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Altered lateralization of the cingulum in deployment-related traumatic brain injury: An ENIGMA military-relevant brain injury study

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Abstract

Traumatic brain injury (TBI) in military populations can cause disruptions in brain structure and function, along with cognitive and psychological dysfunction. Diffusion magnetic resonance imaging (dMRI) can detect alterations in white matter (WM) microstructure, but few studies have examined brain asymmetry. Examining asymmetry in large samples may increase sensitivity to detect heterogeneous areas of WM alteration in mild TBI. Through the Enhancing Neuroimaging Genetics Through Meta-Analysis Military-Relevant Brain Injury working group, we conducted a mega-analysis of neuroimaging and clinical data from 16 cohorts of Active Duty Service Members and Veterans ($n = 2598$). dMRI data were processed together along with harmonized demographic, injury, psychiatric, and cognitive measures. Fractional anisotropy in the cingulum showed greater asymmetry in individuals with deployment-related TBI, driven by greater left lateralization in TBI. Results remained significant after accounting for potentially confounding variables including posttraumatic stress disorder, depression, and handedness, and were driven primarily by

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individuals whose worst TBI occurred before age 40. Alterations in the cingulum were also associated with slower processing speed and poorer set shifting. The results indicate an enhancement of the natural left laterality of the cingulum, possibly due to vulnerability of the nondominant hemisphere or compensatory mechanisms in the dominant hemisphere. The cingulum is one of the last WM tracts to mature, reaching peak FA around 42 years old. This effect was primarily detected in individuals whose worst injury occurred before age 40, suggesting that the protracted development of the cingulum may lead to increased vulnerability to insults, such as TBI.

KEYWORDS
DTI, military, traumatic brain injury

1 | INTRODUCTION

The Iraq and Afghanistan conflicts have brought traumatic brain injury (TBI) to the forefront of military medicine. Service Members (SM) experienced ~450,000 TBIs between 2000 and 2021 (Military Health System, n.d), the majority of which were mild TBIs (mTBIs). While many warfighters appear to recover from these "invisible injuries" within weeks (Helmick et al., 2015), some continue to report somatic, cognitive, and psychological symptoms years later (Mac Donald et al., 2017). Deployment-related TBI is associated with worse outcomes than TBI sustained outside deployment (Martindale et al., 2018, 2021; Stein et al., 2015, 2016; Yurgil et al., 2014). Understanding brain structural changes and their relation to neurobehavioral sequelae following blast-related injuries, however, requires further elucidation as research on impact mTBI may not apply as the injury mechanisms differ.

Neuroimaging has revealed persistent alterations in brain structure and function after extracranial injuries have healed (Wilde et al., 2015). Diffusion magnetic resonance imaging (dMRI) is particularly sensitive to axonal neuropathology of TBI, but evidence is mixed regarding alterations in white matter (WM) organization after mTBI. Several studies have reported no TBI-related differences in dMRI metrics (Bolzenius et al., 2018; Davenport et al., 2015; Levin et al., 2010), and those that have reported significant results generally show lower fractional anisotropy (FA) in spatially distributed regions (Davenport et al., 2012; Hayes et al., 2015; Jorge et al., 2012). With the "pothole" approach, group differences irrespective of location can be shown (Davenport et al., 2012; Jorge et al., 2012; Taber et al., 2015). Larger sample sizes may also help address heterogeneity, and big data approaches could facilitate sophisticated modeling to identify patient clusters with different patterns of WM disruption. One prior analysis on a subset of the cohorts included here used nonnegative matrix factorization (NMF), a data-driven approach, to reduce WM measurements to a set of components accounting for a large amount of the variance. This revealed an age-dependent effect of TBI on FA (a common proxy for WM organization), such that the age-related decreases in FA were steeper than expected after TBI (Bouchard et al., 2022). In addition to the pothole approach applied in previous papers and our prior investigation using the NMF approach, examining tract asymmetry may be another method to identify group differences in tract organization that is more robust to spatial heterogeneity.

Several WM tracts have well-established asymmetry, such as left lateralization of the cingulum and arcuate fasciculus, while asymmetry-related findings for other tracts have been mixed (Gong et al., 2005; Park et al., 2004; Song et al., 2015; Takao et al., 2013; Takao, Abe, et al., 2011; Takao, Hayashi, & Ohtomo, 2011; Yin et al., 2013). Tract asymmetry may jointly contribute to the functional lateralization of the brain along with gray matter asymmetries (Ocklenburg et al., 2016). Arcuate fasciculus asymmetry is closely tied to the lateralization of language (Ocklenburg et al., 2013), while greater cingulum asymmetry has been linked to attention and response/set shifting (Gläscher et al., 2012; Luna et al., 2021). We

examined asymmetry of lateralized tracts to be more sensitive to patient heterogeneity and reduce the number of statistical tests. Asymmetry standardizes measures to the individual, making each his/her own reference, thus increasing sensitivity to subtle, heterogeneous effects (Toga & Thompson, 2003).

