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The UCLA Study of Children with Moderate to Severe Traumatic Brain Injury:
Event-Related Potential Measure of Interhemispheric Transfer Time.

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Abstract

Traumatic brain injury (TBI) frequently results in diffuse axonal injury and other white matter damage. The corpus callosum (CC) is particularly vulnerable to injury following TBI. Damage to this white matter tract has been associated with impaired neurocognitive functioning in children with TBI. Event-Related Potentials can identify stimulus-locked neural activity with high temporal resolution. They were used in this study to measure interhemispheric transfer time (IHTT) as an indicator of CC integrity in 44 children with moderate/severe TBI at 3-5 months post-injury compared with 39 healthy control children. Neurocognitive performance was also examined in these groups. Nearly half of the children with TBI had IHTTs that were outside the range of the healthy control group children. This subgroup of TBI children with slow IHTT also had significantly poorer neurocognitive functioning than healthy controls— even after correction for premorbid intellectual functioning. We discuss alternative models for the relationship between IHTT and neurocognitive functioning following TBI. Slow IHTT may be a biomarker that identifies children at risk for poor cognitive functioning following moderate/severe TBI.

Keywords: corpus callosum, pediatric traumatic brain injury, event-related potential, interhemispheric transfer time, neurocognitive functioning

The UCLA Study of Children with Moderate to Severe Traumatic Brain Injury:
Event-Related Potential Measure of Interhemispheric Transfer Time

Traumatic brain injury (TBI) frequently results in diffuse axonal injury, diffuse white matter atrophy, whole brain volume reductions,¹ and injury to unmyelinated brain fibers.² The corpus callosum (CC) is particularly vulnerable to diffuse axonal injury.^{3,4,5,6,7} There are conflicting results on the relation between acute injury severity and the persistence of CC injury. Reductions in CC area persisted from three months up through three years following severe pediatric TBI, while children with mild and moderate TBI had increases in CC size consistent with normal development over this time span.⁸ However, in a different study of children with complicated mild, moderate/severe pediatric TBI, volumetric reductions in CC were negligible at three months post TBI, but significant reductions were found 18 months post-injury in children with TBI.⁷ The reduction over time in CC volume, along with thinning of the CC, are thought to result from Wallerian degeneration following TBI.⁹

The posterior region, or splenium, of the CC is especially vulnerable to TBI^{10,11,12,13} Atrophy of the splenium of the CC has been observed following TBI.^{14,15,16} Lesions in the posterior half of the CC accounted for 80% of all CC injuries in a study of 92 patients (i.e., ages 2-77, mean age 28) with severe TBI.¹⁵ These lesions are thought to be a direct result of the injury including DAI, of secondary injuries, or of impaired or arrested CC development post injury.¹⁵ The anterior CC is also vulnerable to secondary injury mechanisms following TBI such as elevated intracranial pressure,¹⁷ although this finding is less established in the literature. In children with severe TBI, increased intracranial pressure immediately following TBI was correlated with reduced anterior CC size and overall white matter loss five years post TBI.¹⁸

Taken collectively, brain imaging studies have clearly demonstrated the presence of structural damage to the CC following TBI. The present study will test hypotheses about the functional consequences of CC damage.

Interhemispheric Transfer Time (IHTT) has been used to assess the functional integrity of the CC. IHTT refers to the time required for information to pass across the CC from one hemisphere to another. Patients with focal CC damage (patients with commissurotomies, callosotomies, and callosal agenesis) have slow IHTT^{22,23}. Disconnection in the posterior CC is associated with lower crossed-uncrossed differences in visuomotor reaction time, a measure of IHTT.²⁴ In a case study of a patient with interhemispheric disconnection following TBI, Peru and colleagues²⁴ suggested that the posterior CC might be a communication channel for mediating visuo-motor performance speed. The hypothesis that the posterior CC is responsible for the interhemispheric transfer of visual information is supported by other studies, including a study examining commissurotomies in non-epileptic patients²⁵ and case studies of two patients with posterior CC sectioning for tumor removal,²⁶ as well as in a case study of one patient with hemialexia following posterior CC surgical sectioning.²⁷

