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White Matter Microstructure and Connectivity in mTBI Patients with Distinct
Neuropsychiatric Phenotypes

by
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White Matter Microstructure and Connectivity in mTBI Patients with Distinct

Neuropsychiatric Phenotypes

Zachary Rossen

Abstract

Traumatic brain injury (TBI) is highly prevalent and difficult to characterize. Based on the Glasgow Coma Scale, the majority of TBI patients are diagnosed as mild TBI (mTBI), which can be associated with a wide array of outcomes ranging from full recovery to debilitating and long-lasting neurologic symptoms. These neurobehavioral symptoms have large deleterious impacts on not only the patients, but their families, colleagues, and the community. Recent work used a battery of cognitive and behavioral tests early postinjury to classify mTBI patients into phenotypes that predicted clinical outcomes later: patients of the neuropsychiatrically distressed (ND) phenotype exhibited degraded neuropsychological functioning while patients of the emotionally resilient (ER) phenotype recovered well over the first 6 months post-injury. This study aimed to seek a physical explanation of these phenotypes by analyzing diffusion MRI (dMRI) derived parameters including diffusion tensor imaging (DTI) and edge density imaging (EDI). Analyses of longitudinal data from a cohort of 68 patients (30 NDs and 38 ERs) and 40 uninjured controls showed that axial diffusivity (AD) was lower in certain white matter tracts at 6 month post-injury in the ER but not the ND patients. Edge density trended a longitudinal increase in the ND but not the ER patients. The variability of these parameters exhibited a complex pattern that would require future investigations. The current neuroimaging evidence revealed differences in the dynamic healing processes for the ND and ER patients.

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Introduction

Traumatic brain injury (TBI) is the result of a sudden acceleration of the head which causes trauma that disrupts normal brain function. TBI is common and on the rise worldwide mostly due to an increased percentage of the population being reliant on motor vehicles and thus are at increased risk for collisions [1]. The severity of TBI is characterized as mild, moderate, and severe. A patient presenting to the emergency department will usually undergo a non-contrast CT scan and a Glasgow Coma Scale (GCS) evaluation, to assess injury severity. While prior work has shown this evaluation approach to be somewhat predictive of long-term patient outcomes (Glasgow Outcome Scale at 6 months) [2], more granularity of diagnosis could help to address possible future complications of TBI by allocating care and support resources more precisely to patients.

Mild TBI (mTBI), colloquially known as a concussion, is mostly associated with contact sports players and military personnel, although the general public is also at risk for mTBI occurrences via falls and accidents [1]. While the majority of mTBI patients resume functioning in life postinjury, some suffer persistent neurobehavioral symptoms which impact not only the injured individual but also their community. These neuropsychiatric ailments could range from sleep disorders to depression, anxiety, and much more. It is difficult to quantify the prevalence of long-term post-concussion symptoms (lasting more than a handful of days after injury) as many with mTBI do not seek medical care and symptoms can be subjective [3]. Nonetheless, these cases are documented and serious. Ruff et al. suggested a multifaceted and cumulative process was to blame, involving biological factors and setbacks in many facets of one's life after an episode of mTBI.

The pathophysiology of mTBI is a complex spectrum that involves damage both to the macro- and micro-structures of the brain. Major hemorrhage, for which the initial CT scan at intake is probing, is an obvious result of the brain undergoing a force. However, the majority of mTBI

1

sufferers do not necessarily show visible evidence of trauma from a CT scan but are more likely to undergo a process where the chemical environment of the neurons within the brain is thrown off [4]. This chemically induced damage, coupled with the shearing force of the initial impact, can alter the microstructure of neurons. Such alteration may happen both in gray matter (GM) functioning zones as well as in white matter (WM) connections between those zones. In particular, the assessment of WM integrity has been reported in previous studies as associated with long-term neuropsychiatric issues, suggesting that WM microstructural disturbance was involved and possibly at fault for the post mTBI sequelae. Because this microscopic damage is difficult to image and may not even be present at the initial visit to the emergency department post-injury, the current standard diagnostic regime for mTBI provides little insight into prognosis for clinicians.