The Enhancing Neuroimaging Genetics Through Meta-Analysis (ENIGMA) Military-Relevant Brain Injury working group is part of the ENIGMA Brain Injury working group (https://enigma.ini.usc.edu/ongoing/enigma-tbi/), a global collaboration among neuroimaging researchers focusing on various TBI patient populations (Dennis et al., 2020; Tate et al., 2021; Wilde et al., 2021). It was built on the framework created by the ENIGMA consortium, which seeks to achieve greater statistical power through harmonized image processing and meta/mega-analysis (Thompson et al., 2020). The ENIGMA diffusion tensor imaging (DTI) workflow (Jahanshad et al., 2013) has been used to identify altered WM organization across a range of disorders (Kelly et al., 2017; Kochunov et al., 2020), including moderate/severe TBI in pediatric patients (Dennis et al., 2021), and posttraumatic stress disorder (PTSD; Dennis et al., 2019). We used the ENIGMA DTI workflow to test the hypothesis that some structures would display greater asymmetry in participants with a history of TBI.

2 | MATERIALS AND METHODS

2.1 | Study samples

Our analysis included 16 cohorts of Veteran and Active Duty SMs, totaling 1775 participants with TBI history and 823 comparison participants without TBI history. Of the 1775 participants, 1080 had at least one deployment-related injury, 480 had history of nonmilitary TBI only, and 215 did not have information regarding injury context (military vs. nonmilitary). While the majority of cohorts focused on Iraq/Afghanistan Veterans and SMs, two focused on Vietnam Veterans, a significantly older population. Across cohorts, the age range was 18–85 ($M = 41.7 \pm 12.7$) years. Table 1 provides demographic and clinical details on the cohorts. Inclusion and exclusion criteria for each study are in Table S1. All participants provided institutional review board-approved written informed consent. The group with a history of TBI was significantly younger than the group without TBI history ($M = 40.6$ vs. 43.8 years, $p = 3.6 \times 10^{-8}$) and had a greater proportion of males (91% vs. 85%, $p = 2.8 \times 10^{-5}$). The gender-related differences match existing epidemiological trends in military TBI, and the age difference is likely related to military rank and thus potential exposure to TBI.

2.2 | Harmonizing injury data

Details on injuries were collected using a range of tools (see Tables 1 and S2). From these disparate scales, we extracted common variables, as detailed in Note S1.

2.3 | Image acquisition and processing

Acquisition parameters are provided in Table S3. Preprocessing, including eddy current correction, echo-planar imaging-induced

TABLE 1 Demographic information across cohorts

Site	Total no.	TBI	Control	M	F	Age range	Average age (SD)	Severity	TBI scale
ADNIDoD	109	67	42	109	0	60–85	69.6 (4.6)	Mod/severe	Custom
BETTER/UMCU	84	12	72	84	0	21–57	36.2 (9.5)	Mild	Custom
LIMBIC-CENC	1028	837	191	891	137	22–70	40.1 (9.8)	Mild	PCE
Chronic Effects	80	64	16	72	8	23–54	34.7 (7.4)	Mild	Polytrauma
Duke1	105	70	35	86	19	24–46	39.6 (8.8)	Mild	MN-BEST/QCuBE
Duke2	84	50	34	58	26	23–67	40.1 (11.3)	Mild	MN-BEST/QCuBE
HDFT	28	23	5	23	5	24–58	36.9 (8.7)	Mild–moderate	Custom
Houston Blast	42	32	10	39	3	21–54	32.4 (8.0)	Mild	Polytrauma
INTRuST	85	54	31	69	16	18–69	39.4 (12.8)	Mild	Custom
iSCORE	101	30	71	88	13	19–51	35.8 (7.7)	Mild	Custom
NICoE	258	210	48	246	12	19–59	39.4 (6.5)	Mild	OSU
ROVER WISER	53	23	30	34	19	21–58	31.4 (6.4)	Mild	Polytrauma
SPIRE/GBET	53	39	14	47	6	24–50	35.3 (6.9)	Mild–severe	Polytrauma
VA Minneapolis1	124	92	32	120	4	23–62	34.3 (8.5)	Mild	MN-BEST
VA Minneapolis2	130	99	31	121	9	22–59	32.8 (8.4)	Mild	MN-BEST
VETSA	234	73	161	234	0	56–66	61.8 (2.6)	Mild	Custom
Total	2598	1775	823	2321	277	19–85	41.7 (12.7)		

Note: Numbers are shown for total sample, TBI (any) and control groups, and male/female. The age range, average age in years with SD, sample TBI severity, and the TBI scale collected are also listed.
Abbreviation: TBI, traumatic brain injury.

