Title

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Journal

Neurology, 97(3)

ISSN

0028-3878

Authors

Dennis, Emily L
Caeyenberghs, Karen
Hoskinson, Kristen R
et al.

Publication Date

2021-07-20

DOI

10.1212/wnl.0000000000012222

Peer reviewed

RESEARCH ARTICLE

White Matter Disruption in Pediatric Traumatic Brain Injury

Results From ENIGMA Pediatric Moderate to Severe Traumatic Brain Injury

Emily L. Dennis, PhD, Karen Caeyenberghs, PhD, Kristen R. Hoskinson, PhD, Tricia L. Merkley, PhD, Stacy J. Suskauer, MD, Robert F. Asarnow, PhD, Talin Babikian, PhD, Brenda Bartnik-Olson, PhD, Kevin Bickart, MD, PhD, Erin D. Bigler, PhD, Linda Ewing-Cobbs, PhD, Anthony Figaji, MMed, PhD, Christopher C. Giza, MD, Naomi J. Goodrich-Hunsaker, PhD, Cooper B. Hodges, PhD, Elizabeth S. Hovenden, AA, Andrei Irimia, PhD, Marsh Königs, PhD, Harvey S. Levin, PhD, Hannah M. Lindsey, PhD, Jeffrey E. Max, MBBCh, Mary R. Newsome, PhD, Alexander Olsen, PhD, Nicholas P. Ryan, PhD, Adam T. Schmidt, PhD, Matthew S. Spruiell, BS, Benjamin S.C. Wade, PhD, Ashley L. Ware, PhD, Christopher G. Watson, PhD, Anne L. Wheeler, PhD, Keith Owen Yeates, PhD, Brandon A. Zielinski, MD, PhD, Peter Kochunov, PhD, Neda Jahanshad, PhD, Paul M. Thompson, PhD, David F. Tate, PhD, and Elisabeth A. Wilde, PhD

Correspondence
Dr. Dennis
emily.dennis@hsc.utah.edu

Neurology® 2021;97:e298-e309. doi:10.1212/WNL.0000000000012222

Abstract

Objective

Our study addressed aims (1) to test the hypothesis that moderate-severe traumatic brain injury (TBI) in pediatric patients is associated with widespread white matter (WM) disruption, (2) to test the hypothesis that age and sex affect WM organization after injury, and (3) to examine associations between WM organization and neurobehavioral outcomes.

Methods

Data from 10 previously enrolled, existing cohorts recruited from local hospitals and clinics were shared with the Enhancing NeuroImaging Genetics Through Meta-Analysis (ENIGMA) Pediatric Moderate/Severe TBI (msTBI) working group. We conducted a coordinated analysis of diffusion MRI (dMRI) data using the ENIGMA dMRI processing pipeline.

Results

Five hundred seven children and adolescents (244 with complicated msTBI and 263 controls) were included. Patients were clustered into 3 postinjury intervals: acute/subacute, <2 months; postacute, 2 to 6 months; and chronic, ≥6 months. Outcomes were dMRI metrics and post-injury behavioral problems as indexed by the Child Behavior Checklist. Our analyses revealed altered WM diffusion metrics across multiple tracts and all postinjury intervals (effect sizes

From the Department of Neurology (E.L.D., T.L.M., E.D.B., N.J.G.-H., E.S.H., H.M.L., B.S.C.W., B.A.Z., D.F.T., E.A.W.), University of Utah School of Medicine; George E. Wahlen Veterans Affairs Medical Center (E.L.D., N.J.G.-H., H.M.L., D.F.T., E.A.W.), Salt Lake City, UT; Cognitive Neuroscience Unit (K.C., N.P.R.), School of Psychology, Deakin University, Geelong, Australia; Center for Biobehavioral Health (K.R.H.), The Abigail Wexner Research Institute at Nationwide Children's Hospital; Department of Pediatrics (K.R.H.), The Ohio State University College of Medicine, Columbus; Department of Psychology (T.L.M., E.D.B., N.J.G.-H., C.B.H., H.M.L.) and Neuroscience Center (T.L.M., E.D.B.), Brigham Young University, Provo, UT; Kennedy Krieger Institute (S.J.S.); Departments of Physical Medicine & Rehabilitation and Pediatrics (S.J.S.), Johns Hopkins University School of Medicine, Baltimore, MD; Department of Psychiatry and Biobehavioral Sciences (R.F.A., T.B.), Semel Institute for Neuroscience and Human Behavior, Brain Research Institute (R.F.A.), and Department of Psychology (R.F.A.), UCLA; UCLA Steve Tisch BrainSPORT Program (T.B., K.B., C.C.G.), Los Angeles; Department of Radiology (B.B.-O.), Loma Linda University Medical Center; Departments of Neurology (K.B.) and Neurosurgery (C.C.G.), David Geffen School of Medicine at UCLA, Los Angeles, CA; Department of Pediatrics (L.E.-C., C.G.W.), Children's Learning Institute, University of Texas Health Science Center at Houston; Division of Neurosurgery (A.F.) and Neuroscience Institute (A.F.), University of Cape Town, South Africa; Department of Pediatrics (C.C.G.), Division of Neurology, UCLA Mattel Children's Hospital, Los Angeles, CA; Department of Physical Medicine and Rehabilitation (C.B.H.), Virginia Commonwealth University, Richmond; Ethel Percy Andrus Gerontology Center (A.I.), Leonard Davis School of Gerontology, and Department of Biomedical Engineering (A.I.), Viterbi School of Engineering, University of Southern California, Los Angeles; Emma Children's Hospital (M.K.), Amsterdam UMC, University of Amsterdam, Emma Neuroscience Group, the Netherlands; H. Ben Taub Department of Physical Medicine and Rehabilitation (H.S.L., M.R.N., M.S.S., E.A.W.), Baylor College of Medicine; Michael E. DeBakey Veterans Affairs Medical Center (H.S.L., M.R.N.), Houston, TX; Department of Psychiatry (J.E.M.), University of California, San Diego, La Jolla; Department of Psychiatry (J.E.M.), Rady Children's Hospital, San Diego, CA; Department of Psychology (A.O.), Norwegian University of Science and Technology, Trondheim; Department of Physical Medicine and Rehabilitation (A.O.), St. Olavs Hospital, Trondheim University Hospital, Norway; Department of Clinical Sciences (N.P.R.), Murdoch Children's Research Institute; Department of Paediatrics (N.P.R.), University of Melbourne, Australia; Department of Psychological Sciences (A.T.S.), Texas Tech University, Lubbock; Ahmanson-Lovelace Brain Mapping Center (B.S.C.W.), Department of Neurology, University of California, Los Angeles; Department of Psychology (A.L. Ware, K.O.Y.), University of Calgary, Alberta; Hospital for Sick Children (A.L. Wheeler), Neuroscience and Mental Health Program; Physiology Department (A.L. Wheeler), University of Toronto, Ontario; Alberta Children's Hospital Research Institute and Hotchkiss Brain Institute (K.O.Y.) and Departments of Pediatrics and Clinical Neurosciences (K.O.Y.), University of Calgary, Alberta, Canada; Department of Pediatrics (B.A.Z.), University of Utah School of Medicine, Salt Lake City; Maryland Psychiatric Research Center (P.K.), University of Maryland School of Medicine, Baltimore; Imaging Genetics Center (N.J., P.M.T.), Stevens Neuroimaging & Informatics Institute, Keck School of Medicine of USC, Marina Del Rey; and Departments of Neurology, Pediatrics, Psychiatry, Radiology, Engineering, and Ophthalmology (P.M.T.), USC, Los Angeles, CA.