Some evidence for impaired IHTT in TBI is provided by the performance of children with severe TBIs on a verbal dichotic listening task¹⁰ and adults on visual and tactile reaction time tasks²⁰ that required IHTT. Although white matter atrophy was moderately related to visual and tactile reaction time task performance in adults, total CC area was not significantly related to performance on these tasks.²⁰

The current study used electroencephalography (EEG) scalp recordings of visual Event-Related Potentials (ERPs) to measure IHTT. This electrophysiological measure may be a more direct index of IHTT than performance on crossed-uncrossed differences (i.e., motor speed

reaction time tasks) and tachistoscopic measures used in prior studies of individuals with TBI.²² Visual ERPs have been used in previous studies to examine IHTT as an index of CC functioning in patients with focal CC damage and in patients with CC agenesis.^{22,23,28} Longer IHTTs indicate slower transfer of visual information across the posterior visual brain regions.²² While previous studies have examined EEG-ERP measured IHTTs in healthy adults and adults with non TBI CC damage, this is the first study to examine EEG-ERP measured IHTTs in a pediatric TBI sample.

There are cognitive effects of CC damage. CC atrophy following TBI is associated with impaired performance on the WAIS Processing Speed Index,^{18,19,20} and WAIS Verbal, Performance, and Full Scale IQs, Judgment of Line Orientation test, and the Trail Making Test.²¹ CC damage associated with elevated intracranial pressure was correlated with impairments in children's working memory and social interaction skills, and with impaired performance on the copy condition of the Rey-Osterrieth Complex Figure test.¹⁸

The current study utilized visual ERPs to measure post-acute (i.e., 3-5 months after injury) IHTTs in children with moderate to severe TBIs (msTBI) and a group of healthy control children. In a prior paper³ we examined the relation between visual ERP measured IHTTs and brain metabolites measured by magnetic resonance spectroscopy in 10 children with TBIs post-acute, but never compared visual ERP measured IHTTs of children with TBI to controls. Data in this study were collected from all participants on tasks tapping the neurocognitive domains which a recent meta-analysis of studies of cognitive functioning following pediatric TBI²⁹ found that children with msTBI had their greatest impairments. Those domains were: processing speed, working memory, learning/memory, and executive functioning.

It was hypothesized that children with msTBI would have slower visual ERP IHTTs than controls. In addition, it was predicted that slow IHTTs would be associated with deficits in

neurocognitive functioning, including: processing speed, working memory, learning, and executive functioning in children with msTBIs.

Materials and Methods

Participants

msTBI participants were recruited from the pediatric intensive care units of four Los Angeles County trauma hospitals. The overall study was approved by UCLA Institutional Review Boards and the Institutional Review Boards of each facility from which patients were recruited. Participants were invited to participate following a telephone screening for the following inclusion criteria: (1) the child had sustained a moderate to severe closed-head, non-penetrating TBI. Moderate to severe injury was defined as a Glasgow Coma Scale (GCS) score between 3 and 12 on admission to the hospital; children with higher GCS scores were included if their injury produced confirmed abnormalities on clinical brain imaging (e.g., hemorrhage); (2) 8-18 years of age at the time of injury; (3) normal visual acuity or normal vision once corrected with eyeglasses or contact lenses; and, (4) the child's proficiency in the English language, so he/she could understand instructions and participate in the neurocognitive assessments. Participants with a pre-TBI history of developmental, neurological, or psychiatric disorders (e.g., including Attention Deficit Hyperactivity Disorder and previous head injuries) were excluded. Parents provided written informed consent, while children provided written assent to participate in this study. MRI scans, standard neurocognitive evaluations, and another neurobehavioral measure were collected from participants in addition to the EEG/ERP data. The control group included 39 typically developing children ascertained from the same communities as the msTBI patients. Healthy control group children had no history of head trauma and were also required to meet inclusion criteria 2-4. Participants completed the entire protocol, including electrophysiological and neurocognitive evaluations, in one day.