distortion correction, and tensor fitting, was completed at the University of Utah for sites sharing raw data, or locally for others. Recommended protocols and quality control procedures are available on the ENIGMA-DTI and Neuroimaging Informatics Tools and Resources Clearinghouse webpages. These procedures were recommended, but coordination of preprocessing schemes accommodated site- and acquisition-specific pipelines. Once tensors were estimated, they were mapped and projected onto the ENIGMA-DTI template, and averaged within regions of interest (ROIs; http://enigma.ini.usc.edu/protocols/dti-protocols/) in a TBSS-based approach (Smith et al., 2006). Further details and ROI abbreviations are in Note S2. In the seven sites for whom raw data was shared, we extracted motion parameters from the eddy current correction step to determine if motion played a role in our case–control findings. We compared rotation and translation averaged across the X, Y, and Z axes, finding no significant between-group differences (all *p*s >.05). We calculated FA lateralization index and asymmetry for each lateralized ROI:

$$\text{Lateralization index} = \left(\text{FA}_{\text{Left}} - \text{FA}_{\text{Right}}\right) / \left(0.5 * \left(\text{FA}_{\text{Left}} + \text{FA}_{\text{Right}}\right)\right)$$

where asymmetry was the absolute value of the lateralization index. Significant effects with asymmetry were followed post hoc with examinations of the lateralization index. Asymmetry was the primary measure as it would detect alterations irrespective of direction.

2.4 | Statistics

Mega-analysis was performed on individual-level ROI data. Linear mixed effects models were implemented with *lme* in R 3.1.3. Nested random effects controlled for cohort and site, as some studies included multiple data collection sites. Age and gender were included as covariates in all analyses. The average correlation in asymmetry between all ROIs was $r = .13$. For multiple comparisons correction, we used a modified Bonferroni threshold, following recent ENIGMA analyses (Dennis et al., 2019) to calculate the effective number of independent tests based on the observed correlation structure between alternate responses. The equation of Li and Ji (Li & Ji, 2005) yielded an effective number of tests of $V_{\text{eff}} = 16$, yielding a significance threshold of $p < .05/16 = .003125$. Results that did not pass correction for multiple comparisons ($.05 > p > .003125$) are reported in the Supplement for completeness, but not interpreted. Across analyses, Cohen's *d* statistics are reported for group comparisons and unstandardized betas (*b*) are reported for linear regressions.

We calculated corrected *p*-values using the following equation:

$$P_{\text{adj}} = 1 - (1 - p)^{V_{\text{eff}}}$$

where *p* is the unadjusted *p*-value. Corrected *p*-values are shown for primary analyses. We used FDR to correct *p*-values for post hoc analyses.

2.5 | Quadratic age term

We first conducted analyses to determine whether a quadratic age term, age^2, should be included in statistical models along with age and gender, as age has a nonlinear effect on FA (Kochunov et al., 2012). The effect of this term upon the regression was not significant, so age^2 was not included in subsequent analyses.

2.6 | Primary group comparisons

Our primary analysis compared participants with a history of deployment-related TBI to those with no history of TBI, excluding individuals reporting a history of only nonmilitary TBI and participants whose records did not specify the source of TBI. Deployment-related TBI included both combat and noncombat injuries. As a specificity analysis, we examined group differences between participants with a history of nonmilitary TBI to a non-TBI group as well as individuals with a history of blast-related TBI to the non-TBI group.

2.7 | Supplementary analyses

Supplementary analyses on participant subgroups, interactions, injury variables, and symptom inventories are summarized in Note S3.

2.8 | Cognitive function

Across the 16 cohorts included in this study, seven collected the trail making test (TMT), including 1613 participants, 676 of whom had a history of deployment-related TBI. TMT Part A measures visual search and motor speed and Part B measures set shifting (Sánchez-Cubillo et al., 2009). Participants with Part A or Part B completion times greater than 3 SD above the study-wide mean were winsorized to 3 SD above the mean.

3 | RESULTS

3.1 | Primary group comparisons

We found significantly greater FA asymmetry in deployment-related TBI compared with no history of TBI in the cingulum ($d = 0.18$, corrected $p = .0024$), along with greater asymmetry in the superior longitudinal fasciculus (SLF), although this did not survive multiple comparisons correction ($d = 0.10$, corrected $p = .35$). Post hoc analysis of the cingulum revealed greater left lateralization in the TBI group ($d = 0.15$, FDR-corrected $p = .0042$; Figure 1; Benjamini & Hochberg, 1995). We further examined group differences in FA of the left and right cingula and found no significant differences. The higher asymmetry was also present in the blast-related TBI vs. non-TBI comparison, although it did not survive multiple comparisons correction

