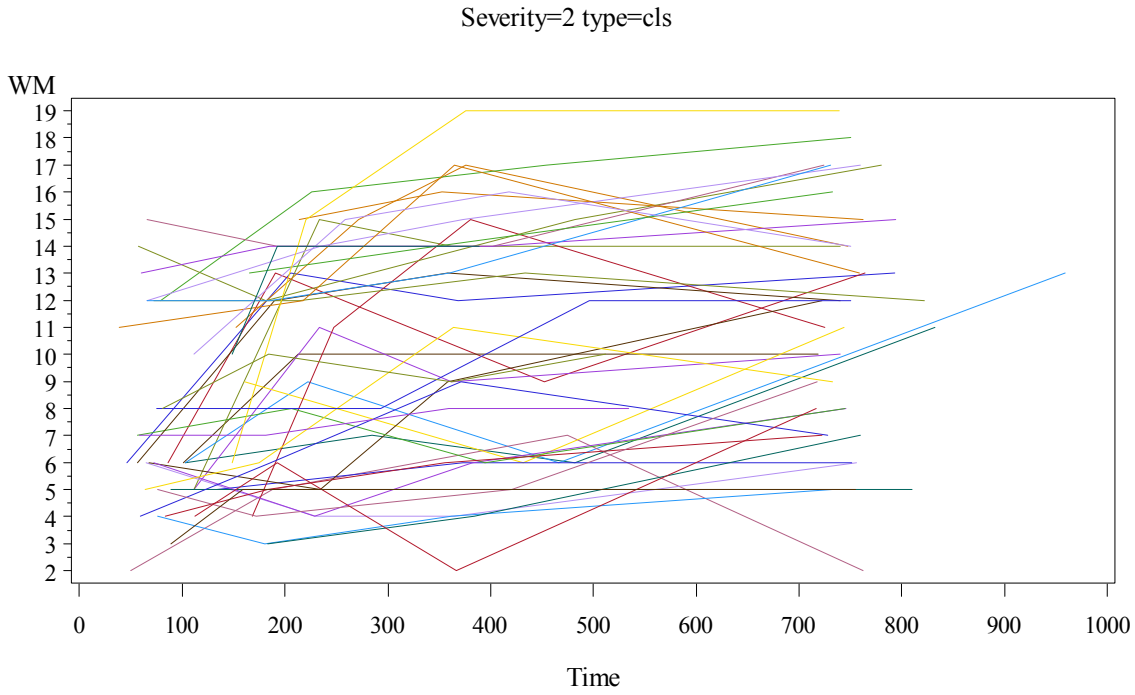


Figure 2. Plots of WM scores over time for children with complicated mild-moderate injuries



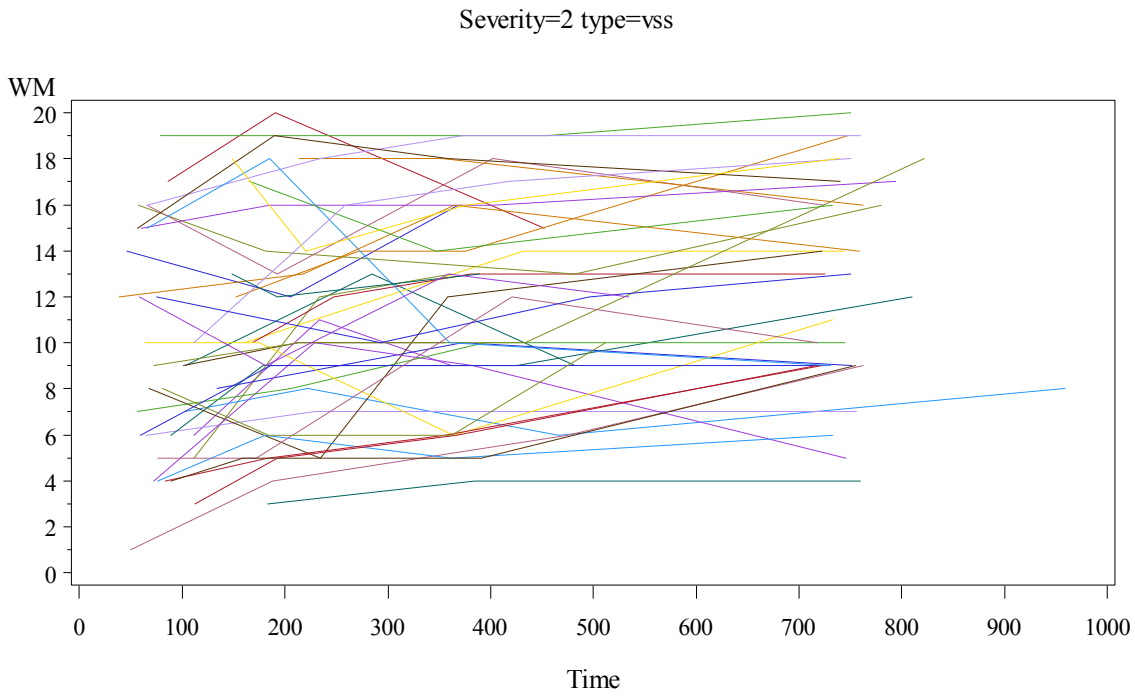


Figure 3. Plots of WM scores over time for children with severe injuries

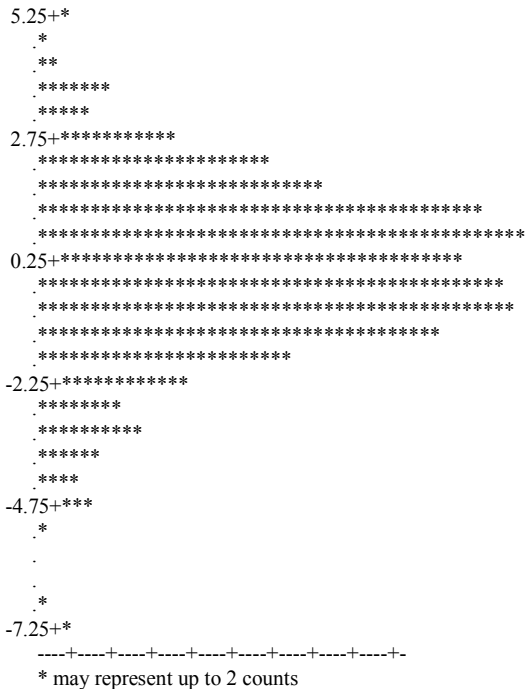


Figure 4. Histogram of residuals of an unconditional means model

Determining Random Effects

The Akaike Information Criterion (AIC) was better (4011.7) when intercept was random as opposed to fixed (4294.1 when intercept fixed), and when curvature was fixed, as opposed to random (4017.6 when curvature random). The AIC value was unchanged when the slope of linear time was included as fixed (4011.3), and thus slope of linear time was included as random. Thus, the overall model was estimated including intercept and the slope of linear time as random and the slope of quadratic time (curvature) as fixed. This resulted in the following model:

