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

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Abstract

In a prospective longitudinal study, the trajectory of verbal and visual-spatial working memory (WM) development was examined 2-, 6-, 12-, and 24-months following complicated-mild to severe pediatric traumatic brain injury (TBI; $n = 55$) relative to an orthopedic injury comparison group ($n = 47$). Individual growth curve modeling revealed an interaction of age, severity, and time for verbal, but not visual-spatial WM. The youngest children with severe TBI had the lowest scores and slowest verbal WM growth. WM outcome is best understood in light of age at injury and TBI severity. Findings support the early vulnerability hypothesis and highlight the need for long-term follow-up.

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; 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, 2004; Roncadin, Guger, Archibald, Barnes, & Dennis, 2004). Because WM has been implicated in the acquisition of academic skills such as reading, reading comprehension, mathematics, and written language (Geary, 2011; Jacob & Parkinson, 2015; Niedo, Abbott, & Berninger, 2014; Peng, Namkung, Barnes, & Sun, 2016; Raghubar, Barnes, & Hecht, 2010; Swanson, 2015), as well as to social cognitive skills (Dennis, Agostino, Roncadin, & Levin, 2009), it is possible that deficits in WM resulting from TBI can lead to poorer functioning in academic and other social settings. Thus, it is important to understand the developmental course of WM following TBI, as well as how injury-related variables such as age at injury and injury severity affect WM development. However, relatively few studies have examined development of WM following pediatric TBI using statistical approaches that model characteristics of change (Levin et al., 2004). To address these gaps in the literature, this study characterized the growth and developmental

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pattern of verbal and visual-spatial domains of WM following head injury in relation to age at injury and injury severity.

Typical working memory development

Working memory 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). The development of the maintenance component of WM begins as early as 7 months of age, with greater ability to store information in memory for a longer duration with increasing age (Diamond, 2002). The three components (the central executive, phonological loop and visuo-spatial sketchpad) of the Baddeley (1996) model of WM were found to be established by 6 years of age, with the maintenance capacity of each component increasing linearly from age 4 through adolescence (Gathercole, Pickering, Ambridge, & Wearing, 2004).

The development of maintenance and manipulation components of verbal and visual-spatial memory spans has been directly compared (Isaacs & Vargha-Khadem, 1989). Significant age effects were found, with verbal memory span (both forward and backward) increasing gradually between the ages of 7 and 15, visual-spatial forward span increasing most significantly between the ages of 9 and 10, and visual-spatial backward span increasing most significantly between the ages of 7 and 8. Developmental increases in memory span were similar for both verbal and visual-spatial material. These findings were extended by Nichelli, Bulgheroni, and Riva (2001) who found a slow, constant improvement in performance on the verbal and visual-spatial span measures, with the verbal measure having an advantage of 1.5 verbal span items over visual span items. The authors attributed the superior performance on the verbal span measure to the use of different processing channels and more frequent use of verbal memory strategies on a daily basis.

Effects of TBI on working memory

Numerous studies have demonstrated that pediatric TBI has a detrimental effect on WM, (Conklin et al., 2008; Gorman et al., 2016; Hanten, Levin, & Song, 1999; Levin et al., 2002, 2004; Mandalis, Kinsella, Ong, & Anderson, 2007). The literature suggests that more severe injuries are related to greater deficits in WM (Levin et al., 2002, 2004; Roncadin et al., 2004) while the literature on the effect of age at injury on WM is not entirely consistent (Gorman et al., 2012; Roncadin et al., 2004). Most studies examining the effect of TBI on WM have utilized primarily verbal measures of WM. However, one more recent study examined the effect of pediatric TBI on measures of both verbal and visual-spatial WM with parallel processing requirements (Gorman et al., 2012). These results suggested that both verbal and visual-spatial WM were significantly impacted by TBI to a similar extent, and that younger age at injury was a significant predictor of poorer maintenance and manipulation performance on visual-spatial WM, but not of an analogous verbal WM task when assessed an average of 4 years after injury. Further investigation of the effects of age at injury on WM, in particular development of WM, was suggested to provide further clarity.

