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Diverging volumetric trajectories following pediatric traumatic brain injury

Emily L. Dennis[a,*], Joshua Faskowitz[a], Faisal Rashid[a], Talin Babikian[b], Richard Mink[c], Christopher Babbitt[d], Jeffrey Johnson[e], Christopher C. Giza[f,i], Neda Jahanshad[a], Paul M. Thompson[a,g], Robert F. Asarnow[b,h,i]

[a] Imaging Genetics Center, Mark and Mary Stevens Institute for Neuroimaging and Informatics, Keck School of Medicine, University of Southern California, Marina del Rey, CA 90292, USA
[b] Department of Psychiatry and Biobehavioral Sciences, Semel Institute for Neuroscience and Human Behavior, UCLA, Los Angeles, CA 90024, USA
[c] Harbor-UCLA Medical Center and Los Angeles BioMedical Research Institute, Department of Pediatrics, Torrance, CA 90509, USA
[d] Miller Children's Hospital, Long Beach, CA 90806, USA
[e] LAC + USC Medical Center, Department of Pediatrics, Los Angeles, CA 90033, USA
[f] UCLA Brain Injury Research Center, UCLA Steve Tisch BrainSPORT Program, Dept of Neurosurgery and Division of Pediatric Neurology, Mattel Children's Hospital, Los Angeles, CA 90095, USA
[g] Departments of Neurology, Pediatrics, Psychiatry, Radiology, Engineering, and Ophthalmology, USC, Los Angeles, CA 90033, USA
[h] Department of Psychology, UCLA, Los Angeles, CA 90024, USA
[i] Brain Research Institute, UCLA, Los Angeles, CA 90024, USA

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ABSTRACT

Traumatic brain injury (TBI) is a significant public health concern, and can be especially disruptive in children, derailing on-going neuronal maturation in periods critical for cognitive development. There is considerable heterogeneity in post-injury outcomes, only partially explained by injury severity. Understanding the time course of recovery, and what factors may delay or promote recovery, will aid clinicians in decision-making and provide avenues for future mechanism-based therapeutics. We examined regional changes in brain volume in a pediatric/adolescent moderate-severe TBI (msTBI) cohort, assessed at two time points. Children were first assessed 2–5 months post-injury, and again 12 months later. We used tensor-based morphometry (TBM) to localize longitudinal volume expansion and reduction. We studied 21 msTBI patients (5 F, 8–18 years old) and 26 well-matched healthy control children, also assessed twice over the same interval. In a prior paper, we identified a subgroup of msTBI patients, based on interhemispheric transfer time (IHTT), with significant structural disruption of the white matter (WM) at 2–5 months post injury. We investigated how this subgroup (TBI-slow, $N = 11$) differed in longitudinal regional volume changes from msTBI patients (TBI-normal, $N = 10$) with normal WM structure and function. The TBI-slow group had longitudinal decreases in brain volume in several WM clusters, including the corpus callosum and hypothalamus, while the TBI-normal group showed increased volume in WM areas. Our results show prolonged atrophy of the WM over the first 18 months post-injury in the TBI-slow group. The TBI-normal group shows a different pattern that could indicate a return to a healthy trajectory.

1. Introduction

Traumatic brain injury (TBI) can have lasting, devastating effects, especially in children whose brains have not fully matured. Some children fully recover, or experience only mild disability, while others experience profound disruption years post-injury. Injury severity is a factor in predicting outcome, but leaves considerable variance in outcome unexplained (Saatman et al., 2008). Our incomplete understanding of recovery prevents clinicians from caring for patients most effectively. Charting longitudinal changes in the brain post-injury is critical for determining how long-term disruption occurs in patients, and may identify targeted interventions, critical windows for such interventions, and clinically useful predictors. Here we examined longitudinal changes in regional brain volume following a moderate/severe TBI (msTBI) in pediatric/adolescent patients.

Group differences in injury severity, type, and location complicate analyses of brain trauma that involve inter-subject registration and group comparisons. MsTBI is associated with volumetric deficits in the

* Corresponding author at: Keck School of Medicine, University of Southern California, 2001 N. Soto Street, Los Angeles, CA 90033, USA.
E-mail address: emily.dennis@ini.usc.edu (E.L. Dennis).

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corpus callosum (CC), and across the gray and white matter in adults (Farbota et al., 2012; Kim et al., 2008; Sidaros et al., 2009) as well as ventricular enlargement (Kim et al., 2008). Subcortical volumetric deficits have been detected in children and adults (Farbota et al., 2012; Kim et al., 2008; Sidaros et al., 2009; Wilde et al., 2007). Additionally, the cerebellum, peduncles, and brainstem show deficits following a brain injury (Farbota et al., 2012; Sidaros et al., 2009). Numerous studies have investigated volumetric deficits in pediatric TBI patients (Levin et al., 2000; Wilde et al., 2007; Wu et al., 2010), and TBM has been used previously to study adult TBI patients (Farbota et al., 2012; Kim et al., 2008; Sidaros et al., 2009), but to our knowledge, our prior paper was the first applying TBM to pediatric/adolescent TBI (Dennis et al., 2016). In our prior paper, we examined msTBI patients cross-sectionally at 2–5 months and 13–19 months post-TBI for regional differences in brain volume. We found expansion of the lateral ventricles at both time points, and reduced volume in clusters throughout all lobes. Here we examined longitudinal changes in those msTBI children. Studies of longitudinal volume changes in adult TBI patients show progressive atrophy across the brain (Farbota et al., 2012; Sidaros et al., 2009). Longitudinal studies of volume change in pediatric patients have mostly focused on the corpus callosum, with msTBI associated with progressive decreases in callosal volume (Levin et al., 2000; Wu et al., 2010).