$Level\ 1$:

$$WM_{ti} = b_{visual0} + b_{verbal0} + b_{visual1} * T_{visual} + b_{verbal1} * T_{verbal} + b_{visual2} * T_{visual}^2 + b_{verbal2} * T_{verbal}^2 + e_{ti}$$

$Level\ 2$:

$$b_{visual0} = \gamma_{visual00} + \gamma_{visual01} * S_i + \gamma_{visual02} * A_i + \gamma_{visual03} * S_i * A_i + \gamma_{visual04} * SES_i + u_{visual01}$$

$$b_{verbal0} = \gamma_{verbal00} + \gamma_{verbal01} * S_i + \gamma_{verbal02} * A_i + \gamma_{verbal03} * S_i * A_i + \gamma_{verbal04} * SES_i + u_{verbal01}$$

$$b_{visual1} = \gamma_{visual10} + \gamma_{visual11} * S_i + \gamma_{visual12} * A_1 + \gamma_{visual13} * S_i * A_i + \gamma_{visual14} * SES_i + u_{visual1i}$$

$$b_{verbal1} = \gamma_{verbal10} + \gamma_{verbal11} * S_i + \gamma_{verbal12} * A_1 + \gamma_{verbal13} * S_i * A_i + \gamma_{verbal14} * SES_i + u_{verbal1i}$$

$$b_{visual2} = \gamma_{visual20} + \gamma_{visual21} * S_i + \gamma_{visual22} * A_i + \gamma_{visual23} * S_i * A_i + \gamma_{visual24} * SES_i$$

$$b_{verbal2} = \gamma_{verbal20} + \gamma_{verbal21} * S_i + \gamma_{verbal22} * A_i + \gamma_{verbal23} * S_i * A_i + \gamma_{verbal24} * SES_i$$

Statistical Assumptions

$$e_{ti} \sim N(0, \sigma^2)$$

$$\begin{matrix} u_{01} \\ u_{1i} \end{matrix} \sim N \begin{matrix} 0 \\ 0 \end{matrix} \begin{matrix} \tau_{00} & \tau_{01} \\ \tau_{10} & \tau_{11} \end{matrix}$$

In sum, the overall model testing all hypotheses included time, and time squared (to look at differences in patterns of acceleration/deceleration) as Level 1 predictors and age at injury and injury severity group as Level 2 predictors, with SES covaried. Intercepts for verbal and

visual-spatial WM and slope of time for verbal and visual-spatial WM were included as random effects (allowing them to vary by person), while all other predictors were fixed.

Level of Performance by Age at Injury and Injury Group

It was hypothesized that at 12 months post-injury (the time point at which the data was centered), children injured at a younger age with severe injuries would demonstrate the poorest level of performance in both verbal and visual-spatial WM at 12 months post-injury. The three-way intercept by age at injury by injury group interaction was examined for both the verbal and the visual-spatial measure to test this hypothesis. The results were not significant ($p > .05$) for the verbal WM measure, $F(1, 371) = 0.01$, $p = .92$, nor for the visual-spatial WM measure, $F(1, 371) = 0.09$, $p = .76$. Because the three-way interactions were not significant, the two way intercept by injury group interactions were examined (which controlled for age at injury). The interaction was not significant for verbal WM, $F(1, 371) = 1.08$, $p = .30$, nor for visual-spatial WM $F(1, 371) = 1.50$, $p = .22$. Visual inspection of the plots in Figures 5-12 shows that children with severe injuries with different age at injury exhibited performance that was below that of children in the complicated mild-moderate group who in turn, performed below the children with orthopedic injuries. However, these differences were not statistically significant ($p > .05$).

Rate of Growth by Age at Injury and Injury Group

To test the hypothesis that children injured at a younger age, with more severe injuries would exhibit the slowest rate of growth (and therefore the flattest slope), the slope by age at injury by injury group interaction was examined for both the verbal WM and visual-spatial WM measures. A significant three-way interaction was found for the verbal WM measure, $F(1, 371) = 10.72$, $p < .01$, with visual inspection of Figures 5-8 showing that

children injured at a younger age with more severe injuries demonstrated a slower rate of growth in WM scores, as compared to the complicated mild-moderate and orthopedic comparison groups, and as compared to older children with severe injuries. A significant three-way interaction was not found for the visual-spatial WM measure, $F(1, 371) = 1.59$, $p = .21$), although visual inspection of Figures 9-12 suggests that this pattern was also present on the visual-spatial WM measure, although it did not reach the critical level of alpha adopted for this study (i.e. $p < .05$). The two-way slope by injury group interaction was examined for visual-spatial WM when age at injury was controlled, and was not significant, $F(1, 371) = 2.79$, $p = .10$.

Differences in Curvature by Injury Group

To determine whether children with more severe injuries exhibited curvature that decelerated over time, relative to the other two injury groups, the slope of the quadratic component of time (curvature) by injury group interaction (when controlling for age at injury) was examined for both WM measures. The two-way interaction was not significant for the verbal measure, $F(1, 371) = 2.42$, $p = .12$, nor for visual-spatial WM, $F(1, 371) = 0.02$, $p = .89$, indicating that the pattern of acceleration/deceleration did not differ by injury group when controlling for age at injury.