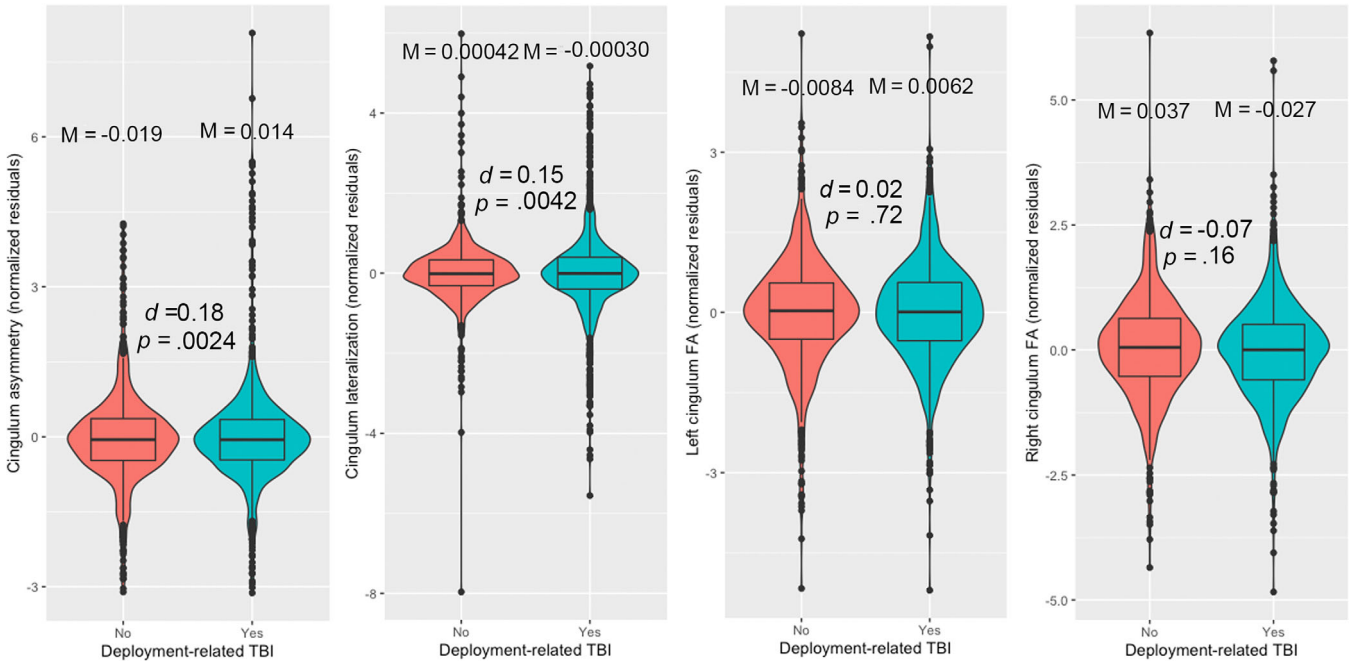

FIGURE 1 Group differences in cingulum asymmetry. Violin plots are shown for the nontraumatic brain injury (TBI) group (red), and deployment-related TBI group (blue) with group *t*-test *p*-values (corrected). The asymmetry analyses were corrected for multiple comparisons across all regions of interest tested using the Li and Ji adjusted Bonferroni correction. The laterality and cingulum fractional anisotropy (FA) analyses were false discovery rate-corrected across the three post hoc tests. The values on the y-axis are the normalized residuals for cingulum asymmetry, laterality index, left FA, and right FA, accounting for age, gender, and the nested random effects of cohort and site. As the cingulum is generally left-lateralized, actual laterality index values are generally positive, but that is not reflected here due to the adjustments and normalization

(d = 0.11, corrected p = .26). As an exploratory analysis in the LIMBIC-CENC cohort, we examined primary blast-related TBI and found no significant group difference in cingulum asymmetry. Primary blast-related TBI is TBI due to overpressure with no simultaneous blunt injury. Blast-related TBI is more commonly secondary or tertiary (with blunt impacts from projectiles or with force propelling the individual into a solid surface). Post hoc, the differences in the deployment-related TBI group remained significant when covarying for PTSD, depression, and both. Comparing individuals with a history of only nonmilitary TBI to the non-TBI group, the effect in the cingulum was not significant. Last, to rule out differences in scan parameters across sites, we examined the effect in the cingulum separately in sites using isotropic versus anisotropic voxels, and in sites using high angular resolution versus low angular resolution (low resolution being 32 directions or fewer). Results were consistent across subanalyses. Results are summarized in Tables 2 and S4 and S5.