Modeling change in cognitive functions post-TBI

Individual growth modeling is one approach to measuring change. The advantages of this approach have been discussed in Francis, Fletcher, Stuebing, Davison, and Thompson (1991). Growth curve modeling has been used to look at level of performance and rate of change in several academic and cognitive skills including academic achievement (Ewing-Cobbs, Barnes, 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 after the initial recovery period during the first 6 months after TBI, younger children with more severe injuries demonstrated a slower rate of development over time relative to younger children with milder injuries, and older children with severe injuries (Ewing-Cobbs, Barnes, et al., 2004; Levin et al., 2001; Thompson et al., 1994). However, Yeates et al. (2002) found a faster rate of development in memory scores in the early recovery period (i.e., 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, Barnes, et al., 2004; Yeates et al., 2002), with discrepancies greater in children injured at an older age with regards to arithmetic (Ewing-Cobbs, Barnes, et al., 2004). Ewing-Cobbs, Barnes, et al. (2004) also found a negative relation between arithmetic level of performance and rate of development, suggesting that children with lower levels of performance exhibited greater rates of development.

To date, a single study has examined verbal WM longitudinally (Levin et al., 2004). The authors administered an N-back task at 1, 3, 6, 12, and 24 months post-injury and the percentage correct score on the N-back task was compared over time in children with mild, moderate and severe injuries. WM performance improved in all three severity groups (mild, moderate, and severe) over the first 3 months post-injury. However, continued improvement was only observed from 12 to 24 months post-injury in the mild and moderate injury groups. Severely injured children's performances tended to decline during this same period, which may be related 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, Wilde, et al., 2008; Wilde et al., 2005). At 12 months post-injury, rate of change (i.e., slope) did not differ by severity groups. Curvature, or the pattern of change, differed significantly, with the mild group showing slight acceleration (i.e., score improvement) and the severe group demonstrated significant deceleration (i.e., score decline). The present study sought 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 examined development 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 development 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 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). 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).

The current study investigated the development of WM in children during the first 2 years following complicated mild-moderate and severe head injury in school-aged children and adolescents in relation to a comparison group of children with orthopedic injuries (OI). The aims of the current study were (a) to use individual growth curve modeling to evaluate the pattern of WM development in children with complicated mild-moderate and severe head injury, as compared to children with OI, using a multivariate approach to examine both verbal and visual-spatial WM at 2, 6, 12, and 24 months post-injury; and (b) to determine whether WM development was affected by age at injury and injury severity. Given literature suggesting that complicated mild injuries place one at increased risk of cognitive sequelae more similar to those seen in moderate injuries (Levin, Hanten, et al., 2008; Williams, Levin, & Eisenberg, 1990), these two groups were combined. We hypothesized that children with severe TBI injured at a younger age would demonstrate the poorest level of performance and a slower rate of development in both verbal and visual-spatial WM at 12 months post-injury than both younger and older children in the complicated mild-moderate and OI groups, and that the WM development of children with more severe injuries would demonstrate curvature that decelerated over time, reflecting initial improvements in performance followed by a performance decline. We also hypothesized that there would be a positive relation between intercepts such that individuals with better performance on verbal WM would perform better on the visual-spatial measure. We expected that individuals with greater rates of development on the verbal measure would have greater rates of development on the visual-spatial measure, and that as level of performance improved, rate of development would slow.

Methods

Participants

Participants included 42 children who sustained severe TBI, 13 children who sustained complicated mild-moderate TBI, and 47 comparison children with orthopedic injuries recruited from a Level 1 Pediatric Trauma Center who were enrolled in a longitudinal, prospective outcome study. Due to the small number of children with complicated mild or moderate TBI, they were combined into a single group, given evidence that they demonstrate similar neurocognitive recovery profiles (Levin, Hanten, et al., 2008). These

participants were drawn from a larger cohort of 119 children enrolled in the study from 2004 to 2007. Inclusion criteria for children in the TBI groups were: (a) TBI resulting from acceleration-deceleration or blunt impact injuries caused by vehicular accidents, falls, or impact with a blunt object; (b) age 6–15 years at the time of injury; and (c) bilingual or primarily English-speaking. Exclusion criteria were determined with a brief questionnaire administered to parents. Exclusion criteria for the TBI groups were: (a) children with injury mechanisms occurring with low frequency that have differing outcomes than acceleration/deceleration injuries (e.g., penetrating brain injuries); (b) children with a prior history of TBI or repeated TBI after enrollment; (c) children of illegal immigrants and families residing outside the catchment area due to difficulty maintaining enrollment; and (d) children with major developmental or psychiatric disorders, including intellectual disability and autism spectrum disorders that may reduce our ability to detect cognitive changes related to the TBI.