Recently researchers have been looking for methods to better predict long-term outcomes in mTBI patients. Brett et al. (2021) showed that mTBI patients can be classified into clinically distinct phenotypes 2 weeks post-injury. The phenotypes were identified via latent profile analysis that fitted a Gaussian mixture model to cluster patient responses to 12 cognitive and behavioral tests included in the NIH Common Data Elements. Each patient was assigned the latent profile of the highest posterior probability. Patients labeled emotionally resilient (ER) were more likely to stave off neuropsychological pathologies. In contrast, patients labeled neuropsychiatrically distressed (ND) were more likely to exhibit compromised neuropsychological functioning [5]. These phenotypes successfully predicted clinical outcomes at 6 months post-injury.

Probing for physiologic biomarkers in these latent profile phenotypes would help unearth more evidence to why some patients are ER vs ND. Diffusion-weighted imaging (dMRI) is a non-invasive way of doing this. Specifically, dMRI can be used to check for white matter microstructural change that could be contributing to resilience. Diffusion tensor imaging (DTI) parameters and

edge density imaging (EDI) are two models derived from dMRI images and can help explain WM integrity and connectivity.

DTI is a subset of diffusion-weighted imaging in which the molecular motion of protons is quantified. What sets DTI apart from DWI is the formation of a tensor matrix by applying diffusion gradients in at least 6 non-collinear directions. This allows for the quantification of the minor and major axis of diffusion. Diffusion in axons is anisotropic, meaning water movement is selective to one principal direction. The most common DTI parameters are fractional anisotropy (FA), mean diffusivity (MD), axial diffusivity (AD), and radial diffusivity (RD). Together these parameters measure how protons are moving in the tissue of interest, white matter in the case of mTBI.

EDI was derived from probabilistic tractography and connectomes. In metaphorical terms, a connectome is the "wiring diagram" of the brain. It is a graphical representation of the structural connections consisting of white matter fibers that rapidly conduct signals between brain areas. Connectomes used to be constructed by examining the subcortical and cortical gray matter parcellations which form network "nodes" but ignore the white matter pathways between nodes. However, clinical evidence emerged to show that white matter is critical to understanding brain pathologies. EDI sets out to fill in the spatial gaps between gray matter regions by estimating "edge density" – the connectome "edges" (links) passing through each voxel. Brain regions more densely connected than others would exhibit high edge density in the trajectories connecting these regions [6-8].

Study Aims

This study aims to probe for a relationship between mTBI phenotypes and patients' white matter structural characteristics, using both classic parametric diffusion tensor imaging and a relatively novel model of white matter connectivity known as edge density imaging (EDI, [6-8]).

Methods

Participants and Inclusion Criteria

The study included 87 mTBI patients and 40 "friend control" (FC) participants from the *Transforming Research and Clinical Knowledge in TBI* (TRACK-TBI) study where over 3,000 participants were enrolled between 2014 and 2018 at 18 academic level 1 trauma centers across the U.S. within 24 hours of injury [4, 9]. The 87 patients were identified with an mTBI phenotype of either *Emotional Resilient* (ER, n = 50) or *Neuropsychiatrically Distressed* (ND, n = 37) [5]. An FC is a friend or family member of an enrolled patient but without an mTBI event. The range of age for participants in the current study was from 18-60 years old.

The TRACK-TBI study has applied a set of inclusion criteria [9]. For the present study, a patient was included if: (1) having been identified as the ER or ND phenotype; (2) having a complete set of T1 and multi-shell diffusion sequences at both time points; (3) all images passed manual quality control with visual inspections on artifacts induced by scanning process or motion, and anatomical abnormalities that could impact the processing pipeline (e.g., very large ventricles, excessive white matter lesions).