Tensor-based morphometry (TBM) is a sensitive method for assessing regional volume change that offers advantages over other volumetric approaches. Longitudinally, TBM generates deformation fields that track local volumetric growth and tissue loss, warping baseline anatomy to match a later scan (Hua et al., 2016; Thompson et al., 2000). The deformation fields indicate regions of volume expansion or contraction in an individual scan, showing changes from the first assessment. TBM analyzes the whole brain, surveying changes without requiring a priori hypotheses about where the changes occur, and without defining regions of interest. TBM does not rely on accurate segmentation of the gray/white matter tissue boundaries, as VBM (voxel based morphometry) does. Tissue segmentation can be problematic in heavily damaged brains.

We previously found a subset of patients within the msTBI group who have markedly poorer neural integrity (Dennis et al., 2015a). MsTBI patients were divided into two groups based on their interhemispheric transfer time (IHTT – the time to transfer information between right and left hemispheres) measured as an event-related potential (ERP) (Ellis et al., 2015). The msTBI group with longer IHTTs (TBI-slow) had poorer WM structural integrity and cognitive impairment relative to healthy controls. The msTBI group with normal IHTTs (TBI-normal), however, had few areas of disrupted WM structural integrity, with no significant cognitive impairment. These differences were not easily explained by demographic or clinical variables. In this paper we compared these three groups, testing for differences in longitudinal changes in regional brain volume. We hypothesized that the TBI-slow group would show greater longitudinal decreases in volume relative to the TBI-normal and control groups.

2. Materials and methods

2.1. Participants

TBI participants were recruited from four Pediatric Intensive Care Units (PICUs) located in Level 1 and 2 Trauma Centers in Los Angeles County. In these institutions, patients with msTBI are routinely admitted to the PICU. A study representative discussed the study goals with the parents of patients, gave them an IRB-approved brochure about the study and obtained permission for the investigators to contact them after discharge from the medical center. Parents additionally signed consent forms allowing access to medical records. IRB approval was obtained by each recruitment site. 35% of patients whose parents agreed to be contacted while the child was in the PICU participated in this study. Out of 124 families contacted at the PICUs, 27 were lost to contact (kept canceling/rescheduling), 21 did not qualify because they did not meet criteria (GCS – Glasgow Coma Scale (Teasdale et al., 1979) – > 12, English skills not sufficient, ADHD,[1] learning disability, braces, etc.), 26 were not interested, and 50 are participating. Of these, not all have longitudinal data. 1 subject was scanned chronically, but data quality issues (artifacts) meant we could not include them, 3 subjects only received functional MRI at the chronic time point, 2 subjects were brought back for the chronic assessment but not scanned, 3 had braces at time 2, 3 were disqualified at time 2 for ADHD or LD (learning disability), 1 family refused to return, 2 moved out of state, 1 was referred by his doctor to the study and had already missed the post-acute window, and 8 were lost to follow-up, meaning they could have moved, changed their phone number, or simply stopped returning our calls. There was no systematic reason for the non-returns. Healthy controls, matched for age, sex, and educational level, were recruited from the community through flyers, magazines, and school postings.

2.1.1. Inclusion criteria

1) non-penetrating msTBI (intake or post-resuscitation GCS score between 3 and 12); 2) 8–18 years of age at the time of injury; 3) right-handed; 4) normal visual acuity or vision corrected with contact lenses/eyeglasses; and 5) English skills sufficient to understand instructions and be familiar with common words (the neuropsychological tests used in this study presume competence in English).

2.1.2. Exclusion criteria

1) history of neurological illness, such as prior msTBI, brain tumor or severe seizures; 2) motor deficits that prevent the subject from being examined in an MRI scanner (e.g., spasms); 3) history of diagnosed psychosis, ADHD, Tourette's Disorder, learning disability, mental retardation, autism or substance abuse. These conditions were identified by parental report and are associated with cognitive impairments that might overlap with those caused by TBI. Participants were excluded if they had metal implants that prevented them from safely undergoing a MRI scan.

Demographic information from our sample is consistent with existing epidemiological information on moderate-severe pediatric/adolescent TBI, both in the male to female ratio and in the types of mechanisms of injury (Keenan and Bratton, 2006). The injury mechanisms for our msTBI group were: 6 motor-vehicle accident (MVA) – pedestrian, 3 MVA – passenger, 6 fall – skateboard, 3 fall – scooter, 2 fall – bike, 1 fall – skiing, 1 assault, 1 uncategorized blunt head trauma. Information on all three groups can be found in Table 1.

2.2. Scan acquisition

Participants were scanned on 3 T Siemens Trio MRI scanners with magnetization-prepared rapid gradient echo imaging (MPRAGE). The T1-weighted images were acquired with the following acquisition parameters: GRAPPA mode; acceleration factor PE = 2; TR/TE/TI = 1900/3.26/900 ms; FOV = 250 × 250 mm; an axial plane acquisition with isotropic voxel size = 1 mm, flip angle = 9°.

2.3. Scan comparison

Part-way through the study, scanning moved from the UCLA Brain Mapping Center (BMC) to the Staglin IMHRO Center for Cognitive Neuroscience (Staglin). Both scanners were 3 T Siemens Trio scanners, and the protocol was maintained. To determine that this scanner change did not introduce bias into our data, we scanned 6 healthy adult volunteers at both the BMC and Staglin centers, 1.5 months apart. We then assessed possible bias in both the T1-weighted images and

[1] Attention Deficit Hyperactivity Disorder.