Go to Neurology.org/N for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

Glossary

AD = axial diffusivity; **BCC** = body of the CC; **BRI** = Behavioral Regulation Index; **BRIEF** = Behavior Rating Inventory of Executive Function; **CBCL** = Child Behavior Checklist; **CC** = corpus callosum; **CR** = corona radiata; **dMRI** = diffusion MRI; **DTI** = diffusion tensor imaging; **ENIGMA** = Enhancing NeuroImaging Genetics Through Meta-Analysis; **FA** = fractional anisotropy; **GCC** = genu of the CC; **GCS** = Glasgow Coma Scale; **GEC** = Global Executive Composite; **HC** = healthy control; **MD** = mean diffusivity; **MI** = Metacognition Index; **msTBI** = moderate/severe TBI; **OI** = orthopedic injury; **PTR** = posterior thalamic radiation; **RD** = radial diffusivity; **ROI** = region of interest; **SLF** = superior longitudinal fasciculus; **TBI** = traumatic brain injury; **TSI** = time since injury; **UNC** = uncinate fasciculus; **WM** = white matter.

range d = −0.5 to −1.3). Injury severity is a significant contributor to the extent of WM alterations but explained less variance in dMRI measures with increasing time after injury. We observed a sex-by-group interaction: female patients with TBI had significantly lower fractional anisotropy in the uncinate fasciculus than controls (β = 0.043), which coincided with more parent-reported behavioral problems (β = −0.0027).

Conclusions

WM disruption after msTBI is widespread, persistent, and influenced by demographic and clinical variables. Future work will test techniques for harmonizing neurocognitive data, enabling more advanced analyses to identify symptom clusters and clinically meaningful patient subtypes.

Diffusion MRI (dMRI) has revolutionized our capabilities to noninvasively visualize white matter (WM) pathways and their role in behavior in healthy and diseased populations.[1,2] Numerous dMRI studies have demonstrated that young patients with traumatic brain injury (TBI) show abnormal WM organization in several fiber tracts such as the corpus callosum (CC).[3-11] These studies have also reported significant, moderate to high correlations between symptoms and decreased WM organization such that increased severity of WM disruption predicts poorer behavioral performance in young patients with TBI.[12,13] The plasticity of the human brain during development supports learning and adaptation, but its hidden cost may be increased vulnerability to injury.[14-16] Despite promising findings, these studies were hampered by sample size (median number of patients with TBI 21) to test specific hypotheses regarding the influence of demographic and clinical variables on WM organization.[10,17]

Enhancing NeuroImaging Genetics Through Meta-Analysis (ENIGMA) is a worldwide consortium for collaborative analyses that leverages large, combined samples to achieve adequate power to address open questions. We have established the ENIGMA Pediatric Moderate/Severe TBI (msTBI) working group, and here we investigate patterns of WM microstructural alterations after TBI. Because changes in WM metrics can be dynamic over the first year after injury, we examined alterations in WM organization across 3 postinjury intervals in line with previous publications[1,18,19] and in accordance with the study designs of the cohorts. We hypothesized that widespread disruptions in WM organization would be evident in the msTBI group and that key demographic factors such as age and sex would moderate outcome.

Methods

Study Design/Context

The ENIGMA Pediatric msTBI Working Group is a subgroup of the ENIGMA Brain Injury Working Group,[20,21] an international collaboration among neuroimaging researchers focused on TBI.[17] The strategy behind this collaboration is to leverage the existing framework of the ENIGMA Consortium[22] to answer questions that can be addressed only with large samples. Through harmonized data processing and meta-analysis, we aim to ensure adequate statistical power to address these questions. The ENIGMA Diffusion Tensor Imaging (DTI) workflow[23] has revealed patterns of altered WM organization across a number of clinical populations,[2] including that with posttraumatic stress disorder.[24] Here we applied these novel analytic methods to pediatric msTBI by analyzing data from >500 participants across 10 cohorts.

Study Samples

Study samples consisted of 10 previously collected cohorts from 7 research sites across 3 countries (table 1). Participants from these cohorts were recruited from hospitals, outpatient rehabilitation clinics, and the surrounding community (in the case of healthy controls [HC]). Details on the recruitment strategies for each separate cohort can be found in table e-1, doi.org/10.5061/dryad.jh9w0vt9q. Generally, inclusion criteria included hospitalization for a TBI with a Glasgow Coma Scale (GCS) score of 3 to 12 or >12 with abnormal imaging findings, age between 5 and 20 years, and local language proficiency necessary to answer questionnaires and scales. Children with developmental or neurologic disorders or a prior TBI were excluded (table e-1). The ENIGMA Pediatric msTBI dMRI analysis included a total of 244 children and adolescents (170 male/74 female patients, age 5–20 years) with complicated

Table 1 Demographic and Clinical Details of Cohorts

Cohort	Design	Chronicity	GCS score	Total, N	TBI (M/F), n Avg age (SD), y	Control (M/F), n Avg age (SD)	Age range, y	Control type
RAPBI	Long	Postacute (2–6 mo)	8.9 (4.1)	91	38 (29/9) 14.7 (2.7)	53 (27/26) 15.5 (2.7)	8–19	HC
		Chronic (7–19 mo)		68	34 (27/7) 16.4 (2.2)	34 (23/11) 16.3 (2.7)	9–20	
Baylor-1	Long	Postacute (3–5 mo)	7.0 (4.3)	70	29 (20/9) 14.1 (2.4)	41 (29/12) 12.3 (2.2)	7–18	OI
		Chronic (12–26 mo)		60	34 (23/11) 14.7 (2.8)	26 (20/6) 13.9 (3.0)	8–19	
Baylor-2	CSX	Acute (1–7 wk)	7.3 (4.9)	24	13 (9/4) 16.2 (2.0)	11 (6/5) 13.1 (1.6)	10–18	OI
		Postacute (3–4 mo)		8	2 (1/1) 14.1 (2.3)	6 (5/1) 13.4 (2.9)	11–19	
Baylor-3	CSX	Acute (2–4 wk)	10.2 (4.8)	8	6 (5/1) 16.5 (3.0)	2 (2/0) 13.8 (1.0)	10–18	OI
		Postacute (3–4 mo)		15	12 (7/5) 15.2 (2.4)	3 (2/1) 17.2 (1.8)	11–18	
		Chronic (12–15 mo)		8	4 (4/0) 14.2 (2.9)	4 (2/2) 15.6 (0.4)	10–17	
Loma Linda University	Long	Acute (1–3 wk)	7.5 (4.2)	58	25 (20/5) 11.8 (3.6)	33 (20/13) 13.2 (3.3)	5–18	HC
		Chronic (11–14 mo)		53	22 (15/7) 12.7 (3.1)	31 (17/14) 14.6 (3.1)	6–19	
Kennedy Krieger	Long	Acute (4–7 wk)	8.0 (3.2)	16	3 (2/1) 13.6 (1.7)	13 (8/5) 15.4 (1.6)	11–18	HC
		Postacute (2–4 mo)		24	11 (7/4) 14.7 (2.3)	13 (8/5) 15.4 (1.6)	11–18	
		Chronic (1–14 y)		33	20 (13/7) 15.4 (2.4)	13 (8/5) 15.4 (1.6)	10–18	
Deakin-1	CSX	Chronic (6 mo–10 y)	NA	41	16 (9/7) 14.1 (3.1)	25 (11/14) 14.5 (2.3)	9–18	HC
Deakin-2	CSX	Chronic (>6 mo)	NA	18	8 (6/2) 16.1 (2.8)	10 (4/6) 12.3 (2.0)	9–20	HC
NCH	CSX	Chronic (1–8 y)	10.7 (4.7)	39	19 (12/7) 12.5 (2.6)	20 (13/7) 12.1 (2.0)	8–17	OI
Amsterdam UMC	CSX	Chronic (1–6 y)	8.2 (2.8)	43	16 (10/6) 9.9 (1.4)	27 (12/15) 10.2 (1.5)	8–13	OI
Total				507	244 (170/74) 14.1 (3.0)	263 (150/113) 13.6 (2.9)		

Abbreviations: Avg = average; CSX = cross-sectional; GCS = Glasgow Coma Scale; HC = healthy controls; Long = longitudinal; NA = not available; OI = orthopedically injured; RAPBI = Recovery After Pediatric Brain Injury Study; TBI = traumatic brain injury.
For each cohort, the design (Long or CSX), chronicity of injury (acute/subacute = <2 months after injury, postacute = 2–6 months after injury, chronic = > 6 months after injury), GCS score (average and SD), total number, number of TBI and control participants, number of male and female participants, age range (average and SD), and type of control group (HC, OI) used are listed.

mild (GCS score >12 but abnormal imaging findings), moderate (GCS score 9–12), or severe (GCS score 3–8) TBI and 263 control children and adolescents (150 male/113 female controls, age 5–20 years). The control sample included both HC and children with orthopedic injuries (OIs). Some evidence suggests that these comparison groups differ, so collecting both HC and controls with OI may be the best design when possible.[25] Five studies were longitudinal and 6 were cross-sectional, yielding 646 scans from 507 participants.