The comparison group was composed of 47 children hospitalized for OI who had no evidence of either head or facial injuries, and no symptoms of concussion. The OI group was included to control for possible pre-injury factors influencing the likelihood of sustaining an injury and to control for the stresses of injury and hospitalization. Exclusion criteria 2–4 were also applied to the OI group. Therefore, the overall sample size was composed of 102 children (42 with severe TBI, 13 with complicated mild or moderate TBI and 47 with orthopedic injuries). Of the original 119 children, 17 were excluded from analyses because they were not able to complete a minimum of two evaluations.

The severity of TBI was assessed using the lowest post-resuscitation Glasgow Coma Scale (GCS) score (Teasdale & Jennett, 1974). Complicated mild TBI was defined as GCS score of 13–15, with neuroimaging evidence of parenchymal injury, moderate TBI was defined as the GCS score of 9–12 and severe TBI as GCS score of 3–8. The severity of OI was assessed using the Abbreviated Injury Scale (Baker, O'Neill, Haddon, & Long, 1974). This scale categorizes the severity of an injury to different anatomic structures as indicated by threat to life. Children with OI had skeletal or body scores 4 indicating minor to severe injuries.

Measures

Hollingshead four factor index—The Hollingshead (Hollingshead, 1975) is a survey designed to measure socioeconomic status (SES). A child participant's parent's education is rated on a 7-point scale, and the child's parent's occupation is rated on a 9-point scale. Education and occupation scores are then weighted to obtain a single SES score (range 8–66).

Wechsler abbreviated scale of intelligence (WASI)—Intellectual Quotient (IQ) was determined with the two-subtest version of the WASI (Wechsler, 1999). The two subtest version consists of a vocabulary measure (Vocabulary Subtest) and a nonverbal reasoning measure (Matrix Reasoning).

Category listening span task (CLS)—The CLS is an experimental measure assessing 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. The outcome measure consisted of the total number of correctly answered trials, including the number of trials below the basal level. No normative information is available.

Visuospatial span (VSS)—The VSS (Cornoldi et al., 2001) was created with the same processing demands as the CLS, and allows for a more direct comparison of verbal and visual-spatial 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 outcome measure for VSS was calculated in the same manner as for CLS. Normative data is also unavailable for VSS.

Procedure

Informed written consent was obtained from the child's guardian. In accordance with guidelines established by the university's Institutional Review Board, 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. Participants were examined individually in an outpatient setting, in a quiet testing room. Participants were evaluated longitudinally at approximately 2, 6, 12, and 24 months post-injury. Each 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 toward the middle of the battery, but were not administered successively to provide variation in task requirements.

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 multivariate general linear mixed model approach was appropriate for the dataset. The model included a multivariate component to examine both verbal and visual-spatial WM within the same model. In order to do this, a model was run including time since injury as a predictor, and residuals were plotted to determine whether the distribution was symmetric and unimodal to determine if a linear approach was appropriate. 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).

Next, 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. Adjusted means presented in Table 1 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.

Results

Demographic and Injury-related Information

Demographic information for each group is presented in Table 2. Groups did not differ significantly 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 3. 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 Four 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).

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, Francis, et al., 2009). That is, because IQ differences may be due to the injury itself, attempting to control for IQ would violate the homogeneity of slopes assumption. Statistics for age at injury in months are presented in Table 3 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.

Working memory 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 Table 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.

Adjusted means

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. Cohen's d values are presented in Table 1. Per Cohen's interpretation, effect sizes range from small to large, but are generally small.

