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Longitudinal Changes of White Matter Microstructure following Traumatic Brain Injury in U.S. Military Service Members

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DISCLAIMER

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SCOPES

1. **Basics of diffusion tensor imaging (DTI)**
2. **Discuss** the findings of “longitudinal changes of white matter microstructure following traumatic brain injury in U.S. military service members”; Brain Communications 2022; 4(3): fcac132. doi: 10.1093/braincomms/fcac132
3. **Multimodal approach**– neuroimaging, neuropsychological function, blood-based biomarkers, non-Gaussian water diffusion imaging.
4. **Subject-specific analysis**
5. **Future directions**

Background - DTI

1. Diffusion Tensor Imaging (DTI) in each voxel:

$$S_j = S_0 \exp(-b_j \mathbf{x}_j^T D \mathbf{x}_j)$$

B value for gradient *j* (known)

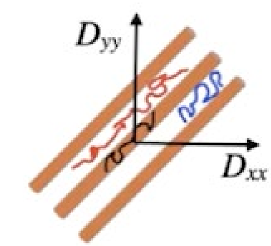
Unit vector representing the direction of gradient (known)

Signal measured after applying a diffusion gradient *j* with direction $\mathbf{x}_j$ and b-value b_j

Signal measured with no diffusion gradient applied

3x3 Diffusion Tensor (unknown)

$$\mathbf{D} = \begin{bmatrix} D_{xx} & D_{xy} & D_{xz} \\ D_{xy} & D_{yy} & D_{yz} \\ D_{xz} & D_{yz} & D_{zz} \end{bmatrix}$$



Q: How easily it diffuse? Directional preference? - anisotropic

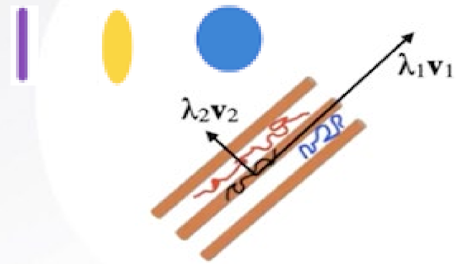
2. DTI Eigenspectrum:

- Once D is estimated, apparent diffusion coefficient (ADC) along the scanner's coordinate system.
- Diagonalize D to get ADC along a local coordinate system in each voxel, determined by the anatomy

$$\mathbf{D} = [\mathbf{v}_1|\mathbf{v}_2|\mathbf{v}_3]^T \begin{bmatrix} \lambda_1 & 0 & 0 \\ 0 & \lambda_2 & 0 \\ 0 & 0 & \lambda_3 \end{bmatrix} [\mathbf{v}_1|\mathbf{v}_2|\mathbf{v}_3]$$

eigenvectors - $\mathbf{v}_1$=direction of max diffusivity

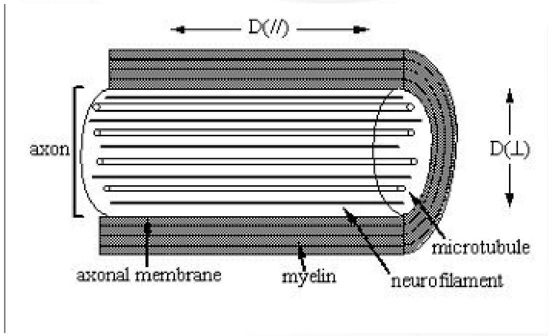
eigenvalues: ADCs along $\mathbf{v}_1, \mathbf{v}_2, \mathbf{v}_3$

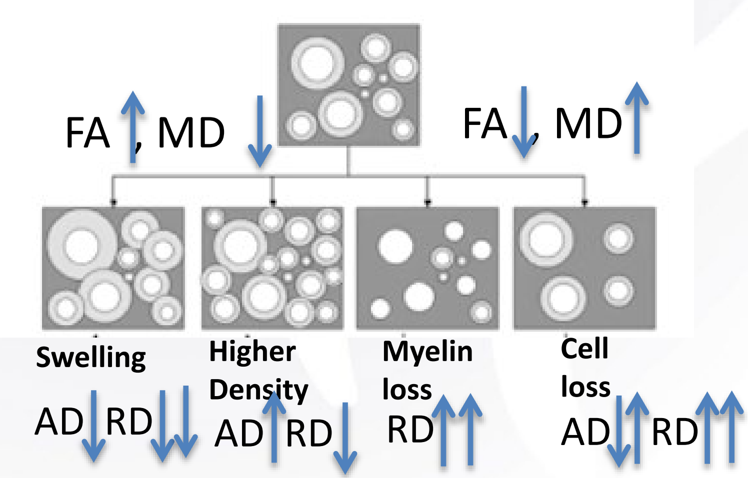


Background - DTI

DTI metrics

- Fractional Anisotropy (FA) = Variance across eigenvalues in [0,1], a summary measure of microstructural integrity
- Mean Diffusivity (MD) = eigenvalues mean
- Axial Diffusivity (AD, parallel ADC) = The main eigenvalue
- Radial Diffusivity (RD, perpendicular ADC) = The mean of two small eigenvalue.
- **Biological interpretations –** different scenarios can have same effects on DTI metrics.





Background - DTI

- **DTI metrics alterations following TBI**

Cell type or compartment	TBI-related alterations	Tissue environment	Expected diffusion changes
Neurons	cell loss necrosis and apoptosis	atrophy, cavitation, *unmasking*	decreased diffusivity and anisotropy, *increased anisotropy*
	axonal injury	axon morphology changes including beading and varicosities	reduction in anisotropy and reduction in diffusion, especially in the axial direction
	neural plasticity sprouting, arborization	increased number of coherent processes and new collaterals	increased anisotropy and/or changed orientation
Oligodendrocytes	demyelination direct damage, chronic pathology	degenerating or lost	decreased anisotropy
	myelination repair remyelination	regenerating	normalized anisotropy
Astrocytes	Hypertrophy	increased number or thickness of glial processes, possibly organized or directional	increased or decreased anisotropy, decreased diffusivity
	proliferation glial scaring	increased cellularity dense glia, increased organization	decreased diffusivity decreased diffusivity, increased anisotropy
Microglia	phagocytosis	amoeboid stage microglia	increased diffusivity
	neural repair and support	rod-microglia	possible increased anisotropy
Intracellular space	cytotoxic edema	cell swelling	decreased diffusivity