3.2 | Cognitive function

In the non-TBI group, there were no detectable significant associations between TMT and cingulum FA. We examined the effect in the cingulum post hoc to test for functional consequences of the shift in asymmetry. As a post hoc test, we corrected for multiple comparisons across eight tests using FDR (TMT-A and TMT-B with cingulum asymmetry, laterality, and left and right cingulum FA). There were no significant associations with asymmetry in the deployment-related TBI group. There were slight trend associations in the deployment-related TBI group between the lateralization index of the cingulum and TMT-A and TMT-B time ($b = -5.5 \times 10^{-4}$, p = .16; $b = -1.8 \times 10^{-4}$, p = .16, respectively; Figure S1). Within the deployment-related TBI group, FA of the left cingulum was negatively associated with TMT-A and TMT-B ($b = -5.0 \times 10^{-4}$, p = .042; $b = -1.7 \times 10^{-4}$, p = .042, respectively, Figure 2).

4 | DISCUSSION

We examined WM asymmetry in 2598 military SM and Veterans, reporting a primary finding of greater asymmetry in the cingulum among individuals with a history of deployment-related TBI compared to those with no lifetime history of TBI. This was driven by greater left lateralization in the TBI group. The cingulum is a key structure in the limbic system, connecting medial aspects of the frontal and parietal lobes (not including the hippocampal cingulum, as the dorsal and hippocampal were distinct in this study; Budisavljevic et al., 2016) and supporting a number of important executive functions, including working memory, inhibition, and processing speed (Bettcher et al., 2016). The cingulum is also one of the last tracts to mature, with an average age-at-peak FA of 42 years old (Lebel et al., 2012). This

TABLE 2 Group differences in tract asymmetry.

ROIs	Deployment-related TBI ($N = 1872$)			Blast-related TBI ($N = 1509$)			Primary blast TBI ($N = 337$)			HX of TBI with LOC		
	d [95% CI]	Uncorrected *p*	Corrected *p*	*d* [95% CI]	Uncorrected *p*	Corrected *p*	*d* [95% CI]	Uncorrected *p*	Corrected *p*	*d* [95% CI]	Uncorrected *p*	Corrected *p*
ACR	−0.01 [−0.11, 0.08]	.75	1	−0.02 [−0.11, 0.07]	0.63	1	−0.06 [−0.16, 0.03]	.17	.95	0.06 [−0.04, 0.15]	.24	.99
ALIC	0.04 [−0.05, 0.13]	.35	1	0.03 [−0.06, 0.12]	0.52	1	0.05 [−0.04, 0.14]	.32	1	0.05 [−0.04, 0.14]	.29	1
CGC	**0.18 [0.08, 0.27]**	**.00015**	**.0024**	*0.11 [0.02, 0.20]*	*0.019*	*.26*	−0.06 [−0.15, 0.04]	.23	.98	0.06 [−0.04, 0.15]	.25	.99
CGH	0.01 [−0.08, 0.10]	.81	1	0.01 [−0.08, 0.10]	0.82	1	−0.04 [−0.13, 0.05]	.39	1	0.02 [−0.07, 0.11]	.66	1
CST	−0.08 [−0.17, 0.01]	.086	.76	−0.05 [−0.14, 0.04]	0.24	.99	−0.07 [−0.16, 0.02]	.12	.87	−4.1 e-3 [−0.09, 0.09]	.93	1
CR	0.06 [−0.03, 0.15]	.2	1	0.04 [−0.05, 0.13]	0.41	1	0.04 [−0.05, 0.14]	.34	1	*0.12 [0.03, 0.21]*	*.009*	*.13*
EC	−0.04 [−0.13, 0.05]	.42	1	−0.02 [−0.11, 0.07]	0.73	1	0.09 [0.00, 0.18]	.056	.6	−0.04 [−0.13, 0.05]	.39	1
FX/ ST	0.03 [−0.06, 0.12]	.46	1	0.02 [−0.07, 0.11]	0.62	1	−0.07 [−0.16, 0.02]	.14	.91	0.03 [−0.06, 0.12]	.54	1
IC	0.05 [−0.04, 0.14]	.3	1	0.04 [−0.05, 0.13]	0.39	1	*0.11 [0.02, 0.20]*	*.017*	*.24*	0.02 [−0.07, 0.11]	.68	1
PCR	0.04 [−0.05, 0.13]	.39	1	0.04 [−0.05, 0.13]	0.42	1	0.02 [−0.07, 0.12]	.6	1	0.06 [−0.03, 0.16]	.17	.95
PLIC	1.0 e-3 [−0.09, 0.09]	.98	1	−0.01 [−0.10, 0.08]	0.78	1	5.1 e-3 [−0.09, 0.10]	.91	1	−0.03 [−0.12, 0.06]	.46	1
PTR	0.07 [−0.02, 0.16]	.12	.87	0.06 [−0.03, 0.15]	0.19	.97	0.05 [−0.04, 0.14]	.27	.99	0.07 [−0.02, 0.16]	.15	.93
RLIC	3.0 e-3 [−0.09, 0.09]	.95	1	0.02 [−0.07, 0.11]	0.71	1	0.08 [−0.01, 0.17]	.088	.77	0.04 [−0.05, 0.13]	.42	1
SCR	0.06 [−0.03, 0.15]	.22	.98	0.09 [0.00, 0.18]	0.055	.6	0.05 [−0.04, 0.14]	.31	1	−1.5 e-3 [−0.09, 0.09]	.97	1
SFO	−0.03 [−0.12, 0.06]	.55	1	0.02 [−0.07, 0.11]	0.69	1	0.02 [−0.07, 0.11]	.73	1	0.04 [−0.06, 0.13]	.44	1
SLF	*0.10 [0.01, 0.19]*	*.027*	*.35*	0.06 [−0.03, 0.15]	0.18	.96	0.03 [−0.06, 0.12]	.57	1	0.14 [0.05, 0.23]	**.0018**	**.028**
SS	0.07 [−0.02, 0.16]	.13	.89	0.05 [−0.04, 0.14]	0.26	.99	−0.06 [−0.15, 0.04]	.24	.99	0.06 [−0.03, 0.15]	.18	.96
TAP	−0.08 [−0.18, 0.01]	.068	.68	−0.02 [−0.11, 0.07]	0.63	1	0.03 [−0.06, 0.12]	.53	1	−0.02 [−0.11, 0.07]	.66	1
UNC	0.02 [−0.07, 0.11]	.67	1	0.02 [−0.07, 0.11]	0.67	1	0.03 [−0.06, 0.13]	.45	1	0.04 [−0.05, 0.13]	.35	1