Polynomial trend of the data and appropriateness of a general linear mixed model

To determine the appropriate form of the data (linear, quadratic or cubic), scores for the CLS and VSS measures were plotted as a function of time since injury for each level of injury. A quadratic trend best approximated the curvature of the growth curves, as WM scores appeared to increase from the 2 to 6 months evaluations and from the 6 to 12 months evaluations, but not between the 12 and 24 months evaluations. 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. Residuals of this model were then plotted and revealed a distribution that was symmetric and unimodal, suggesting that a general linear mixed model was appropriate.

Determining random effects

The Akaike Information Criterion (AIC) was better when intercept was random as opposed to fixed, and when curvature was fixed, as opposed to random. The AIC value was unchanged when the slope of linear time was included as fixed, and thus slope of linear time was included as random. Thus, 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

A three-way intercept by age at injury by injury group interaction was examined for both the CLS and the VSS measure to test whether children injured at a younger age with severe injuries would demonstrate the poorest level of performance at 12 months post-injury (the time point at which the data were centered). The results were not significant for the CLS measure, $F(1, 371) = 0.01, p = .92$, nor for the VSS 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 CLS, $F(1, 371) = 1.08, p = .30$, nor for VSS $F(1, 371) = 1.50, p = .22$. Visual inspection of the plots in Figures 1 and 2 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 development by age at injury and injury group

The slope by age at injury by injury group interaction was examined for both measures to test whether children injured at a younger age, with more severe injuries would exhibit the slowest rate of development. A significant three-way interaction was found for CLS, $F(1, 371) = 10.72, p < .01$, with visual inspection of Figure 1 showing that children injured at a younger age with more severe injuries demonstrated a slower rate of development 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 VSS measure, $F(1, 371) = 1.59, p = .21$, although visual inspection of Figure 2 suggests that this pattern was also present on the VSS measure, it did not reach statistical significance. The two-way slope by injury group interaction was examined for VSS when age at injury was controlled, and was not significant, $F(1, 371) = 2.79, p = .10$.

Differences in curvature by injury group

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

Post hoc analyses

Visual inspection of Figures 1 and 2 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 CLS $F(1, 369) = 0.41, p = .52$, and VSS $F(1, 369) = 1.83, p = .07$ did not reach statistical significance. However, the trend for the VSS score suggests that there was less difference in performance of the older groups at 24 months and that the severe TBI group closed the gap

while performance of the younger children with mild-moderate and severe TBI remained below that of the OI group.

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 CLS and VSS (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 development of verbal and visual-spatial WM

To determine whether there was a positive relation between rate of development (slopes) between the two WM measures (suggesting that individuals with greater rates of development on the verbal measure would also have greater rates of development 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, $z = 0.34$, $p = .73$.

Relation between level of performance and rate of development of verbal and visual-spatial WM

The covariances between the intercept and slope of the verbal and visual-spatial WM measure were examined to determine whether there was a negative relation between slope and intercept for CLS and VSS (suggesting that as level of performance improved, rate of development would slow). On the CLS measure, the relation was neither statistically significant, nor negative, $z = 1.26$, $p = .21$, and for the VSS measure, the relation was negative, but not statistically significant, $z = -1.08$, $p = .28$.

Discussion

Summary of findings

The primary aim of the present study was to characterize the pattern of development of verbal and visual-spatial WM across the first 2 years after injury in children with complicated mild-moderate and severe TBI as compared to a sample of children with orthopedic injuries. Age at injury and injury severity were expected to influence the trajectory of WM outcomes. The secondary aim examined the relation between change over time in verbal and visual-spatial WM measures. Both aims were evaluated using individual growth curve modeling and using a multivariate approach so that level, slope, and curvature of both verbal and visual-spatial WM could be considered within a single model. Contrary to our first hypothesis, the level of WM performance of children in all three injury groups did not differ significantly when data were centered at 12 months post-injury. Regarding the slope, severely injured children had a slower rate of recovery for verbal WM than the other groups. The rate of change did not decelerate over time, suggesting that they continued to develop verbal WM skills, albeit at a slower rate than children with lesser injuries. In

contrast to verbal WM, injury severity did not interact with visual-spatial WM scores. Age at injury also influenced the trajectory of verbal WM scores. The three-way interaction of age, injury severity, and time was significant. When children were injured at a younger age, more severe injuries were associated with a slower rate of improvement in WM scores, as compared to the complicated mild-moderate and orthopedic comparison groups. This pattern approached significance for visual-spatial WM.