Hutchinson E.B. *et al* JNR 2017

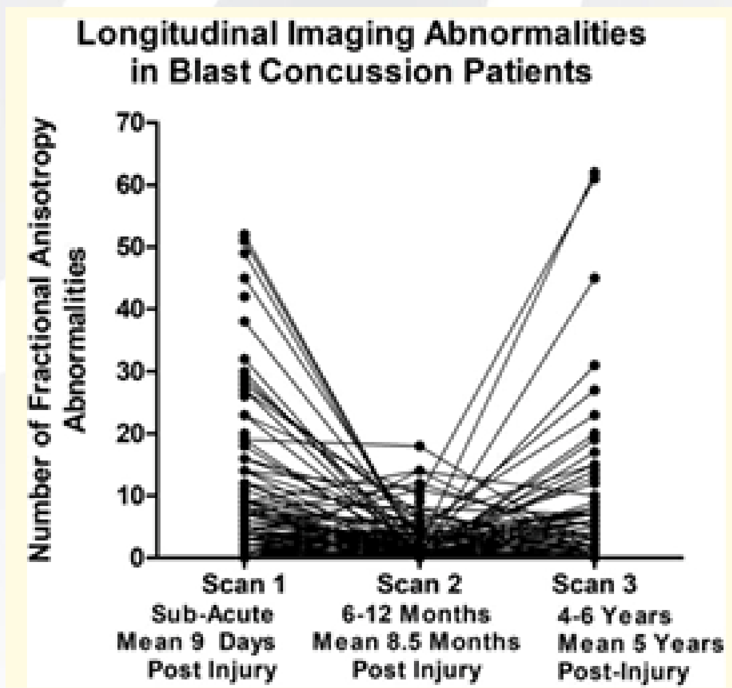
Longitudinal DTI following TBI

doi:10.1093/braincomms/fcz031 BRAIN COMMUNICATIONS 2019: Page 1 of 13 | 1

BRAIN COMMUNICATIONS

Longitudinal neuroimaging following combat concussion: sub-acute, 1 year and 5 years post-injury

Christine L. Mac Donald,[1] Jason Barber,[1] Jalal Andre,[2] Chris Panks,[1] Kody Zalewski[1] and Nancy Temkin[1,3]



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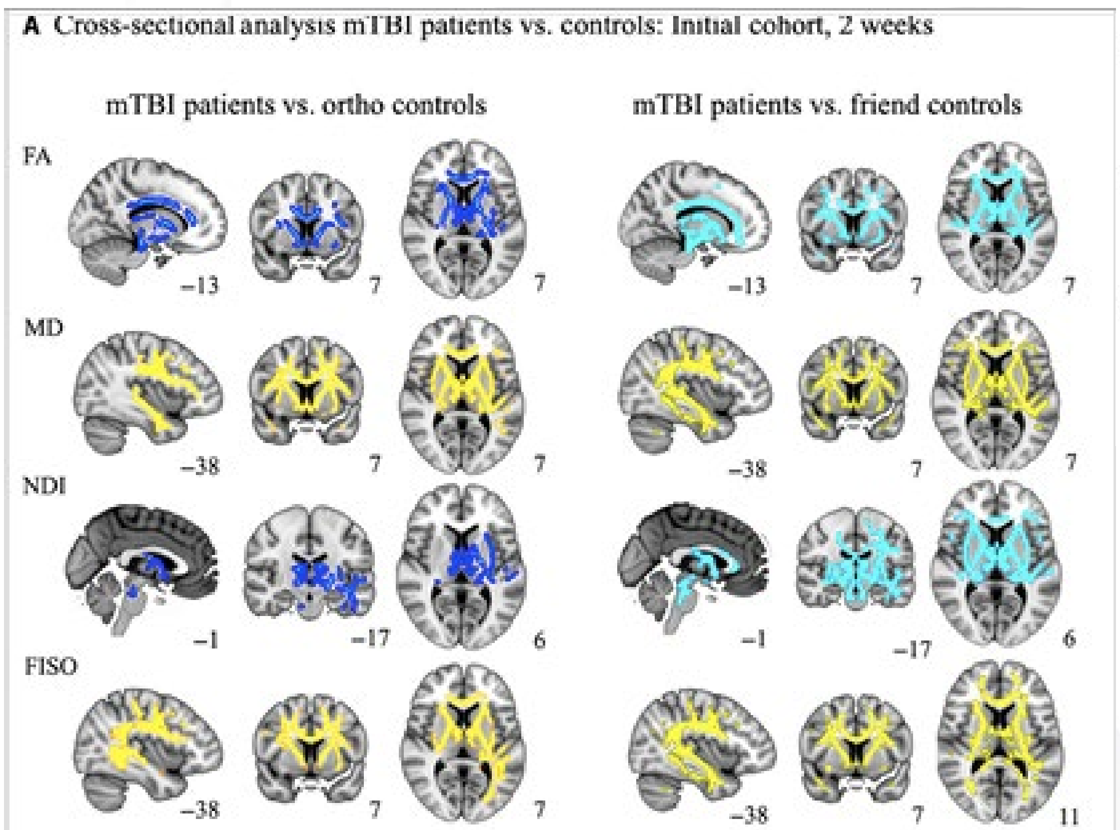
Longitudinal DTI following TBI

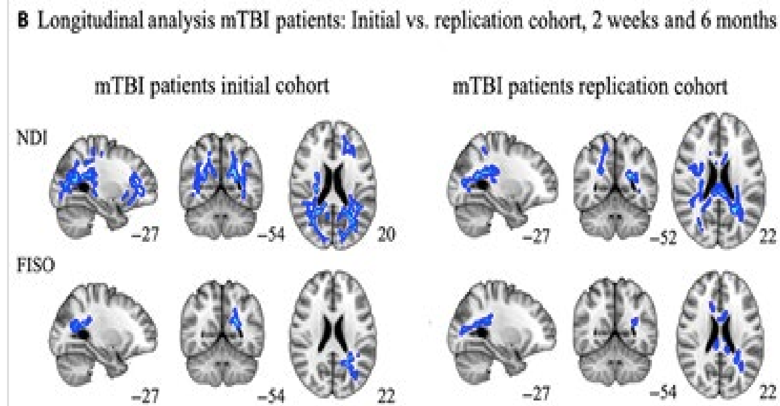
SCIENCE ADVANCES | RESEARCH ARTICLE

NEUROSCIENCE

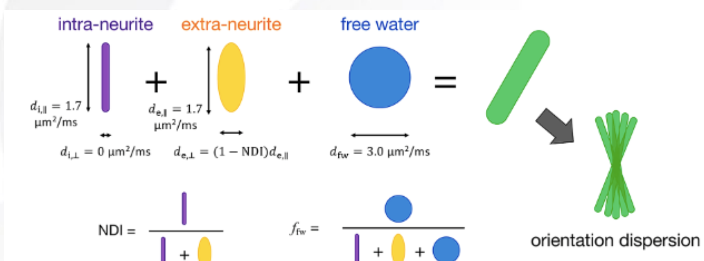
The evolution of white matter microstructural changes after mild traumatic brain injury: A longitudinal DTI and NODDI study