Note: Results from group analyses are shown comparing deployment-related TBI to no TBI, blast-related TBI to no TBI, and primary blast TBI to no TBI, along with total sample size for each comparison. Cohen's *d*, 95% CI, and uncorrected *p*-values are shown, **bolded** statistics are those that survive correction for multiple comparisons, *italicized* statistics are those that do not survive multiple comparisons correction (.05 > *p* > .003125). Primary blast TBI is blast overpressure with no concurrent blunt injury.

Abbreviations: ACR, Anterior corona radiata; ALIC, anterior limb of internal capsule; CGC, cingulum; CGH, hippocampal cingulum; CR, corona radiata; CST, corticospinal tract; EC, external/extreme capsule; FX/ST, fornix-stria terminalis; IC, internal capsule; LOC, loss of consciousness; PCR, posterior corona radiata; PLIC, posterior limb of internal capsule; PTR, posterior thalamic radiation; RLIC, retrolenticular limb of internal capsule; ROI, Region of interest; SCR, superior corona radiata; SFO, superior fronto-occipital fasciculus; SLF, superior longitudinal fasciculus; SS, sagittal stratum; TAP, tapetum; TBI, traumatic brain injury; UNC, uncinate.

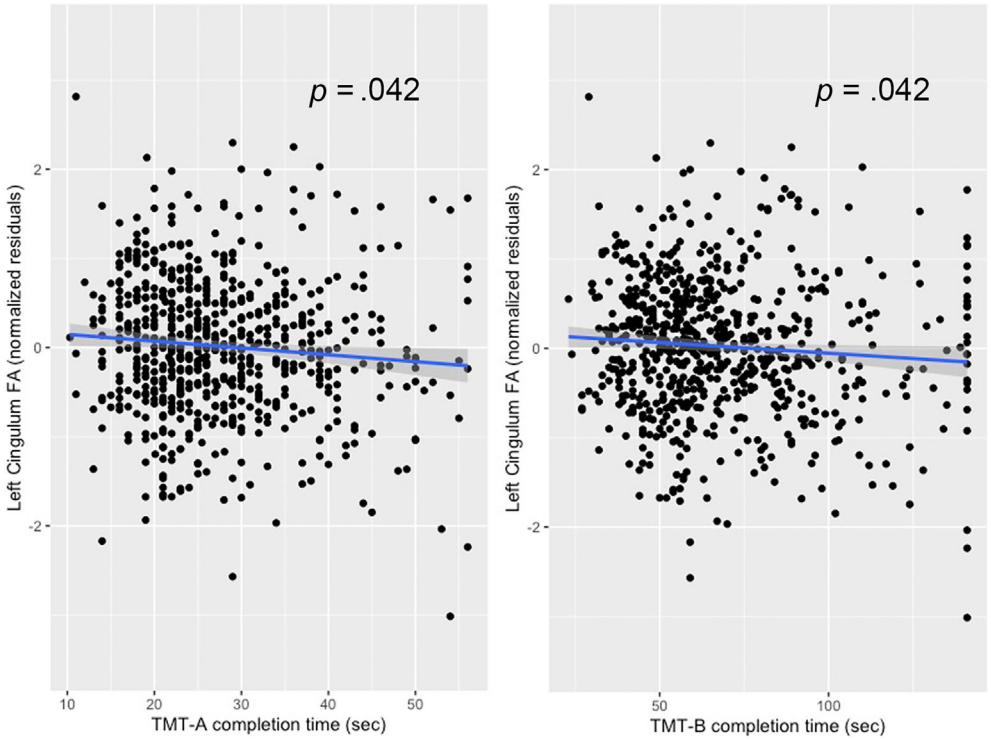

FIGURE 2 Group differences in tract asymmetry. Results from group analyses are shown comparing deployment-related traumatic brain injury (TBI) to no TBI, blast-related TBI to no TBI, and primary blast TBI to no TBI, along with total sample size for each comparison. Cohen's *d*, 95% CI, and uncorrected *p*-values are shown, bolded statistics are those that survive correction for multiple comparisons, italicized statistics are those that do not survive multiple comparisons correction (.05 > *p* > .003125). Primary blast TBI is blast overpressure with no concurrent blunt injury. ACR, anterior corona radiata; ALIC, anterior limb of internal capsule; CGC, cingulum; CGH, hippocampal cingulum; CR, corona radiata; CST, corticospinal tract; EC, external/extreme capsule; FX/ST, fornix-stria terminalis; IC, internal capsule; PCR, posterior corona radiata; PLIC, posterior limb of internal capsule; PTR, posterior thalamic radiation; RLIC, retrolenticular limb of internal capsule; ROI, Region of interest; SCR, superior corona radiata; SFO, superior fronto-occipital fasciculus; SLF, superior longitudinal fasciculus; SS, sagittal stratum; TAP, tapetum; UNC, uncinate.

prolonged maturation may render the cingulum more vulnerable to environmental impacts, and prior structural equation modeling did not show significant genetic contributions to cingulum asymmetry, supporting the hypothesis that environment plays an outsized role (Jahanshad et al., 2010). This age-at-peak happens to coincide with the average age of our sample (41.7 years). Indeed, when we ran the analysis after separating participants whose worst injury occurred before age 40 versus those whose injury occurred after age 45, only the comparison in the younger group remained significant. This analysis excluded Vietnam Veterans as the remoteness of their injuries may implicate different injury-related and age-related processes. Heterogeneity across cohorts and the general reliance on self-reports of injuries, including their timing and severity, mean that this must be interpreted with caution, but this does present a hypothesis that can be addressed more directly in individual studies. As the sample size differed greatly between these analyses (855 younger vs. 106 older TBI participants), we cannot rule out decrease in statistical power as the reason for the difference; however, the result does lend support to the interpretation that the cingulum is particularly vulnerable to injury because of its long maturation.