Standard Protocol Approvals, Registrations, and Patient Consents

Original studies were reviewed by the individual institutional review board for each respective institution. All participants provided written or verbal informed assent, while parents provided written informed consent approved by local institutional review boards.

Image Acquisition and Processing

Apart from 1 cohort, all sites shared raw imaging data with the central site (University of Utah), where they were processed and analyzed. The remaining site processed, quality checked, and analyzed data according to the same set of standardized scripts (accessible on the ENIGMA website: enigma.ini.usc.edu/protocols/dti-protocols/). The acquisition parameters for each cohort are provided in table e-2, doi.org/10.5061/dryad.jh9w0vt9q. Preprocessing, including eddy current correction, echo-planar imaging–induced distortion correction, and tensor fitting, was performed at the University of Utah. All data were visually quality checked at multiple stages according to the recommended protocols and quality control procedures of the ENIGMA-DTI and Neuroimaging Informatics Tools and Resources Clearinghouse webpages, including careful inspection of registrations. Fractional anisotropy (FA) is a measure of the degree to which water is diffusing preferentially along the direction of axons and has been interpreted as a proxy for myelin integrity, although it can also be altered by inflammation and axonal packing.[26] Mean diffusivity (MD) measures the magnitude of diffusion (regardless of direction) in a voxel (averaged across the 3 eigenvectors); radial diffusivity (RD) is diffusion perpendicular to the largest

eigenvalue (typically along the axon); and axial diffusion (AD) is diffusion along the axon. Once tensors were estimated (FA/MD/RD/AD), they were mapped to the ENIGMA DTI template, projected onto the WM skeleton, and averaged within 24 regions of interest (ROIs) from the Johns Hopkins Atlas, some of which overlap (e.g., genu [GCC], body [BCC], and splenium of CC and total CC, enigma.ini.usc.edu/protocols/dti-protocols/). Further details and ROI abbreviations may be found in appendix e-1. Across all sites (except the single site that did not share raw imaging data), to determine whether motion may have confounded group differences, we extracted motion parameters from the eddy current correction procedure. Rotation and translation were averaged across the X, Y, and Z axes. We found greater average rotation (t = 2.4, p = 0.018) in the control group. Therefore, we repeated group comparisons while covarying for rotation.

Statistical Analysis

For each cohort, a linear model was fit using the lm, ppcor, and matrixStats packages in R 3.5.3 (r-project.org/), with the ROI FA as the response variable and group and covariates as predictors. For cohorts/studies with >1 data collection site, participants at each site were analyzed as a separate cohort. As in prior ENIGMA disease working group meta-analyses,[24,27] the central computational site (University of Southern California) conducted a random-effects inverse variance–weighted meta-analysis in R (metafor package, version 1.99-118 http://www.metafor-project.org/) to combine effect sizes estimated for each individual cohort. The Cohen d for the main effect of group and unstandardized β coefficients (regression parameters) for continuous predictors were computed with 95% confidence intervals. We used the Cohen d calculation, which accounts for covariates in the fixed-effects model, using the following equation:

$$d = \frac{M1 - M2}{pooled\ \ SD} \quad \text{where pooled SD} = \sqrt{\frac{SD_1^2 + SD_2^2}{2}}$$

Heterogeneity scores (I^2) for each test were computed, indicating the percent of total variance in effect size explained by heterogeneity across cohorts. As the most commonly reported dMRI metrics,[1,11] FA and MD averaged within ROIs across hemispheres were the primary imaging measures. In our post hoc analyses, we extracted the underlying eigenvalues because they may show more specific associations with certain pathologic processes and reflect WM disruption.[28] Specifically, we computed axial ($\lambda\|$), and radial ($\lambda^{\perp}$) diffusivity as indirect markers of axonal and myelin damage, respectively (for a recent review, see reference 28). Lateralized ROIs were examined post hoc when a significant effect was found for the bilateral average. The corticospinal tract was not analyzed because its diffusivity measurements have poor reliability, likely due to registration issues.[23] The average correlation in FA and MD between all pairs of ROIs was r = 0.4568. A Bonferroni correction is considered too conservative when there are correlations among the multiple dependent measures being tested.[29] Therefore, we followed recent ENIGMA analyses[24] and calculated the effective number of independent tests based on the observed correlation structure between the regional measures. The equation of Li and Ji[29] yielded V_{eff} = 20, giving a significance threshold of $p < 0.05/20 = 0.0025$.

Data Availability

All analyses were conducted with generalizable scripts available on the ENIGMA GitHub repository: github.com/ENIGMA-git/ENIGMA/tree/master/WorkingGroups/EffectSize_and_GLM. Individual ROI-level data were processed using a set of R scripts with regressions customized for the current ENIGMA Pediatric msTBI dMRI analysis workflow, which is available on a set of Google spreadsheet configuration files by request. Data are available to researchers who join the working group and submit a secondary analysis proposal to the group for approval.

Nonlinear Age Term

We first examined whether a nonlinear age term should be included in statistical models along with age and sex because increases and decreases in diffusion metrics over the lifespan do not follow a linear trend.[30] Age^2 was significantly associated with all diffusion metrics for a number of ROIs, so it was included in all subsequent models.

Primary Group Comparisons

Data were binned into 3 postinjury intervals based on prior publications[1,18]: acute to subacute (MRIs acquired 1 week–2 months after injury), postacute (2–6 months after injury), and chronic (6 months–14 years after injury).[11] Binning participants into postinjury windows is an imperfect approach because injury and recovery processes are continuous and nonlinear over time. However, fundamentally different neurobiological processes are at play in different postinjury windows, necessitating some division. On the basis of what we know of the time course of neuropathology, treatment, and rehabilitation, and functional recovery,[31,32] we can consider 3 separate phases: acute/subacute, acute pathology such as bleeding and edema peak and resolve; postacute, secondary injury and microstructural alterations become more clear as gross pathology no longer dominates, and recovery processes may begin; and chronic, some recovery of function continues, but the brain is in a more stable state. The boundaries between time intervals were initially informed by published reviews and meta-analyses[1,18,19,31,32] and tailored to fit our datasets. Figure e-1 (doi.org/10.5061/dryad.jh9w0vt9q), displays a histogram of times since injury showing 3 primary bins. As there is a long tail, the graph is truncated at 3 years after injury, with all participants scanned >3 years after injury represented in the final bin. Analyses were repeated with the 7 participants between 28 and 42 weeks after injury excluded from the chronic phase for a cleaner break, and results were virtually identical. Within each time period, we compared groups of patients with TBI and controls. Sites with <5 participants in any cell were not included in meta-analyses. Six cohorts collected data on HC, while 5 studies recruited children with OIs

(matched for time since injury [TSI] to the TBI group) as controls. To examine the impact of control group, all group comparisons were repeated separately for those cohorts that recruited HC or OI comparison groups.

Interactions

We examined potential interactions between group and age or sex within the 3 postinjury windows.

Injury Variables

Within the msTBI group, we examined linear relationships using regression analyses between dMRI measures and 3 injury variables: age at injury (controlling for age at scan), GCS score, and TSI.