Eighty-three children were entered into this study. Six children (5 children with msTBI and 1 control child) were removed from data analysis due to unreadable ERP results. These children's ERPs were unreadable due either to excessive eye-movements, muscle tension-related artifacts, or other "noise" which made the peak points on their parietal and occipital EEG waveforms unidentifiable. Three additional children (2 controls and 1 child with TBI) were removed from data analysis due to missing mastoid EEG channels. To remain consistent with inclusion criteria, one additional child with msTBI was removed from data analysis after we learned that this child was diagnosed with ADHD prior to the msTBI. There were 44 children with TBI and 39 healthy control participants included in the analyses presented below.

Preliminary review of the distribution of IHTT scores of the msTBI and control participants (see Figure 1) revealed that the distribution of scores in the msTBI group was highly skewed, with a substantial number of the scores of the msTBI group outside of the normal range. Just over half ($n = 26$) of the msTBI group had IHTT scores within 1.5 standard deviations of the normal range. The balance of the TBI group had very slow IHTTs, outside of the normal range. The normal range was defined based on the IHTT scores for the healthy control group. The cutoff for including participants in the slow IHTT group was an IHTT greater than the 1.5 standard deviations of the range in the healthy controls. Consequently, the TBI group was split into two subgroups: normal IHTT TBI ($n=26$) and slow IHTT ($n=18$) TBI children. (See results section for more details).

INSERT FIGURE 1 ABOUT HERE

The demographic and clinical characteristics of the three groups are presented in Table 1. A 3 x 1 analysis of variance revealed that the normal range IHTT and slow IHTT msTBI groups and healthy control group did not significantly differ in age. Chi-square tests revealed that the three

groups also did not significantly differ in gender or handedness. Hand dominance was based upon self-report from participants. The normal IHTT and slow IHTT msTBI groups did not differ in their worst GCS recorded during the first 24 hours of injury, nor were these two groups different on the average time since injury at time of study participation. Worst GCS score was not available for one normal IHTT msTBI group participant. Table 1 presents the demographic characteristics and injury severity of the groups in this study.

INSERT TABLE 1 ABOUT HERE

Procedure

Neurocognitive tests: A cognitive performance composite index was computed that summarized performance on five tests that tapped the cognitive domains most sensitive to the effects of moderate and severe pediatric TBI in a recent meta-analytic review.²⁹ The tests included in the cognitive composite index are briefly described below. Principal Components Analysis confirmed that these five tests shared sufficient common variance in both children with msTBI and healthy controls that they could be combined into a composite score with unit weighting (Moran et al., 2015, submitted for publication). The five tests included the following:

Psychomotor processing speed. The Processing Speed Index (PSI) score from the Wechsler Intelligence Scale for Children- Fourth Edition or Wechsler Adult Intelligence Scale- Third Edition, depending on age, was used.^{30,31}

Working memory. The Working Memory Index (WMI) score from the Wechsler Intelligence Scale for Children- Fourth Edition or Wechsler Adult Intelligence Scale- Third Edition, depending on age, was used.^{30,31}

Verbal learning. The index of verbal learning was T-scores for the total words learned over five trials of the California Verbal Learning Test Children’s Version (CVLT-C) or Second Edition (CVLT-II), depending on age.^{32,33}

Executive functioning. The index of executive function was derived from the Inhibition/Switching condition of the Color-Word Interference subtest, from the Delis-Kaplan Executive Functioning System battery.³⁴

IQ Estimate. The Vocabulary and Matrix Reasoning subtests of the Wechsler Abbreviated Scale of Intelligence (WASI)³⁵ were used to generate a two subtest estimate of Full Scale IQ for all participants.