The length, orientation, and proximity of the cingulum to the falx and ventricles may contribute to strain and shear forces on the tract during impact (Bigler, 2007; Ware et al., 2019; Zhou et al., 2022). Disentangling the effects of blast-related versus impact-related TBI is difficult, especially in our analysis of heterogeneous legacy datasets. The differences between blast-related TBI and no TBI were not significant after multiple comparisons correction and the effect size was smaller, but the sample size was smaller, and blast-related injuries in military settings often also involve a co-occurring impact. An exploratory analysis in the small subset of the sample with data on primary blast TBI (blast TBI due to overpressure with no concurrent blunt injury; 146 vs. 191) did not yield significant results for the cingulum, lending support to the interpretation that the biomechanical forces of TBI may affect the cingulum more than the pressure forces of blast-related TBI. Targeted analysis in animal studies and well-characterized cohort studies are necessary to confirm this finding.

Left lateralization of cingulum FA is a well-documented phenomenon in healthy (primarily right-handed) individuals (Gong et al., 2005; Takao et al., 2013; Takao, Hayashi, & Ohtomo, 2011) and is linked with cingulum-related cognitive functions (Caeyenberghs et al., 2016; Luna et al., 2021; Metzler-Baddeley et al., 2012). Development, aging, and sex do not appear to contribute to laterality of the whole cingulum (Takao, Abe, et al., 2011; Trivedi et al., 2009), although aging

effects have been reported for the subcallosal cingulum (Sibilia et al., 2017). In tracts that are more asymmetric, the nondominant hemisphere may be more susceptible to damage, as neural resources may be diverted to maintaining integrity of the dominant hemisphere. Lower FA in the right cingulum may be due to less myelination, or to less organized or less densely packed fibers. A recent, large study of young adults using multishell dMRI showed that the neuronal density of the left cingulum was greater than that of the right, while the orientation dispersion index was higher on the right, indicating less coherence in fiber direction (Tsuchida et al., 2021). Lower fiber density could mean greater elasticity and thus more stretch during impact; finite element modeling consistently indicates high axonal strain in the cingulum (Chatelin et al., 2011; Zhang & Gennarelli, 2011; Zhao et al., 2019). Less asymmetry may partially explain the lack of significant group differences in females, as some studies have found lower tract asymmetry in women than men (Jahanshad et al., 2010; Thiebaut de Schotten et al., 2011), but the much smaller female sample size ($n = 199$) limited statistical power and thus limits our ability to draw conclusions from the female-only analyses.