Neurobehavioral Measures

Six of the cohorts collected the parent version of the Behavior Rating Inventory of Executive Function (BRIEF),[33] although 2 cohorts had too few participants (<5) with both BRIEF and high-quality dMRI to be included in analyses. Among these, we conducted linear regressions on the normative T scores from 2 summary indices (Behavioral Regulation Index [BRI] and Metacognition Index [MI]) and the Global Executive Composite (GEC) within the TBI group. The BRI assesses behavior that is considered to be related to inhibition, shifting, and emotional control, while the MI assesses behavior considered to be related to the ability to plan, initiate, and monitor activity and performance along with working memory. GEC is a measure of behavior considered to be related to overall executive functioning. There were insufficient data to examine associations between WM organization and BRIEF scores in the acute-phase sample. In the postacute-phase sample, 56 participants in the TBI group had BRIEF data. The average (μ), SD (σ), and range of the T scores were as follows: for GEC, $\mu = 52.8$, $\sigma = 11.8$, and range = 36 to 74; and for BRI, $\mu = 51.9$, $\sigma = 12.0$, and range = 37 to 79; for MI, $\sigma = 53.3$, $\sigma = 11.4$, and range = 36 to 78. In the chronic phase, 86 participants in the TBI group had BRIEF data. The average, SD, and range of the T scores were as follows: for GEC, $\mu = 51.2$, $\sigma = 10.5$, and range = 32 to 76; for BRI, $\mu = 50.5$, $\sigma = 10.7$, and range = 36 to 77; and for MI, $\mu = 51.5$, $\sigma = 10.5$, and range = 30 to 75. Outliers, defined as being >3 SDs away from the age-adjusted population mean, were removed (any T score <21 or >79).

Four of the cohorts included the Child Behavior Checklist (CBCL), a parent report of emotional and behavioral functioning,[34] although 1 cohort had too few participants with CBCL score and dMRI of acceptable quality to be included in analyses. Among these 3 cohorts, we conducted linear regressions assessing associations with FA on the T scores from 3 summary indices: Internalizing Problems (e.g., depressive, anxious, and somatic symptoms), Externalizing Problems (e.g., aggressive and rule-breaking behaviors), and Total Problems (e.g., all of the above plus social, attention, and thought problems scales). These were assessed in the chronic phase because not enough cohorts collected these measures in other phases. Outliers were removed (any T score <21 or >79). The average, SD, and range of scores were as follows: Internalizing Problems, $\mu = 51.2$, $\sigma = 12.1$, and range = 33 to 79; Externalizing Problems, $\mu = 48.3$, $\sigma = 11.0$, and range = 33 to 76; and Total Problems, $\mu = 49.9$, $\sigma = 12.2$, and range = 24 to 76.

Results

Primary Group Comparison

In the acute/subacute phase (38 with TBI/44 controls), postacute phase (78 with TBI/107 controls), and chronic phase (160 with TBI/190 controls), we found significantly lower FA and higher MD in the TBI group across a large number of ROIs, particularly central WM tracts and regions (table 2). Effect sizes across ROIs for each time point are shown in figures 1 and 2. Due to space constraints, only effects with FA are visualized. Forest plots for the sites contributing to the group comparisons are shown in figures e-2 through e-4, doi.org/10.5061/dryad.jh9w0vt9q. Follow-up analyses including average rotation as a covariate yielded results consistent with our main analyses (for details, see appendix e-1 and figure e-5). Post hoc analyses of other diffusion metrics revealed higher RD in all postinjury phases. Acutely, AD was significantly lower across ROIs. Postacutely and chronically, AD was lower in segments of the CC and higher in other ROIs (figures e-6 to e-8). Generally, significant results for bilateral ROIs were accompanied by significant results in the lateralized ROIs as well.

Interactions

A significant group-by-sex interaction was found in the postacute phase for FA in the uncinate fasciculus (UNC; $\beta = 0.043$, $p = 0.0012$), with no effects with MD. Further analyses detected no effect of group in male participants, while female participants with TBI had lower FA than female controls (figure 3). Post hoc analyses revealed a significant group-by-sex interaction in the UNC for RD as well ($\beta = -3.1 \times 10^{-5}$, $p = 0.027$), but not for AD. In the chronic phase, there were only borderline interaction effects with age or sex ($0.005 < p < 0.05$, figure e-9, doi.org/10.5061/dryad.jh9w0vt9q).

Control Populations

When conducting separate meta-analyses across sites that recruited HC vs OI controls, we obtained results that were generally consistent with the main analyses, although differences were not quite as extensive in the chronic phase for the OI comparison (figure e-10, doi.org/10.5061/dryad.jh9w0vt9q). There was not a large enough sample (<5 per cell) in the acute phase to examine TBI vs OI controls.

Injury Variables

Within the TBI group, significant associations were found with age at injury in the postacute phase in the posterior thalamic radiation (PTR) and superior longitudinal fasciculus

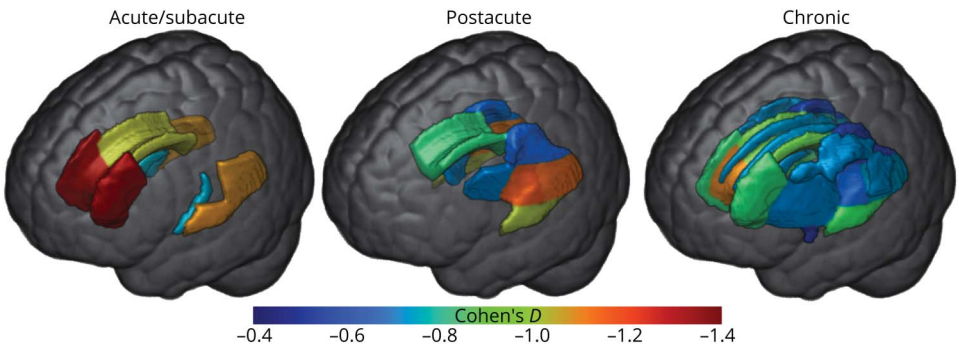
Table 2 Group Differences in FA in the Acute/Subacute, Postacute, and Chronic Phases