E. M. Palacios[1], J. P. Owen[2], E. L. Yuh[1,3], M. B. Wang[1], M. J. Vassar[3,4], A. R. Ferguson[3,4,5], R. Diaz-Arrastia[6], J. T. Giacino[7,8], D. O. Okonkwo[9], C. S. Robertson[10], M. B. Stein[11,12], N. Temkin[13], S. Jain[12], M. McCrea[14], C. L. MacDonald[13], H. S. Levin[15], G. T. Manley[3,4], P. Mukherjee[1,3,16]*, TRACK-TBI Investigators†





Neurite Orientation Dispersion and Density Imaging (NODDI)



Kamiya K. et al 2020

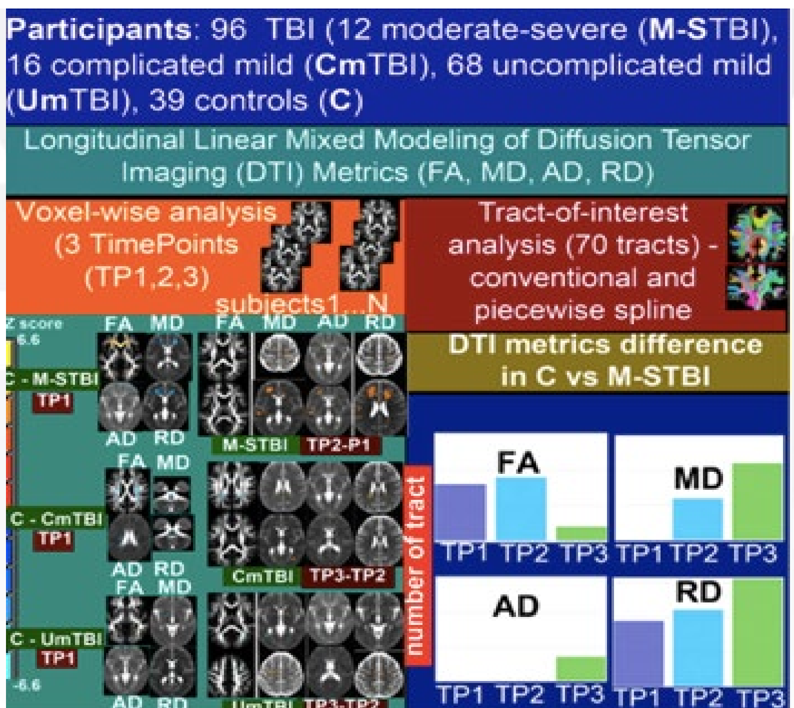
Longitudinal DTI following TBI

https://doi.org/10.1093/braincomms/fcac132 BRAIN COMMUNICATIONS 2022: Page 1 of 15 | 1

BRAIN COMMUNICATIONS

Longitudinal changes of white matter microstructure following traumatic brain injury in U.S. military service members

Ping-Hong Yeh,[1] Sara. M. Lippa,[1] Tracey A. Brickell,[1,2,4,5,6] John Ollinger,[1] Louis M. French[1,2,4] and Rael T. Lange[1,2,3,5,6]



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Study Design

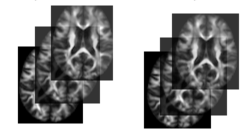
143 participants selected from initial 351 participants

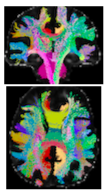
Interview, injury history taking, initial structural MRI assessment

excluding 37 TBI with unsatisfactory MRI data, 7 equivocal mild TBI, 1 control

96 TBI (12 Moderate-Severe TBI, 16 Complicated Mild TBI, 68 Uncomplicated Mild TBI),
39 non-TBI Controls (31 injured controls, 8 non-injured controls)

MRI data preprocessing





Automated 70 white matter bundles segmentation (TractSeg)

DTI metrics mapping and averaging

Tract-of-interest analysis by linear mixed-effect modeling using SAS package PROC MIXED

TP1, TP2, TP3

Group analysis with effects from multiple sessions at individual subject level, random effects of individual intercept, and covariates of gender and age

TP1, TP2, TP3, TP4, TP5

Piecewise linear splines with knot at 700 days since injury by modeling group effect and time since injury effect, random effects of individual intercept, repeated scans effect with covariates of gender and age

Longitudinal whole brain DTI metrics spatial normalization

TP1, TP2, TP3

Whole brain voxel-wise analysis by linear mixed-effect modeling using AFNI package 3dLMEr