Alterations in cingulum microstructure have been reported previously in mTBI (Kinnunen et al., 2011; Kraus et al., 2007; Niogi et al., 2008; Rutgers et al., 2008; Wu et al., 2010), including military-specific mTBI (Mac Donald et al., 2011; Yeh et al., 2014; Yurgelun-Todd et al., 2011), as well as across psychiatric disorders (Abdul-Rahman et al., 2011; Kochunov et al., 2020; Lochner et al., 2012). In healthy individuals, greater cingulum asymmetry has been associated with better attentional control and executive function (Luna et al., 2021). Other studies have reported that alterations in WM asymmetry are associated with cognitive deficits (Gómez-Gastiasoro et al., 2019). Two prior studies examining WM asymmetry in mTBI reported increased asymmetry in the corticospinal tract (CST; Maruta et al., 2020; Vakhtin et al., 2020). Unfortunately, this midline tract was not separated into left and right components in the ENIGMA atlas, so we did not have the opportunity to replicate that finding. Several studies in participants with TBI have reported associations between WM microstructural organization in the right cingulum and cognitive function, including reaction time and set shifting (Bonnelle et al., 2011; Kinnunen et al., 2011; Sugiyama et al., 2009). Prior studies have shown that deployment-related TBI is associated with poorer TMT performance, even when compared to nondeployment TBI (Martindale et al., 2021). We report that lower FA of the left cingulum is linked with slower processing speed and set shifting in the TBI group, echoing the findings of Gläscher et al., 2012 and Luna et al., 2021, but this association was not present in the non-TBI comparison group. Altered asymmetry of the cingulum in our sample was driven by an exaggerated laterality index, but no significant changes in either hemisphere. This suggests that asymmetry differences may be due to minor changes in both hemispheres, or that the anatomic location of the changes differ across participants.

Our study has several limitations. First, as a retrospective analysis of data collected across different studies, there are many sources of heterogeneity in our data that we cannot fully characterize or account for. Differences in TBI history assessment limited the analyses to the most common denominators, which were often more general variables than individual sites collected. Our results present several interesting hypotheses that future studies can interrogate in greater detail, such as whether the cingulum is vulnerable because of its extended maturation, whether females are less vulnerable to alterations in cingulum asymmetry because they have less natural cingulum asymmetry, or whether the right cingulum is more vulnerable due to less densely packed fibers. Second, most of the TBI history for our cohorts was self-reported, which has inherent issues with reliability. We report all analyses of injury variables (such as duration of loss of consciousness) for completeness, but do not interpret these results. Third, TBSS is limited as a tensor-based approach compared to a tractography approach, so we cannot fully attribute results to particular fiber bundles. Fourth, we were limited in the clinical endpoints we could examine to those that were most general (e.g., categorical variable for current depression), most commonly collected (e.g., TMT), or already harmonized (e.g., PCL versions; Kennedy, 2022). Work is ongoing in the ENIGMA Clinical Endpoints working group (a subgroup of the Brain Injury working group) to develop additional harmonized measures across multiple domains. Thus, future studies will be able to examine how TBI-related alterations in brain structure and function correspond to changes in memory, attention, and inhibition, among others. Fifth, as a cross-sectional study, we cannot examine whether asymmetry differences predate injury, or how the differences in asymmetry evolve over the lifespan. Sixth, there were significant differences between our groups in age and gender. These match epidemiological trends, and age and gender were included as covariates in all analyses. Lastly, while one cohort came from the Netherlands, the rest of the cohorts were from the United States, which may limit the generalizability of our results to other military contexts.

5 | CONCLUSIONS

Our effect sizes are small, but in line with other ENIGMA analyses (Dennis et al., 2019; Kochunov et al., 2020). Given the many sources of heterogeneity in our sample, and the existing, often inconclusive, literature on dMRI alterations in military-relevant TBI (predominantly mTBI), small effect sizes are expected. The necessary sample size to find an effect of this size with 80% power and a significance threshold of 5% is 972, far larger than most published work on dMRI in military brain injury, highlighting the importance of collaborative projects. Our work points to subtle alterations in the balance of the brain after TBI, and suggests a phenomenon of heightened vulnerability of the nondominant hemisphere, perhaps as neural resources are diverted to support the dominant hemisphere. These alterations have functional consequences, as they were associated with slower processing speed and set shifting. Future targeted studies in individual, well-characterized cohorts or animal models will further elucidate specific

underlying mechanisms and functional implications for alterations in tract asymmetry.

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CONFLICT OF INTEREST

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DATA AVAILABILITY STATEMENT

Researchers interested in accessing the data described here must first join the ENIGMA Military-Relevant Brain Injury group and agree to abide by the Memorandum of Understanding governing data sharing and authorship. All projects are opt-in, so the specific cohorts available will differ.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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