	Acute			Postacute			Chronic		
ROI	Meta d	Meta *p* Value (uncorrected)	95% CI	Meta d	Meta *p* Value (uncorrected)	95% CI	Meta d	Meta *p* Value (uncorrected)	95% CI
Average FA	−1.15[a]	1.7E-06[a]	−1.63, −0.68	−1.10[a]	1.7E-06[a]	−1.55, −0.65	−1.08[a]	4.1E-07[a]	−1.50, −0.66
ACR	−1.37[a]	3.2E-08[a]	−1.86, −0.89	−1.07[b]	0.0071[b]	−1.85, −0.29	−0.86[a]	1.0E-05[a]	−1.24, −0.48
ALIC	−0.28	0.57	−1.24, 0.68	−0.44	0.11	−0.98, 0.10	−0.34[b]	0.011[b]	−0.60, −0.08
BCC	−1.02[a]	1.7E-05[a]	−1.49, −0.56	−0.85[a]	0.0013[a]	−1.37, −0.33	−0.95[a]	4.2E-08[a]	−1.29, −0.61
CC	−1.33[a]	0.0011[a]	−2.13, −0.53	−1.00[a]	0.00047[a]	−1.56, −0.44	−1.05[a]	2.6E-08[a]	−1.42, −0.68
CGC	−0.19	0.40	−0.63, 0.25	−0.60[b]	0.012[b]	−1.07, −0.13	−0.72[a]	2.0E-06[a]	−1.02, −0.42
CGH	−0.02	0.97	−1.08, 1.04	−0.28	0.072	−0.58, 0.02	−0.30[b]	0.044[b]	−0.59, −0.01
CR	−1.12[b]	0.0065[b]	−1.93, −0.31	−0.92[b]	0.0043[b]	−1.56, −0.29	−0.78[a]	2.0E-05[a]	−1.13, −0.42
EC	−0.58[b]	0.011[b]	−1.03, −0.14	−0.22	0.29	−0.64, 0.19	−0.70[a]	0.0016[a]	−1.13, −0.26
FX	−0.75[a]	0.0011[a]	−1.21, −0.30	−0.37	0.076	−0.78, 0.04	−0.71[a]	0.00047[a]	−1.11, −0.31
FXST	−0.75[a]	0.0012[a]	−1.20, −0.29	−0.51[b]	0.031[b]	−0.96, −0.05	−0.37[b]	0.038[b]	−0.72, −0.02
GCC	−1.36[a]	3.8E-08[a]	−1.85, −0.88	−1.47[b]	0.047[b]	−2.92, −0.02	−1.11[a]	6.7E-10[a]	−1.46, −0.76
IC	−0.34	0.19	−0.85, 0.17	−0.90[a]	8.2E-06[a]	−1.30, −0.51	−0.50[a]	0.00016[a]	−0.77, −0.24
PCR	−0.61	0.16	−1.48, 0.25	−0.64[a]	0.0024[a]	−1.05, −0.23	−0.53[a]	9.3E-05[a]	−0.79, −0.26
PLIC	−0.01	0.99	−0.83, 0.81	−0.69[a]	9.9E-05[a]	−1.04, −0.34	−0.22	0.054	−0.44, 0.00
PTR	−1.08[a]	5.9E-06[a]	−1.55, −0.62	−1.14[a]	2.6E-12[a]	−1.46, −0.82	−0.73[a]	2.1E-05[a]	−1.07, −0.39
RLIC	−0.43	0.27	−1.19, 0.33	−1.19[a]	0.00012[a]	−1.80, −0.58	−0.65[a]	1.7E-06[a]	−0.92, −0.39
SCC	−0.90[b]	0.0036[b]	−1.51, −0.29	−0.54[b]	0.0034[b]	−0.90, −0.18	−0.77[a]	1.2E-06[a]	−1.08, −0.46
SCR	−0.56	0.26	−1.55, 0.43	−0.40[b]	0.0093[b]	−0.69, −0.10	−0.41[b]	0.0041[b]	−0.69, −0.13
SFO	−0.51[b]	0.024[b]	−0.95, −0.07	−0.43[b]	0.032[b]	−0.82, −0.04	−0.28[b]	0.021[b]	−0.52, −0.04
SLF	−0.52[b]	0.022[b]	−0.96, −0.08	−0.67[b]	0.0031[b]	−1.12, −0.23	−0.71[a]	5.8E-06[a]	−1.02, −0.40
SS	−1.09[a]	4.8E-06[a]	−1.56, −0.63	−1.01[a]	5.4E-09[a]	−1.35, −0.67	−0.89[a]	8.2E-10[a]	−1.18, −0.61
TAP	−0.51[b]	0.045[b]	−1.01, −0.01	−0.29	0.053	−0.59, 0.00	−0.55[a]	0.00020[a]	−0.84, −0.26
UNC	−0.67[b]	0.0084[b]	−1.17, −0.17	−0.16	0.30	−0.45, 0.14	−0.51[a]	0.00045[a]	−0.79, −0.22

Abbreviations: CI = confidence interval; FA = fractional anisotropy; ROI = region of interest. ROI abbreviations are explained in appendix e-2, doi.org/10.5061/dryad.jh9w0vt9q.
The Cohen d values, uncorrected *p* values, and the 95% confidence intervals for the d statistic are shown for the group comparisons.
[a] Results are significant when corrected for multiple comparisons.
[b] Results are marginally significant (based on the Li and Ji[29] adjusted Bonferroni correction, $0.05 > p > 0.0025$).

(SLF) ($\beta = 0.20$, $p = 0.00023$; $\beta = 0.18$, $p = 1.3 \times 10^{-5}$, respectively), with higher FA in patients who were older at the time of injury (figure e-11, doi.org/10.5061/dryad.jh9w0vt9q). There were no associations between age at injury and MD, RD, or AD. Postacutely, significant associations were seen between TSI and the FAs of the BCC and GCC ($\beta = -0.0075$, $p = 0.00010$; $\beta = -0.0049$, $p = 0.0041$, respectively) with lower FA in patients further from injury (figure e-11). There were no associations between TSI and MD or AD, and RD showed a significant positive association with TSI. We found significant associations with GCS score within the TBI group at all time points (figure e-11); in all cases, higher GCS score (i.e., less severe injury) was associated with higher FA. Acutely, an association was found between GCS score and average FA, along with FA of the anterior limb of the interior capsule, several corona radiata (CR) segments, FX, PTR, SCC, SS, and TAP. RD was negatively associated with GCS score acutely, and there were no associations with MD or AD. Postacutely, GCS score was associated with average FA, along with FA of the CR segments, BCC, and SLF. MD and RD were negatively associated with GCS score, and there were no associations with AD. Chronically, GCS score was associated with FA of the FX and SS ($\beta = 0.010$, $p = 7.0 \times 10^{-6}$; $\beta = 0.0033$, $p = 5.8 \times 10^{-5}$, respectively). RD was negatively associated with GCS score chronically, and there were no associations with MD or AD.

Figure 1 Group Differences in FA in the Acute/Subacute, Postacute, and Chronic Phases



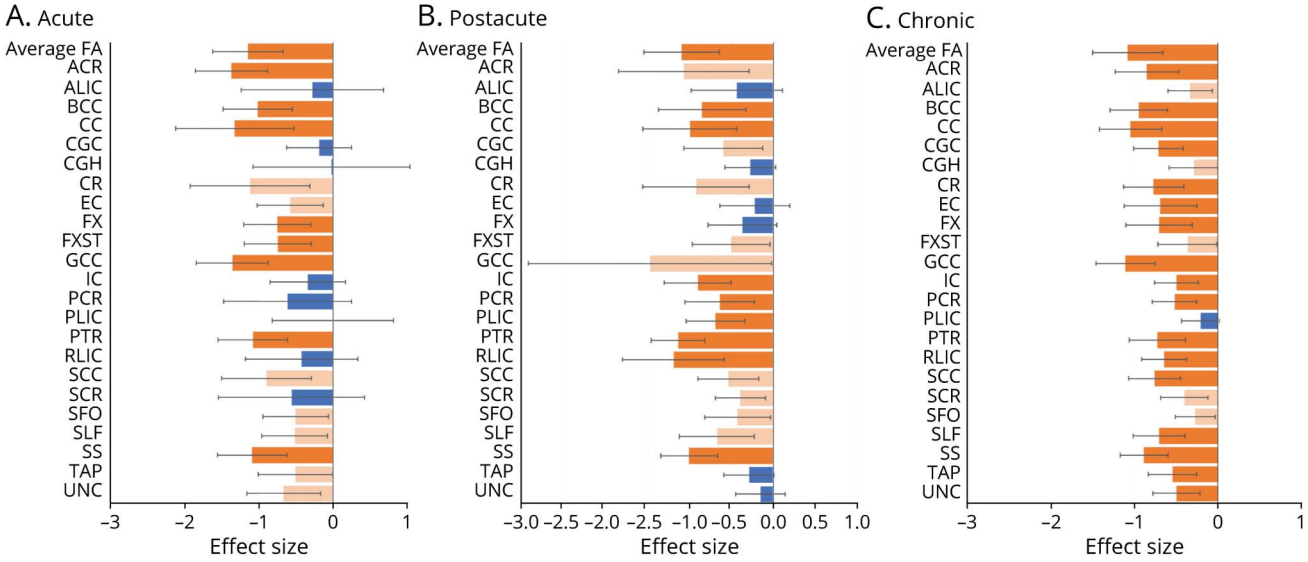
Effect sizes are shown for significant results from the primary group comparison, covarying for sex, age, and age^2. The Cohen's d statistics for midline and bilateral regions of interest (ROIs) are displayed according to the color bar below. Because traumatic brain injury (TBI) was coded as 1 and controls as 0, negative effect sizes indicate lower fractional anisotropy (FA) in the TBI group. Only regions surviving correction for multiple comparisons are shown ($p < 0.0025$). Statistical details for all ROIs are shown in table 2.