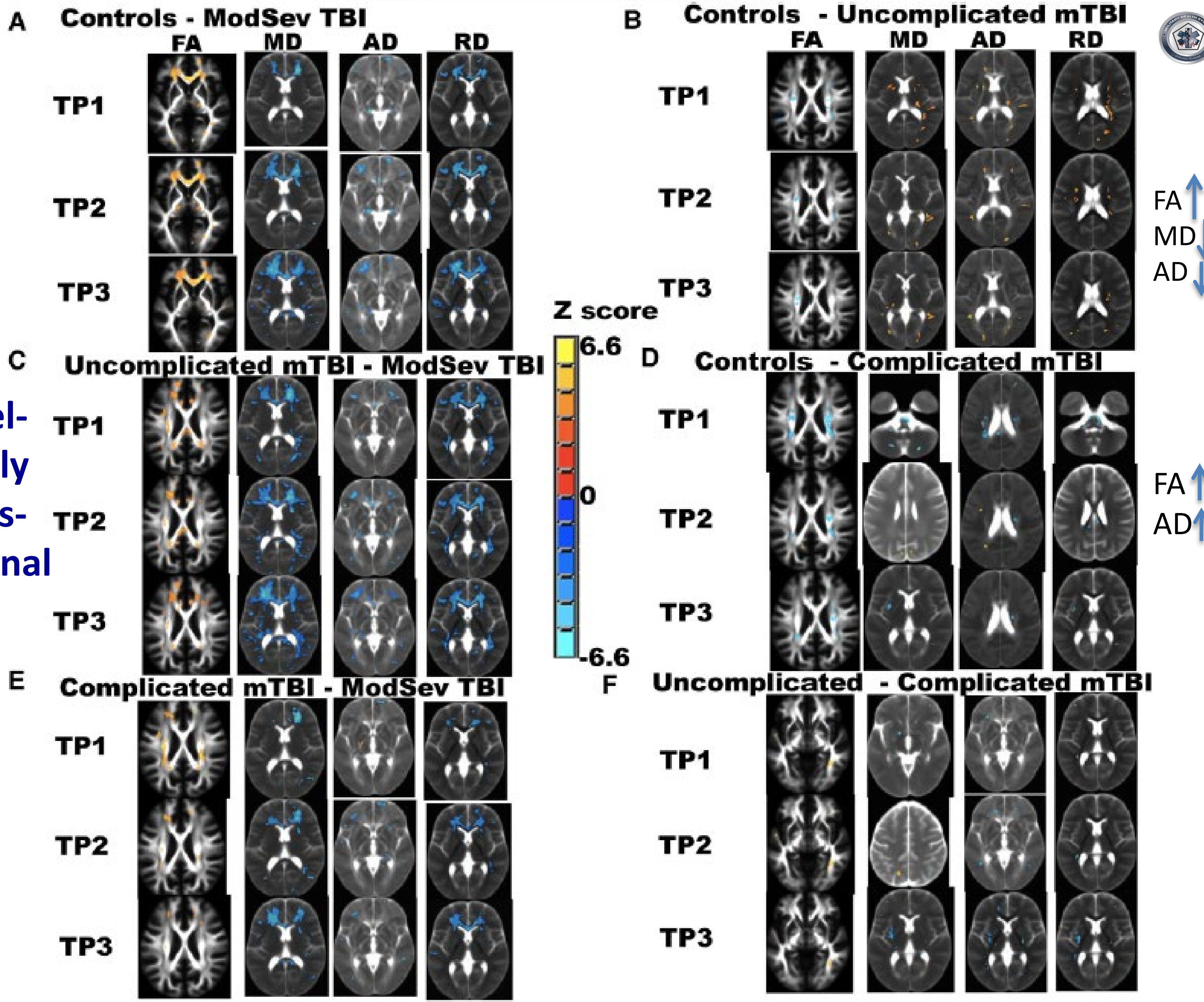
Group analysis with effects from multiple sessions at individual subject level, random effects of individual intercept, and covariates of gender and age

Participants*

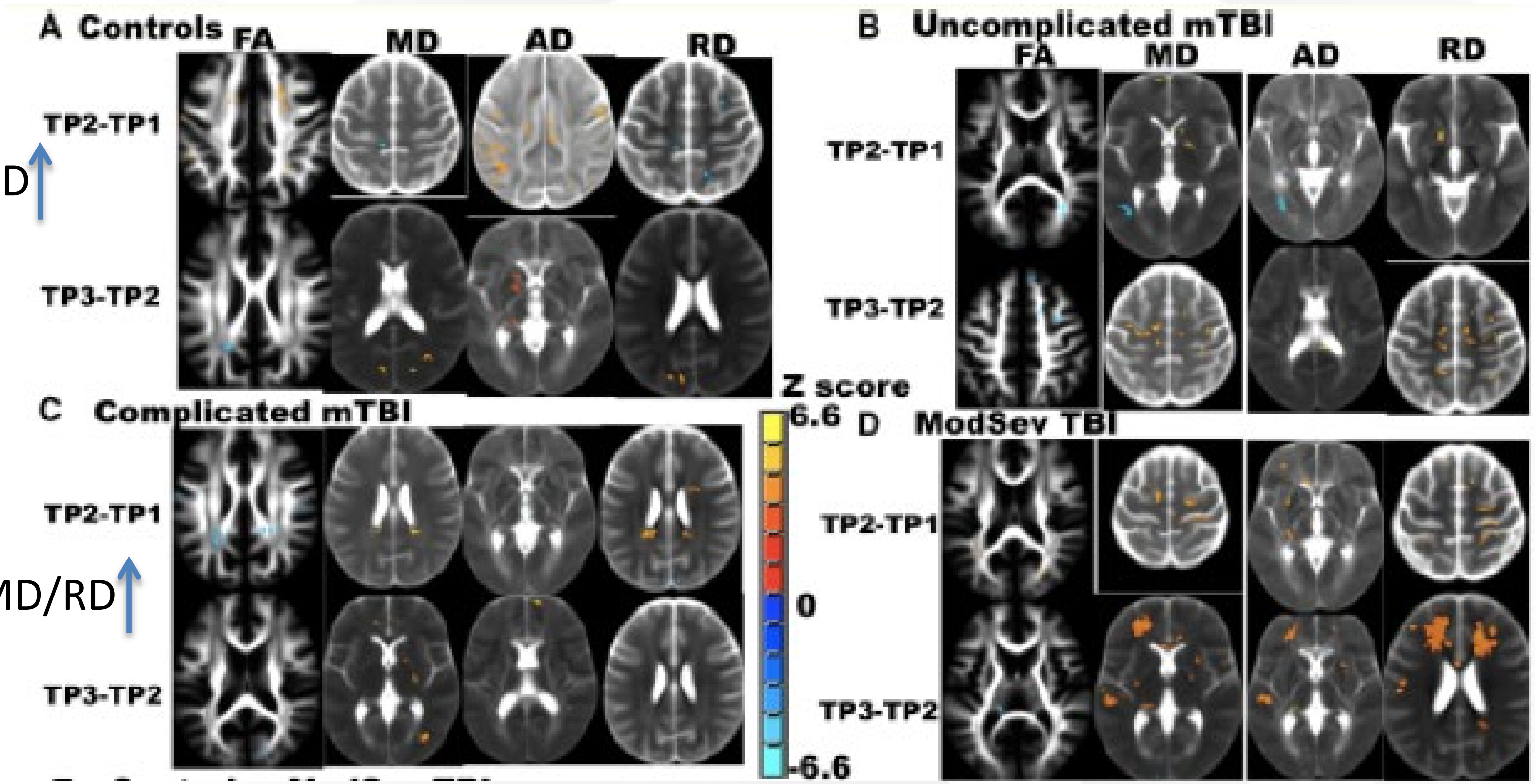
Group\TP	TP1	TP2	TP3	TP4	TP5
Controls (M/F)	28/3	34/4	12/1	4/1	1/0
Age	38.0 ± 11.4	40.1 ± 10.4	36.5 ± 13.4	32.5 ± 9.5	31
Days since injury	882.5 ± 1172.6	1137.0 ± 1956.4	1273.3 ± 1195.0	1250 ± 353.3	1851
Uncomplicated mTBI (M/F)	45/2	66/2	14/1	5/0	1/0
`Age	33.5 ± 9.5	36.5 ± 9.8	37.9 ± 9.3	39.9 ± 8.4	44
Days since injury	1062 ± 1240.0	1732.8 ± 1316.4	1786.2 ± 399.5	2180.0 ± 1891.0	1823
Complicated mTBI (M/F)	13/2	14/2	6/1	1/1	—
Age	33.7 ± 11.1	36.0 ± 11.6	41.7 ± 9.3	47.0 ± 1.4	—
Days since injury	181.4 ± 95.7	597.4 ± 343.7	1437.1 ± 426.8	1840.5 ± 426.8	—
ModSev TBI (M/F)	10/1	10/1	7/1	3/1	1/0
Age	29.8 ± 8.4	30.8 ± 8.9	30.3 ± 6.6	32.5 ± 9.6	28
Days since injury	278.1 ± 282.2	692.0 ± 514.3	1293.9 ± 526.9	1661.8 ± 376.2	1850