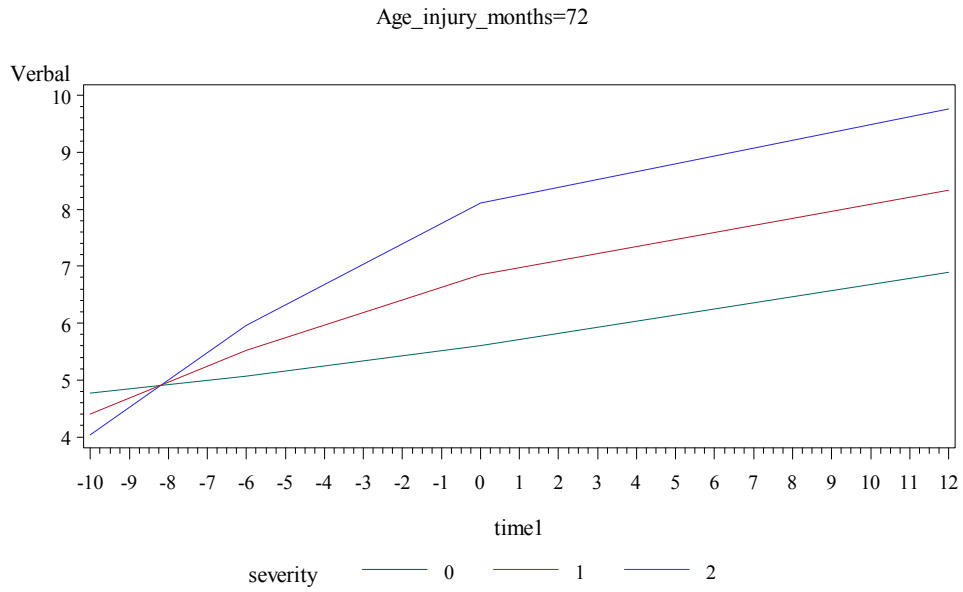


Figure 5. Total number of correctly answered items on the verbal WM measure plotted over time for children injured at 72 months

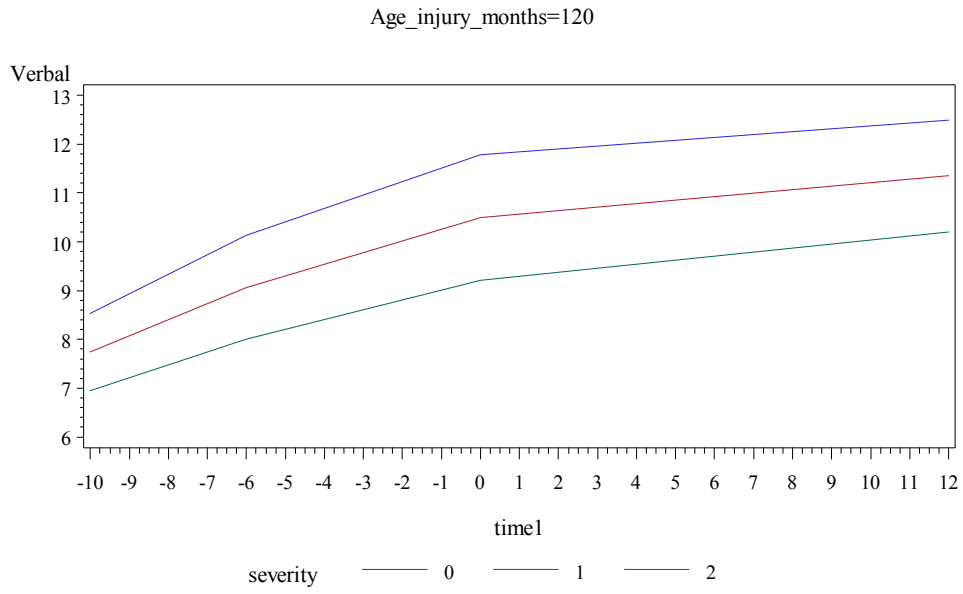


Figure 6. Total number of correctly answered items on the verbal WM measure plotted over time for children injured at 120 months

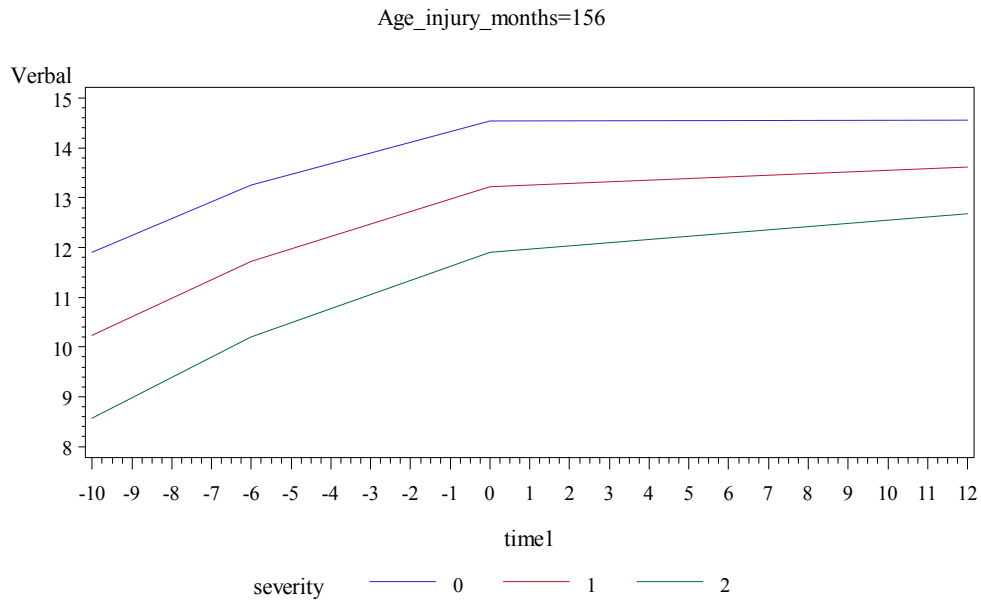


Figure 7. Total number of correctly answered items on the verbal WM measure plotted over time for children injured at 156 months