Neurobehavioral Function

In the postacute and chronic phases, 56 and 86 participants, respectively, in the TBI group had BRIEF scores. In the postacute phase, better behavioral regulation was associated with higher average skeleton FA ($\beta = -0.00060$, $p = 0.0028$, figure e-12, doi.org/10.5061/dryad.jh9w0vt9q) and lower RD. There were no associations with MD or AD. No associations survived correction for multiple comparisons in the chronic phase. For MI, in the chronic phase, we found a significant negative association with the FA of the UNC ($\beta = -0.0028$, $p = 8.6 \times 10^{-5}$, figure e-12) and a positive association with RD. There were no associations with MD or AD. No associations survived correction for multiple comparisons in the postacute phase. For GEC, a number of associations were found in both the postacute and chronic phase with FA and MD, although none survived correction for multiple comparisons at either time point (figure e-12).

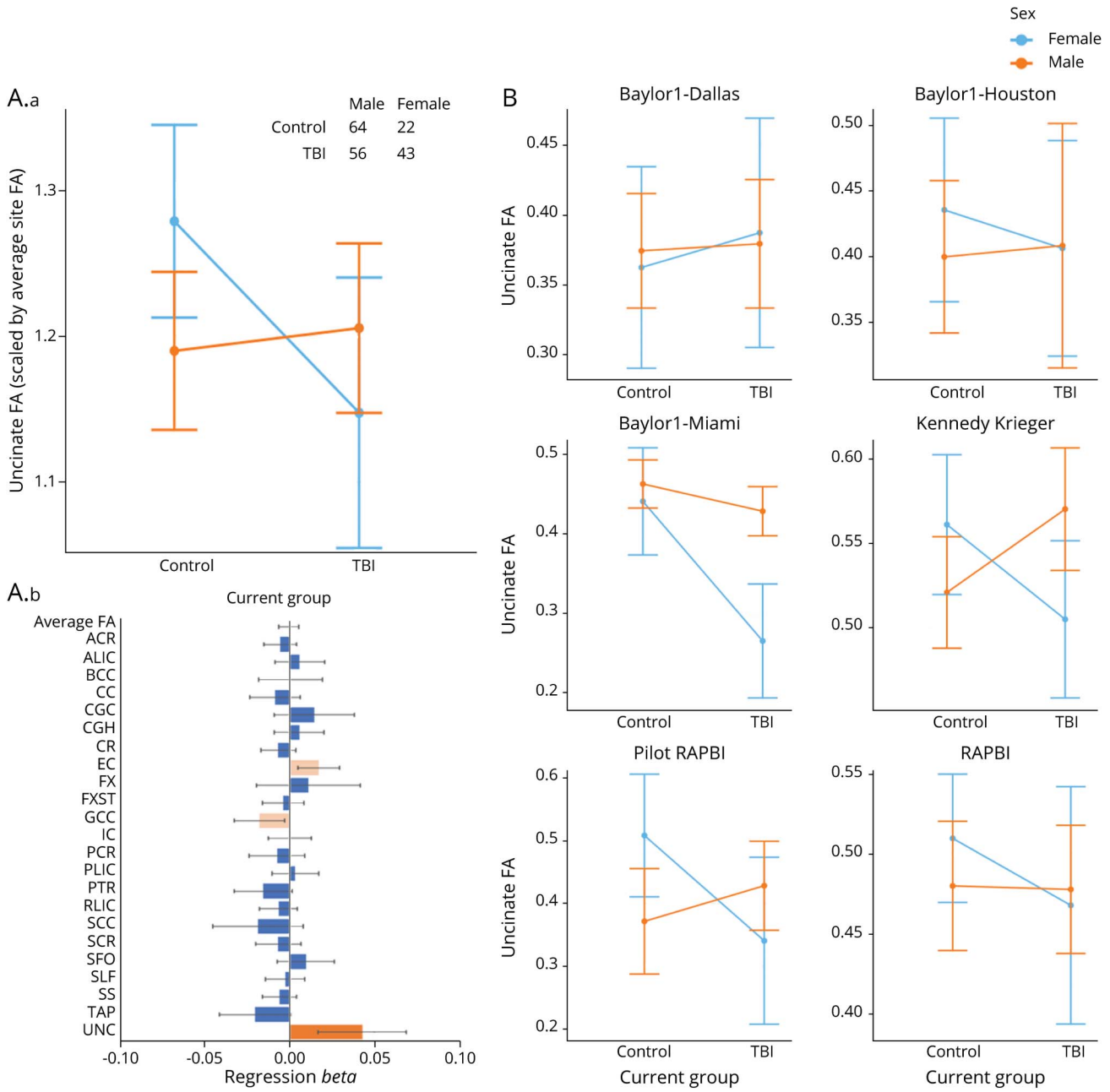
There were 69 participants across 3 sites in the TBI group with CBCL scores. Across the TBI group, no significant associations were found between FA and CBCL Internalizing, Externalizing, or Total Problems scores. Given the significant group-by-sex interaction with FA and RD in the UNC (a key structure for emotion regulation), we also examined the CBCL scores in the female participants in the TBI group only. Across the 3 sites, 21 female participants in the TBI group had CBCL scores. We found a significant negative association between total problems and FA in the UNC and SS ($\beta = -0.0027$, $p = 0.0017$ and $\beta = -0.0014$, $p = 0.0024$, respectively,

Figure 2 Group Differences in the (A) Acute, (B) Postacute, and (C) Chronic Phases



Effect sizes are shown for the primary group comparison in the acute, postacute, and chronic phases, covarying for sex, age, and age^2. The Cohen d statistics are shown across all midline and bilateral regions of interest (ROIs), along with average fractional anisotropy (FA), with bars indicating the 95% confidence interval. Because traumatic brain injury (TBI) was coded as 1 and controls as 0, negative effect sizes indicate lower FA in the TBI group. ROI abbreviations are explained in appendix e-2, doi.org/10.5061/dryad.jh9w0vt9q. Dark orange bars indicate significance ($p < 0.0025$); light orange bars indicate effects that did not withstand multiple-comparisons correction ($0.05 > p > 0.0025$); and blue bars are not significant ($p > 0.05$).

Figure 3 Group-by-Sex Interactions



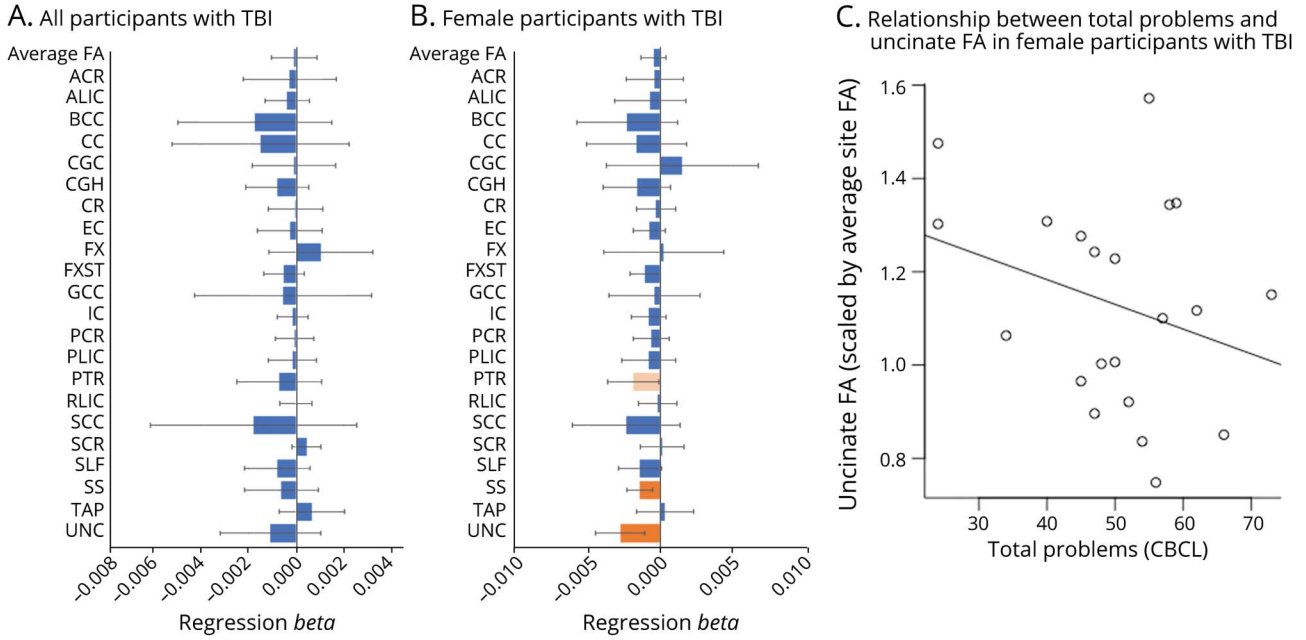
Results are shown for the postacute phase. Shown are unstandardized regression β values for 23 regions of interest regions of interest (ROIs) and average fractional anisotropy (FA) (A.b). ROI abbreviations are explained in appendix e-2, doi.org/10.5061/dryad.jh9w0vt9q. Dark orange bars indicate significance ($p < 0.0025$); light orange bars indicate effects that did not withstand multiple-comparisons correction ($0.05 > p > 0.0025$); and blue bars are not significant ($p > 0.05$). Error bars are 95% confidence interval. A plot probing the significant interaction effect in the uncinate is shown (B).