*All subjects enrolled into the study voluntarily agreed to participate and gave written informed consent. This study was approved by the Institutional Review Board of The Walter Reed National Military Medical Center (WRNMMC), Bethesda, Maryland

Voxel-wisely Cross-sectional



Voxel-wisely longitudinal



AD↑

MD/RD↑

MD/RD↑

MD/RD↑↑

AD↑

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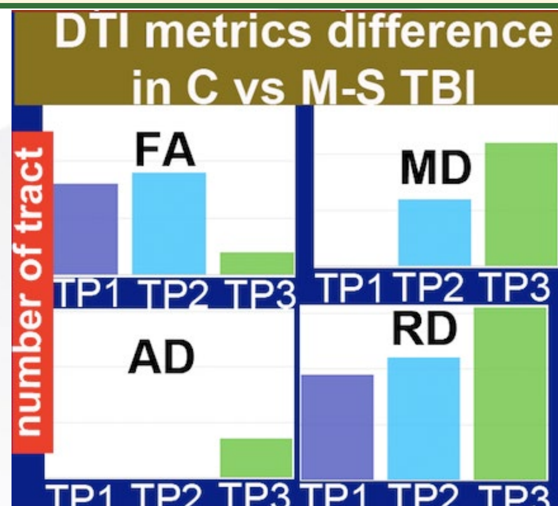
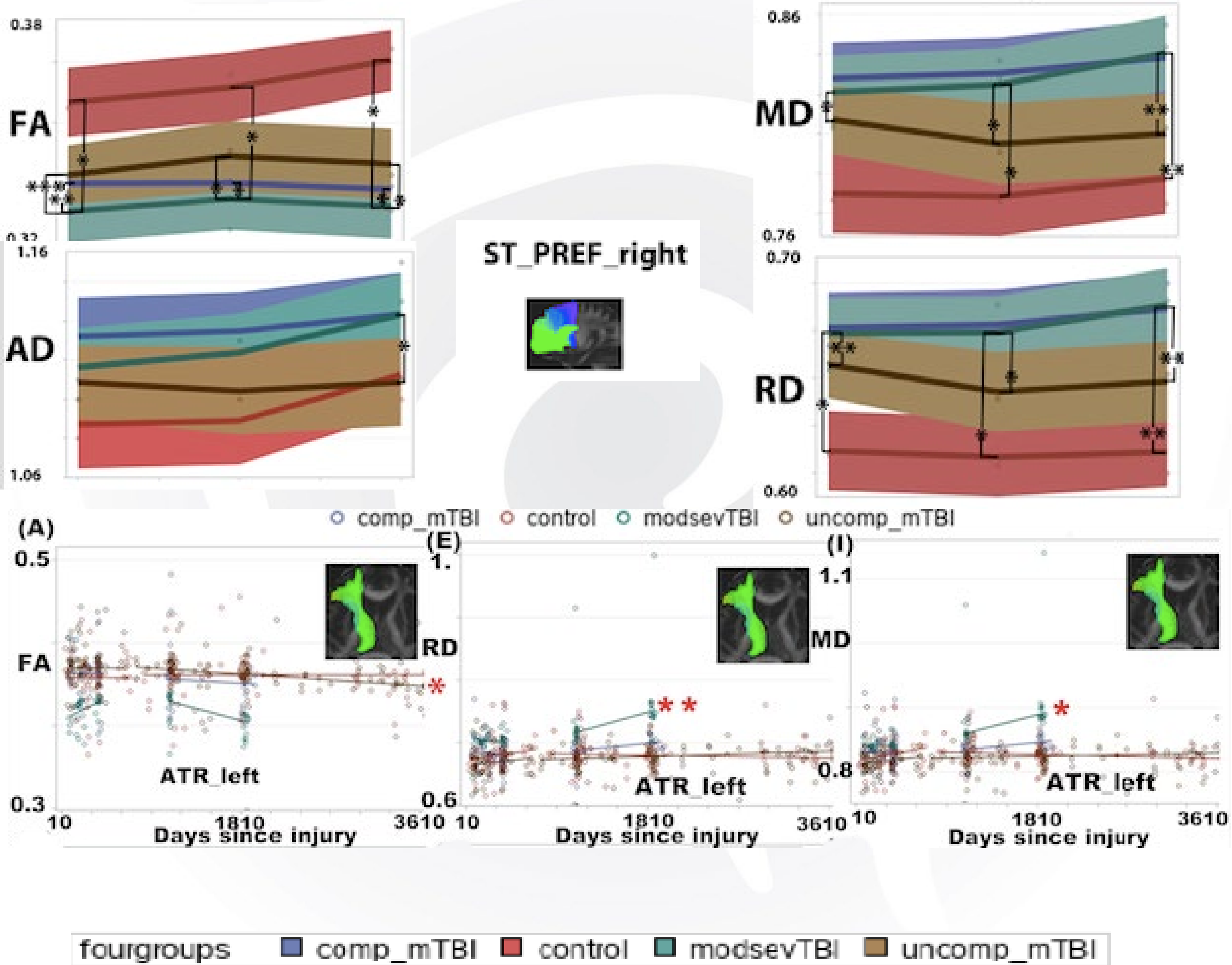
Tract-of-Interest Analysis