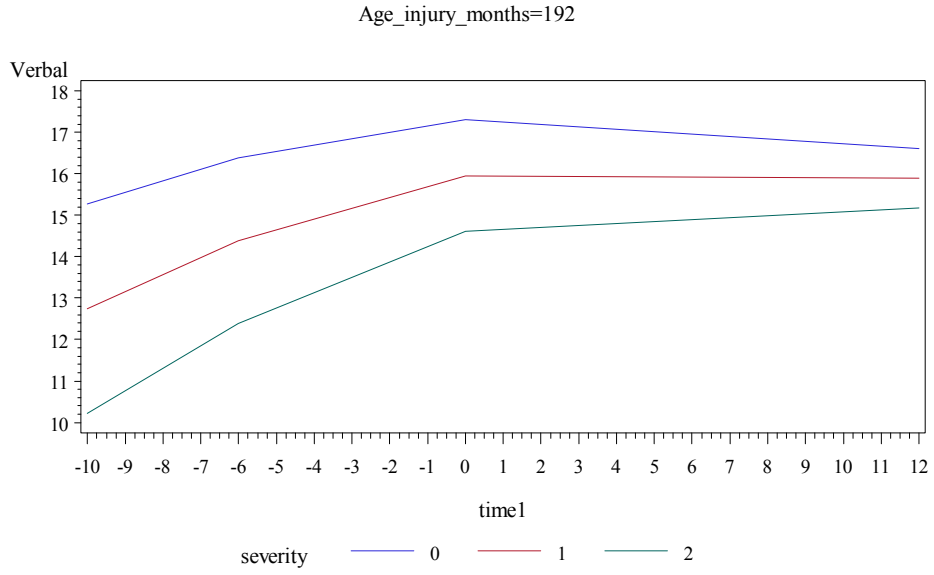


Figure 8. Total number of correctly answered items on the verbal WM measure plotted over time for children injured at 192 months

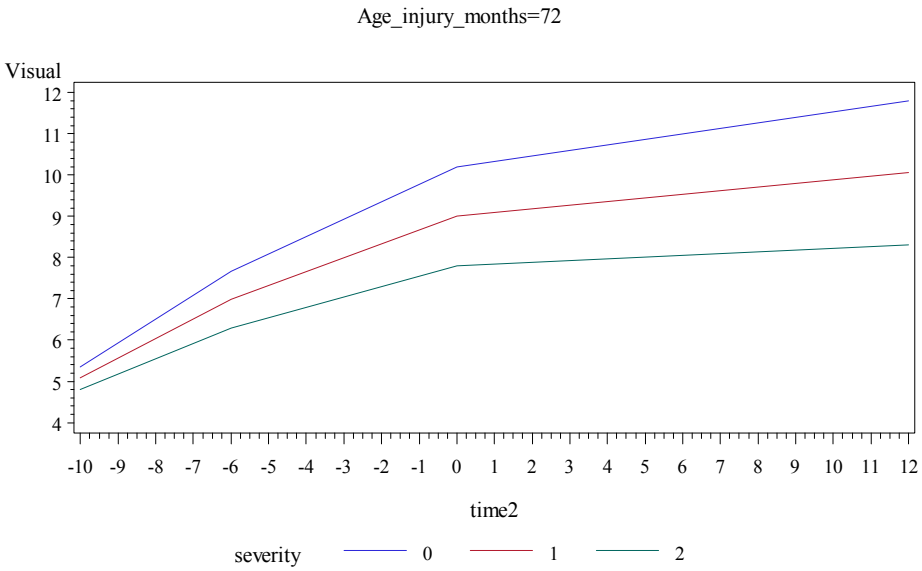


Figure 9. Total number of correctly answered items on the visual-spatial WM measure plotted over time for children injured at 72 months

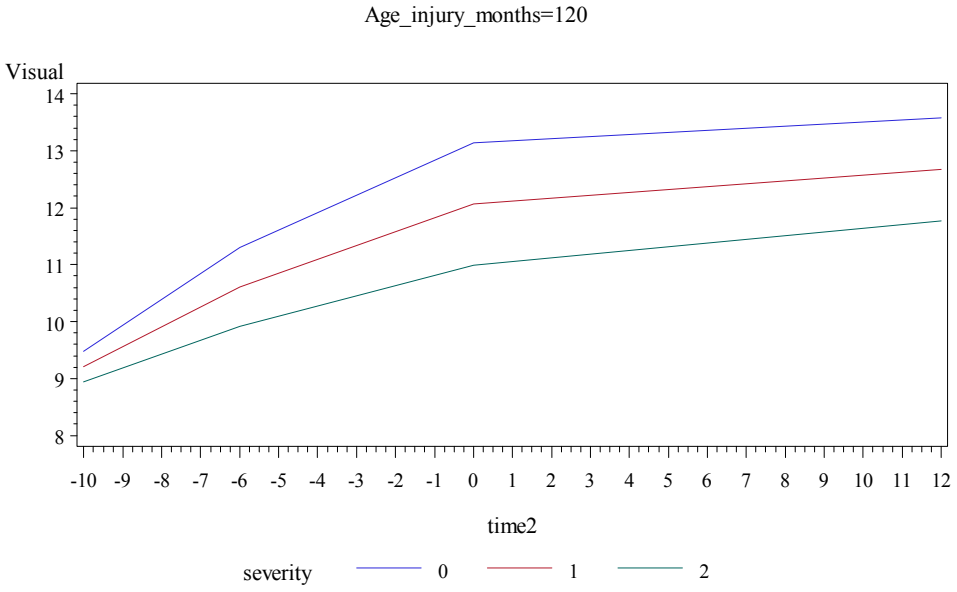


Figure 10. Total number of correctly answered items on the visual-spatial WM measure plotted over time for children injured at 120 months

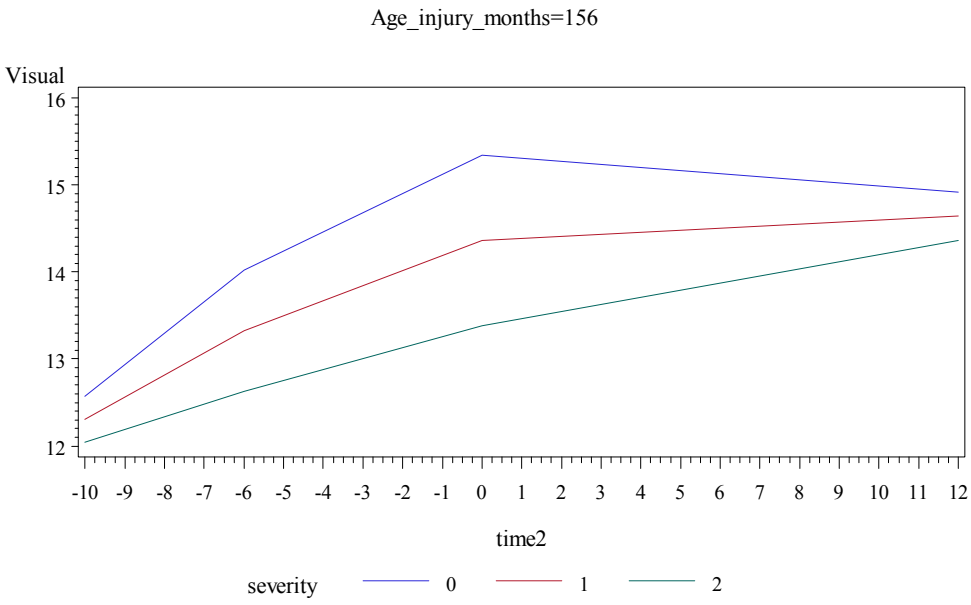


Figure 11. Total number of correctly answered items on the visual-spatial WM measure plotted over time for children injured at 156 months