Regarding the relation between the two domains of WM, the level of performance on verbal and visual-spatial WM was positively related. Despite the similar level of performance across domains, the rates of development of verbal and visual-spatial WM were not positively related. Moreover, contrary to expectation, the rate of development on each of the WM measures did not decrease as the level of performance increased.

Levels of performance

With regard 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. Plot inspection suggested 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 development. Perhaps with a larger sample size, injury group differences in levels of performance may have been detected, particularly given that effect sizes were generally small.

Of interest is the finding that there was not a statistically significant difference in levels of performance between injury groups. 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, 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. 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). 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 development

Interestingly, the relation between the rate of development of WM varied as a function of age at injury. 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 development 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 development 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 & Alexander, 1977; Goldman, Rosvold, & Mishkin, 1970), with more recent studies providing support for this notion (Chapman et al., 2010; Ewing-Cobbs, Prasad, et al., 2004; Ryan et al., 2015). With regard 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, Wendelken, Donohue, Van Leijenhorst, & Bunge, 2006), it is not surprising that children in the younger age at injury groups demonstrated the slowest rate of development resulting in discrepancies in levels of performance that appeared to increase over time.

The interaction between rate of development, age at injury, and injury group has implications for the “plasticity” versus “early vulnerability” debate. Early support for the notion of plasticity arose following primate research of Margaret Kennard (Kennard, 1938, 1940, 1942; Teuber, 1974). However, the relation between age at injury and outcome is more complex. 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). 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, Barnes, et al., 2004), reading (Barnes, Dennis, & Wilkinson, 1999; Chadwick, Rutter, Thompson, & Shaffer, 1981; Shaffer, Bijur, Chadwick, & Rutter, 1980), language (Chapman, 1995; Ewing-Cobbs, Brookshire, Scott, & Fletcher, 1998; Ewing-Cobbs et al., 1987; 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 (Johnston, 2009; Kolb, Monfils, & Sherren, 2008; Schneider & Koch, 2005). With regard to WM, WM capacity increases linearly between ages 4 through early adolescence (Gathercole et al., 2004). 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 2 year post-injury follow-up period, while children injured at 9 years of age and older were making greater gains in WM over the 2-year time period. Thus, the present findings suggest that WM is particularly vulnerable to disruption following early brain insult.

Rates of development of verbal and visual-spatial WM were not statistically significantly positively related. This does not imply that rate of development 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, as previous studies have shown parallel development of both verbal and visual-spatial WM, (Gathercole et al., 2004; Isaacs & Vargha-Khadem, 1989; Nichelli et al., 2001). Perhaps the lack of a significant positive relation of verbal and visual-spatial WM development 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 development.

Results also indicated that at 12 months post-injury, level of performance was not significantly related to the rate of development for either WM measure. Thus, at 12 months post-injury, development was constant irrespective of level of performance at this time. This is likely the result of plateauing rates of development by 12 months post-injury, as the majority of recovery from TBI occurs within the first year.

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 development during this same post-injury period for children with mild and moderate injuries. In the current study, children with severe injuries continued to improve between 12 and 24 months, although the rate of development 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, an idea which has been supported by research evaluating change in academic achievement following TBI (Ewing-Cobbs, Barnes, et al., 2004).

Limitations

The implications of the current study should be interpreted within the context of several limitations related to power, sample size, and measurement characteristics of the WM scales. First, 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 would have been required to detect the generally small to medium effect sizes in our study. In addition, the complicated mild-moderate sample consisted of only 13 participants. The small sample size may have contributed to unanticipated findings such as the complicated-mild-moderate TBI group having mean visual-spatial WM scores higher than those of the orthopedic group, the non-significant group differences on level of performance for either WM measure or the non-significant (albeit approaching significance) rate of development by injury group by age at injury interaction for the visual-spatial measure. 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 (Francis et al., 1991). However, this limitation is not unique to the present study, as