Visual ERP measure of IHTT. This study used visual ERPs to measure IHTT. IHTT is defined as the time required to transfer stimulus-locked neural activity between the left and right brain hemispheres. Electroencephalography was recorded while participants completed a computerized, pattern matching task with bilateral field advantage. A BIOSEMI system was used to acquire ERPs. The low pass filter= 40Hz, high pass filter= 0.16Hz, bandwidth (3dB)= 134Hz and sample rate = 512Hz.

Participants were exposed to two distinct visual patterns (geometric shapes of 9 to 11 letter “o”s) following a gaze-fixation (a colon) in the center of the visual field. These patterns were presented randomly to two of the four visual fields (upper and lower; left and right). This created four bilateral and two unilateral conditions (right and left visual fields; RVF and LVF). Participants were asked to determine if the two patterns presented during each trial constituted a “match” or a “non-match”. “Match” and “non-match” responses were made by pressing the “M” and “N” keys of a computer keyboard. Participants alternated between pressing with the right hand – with their index finger on the “N” key and their middle finger on the “M” key – or with

the left hand – with their index finger on the “M” key and middle finger on the “N” key – for each trial. The responding hand was alternated in 8 blocks of 97 trials. Each participant’s cross-callosal IHTT was calculated using the electroencephalographic visual ERPs which were collected during the unilateral conditions. Greater detail on this methodology is described elsewhere.³⁶

ERP recording. While participants performed the pattern matching task, visual ERPs were recorded, synchronized to the onset of the pattern presentation. A 16 channel cap plus two grounders was used to record EEG. Parietal and occipital electrode sites were used because previous studies have shown these lateral sites produce large visual ERPs which yield clear evoked potential IHTTs.^{37,38,39} In addition, electrodes were placed above, below, and at the outer cantus of each eye for the recording of eye movements. Electrodes placed on the mastoid bones (i.e., behind the ears) of participants were used as linked-ears references. This reference point has been shown to provide a more valid estimate of IHTT than mid-frontal reference points.²⁸ ERPs at each recording electrode from each trial were stored on a computer disk for later averaging.

For each electrode, ERPs were averaged for the 2 x 2 combinations of LVF versus RVF. Averaged ERPs were displayed on a computer visual display and the N1 component identified blind to participant group. For each of the parietal or occipital recording electrodes – contingent upon which set provided the most clearly identifiable nodes and peaks – the latency and amplitude of these components were stored in a computer file for statistical analysis. IHTT was calculated by averaging ERP waveforms at the P3 or O1 (left hemisphere) and P4 or O2 (right hemisphere) electrode sites. Next, the peak latency (in milliseconds) of the early N1 evoked potential components was determined. Then, the latencies of the ipsilateral and contralateral conditions were subtracted to determine the overall IHTT for each visual field. Finally, the RVF

and LVF IHTTs were averaged to compute the overall IHTT for each participant. The average of left to right visual field and right to left visual field IHTTs for each participant were used in the remaining analyses. Longer IHTTs indicate slower transfer of visual information across the posterior brain regions. Accuracy of pattern matching was not recorded in this study. Previous studies have demonstrated that true deficits in IHTT are reflected in slower reaction times rather than response accuracy, particularly in individuals with agenesis of the corpus callosum.^{40,41}

Data Analysis

Analyses reported include independent samples *t*-tests, Pearson correlations, ANCOVA, and Univariate ANOVA tests. Data were analyzed using statistics program R and in SPSS v21.