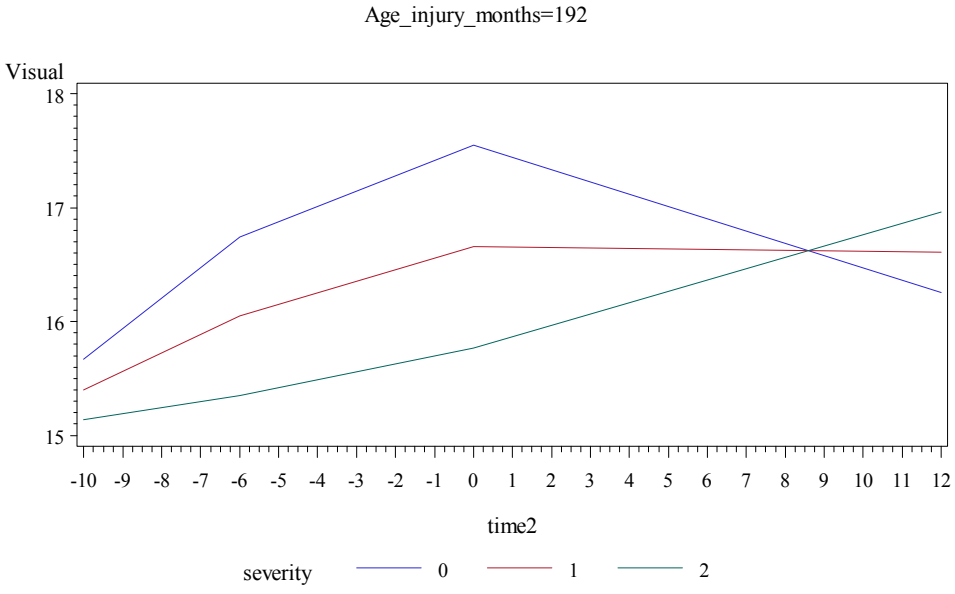


Figure 12. Total number of correctly answered items on the visual-spatial WM measure plotted over time for children injured at 192 months

Relation between Level of Performance on Verbal and Visual-Spatial WM

In order to determine whether there was a positive significant relation between level of performance (intercepts) on verbal and visual-spatial WM (reflecting that individuals with better levels of performance on verbal WM also performed better on the visual-spatial measure), the significance of the covariance between the two intercepts was examined. The result indicated a positive, significant relation, $z = 4.99$, $p < .0001$, suggesting that children who performed better at 12 months on the verbal WM measure, also performed better on the visual-spatial WM measure.

Relation between Rate of Growth of Verbal and Visual-Spatial WM

It was hypothesized that there would be a positive relation between rate of growth (slopes) between the two WM measures, suggesting that individuals with greater rates of growth on the verbal measure would also have greater rates of growth on the visual-spatial measure. The significance of the covariance between the two slopes was examined. Although the value of the estimate was positive, it was not statistically significant, $z = 0.34$, $p = .73$, suggesting that the rates of growth between verbal and visual-spatial WM were not significantly positively related.

Relation between Level of Performance and Rate of Growth of Verbal and Visual-Spatial WM

It was hypothesized that there would be a negative relation between slope and intercept for both verbal and visual-spatial WM, suggesting that as level of performance improved, rate of growth would slow. The covariances between the intercept and slope of the verbal and visual-spatial WM measure were examined. On the verbal measure, the relation was neither statistically significant, nor negative, $z = 1.26$, $p = .21$, and for the visual-spatial

measure, the relation was negative, but not statistically significant, $z = -1.08$, $p = .28$. This suggested that performance at 12 months post-injury was not significantly negatively related to the rate of growth for either WM measure.

Post hoc Analyses

Visual inspection of Figures 5-12 suggested that with increasing time post-injury, differences in level of performance between injury groups became larger in children injured at a younger age, and smaller in children injured at an older age. Thus, the analyses were repeated centering time post-injury at 24 months and the three-way intercept by age at injury by injury group interaction for both WM measures were examined. The interactions for verbal WM $F(1, 369) = 0.41$, $p = .52$, and visual-spatial WM $F(1, 369) = 1.83$, $p = .07$ did not reach statistical significance.

Discussion

Summary of Findings

The aim of the present study was to characterize the pattern of growth of verbal and visual-spatial WM using age at injury and injury severity as predictors in children with complicated mild-moderate and severe TBI as compared to a sample of children with orthopedic injuries. This aim was evaluated using individual growth curve modeling and using a multivariate approach so that both verbal and visual-spatial WM could be considered within a single model. With regards to levels of performance, I hypothesized that children injured at a younger age with severe injuries would demonstrate the poorest level of performance in both verbal and visual-spatial WM at 12 months post-injury. If a significant three-way interaction was not found, I hypothesized that children with more severe injuries would have a poorer level of performance, while controlling for age at injury. When age at

injury was not held constant, injury groups did not differ significantly on level of performance, nor did injury groups differ on level of performance when holding age at injury constant. I also hypothesized that there would be a positive relation between levels of performance of verbal and visual-spatial WM, such that individuals with better performance on verbal WM would perform better on the visual-spatial measure. Level of performance on verbal WM was found to be positively related to level of performance on visual-spatial WM. With regards to rate of growth, I hypothesized that children injured at a younger age with severe injuries would demonstrate the slowest rate of growth in both verbal and visual-spatial WM at 12 months post-injury, and if a significant three-way interaction was not found, I hypothesized that there would be a significant two-way slope by injury group interaction, with children with more severe injuries demonstrating a slower rate of growth, while controlling for age at injury. Differences in rate of growth on the verbal WM measure revealed that children with severe injuries injured at a younger age had the slowest rate of growth. This pattern was also observed for visual-spatial WM, although it did not reach statistical significance. I also hypothesized that there would be a positive relation between rates of growth between the two WM measures, suggesting that individuals with greater rates of growth on the verbal measure would have greater rates of growth on the visual-spatial measure. However, rates of growth of verbal and visual-spatial WM were not significantly positively related. I hypothesized that there would be a negative relation between slope and intercept, with children with higher levels of performance having slower rates of growth. However, level of performance and rate of growth on each of the WM measures were not significantly negatively related. Lastly, I hypothesized that the growth patterns of children with more severe injuries would demonstrate curvature that decelerated over time (reflecting

initial improvements in performance, followed by a performance decline), while controlling for age at injury. However, significant differences between injury groups were not observed for the pattern of acceleration/deceleration (curvature), when age at injury was held constant.