		Cross-sectional			Trajectory	
		TP1	TP2	TP3	TP2–TP1	TP3–TP2
FA	Controls > ModSev TBI	16 tracts	18 tracts	4 tracts	—	—
	Complicated mTBI > ModSev TBI	10 tracts	5 tracts	3 tracts	—	—
	Uncomplicated mTBI > ModSev TBI	30 tracts	17 tracts	17 tracts	—	—
	Controls	—	—	—	1 tract (positive)	
MD	ModSev TBI > controls	—	12 tracts	22 tracts	—	—
	ModSev TBI > complicated mTBI	—	3 tracts	3 tracts	—	—
	ModSev TBI > uncomplicated mTBI	7 tracts	19 tracts	30 tracts	—	—
	ModSev TBI	—	—	—	1 tract (positive)	3 tracts (positive)
AD	ModSev TBI > controls	—	—	7 tracts	—	—
	ModSev TBI > complicated mTBI	—	—	1 tract	—	—
	ModSev TBI > uncomplicated mTBI	—	1 tract	11 tracts	—	—
	ModSev TBI	—	—	—	—	1 tract (positive)
RD	ModSev TBI > controls	3 tracts	20 tracts	22 tracts	2 tracts	1 tract
	ModSev TBI > complicated mTBI	4 tracts	5 tracts	7 tracts	—	—
	ModSev TBI > uncomplicated mTBI	19 tracts	22 tracts	31 tracts	—	—
	ModSev TBI	—	—	—	1 tract (positive)	1 tract (positive)



Tract-of-Interest Analysis



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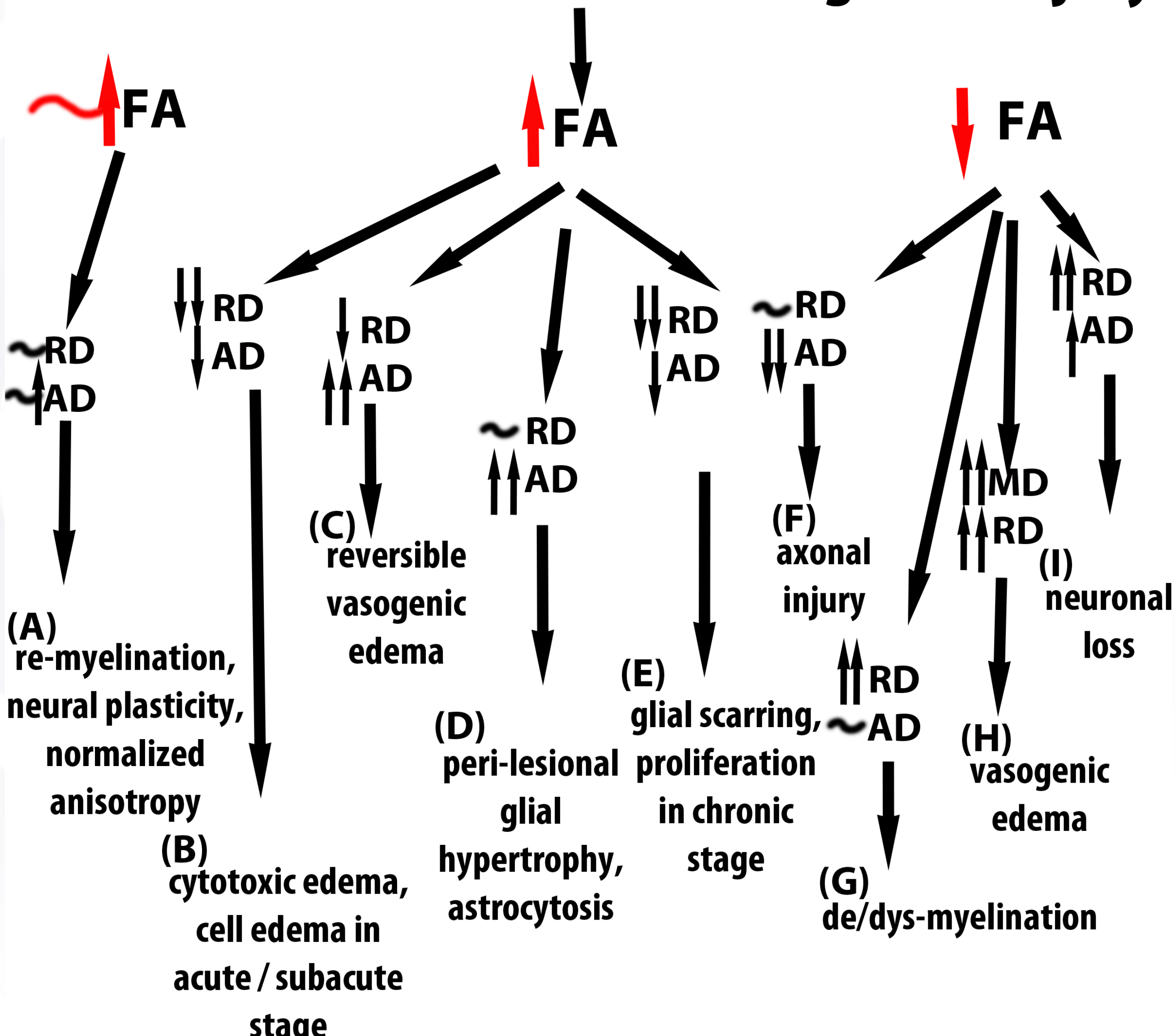
Possible Biological Alterations

MILITARY HEALTH SYSTEM
STRONG TO SAVE

Patterns of DTI metrics following head injury



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Blood Biomarkers & DTI following TBI

JOURNAL OF NEUROTRAUMA 36:2190–2199 (July 15, 2019)

DOI: 10.1089/neu.2018.6269

Plasma Tau and Amyloid Are Not Reliably Related to Injury Characteristics, Neuropsychological Performance, or White Matter Integrity in Service Members with a History of Traumatic Brain Injury

Sara. M. Lippa,[1–3] Ping-Hong Yeh,[2] Jessica Gill,[4] Louis M. French,[1,2,5]
Tracey A. Brickell,[1–3,5] and Rael T. Lange[1–3,6]