Results

Interhemispheric Transfer Times

The TBI group (mean=15.5ms, SD=10.4) had a significantly slower IHTT than the control group (mean=9.4ms, SD=5.6), ($F(1,83)= 10.5, p=.002, \eta_p^2=.12$). As noted above, given the heterogeneity of IHTT scores in the TBI group, the TBI group was divided into: 1) a “normal IHTT” TBI group and, 2) a second “slow IHTT” TBI group for further data analysis. The cutoff for the “slow IHTT” TBI group was an IHTT of 18ms or greater (I think I mentioned above, but how was the cutoff determined, a SD below control’s mean?). The mean IHTT for the normal IHTT TBI, slow IHTT TBI, and control groups are presented in Table 1. As would be expected, the slow IHTT TBI group had a significantly slower IHTT than the control group and the normal IHTT TBI group ($F(1,83)= 64.8, p < .001, \eta_p^2=.62$).

Parent Education

There is a wide range of pre-injury cognitive functioning in children who incur TBIs. Since pre-injury cognitive function accounts for substantial variance in post-injury cognitive outcomes, it is important to control for the effects of pre-injury level of cognitive function. Parental level of education is a good predictor of a child’s cognitive functioning^{42,43} and can therefore be used to control for what the child’s level of cognitive function was absent the TBI. Parental education level was self-reported by parents. Parental education was missing for one participant in the control group. In instances where parents differed in their educational level, the higher educational level was selected.

The parental education of the slow IHTT TBI group was significantly lower than that of controls ($F(2,82)=4.5, p=.02, \eta_p^2=.10$), and was non-significantly lower than the normal IHTT TBI group. The healthy controls and normal IHTT TBI group did not significantly differ on

parent education, although the mean parent education was somewhat lower for the normal IHTT TBI group than controls (see Table 1). Pearson correlations were performed to examine the relationship between parent education and IQ for study participants, by group. This analysis revealed that parent education was not significantly correlated with IQ for the normal IHTT TBI group ($r=.28, p=.17$). However, parent education was significantly correlated with IQ for both the slow IHTT TBI group ($r=.57, p=.01$) and for the healthy control group ($r=.56, p<.001$). As a consequence, parent education was used as a covariate for secondary analysis of the neurocognitive variable in this study to further evaluate differences between the three groups.

Neurocognitive Test Performance

The performance of the two TBI groups was compared to the healthy control children on the cognitive composite index score and IQ using 3 x 1 ANOVAs with the Bonferroni statistic used for post-hoc comparisons. When there were group differences, the initial analyses were followed up with analyses of covariance with parental education as the covariate to correct for potential differences in pre-injury neurocognitive function. Cognitive composite index scores were not available for 2 normal IHTT TBI participants due to missing data in more than one neurocognitive subtest for these participants (e.g., no PSI subtests taken due to participants' physical motor impairments). The results of comparisons between the remaining participants are summarized in Table 2.

INSERT TABLE 2 HERE

Cognitive composite index. There was a significant difference between the three groups on the cognitive composite index ($F(1,81)=7.9, p=.001, \eta_p^2=.17$). Post-hoc comparisons revealed that the slow IHTT TBI group had significantly poorer neurocognitive performance than the control group. There were no statistically significant differences in the cognitive composite index

between the normal IHTT TBI group and the healthy control group, nor between the two TBI groups. The observed differences between the healthy control and slow IHTT TBI groups survived correction for parental education ($F(1,80)=5.2, p=.008, \eta_p^2=.12$). A secondary, pairwise comparison (i.e., 2X1 ANOVA of controls and the slow IHTT TBI group) produced similar results ($F(1,56)=8.1, p=.006, \eta_p^2=.13$). The relation between IHTT and the cognitive composite index scores was not linear in patients with TBI. The correlation between IHTT and cognitive composite index scores in the overall TBI group was not significant. Figure 2 presents the distribution of the cognitive composite index scores in the three groups.

INSERT FIGURE 2 HERE

Two-subtest IQ Initially, there was a significant difference in the Two-Subtest IQs of the three groups ($F(1,83)=4.3, p=.02, \eta_p^2=.10$). The slow IHTT TBI group had a significantly lower IQ than controls ($p=.01$), while the difference between controls and the normal IHTT TBI group did not reach significance ($p=.90$) and, similarly, there was no significant difference between the two TBI groups ($p=.20$). However, when parent education was corrected for, there were no significant differences between the three groups ($p=.14$). As noted previously, IQ was significantly correlated with parent education for the healthy control and slow IHTT TBI groups, but not for the normal IHTT TBI group.