figure 4) and a significant positive association with UNC RD, with lower FA and higher RD in patients whose parents reported more problems.

Discussion

Here we present the largest-ever study using dMRI to examine altered WM microstructural organization in pediatric patients with msTBI. In a sample of >500 children and adolescents from 10 cohorts across 3 countries, we report widespread disruption of WM microstructural organization along all postinjury time windows. Results were more extensive with FA than MD, and alterations were nearly always paired with alterations in RD. We found that female patients may have a particular vulnerability to WM disruption, especially in the UNC, a frontolimbic tract, which may underlie a heightened risk of behavioral or emotional problems after injury. Our

Figure 4 Associations With CBCL Total Problems Score



Linear associations with Child Behavior Checklist (CBCL) Total Problems score in the full traumatic brain injury (TBI) group (A) and in the female TBI subset (B). Shown are unstandardized regressions for 23 regions of interest (ROIs) and average fractional anisotropy (FA). ROI abbreviations are explained in appendix e-2, doi.org/10.5061/dryad.jh9w0vt9q. Dark orange bars indicate significance ($p < 0.0025$); light orange bars indicate effects that did not withstand multiple-comparisons correction ($0.05 > p > 0.0025$); and blue bars are not significant ($p > 0.05$). Error bars are 95% confidence interval. A plot probing the association between total problems and uncinate FA in the female TBI group is shown (C).

results indicate that disruption of WM, particularly in callosal fibers, can persist for years after injury.

In group comparisons, central WM ROIs (CC, CR, internal capsule) exhibited the most extensive disruptions, although, by the chronic phase, nearly every ROI showed significant group differences. This could, for a variety of reasons, be associated with either pathology and methodology. The CC, in particular, may be most vulnerable to injury because the falx cerebri exacerbates lateral forces during an impact.[35] Methodologically, modeling crossing fibers is a known challenge in dMRI that can affect calculations in certain areas such as the CR and may mean that alterations in FA are more consistently detected in regions with few mixed fiber populations such as the CC. Lower FA paired with higher MD and RD could indicate demyelination but also could reflect axonal degeneration, inflammation, or changes in axonal density.[11] In the acute/subacute phase, we report lower AD, perhaps reflecting axonal disruption shortly after injury. In the postacute and chronic phases, however, the directions of AD effects were mixed, with higher AD in the CR and lower AD in the CC. Higher AD could reflect recovery but also could result from selective degeneration of neuronal populations. Lower AD in the CC, where the fibers are more unidirectional, suggests axonal degeneration. If callosal projections are interrupted, this could lead to higher AD values in areas where they would have otherwise crossed other fiber bundles such as the CR. Higher-resolution multishell dMRI, which can be used to model intracellular and extracellular diffusion, could reveal whether neurite density is lower and whether there are more unidirectional axonal bundles in the CR farther from injury. This would be expected in the presence of selective degeneration of callosal fibers.

We found a group-by-sex interaction for UNC FA and RD. Female patients with msTBI had lower UNC FA and higher RD compared to controls, whereas the effect of TBI was not significant in male patients. The UNC connects the ventral prefrontal cortex and the amygdala and is a key structure for emotion regulation. Around half of children sustaining an msTBI may go on to develop novel psychiatric disorders later in life,[36] and there is a significant and specific relationship between novel psychiatric disorders in children with msTBI and WM organization.[37] In prior studies, lower FA in the UNC after TBI was associated with reduced emotional control and increased vulnerability to novel psychiatric disorder.[37,38] Another study reported greater prevalence of internalizing disorders in female compared to male patients,[39] although this disparity is also present outside of TBI.[40] We also show a significant association between UNC FA and RD and the Total Problems score from the CBCL in female patients with TBI. This association was not present in the full TBI group, suggesting that the particular vulnerability of the UNC in female patients may lead to a greater likelihood of behavioral or emotional problems after injury. This analysis was underpowered, however, because our sample of female patients with TBI was small and only 3 sites collected the CBCL. A central future aim of the ENIGMA Pediatric msTBI working group is harmonizing different scales to extract

common domain scores across cohorts and to analyze the neural underpinnings of psychiatric symptoms after TBI.[41]

Premorbid factors that are associated with brain structure may predispose children to injury (e.g., hyperactivity), and for this reason, some studies include controls with OI instead of HC. When we conducted separate meta-analyses of cohorts collecting HC vs controls with OI, results were generally consistent. Using the OI group as a comparison to the TBI group revealed more extensive differences in dMRI in the postacute phase than when using the HC group as a control. The opposite is true for the chronic phase, although statistical power presumably differed in the chronic phase given the differing sample sizes (chronic phase: 73 with TBI vs 77 with OI, 100 with TBI vs 119 HC). This difference could also reflect effects of injury that are not restricted to the head. One study of mild TBI including both HC and controls with OI found little difference between the mild TBI and OI groups,[25] although there were differences between the HC and injury groups. However, another study that included more severely injured patients reported mixed results.[8] The effects of hospitalization, pain, medications, psychological trauma from the injury event, and systemic biological responses associated with secondary injury (such as inflammation and immune response) could all contribute to alterations in brain structure and function even when the brain itself is not directly injured.[42,43] In addition, there can be inconsistencies in the rigor of screening for/reporting of occult minor head trauma in which substantial forces are applied to the body but the treatment focus is on extracranial injury.

We examined a number of clinical variables within the TBI group, including age at injury, GCS score, and TSI. Older patients may fare better; we found significant associations with age at injury for the FA of the SLF and PTR, 2 regions that are still maturing throughout adolescence.[44,45] However, these associations were present only in the postacute phase, suggesting that the long-term effect is minimal, possibly reflecting late catch-up recovery in younger children with TBI in the chronic phase. TSI similarly showed an effect only in the postacute phase. This is not surprising, however, because diffusivity calculations in the acute phase may be influenced by acute pathologies such as swelling or breakdown of the blood-brain barrier.[46] The lack of detectable associations in the chronic phase (range of postinjury time intervals 0.5–14 years) may be influenced by variability among cohorts, or it could indicate that the impact of TBI on WM organization may stabilize within the first year or so of injury. Longitudinal studies with >2 assessments are critical to answer this important question. GCS score was significantly positively associated with FA and negatively associated with RD at all time points, suggesting that more severe injury is associated with poorer WM organization.