Note on the Critical Level of Alpha Utilized in this Study

It should be noted at the outset, that while some of the statistical values testing the hypotheses in this study did not reach the critical value of alpha, this does not necessarily imply the absence of hypothesized effects. As can be discerned from the plotted data, the overall pattern of growth of verbal and visual-spatial WM was as expected, although statistical significance was not always obtained at the critical level of alpha adopted for this study ($p < .05$). This may in part be due to insufficient power to detect small to medium effect sizes. Furthermore, the pattern of growth was similar for both verbal and visual-spatial WM, although for some hypotheses, the critical level of alpha was met only for verbal WM. Thus, it is not apparent that effects are present only for verbal WM given that similar patterns were observed for both verbal and visual-spatial WM measures. Rather, given the current sample size, the verbal WM measure may have been more robust with regards to detection of small to medium effect sizes. Indeed, the average root mean square error value over time was smaller for the verbal measure than for the visual-spatial measure. Additionally, the correlations between scores at each time point were greater for the verbal measure, suggesting greater stability over time, or greater reliability, of the verbal measure. Thus, with regards to interpretation, patterns of performance and growth will be emphasized to a greater degree than whether the critical level of alpha was obtained.

Levels of Performance

With regards to levels of performance, there were no statistically significant differences between injury groups at different age at injuries for either verbal or visual-spatial WM at 12 months post-injury. Inspection of plots showed that with increasing time since injury, differences between injury groups in level of performance became larger for children injured at a younger age, but smaller for children injured at an older age, likely due to differences in rate of growth, which will be discussed in further detail below. Alternatively, by 24 months post-injury there may have been a significant three-way interaction, but this was not found in a post-hoc analysis. Perhaps with a larger sample size, group differences in levels of performance may have been detected.

Of interest is the finding that there was not a statistically significant difference in levels of performance between injury groups when age at injury was held constant. This might seem to contrast with the existing literature showing significant differences in WM levels of performance between injury groups (Conklin et al., 2008; Hanten et al., 1999; Levin et al., 2002; Levin et al., 2004; Mandalis et al., 2007). However, much of the existing literature has obtained significant differences in levels of performance between injury groups without considering age at injury. This suggests that WM outcome may be best understood in light of both the developmental level of the brain at the time at which the injury occurred, and the severity of the injury.

Level of performance on verbal and visual-spatial WM at 12 months post-injury was significantly positively related, with children who obtained higher scores on the verbal WM measure obtaining higher scores on the visual-spatial WM measure. This is consistent with the significant correlation between the two WM measures reported earlier. The two WM

measures may be related because they tap a component of WM that is shared by both verbal and visual-spatial domains, namely, central executive processes (Gorman et al., 2012). Central executive processes involve the ability to focus attention on relevant information, retrieve information from long term memory and maintain and manipulate integrated information (Baddeley, 1996, 2002). This notion is further supported by the findings of Gathercole et al. (2004), who found that the central executive was closely linked to both the phonological loop (underlying verbal WM) and the visuospatial sketchpad (underlying visual-spatial WM).

Rates of Growth

Interestingly, the relation between the rate of growth of WM and the injury groups varied at different age at injuries. This interaction was statistically significant for the verbal WM measure, and the same relation appeared to be present for visual-spatial WM based on visual-inspection of the plots, although it did not meet the critical level of alpha. Children with more severe injuries who were injured at a younger age had a slower rate of WM growth than either children injured at a younger age with less severe injuries, or children injured at an older age with severe injuries. This slower rate of growth appeared to underlie the apparent widening over time of performance levels between injury groups for the younger children. This pattern may be related to the notion of deficits that may emerge later in children injured at an earlier age, first posited by Goldman-Rakic and colleagues (Goldman, 1971, 1974; Goldman, Rosvold, & Mishkin, 1970; Goldman & Alexander, 1977), who found that the ability for primates to complete a task was dependent upon the developmental stage of the brain structure believed to underlie that task (Segalowitz & Hiscock, 2002). What was initially thought to be plasticity (discussed in greater detail below)

actually was the consequence of a lesion within a brain structure that had not yet become necessary for performing that task. With further growth and development, which would have made the underlying brain structure essential to complete the task, deficits were observed (Segalowitz & Hiscock, 2002).

Goldman and Alexander (1977) showed that dorsolateral cortex damage did not contribute to delayed-response performance (believed to involve working memory) (Baddeley, 1981; Olton, 1983) until approximately 3 years of age, thus resulting in relatively normal performance on the task prior to that time. Ewing-Cobbs et al. (2004) provided support for this hypothesis in a sample of children who sustained head injury prior to 6 years of age. They found that younger children between 11 and 35 months at the time of testing performed comparably to a non-injured group of children, while older children between 36 and 71 months at the time of testing performed more poorly than comparison children on a self-ordered WM task (Stationary Boxes).

With regards to the current study, given the maintenance and manipulation requirements of the WM measures utilized, and the finding that there are significant developmental changes in maintenance and manipulation of information in school-aged children and adolescents (Crone et al., 2006), it is not surprising that children in the younger age at injury groups demonstrated the slowest rate of growth resulting in discrepancies in levels of performance that appeared to increase over time.