Correlation b/w Plasma Aβ42 and DTI metrics

	Uncomplicated mild (n=47)				*Complicated mild* (n=19)				*Moderate+* (n=22)			
	FA	*MD*	*RD*	*AD*	*FA*	*MD*	*RD*	*AD*	*FA*	*MD*	*RD*	*AD*
WHOLE BRAIN	.048	.059	.014	.117	.172	–.119	–.169	–.009	.390	–.547[a]	–.502[a]	–.546[a]
F MAJOR	.054	–.061	–.077	–.003	.277	–.215	–.254	–.097	.499[a]	–.612[a]	–.608[b]	–.218
F MINOR	.013	.150	.106	.131	.343	–.245	–.316	.005	.173	–.394	–.336	–.424
L ATR	–.135	.191	.200	.060	.198	.009	–.083	.150	.077	–.385	–.295	–.363
L CAB	.180	.001	–.081	.127	.035	–.126	–.132	–.101	.414	–.362	–.393	–.235
L CCG	–.133	.051	.153	–.119	.186	–.160	–.217	.074	.025	–.286	–.199	–.229
L CST	–.039	–.018	.008	–.043	–.005	–.062	–.019	–.043	.189	.026	–.048	.109
L ILF	.120	–.103	–.146	.024	.047	–.101	–.078	–.097	.225	–.432	–.370	–.455
L SLFP	.048	.041	–.002	.066	–.122	–.170	–.075	–.229	.193	–.253	–.238	–.223
L SLFT	.078	.246	.090	.260	–.186	–.067	.085	–.172	.194	–.149	–.170	–.056
L UNC	.144	–.083	–.126	.027	.058	–.010	–.014	–.004	.165	–.170	–.165	–.1 42
R ATR	–.037	.192	.164	.146	–.104	–.175	–.092	–.253	.130	–.429	–.390	–.330
R CAB	.049	.032	.021	.044	.246	–.042	–.111	.097	.174	–.455[a]	–.409	–.428
R CCG	–.154	.127	.189	–.050	.236	.107	–.052	.217	.068	–.383	–.253	–.420
R CST	–.013	.033	.019	.030	.268	–.129	–.257	.084	.161	–.416	–.308	–.431
R ILF	.067	–.081	–.101	–.016	.040	.002	.013	–.009	.273	–.657[b]	–.537[a]	–.729[b]
R SLFP	.025	–.036	–.018	–.043	.065	–.106	–.113	–.042	.249	–.492[a]	–.489[a]	–.392
R SLFT	–.026	–.023	.022	–.087	.079	.020	–.015	.048	.448	–.573[a]	–.576[a]	–.412
R UNC	.016	.046	.027	.051	.019	.177	.114	.192	.348	–.300	–.314	–.181

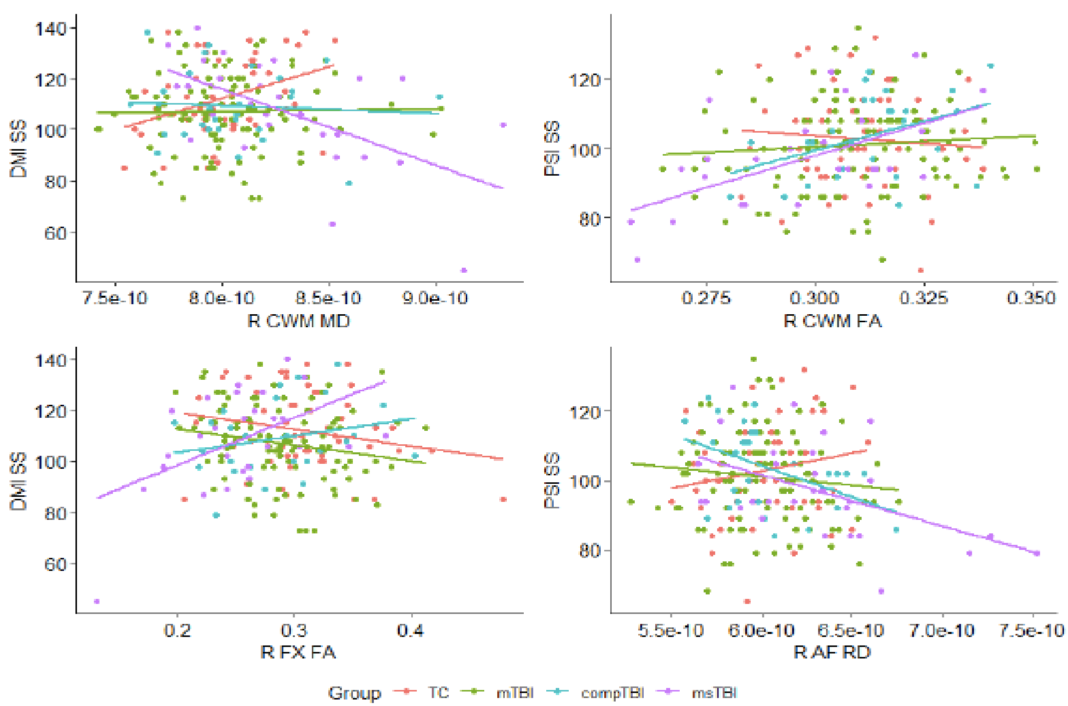
Cognition & DTI following TBI

Journal of Neurotrauma > VOL. 0, NO. ja | normal

White Matter Integrity Relates to Cognition in Service Members and Veterans Following Complicated Mild, Moderate, and Severe TBI, but not Uncomplicated Mild TBI

Dr. Sara M Lippa, Dr. Ping-Hong Yeh, Dr. John M Ollinger, Dr. Tracey A Brickell, Dr. Louis M. French, and Dr. Rael T Lange

Published Online: 7 Sep 2022 | https://doi.org/10.1089/neu.2022.0276



TBI Subject-Specific Analysis

Neuroimage. 2016 Feb 1;126:151-63. doi: 10.1016/j.neuroimage.2015.11.046. Epub 2015 Nov 27.