ratio scale data are seldom available within the field of psychological research (Howell, 2007). It should also be kept in mind that the WM measures utilized in the current study were translated and not normed and there was no typically developing comparison group. Thus, it cannot be determined whether the scores obtained by the children in this study were below that of a normative sample. However, raw scores represent the best characterization of development for each child, as scaled scores eliminate age-related change (Francis et al., 1991). Therefore, the use of raw scores does not limit interpretation of the findings. Furthermore, bilingual children were not excluded from this study. This is noteworthy, given that some studies have shown that bilingualism confers an advantage on working memory tasks (Sorge, Toplak, & Bialystok, 2017; Veenstra et al., 2016). However, the relationship between bilingualism and better working memory performance has not been consistently demonstrated (Engel De Abreu, 2011; Gathercole et al., 2014; Loe & Feldman, 2016).

Future directions

The findings of the current study could be extended by future research incorporating neuroimaging techniques with longitudinal studies of WM development 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 development following head injury. Neuroimaging techniques might also be utilized to determine more precisely which components of the networks 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 development 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 development of WM following head injury may help guide clinical interventions implemented in both school and home environments. It would also be of interest to determine whether developmental trajectories of academic achievement in reading, writing, and math, as well as in social cognition, might be similar to the trajectory of WM following TBI, given that WM has been shown to be related to these areas. The effects of age at injury and injury severity on developmental trajectories post-TBI in other cognitive domains should also be investigated to determine whether the relations found in the current study extend to other areas of cognition. Lastly, there is a strong need for TBI pediatric interventions tailored to the developing brain so that our understanding of WM development (or lack thereof) and the development of other cognitive domains post-injury can be specifically targeted with empirically-based cognitive interventions. While still a young area of research, several studies have investigated the efficacy of certain interventions such as cognitive training programs, on cognitive performance in attention, memory, and daily functioning (Catroppa et al., 2015) as well as on specific aspects of WM (Phillips et al., 2016). The findings of these studies are encouraging, with positive effects of cognitive training found at 3 months (Phillips et al., 2016) and 6 months (Catroppa et al., 2015) post-injury. However, additional

research is needed to determine whether cognitive interventions have a positive impact on the long-term developmental trajectory of WM and other skills.

Conclusions

In summary, the current study further elucidates the complex relation between severity of TBI, age at which TBI was sustained, and outcomes in WM. Children who sustain a severe injury at a younger age are at greatest risk of WM deficits and show the slowest rates of development. This highlights the importance of continued follow-up of these children for several years after injury. Functional deficits related to WM may increase over time indicating that the need for interventions over time may also increase. Thus, repeat neuropsychological evaluations would play a critical role in determining appropriate interventions or accommodations to improve outcomes with this population.

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Figure 1.

Expected verbal working memory by severity and age at injury. Dotted lines represent children injured at a younger age by orthopedic, mild/moderate and severe injury groups. Solid lines represent children injured at an older age of same injury severity groups.

Figure 2.

Expected visual spatial working memory by severity and age at injury. Dotted lines represent children injured at a younger age by orthopedic, mild/moderate and severe injury groups. Solid lines represent children injured at an older age of same injury severity groups.

Table 1

Cohen's d for group comparisons.

	Orthopedic vs. Complicated Mild-Moderate TBI	Complicated Mild-Moderate TBI vs. Severe TBI	Orthopedic vs. Severe TBI
Category Listening Span			
2 months post-injury	0.27	0.28	0.55
6 months post-injury	0.28	0.17	0.45
12 months post-injury	0.38	0.26	0.64
24 months post-injury	0.58	0.10	0.49
Visual Spatial Span			
2 months post-injury	0.13	0.26	0.14
6 months post-injury	0.13	0.41	0.29
12 months post-injury	0.38	0.95	0.56
24 months post-injury	0.08	0.47	0.39

Table 2

Percentage of ethnicities and genders.

	Orthopedic	Complicated Mild-Moderate TBI	Severe TBI
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 3

Means and standard deviations of demographic and injury-related variables.

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

Table 4

Correlations of working memory measures 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
	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.^{*}
 $p < .0001$.

Table 5

SES and age at injury adjusted means, root mean square errors, and R^2 values.

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

Note.

* denotes unadjusted root mean square error.

** denotes unadjusted R^2 .