The interaction between rate of growth, age at injury and injury group has implications for the "plasticity" versus "early vulnerability" debate. Plasticity has been defined as an intrinsic property of the central nervous system reflecting its capacity to respond in a dynamic manner to the environment and experience through modification of

neural circuitry (Anderson, Spencer-Smith, & Wood, 2011). Early support for the notion of plasticity arose following primate research of Margaret Kennard, which showed that unilateral motor cortex injury in infancy resulted in better outcomes than those in adults (Kennard, 1938, 1940, 1942). Decades later, this resulted in what is known as the Kennard principle (Teuber, 1974) stating that the earlier one suffers brain damage, the less severe the behavioral loss. However, the relation between age at injury and outcome is more complex. For instance, early diffuse injuries (as are frequently seen in TBI) are associated with poorer recovery (Catroppa, Anderson, & Stargatt, 1999; Stevens, Raz, & Sander, 1999) than are smaller more focal lesions (Aram & Eisle, 1994; Ballantyne, Spilkin, Hesselink, & Trauner, 2008).

Another factor influencing growth is developmental level at time of insult (Dennis, 1989). Indeed, Kennard (1938) found that the effects of motor cortex lesions in primates was dependent upon the development of the motor cortex at the time of lesion, noting that if a brain region is functionally developed in infancy, the effects of a lesion is similar in both infants and adults (Dennis, 2010). Hebb (1942) suggested that a young brain in a rapid stage of development is more vulnerable to injury because normal cognitive development is dependent upon the integrity of particular brain structures in certain stages of development (early vulnerability). Thus, brain injury at a younger age, when the brain is still in a rapid stage of development, places one at increased risk for cognitive deficit. Sustaining insult when skills are developing may influence the rate, mastery, and strategy of these skills so development might be slowed, ultimate levels achieved depressed and children may need to implement compensatory strategies to achieve in the skill area (Anderson et al., 2011).

Possible underlying neurological mechanisms contributing to early vulnerability include the finding that the immature brain may allow more diffuse transmission of traumatic forces due to discrepancies in degree of myelination and water content (Bittigau et al., 1999; Bittigau, Sifringer, Felderhoff-Muesser, & Ikonomidou, 2004; Giza, Mink, & Madikians, 2007), and interruption to dendritic development which affects neural connectivity (Purpura, 1975, 1982; Webb, Monk, & Nelson, 2001). Many studies have supported early vulnerability in numerous cognitive domains including overall cognitive functioning (Anderson et al., 2009; Anderson, Catroppa, Morse, Haritou, & Rosenfeld, 2005; Levin, Ewing-Cobbs, & Eisenberg, 1995), academic achievement (Ewing-Cobbs et al., 2004), reading (Barnes et al., 1999; Chadwick, Rutter, Thompson, & Shaffer, 1981; Shaffer, Bijur, Chadwick, & Rutter, 1980), language (Chapman, 1995; Ewing-Cobbs et al., 1987; Ewing-Cobbs, Brookshire, Scott, & Fletcher, 1998; Ewing-Cobbs, Miner, Fletcher, & Levin, 1989), written language (Ewing-Cobbs et al., 1987), attention (Dennis, Wilkinson, Koski, & Humphreys, 1995; Kaufmann, Fletcher, Levin, Miner, & Ewing-Cobbs, 1993), perceptual-motor and spatial skills (Anderson & Moore, 1995), and verbal WM in children with moderate TBI (Roncadin et al., 2004).

It has also been suggested that brain disruption or insult during a critical, or sensitive period of development can lead to cessation of development, or alteration of its course (Schneider & Koch, 2005; Kolb, Monfils, & Sherren, 2008; Johnston, 2009). With regards to WM, WM capacity increases linearly between ages 4 through early adolescence (Gathercole et al., 2004). Furthermore, Dempster (1981) found that backward digit span (which requires both maintenance and manipulation of information) increased five-fold between the ages of 6 to 13, suggesting substantial development in WM during this time period. This is consistent

with the current findings, with plot inspection suggesting that children injured between 6 and 8 years of age made fewer gains over the two year post-injury follow-up period, while children injured at 9 years of age and older were making greater gains in WM over the two year time period. Thus, the present findings suggest that WM is particularly vulnerable to disruption following early brain insult.

Rates of growth of verbal and visual-spatial WM were not statistically significantly positively related. This does not imply that rate of growth between the two WM tasks differed, as between-task effects were not analyzed. The non-significant positive relation is not likely due to a lack of relation between the developmental trajectories of verbal and visual-spatial WM. Previous studies have shown parallel development of both verbal and visual-spatial WM, suggesting a positive relation (Gathercole et al., 2004; Nichelli et al., 2001; Isaacs & Vargha-Khadem, 1989).

Perhaps the lack of a significant positive relation of verbal and visual-spatial WM growth was related to proposed differences in processing channels and learned knowledge. Verbal WM strategies are more frequently utilized and emphasized in a school setting (Nichelli et al., 2001). Children may have more already established strategies to compensate for difficulties with WM which may lead to differences in rates of growth. Results also indicated that at 12 months post-injury, level of performance was not significantly related to the rate of growth for either WM measure. Thus, at 12 months post-injury, growth was constant irrespective of level of performance at this time. This is likely the result of plateauing rates of growth by 12 months post-injury, as the majority of recovery from TBI occurs within the first year. It is possible that if time since injury had been centered earlier in the post-injury period (e.g. at 2 or 6 months), significant relations would have been detected.

Curvature

Lastly, this study attempted to extend the findings of Levin et al. (2004) who found significant WM performance declines in the severe injury group between 12 and 24 months post-injury, but continued growth during this same post-injury period for children with mild and moderate injuries. The authors attributed this decline to degenerative brain changes secondary to the initial injury. In the current study, children with severe injuries continued to improve between 12 and 24 months, although the rate of growth had slowed over time (but deceleration over time occurred for all three injury groups). The current study examined acceleration/deceleration injury group differences while holding age at injury constant, while age at injury was not considered by Levin et al. (2004). Perhaps performance declines may be more related to both age at injury and injury severity. Support for this possibility comes from Ewing-Cobbs et al. (2004) who examined academic achievement following head injury. The authors looked at growth by severity and age at injury. With regards to arithmetic, children injured at younger ages with mild-moderate and severe injuries exhibited declines in arithmetic scores between baseline and 5 years post-injury whereas older children with both mild-moderate and severe injuries continued to improve over this time. Thus, the rates of acceleration/deceleration in pattern of growth following injury may rely upon age at injury, as well as injury severity.