Discussion

Children with moderate to severe TBIs were studied on average within three months post-TBI. Overall, the TBI group had significantly longer IHTTs than the healthy control group. Just under half of the children with TBIs had IHTT scores outside the normal range (i.e., more than 1.5 standard deviations longer than the mean IHTT score of the healthy control group). The slow IHTT TBI group has impaired interhemispheric communication. This finding is consistent with the results of two prior studies, which used a verbal dichotic listening task in children with severe TBIs¹⁰ as well as visual and tactile reaction time tasks in adults with TBI²⁰ to assess interhemispheric communication. Because the ERP IHTT task is an electrophysiological measure of IHTT, it provides a more direct indication of the functional integrity of the CC than performance based measures. By providing a relatively direct measure of the functional integrity of the CC, the ERP IHTT is a very useful complement to the increasingly sensitive MRI measures such as high resolution DTI, used to assess the structural integrity of the CC.

In children with TBI the slow IHTT group, but not the normal IHTT group, had neurocognitive impairments. After correcting for parental education (to control for pre-injury level of cognitive function), the slow IHTT TBI group performed significantly more poorly than healthy controls on the cognitive composite index score. While the normal IHTT TBI group performed more poorly than the healthy control group on this index score, the differences between the normal IHTT TBI group and the control group did not reach significance. The slow and normal IHTT TBI groups did not significantly differ from each other in neurocognitive functioning, although the slow IHTT TBI group tended to have lower scores on the cognitive composite index score than the normal IHTT TBI group. The worst neurocognitive performance in the current study was found in children who had both incurred a TBI and had slow IHTT. A

slow IHTT following a moderate to severe TBI captures some, but not all, of the variance in the adverse effect of a TBI on neurocognitive functioning.

There are two non-mutually exclusive hypotheses about the mechanisms underlying the effect of slow IHTT on neurocognitive function following TBI. Both explanations assume that slow IHTT following a TBI reflects decreased functional integrity of the CC. The first explanation is that many higher order cognitive processes (i.e., particularly those that are computationally demanding) involve the coordinated activity of processing nodes in both hemispheres.⁴⁴ Damage to the CC disrupts interhemispheric collaboration.

The second hypothesis stems from the observation that, given the diffuse damage to white matter tracts caused by moderate and severe TBIs, white matter damage is not restricted to the CC. The disruption to the functional integrity of the CC reflected in slow IHTT in many, but not all, children with TBI may be a reflection of more general damage to white matter tracts. In effect, the disruption of the functional integrity of the CC may be a specific instance of a more general problem.

Conclusions and Directions for Future Research

This study was the first to examine IHTT in children at a circumscribed time point during the first year post-TBI; about three months post-injury. This paper does not address the question of the course of IHTT after the post-acute phase, nor how well IHTT predicts longer term outcomes. When more longitudinal data is available, we will determine whether IHTT normalizes during the first year post-TBI and whether normalization of IHTT predicts neurocognitive function during this time frame. Future research should examine the correlation between IHTT and structural indices of white matter damage. When more brain imaging data is available, we will examine the relationship between measures of white matter damage (including

high resolution DTI) in the CC and long projection tracts outside of the CC and IHTT using this ERP method. This is one way to address the second hypothesis. In a very small subset (n = 4) of the patients in the current study studied post-acutely, we found that IHTT measured by EEG-ERP was inversely and significantly correlated with posterior CC N-acetyl acetate levels (neuronal/axonal integrity) and positively correlated with posterior CC choline (membrane degeneration/inflammation) and creatine (energy metabolism) levels.³ We will determine if these results can be replicated in a larger sample.

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