A limitation of our study is the variability among sites, scan parameters, recruitment criteria, and collected measures. This heterogeneity limits our ability to characterize the groups in great detail and limits our power for some analyses even with our large sample size, particularly those involving behavioral measures. For example, the associations we report with CBCL Total Problems score in female patients with TBI need to be replicated in a larger sample. However, this discovery was possible only with the relatively large sample that we had and demonstrates the potential of ENIGMA analyses to generate hypotheses that future research can interrogate in greater depth. The ENIGMA Pediatric msTBI group will conduct follow-up analyses when we have established harmonization procedures that enable us to measure behavioral and psychological disruption across measures. Another limitation is the inability to control for preinjury behavioral problems and psychiatric diagnoses. The broad variability across sites in the timing of assessments may limit results because the first year after injury is especially dynamic from a neural reorganization perspective. We attempted to address this by establishing postinjury intervals, but biological changes occur along more of a continuum than in discrete periods during recovery from injury, and the scale and granularity of this continuum differ across patients. Variability in study parameters is, to some extent, a strength, because it supports the generalizability of our results. Our analysis includes a good portion of the dMRI data that currently exist for pediatric msTBI cohorts, but it is a small field. An important limitation of the present study is the use of DTI.[47] This is the most commonly used approach to date for the study of WM microstructure in TBI.[1] DTI provides general information on the local orientation of WM fibers and metrics describing the FA, MD, and eigenvalues (AD and RD). However, DTI is less accurate in areas of crossing fibers, leading to problems with interpretation and limited biological specificity of the DTI metrics.[48] One approach to address these challenges is a statistical analysis framework called fixel-based analysis,[49] where a fixel refers to a specific fiber population within a voxel. This framework allows fiber-specific metrics to examine microstructural (fiber density) and macrostructural (fiber cross section) WM changes (for a critical review, see reference 50). Future studies are needed to validate the diffusion metrics against gold standard histologic measures for a better understanding of the cellular processes after pediatric TBI. Finally, multimodal MRI data, incorporating regional volumes, and more advanced dMRI data (higher b value and/or multishell), along with more longitudinal investigations, are needed to further explain our results. Future data collection (ideally with a greater degree of harmonization) and machine learning approaches may reveal clinically significant patient subtypes based on demographic, clinical, and imaging variables.

Acknowledgment

The authors thank Dr. Mark Logue for statistical consultation. They also acknowledge the participation of the children and family members and the efforts of our many colleagues that make this work possible.

Study Funding

Funding provided by K99NS096116 (E.L.D.); R61NS120249 (E.L.D., D.F.T., E.A.W.); R01NS05400 (B.B.-O.); National Health

and Medical Research Council Career Development Fellowship (K.C.); NRF SARChI Chair of Clinical Neurosciences (A.F.); UCLA Easton Clinic for Brain Health, Stan and Patty Silver, UCLA Brain Injury Research Center, R01HD061504 (C.C.G.); K01HD083459 (K.R.H.); R01NS100973, Department of Defense contract W81XWH-18-1-0413 and a Hanson-Thorell Research Scholarship (A.I.); R01HD088438 (JEM); K12HD001097, K23HD06161, UL1TR001079, 1S10OD021648 (S.J.S.); U54EB020403, R01MH116147, R56AG058854, P41EB015922, R01MH111671 (P.M.T.); K99MH119314, NARSAD 27786 (B.S.C.W.); and Ronald and Irene Ward Chair in Pediatric Brain Injury, funded by the Alberta Children's Hospital Foundation (K.O.Y.).

Disclosure

P.M.T. received partial research support from Biogen, Inc, for research unrelated to this manuscript. J.E.M. reports medico-legal consultation approximately equally for plaintiffs and defendants at ≈10%. C.C.G. reports consulting for the National Basketball Association, National Football League, *National Hockey League Players' Association*, and Los Angeles Lakers, serving on the Advisory Board for Highmark Interactive, Novartis, Major League Soccer, National Basketball Association, US Soccer Federation, and medico-legal consultation for 1 to 2 cases annually. D.F.T. and E.D.B. additionally report medico-legal consultation. All other authors report no relevant financial disclosures. Go to Neurology.org/N for full disclosures.

Publication History

Received by *Neurology* August 27, 2020. Accepted in final form April 14, 2021.

Appendix Authors

Name	Location	Contribution
Emily L. Dennis, PhD	University of Utah, Salt Lake City	Designed analyses, processed and analyzed data, performed statistical analysis, drafted initial manuscript
Karen Caeyenberghs, PhD	Deakin University, Melbourne, Australia	Provided data, designed analyses, edited initial manuscript
Kristen R Hoskinson, PhD	The Abigail Wexner Research Institute at Nationwide Children's Hospital, Columbus, OH	Provided data, designed analyses, edited initial manuscript
Tricia L. Merkley, PhD	Department of Psychology, Brigham Young University, Provo, UT	Designed analyses, edited initial manuscript
Stacy J. Suskauer, MD	Kennedy Krieger Institute, Baltimore, MD	Provided data, designed analyses, edited initial manuscript
Robert F. Asarnow, PhD	UCLA, Los Angeles, CA	Provided data, edited manuscript
Talin Babikian, PhD	UCLA, Los Angeles, CA	Designed analyses, edited manuscript

Appendix *(continued)*

Name	Location	Contribution
Brenda Bartnik-Olson, PhD	Loma Linda University Medical Center, CA	Provided data, edited manuscript
Kevin Bickart, MD, PhD	UCLA, Los Angeles, CA	Designed analyses, edited manuscript
Erin D. Bigler, PhD	University of Utah, Salt Lake City	Edited manuscript
Linda Ewing-Cobbs, PhD	University of Texas Health Science Center at Houston	Edited manuscript
Anthony Figaji, MMed, PhD	University of Cape Town, South Africa	Edited manuscript
Christopher C. Giza, MD	UCLA, Los Angeles, CA	Provided data, edited manuscript
Naomi J. Goodrich-Hunsaker, PhD	University of Utah, Salt Lake City	Designed analyses, edited manuscript
Cooper B. Hodges, PhD	Virginia Commonwealth University, Richmond	Edited manuscript
Elizabeth S. Hovenden, AA	University of Utah, Salt Lake City	Edited manuscript
Andrei Irimia, PhD	University of Southern California, Los Angeles	Designed analyses, edited manuscript
Marsh Königs, PhD	University of Amsterdam, the Netherlands	Provided data, edited manuscript
Harvey S. Levin, PhD	Baylor College of Medicine, Houston, TX	Provided data, edited manuscript
Hannah M. Lindsey, PhD	University of Utah, Salt Lake City	Edited manuscript
Jeffrey E. Max, MBBCh	Department of Psychiatry, University of California, San Diego, La Jolla	Edited manuscript
Mary R. Newsome, PhD	Michael E. DeBakey Veterans Affairs Medical Center, Houston, TX	Designed analyses, edited manuscript
Alexander Olsen, PhD	Norwegian University of Science and Technology, Trondheim, Norway	Designed analyses, edited manuscript
Nicholas P. Ryan, PhD	Murdoch Children's Research Institute, Melbourne, Australia	Designed analyses, edited manuscript
Adam T. Schmidt, PhD	Texas Tech University, Lubbock	Edited manuscript
Matthew S. Spruiell, BS	Baylor College of Medicine, Houston, TX	Edited manuscript
Benjamin S.C. Wade, PhD	University of Utah, Salt Lake City	Statistical support, edited manuscript
Ashley L. Ware, PhD	University of Calgary, Alberta, Canada	Edited manuscript
Christopher G. Watson, PhD	University of Texas Health Science Center at Houston	Edited manuscript
Anne L. Wheeler, PhD	Hospital for Sick Children, Toronto, Ontario, Canada	Edited manuscript
Keith Owen Yeates, PhD	University of Calgary, Alberta, Canada	Edited manuscript

Appendix *(continued)*

Name	Location	Contribution
Brandon A. Zielinski, MD, PhD	University of Utah, Salt Lake City	Edited manuscript
Peter Kochunov, PhD	University of Maryland School of Medicine, Baltimore	Designed processing workflow, edited manuscript
Neda Jahanshad, PhD	Keck School of Medicine of USC, Marina del Rey, CA	Designed processing workflow, edited manuscript
Paul M. Thompson, PhD	Keck School of Medicine of USC, Marina del Rey, CA	Designed processing workflow, edited manuscript
David F. Tate, PhD	University of Utah, Salt Lake City	Edited manuscript
Elisabeth A. Wilde, PhD	University of Utah, Salt Lake City	Provided data, designed analyses, edited initial manuscript

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