Clinical Implications

The current findings have important clinical implications. The present findings can better inform psychoeducational information provided to parents and teachers of children who sustain a head injury. Parents and teachers can be informed that the child's ability to successfully complete multi-step instructions (which can negatively affect academic

performance) may be adversely impacted and that the degree of this impact is related to the age at which the child sustained injury and the severity of the injury. However, each child's post-injury cognitive growth trajectory is unique, which highlights the importance of long-term follow-up evaluations to monitor cognitive changes that may not initially be apparent (particularly for children who sustain severe injury at a younger age who may experience cognitive deficits that emerge at a later time). Monitoring of possible cognitive changes also provides the opportunity to intervene if WM deficits emerge, and to tailor intervention that targets the child's WM difficulties. Very few high quality intervention studies have been conducted with children following TBI (Ylvisaker, 2005), and the benefits of WM-specific cognitive training are not well-established (Melby-Lervag & Hulme, 2012).

It has been suggested that WM reflects a general attentional resource, and that if WM is trained, benefits can be seen in a variety of cognitive tasks that rely on attentional capacity (Shipstead, Redick, & Engle, 2010) such as word decoding, arithmetic, attentional control, behavioral inhibition and language abilities (Chein & Morrison, 2011; Holmes et al., 2010; Klinberg, 2010; Perrig, Hollenstein, & Oelhafen, 2009). With regards to WM training following acquired brain injuries, including TBI, encephalitis, anoxia, and brain malignancies, Hagberg-van't Hooft (2005) found that 17 weeks of daily 30 minute training resulted in significant immediate and long-term improvement (at a 6 month follow-up) in the child's school achievement, according to both neuropsychological measures and parent report measures. However, a recent meta-analysis of the effects of WM training programs indicated that the immediate benefits of WM training are seen only on similar WM measures, and do not generalize to other cognitive domains including word reading and arithmetic (Melby-Lervag & Hulme, 2012). Furthermore, the initial benefits on similar WM measures

were not maintained at an average follow-up of 9 month post-training. Thus, the effect of WM interventions on academic achievement and other aspects of behavior involving WM requires additional research. Perhaps the results of the current study might aid in determining which children might be most appropriate for WM-specific interventions and at what point in recovery (e.g. if the WM growth rate might be improved in younger children with severe injuries who receive WM training).

Limitations

The implications of the current study should be interpreted within the context of several limitations. First, as previously discussed, power estimates suggested that the present study may have lacked sufficient power to detect small to medium differences between injury groups. While similar studies suggested that the size of the current sample should have been sufficient to detect medium to large effect sizes (Gorman et al., 2012), a larger sample may have been required to detect small to medium effect sizes in the current study.

When interpreting the current results it should also be kept in mind that the measurement scale of the data was not on a ratio data scale, which has been considered the optimal data scale for use in growth curve analysis because the ratio scaling most appropriately models change (Francis et al., 1991). However, this limitation is not unique to the present study, as ratio scale data is seldom available within the field of psychological research (Howell, 2007).

When considering the nature of the data, it should also be kept in mind that the WM measures utilized in the current study were not normed. Thus, it cannot be determined whether the scores obtained by the children in this study were below that of a normative sample. However, regardless of whether normative data would have been available for the

WM measures, raw scores would have been entered into the growth curve model because raw scores represent the best characterization of growth for each child. Scaled scores would not have represented changes in performance over time because age-related change is eliminated by the scaling methods (Francis et al., 1991). The measures used in the current study also lacked estimates of reliability. While within test correlations at each time point were high ($p < .0001$), calculating the reliability of the measures could provide further support for the use of these measures in longitudinal WM studies.

Another limitation of the current study is that a comparison group of non-injured children was not available for inclusion. An orthopedic comparison group was utilized which is advantageous because it controls for pre-morbid injury characteristics such as impulsivity and attentional difficulties that may predispose children to injury (Fay et al., 2009; Keenan, Hall, & Marshall, 2008). It also helps control for behavioral and psychosocial difficulties such as agitation, apathy, emotional lability, sleep disturbance, depression and diminished self-esteem (Barry, Taylor, Klein, & Yeates, 1996; Mangeot, Armstrong, Colvin, Yeates, & Taylor, 2002; Tham et al., 2012; Yeates et al., 2001) that are often seen in children as they adjust to cognitive and/or physical limitations following injury (Semrund-Clikeman, 2001). However, detailed measures of psychosocial functioning and psychiatric symptoms were not analyzed in this study. This must be kept in mind because psychiatric symptoms, in particular depression, have been associated with poor memory performance, particularly in children with more severe levels of depression (Lauer et al., 1994). Because measures assessing psychiatric symptoms were not included in this study, it is not clear whether children in the sample experienced depression, which could have impacted their performance. Furthermore, because children with orthopedic injuries may not represent a typically-developing sample

(Fay et al., 2009; Keenan et al., 2008), the findings pertaining to group differences do not represent differences between children with head injuries and typically-developing children. A comparison of the developmental WM trajectories of typically-developing children, children with orthopedic injuries, and children with mild-moderate and severe TBI is needed. Future studies might consider utilizing such a two comparison-group design.

When considering the sample utilized in the current study it should also be kept in mind that the complicated mild-moderate sample consisted of only 13 participants. The small sample size may have contributed to unanticipated findings such as this group having mean VSS scores higher than those of the orthopedic group, and having the lowest mean SES. Thus, the results of the current study must be interpreted with this in mind.

Future Directions

The findings of the current study could be extended by future research incorporating neuroimaging techniques with longitudinal studies of WM growth following head injury. Future studies might consider utilizing the findings of the current study with neuroimaging studies of the neural correlates of WM (Wilde et al., 2011) which could provide a better understanding of underlying neurological mechanisms associated with differences in trajectories of WM growth following head injury. Neuroimaging techniques might also be utilized to determine more precisely which regions of the brain are activated by the verbal and visual-spatial WM measures utilized in this study, which could elucidate the brain regions associated with maintenance and manipulation of verbal and visual-spatial information. Furthermore, future research might also consider the implications of post-injury WM growth on academic performance. It has been suggested that academic difficulties experienced by children with TBI may be more related to deficits in general

neuropsychological abilities (e.g. memory and attention) as opposed to more specific disabilities in reading or mathematics (Barnes, Fuchs, & Ewing-Cobbs, 2010). If WM partially underlies academic deficits seen in children with TBI, then understanding the growth of WM following head injury may help guide clinical interventions implemented in both school and home environments. Lastly, there is a strong need for TBI pediatric interventions tailored to the developing brain so that our understanding of WM growth (or lack thereof) and the growth of other cognitive domains post-injury can be specifically targeted with empirically-based cognitive interventions.

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