Tract Orientation and Angular Dispersion Deviation Indicator (TOADDI): A framework for single-subject analysis in diffusion tensor imaging

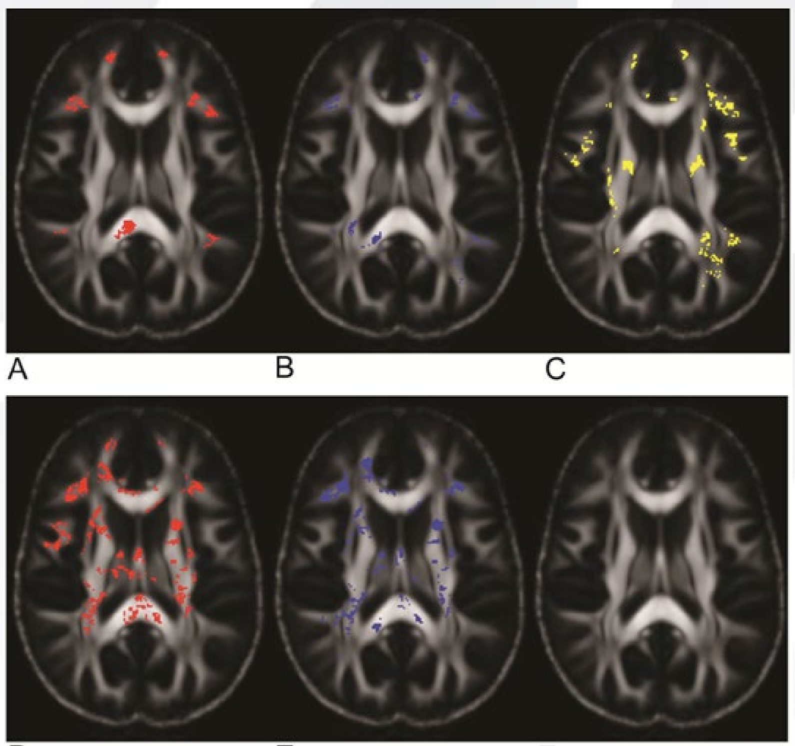
Cheng Guan Koay [1], Ping-Hong Yeh [2], John M Ollinger [3], M Okan İrfanoğlu [4], Carlo Pierpaoli [5], Peter J Basser [5], Terrence R Oakes [3], Gerard Riedy [6]

One-to-Many Analysis

mTBI - I | mTBI - II | control

Orientation Deviation

Elliptical Cone of Uncertainty



TBI Subject-Specific Analysis

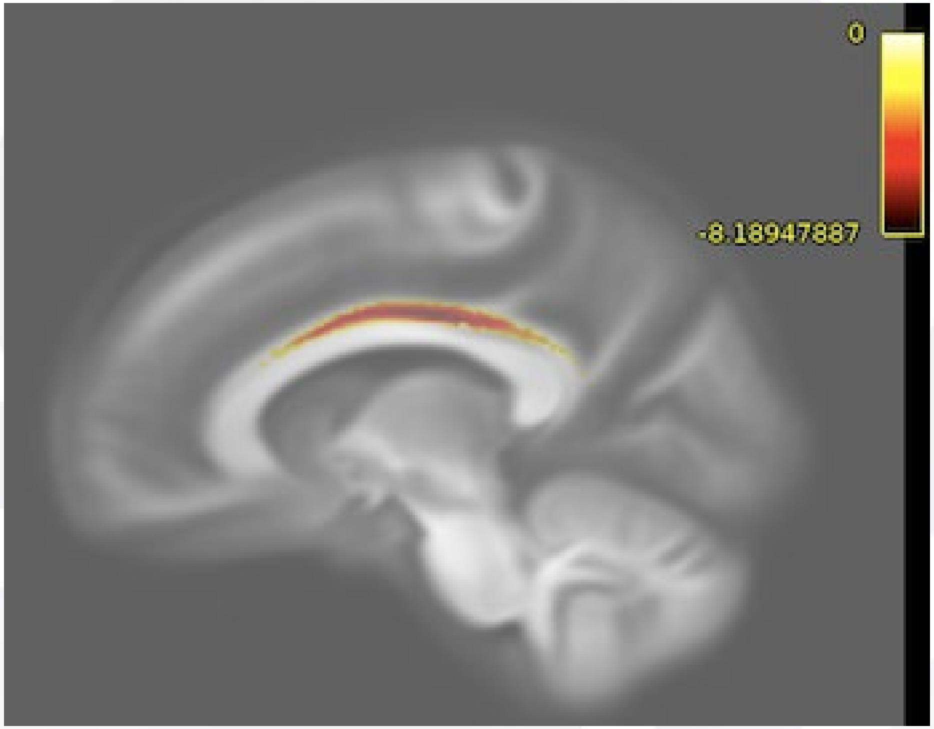
Detection of White Matter Bundles Anomalies in Service Members with Chronic Mild Traumatic Brain Injury Using a Geodesic Learning Framework

Ping-Hong Yeh[1], J. Cheng Guan Koay[1], Chihwa Song[1], Rujirutana Srikanchana[1], Grant Bonavia[1,2], Gerard Riedy[1,2], John Ollinger[1]

[1]National Intrepid Center of Excellence Walter Reed National Military Medical Center, [2]Uniformed Services University of the Health Sciences, Bethesda, MD

One-to-Many Analysis

Manifold dimensionality reduction to capture control variability



Presented at 2022 MHSRS

Tract-weighted fiber orientation distribution (TW_FOD) z-score in one mTBI patient, who had lower TW_FOD in the right cingulum bundle .

Conclusion

1. Moderate-severe TBI had more spatially extensive white matter changes (lower FA, higher MD) than non-TBI controls and mild TBI over the frontal white matter tracts, and without evidence of recovery.
2. Mild TBI had less spatially extensive white matter disruption, mainly over the posterior portion of the brain, and there was no difference of white matter integrity between uncomplicated mild TBI and complicated mild TBI.
3. Our results suggest TBI patients have varying trajectories of white matter microstructural changes.

Conclusion

4. DTI limitations – crossing fibers, many things can lead to FA changes, e.g. axonal injury vs organizational changes.
5. Multi-modal approach using multi-variate pattern learning algorithms to characterize multi-system multi-symptom relationship by integrating **non-Gaussian** dMRI, clinical symptoms, neuropsychological testing, blood biomarkers
6. Evaluate sensitivity and specificity of TBI subject-specific analysis

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- **Neuroimaging Group:** John Ollinger, Grant Bonavia, Gerard Riedy, Cheng Guan Koay, Wei Liu, Chihwa Song, Andy Srikanchana, Adam Cliffton, Joseph Hindinger, Rebecca Sandlain, Bella Salmon and all NICoE staff.
- **JHU: Jessica Gill**
- **All Participants**