After processing n = 12 ER and n = 7 ND were excluded due to artifact which were first thought to be minor, but unfortunately did cause poor EDI map generation. The final population was 38 *Emotional Resilient* and 30 *Neuropsychiatrically Distressed.*

Table 1: Table depicting the demographic and injury characterics of the TRACK-TBI patients

Characteristic	All mTBI (n = 68)	ER Patients (n = 38)	ND Patients (n = 30)
Age (year)	39.9 ± 16.5	41.7 ± 16.4	39.7 ± 15.7
Sex			
Male	39	22	17
Female	28	16	13
Race			
White	52	30	22
Black	11	3	8
Asian	2	2	0
Mixed race	2	2	0
Unknown	1	1	0
Ethnicity			
non-Hispanic	52	31	21
Hispanic	16	7	9
Highest level of care			
ED Discharge	16	9	7
Non ICU admit	32	20	12
ICU admit	20	9	11
Acute Cranial Injury			
CT+	35	14	21
CT-	29	21	8
Missing	4	3	1

MRI Acquisition

Whole-brain MR imaging sessions with structural and diffusion sequences were conducted using 3T scanners at 2 weeks and 6 months post-injury for patients and at two visits 6-month apart for the control population. Scanner models involved all major manufacturers (Siemens, GE, Philips) but data were collected using unified protocols. The diffusion sequences were acquired using multislice single-shot spin-echo echo-planar imaging (EPI) with multishell at $b = 1000$ s/mm^2 and 3000 s/mm^2 for 64 diffusion-encoding directions, and at $b = 0$ s/mm^2. The voxel size is 2.7-mm in all three dimensions.

MaPPeRTrac (Massively Parallel, Portable, and Reproducible Tractography)

The MaPPeRTrac framework consists of 3 consecutive, data-dependent steps for DTI processing and EDI computation [10]. The workflow uses software libraries including FSL and FreeSurfer. The T1 and diffusion images were organized in the BIDS format [8]. In *Step 1*, diffusion images are corrected for artifacts and noise and used to fit DTI parameters. Then the T1 is used for the cortical and subcortical parcellation, followed by nonlinear registration between individual native diffusion space and T1 space. In *Step 2*, Markov Chain Monte Carlo (MCMC) sampling is run to estimate fiber orientations in the diffusion space at each voxel. Then in *Step 3*, probabilistic tractography is performed to derive the connectome matrix and the EDI map.
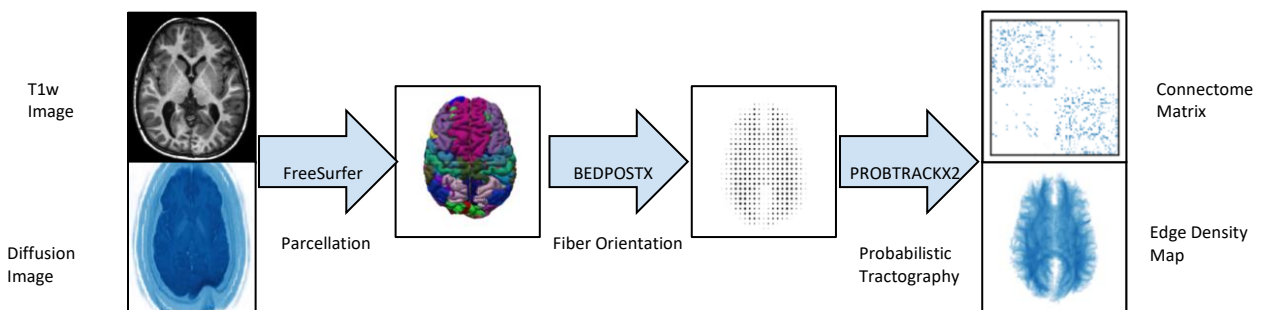

Figure 2: The pipeline schematic of MaPPeRTrac (adapted from Moon et al. 2022 [7]).

UCSF Wynton HPC (High Performance Computing cluster)

The computation challenges of the MaPPeRTrac workflow demand HPCs. The current study uses UCSF Wynton HPC to run the bulk majority of analyses. At its current state, Wynton has 217 GPUs across 56 nodes and 449 computer nodes with 12572 physical cores [9].

Tract Based Spatial Statistics (TBSS)

TBSS is an FSL toolbox to analyze a multi-subject dMRI dataset. The basic workflow is to register a group of FA images to the FMRIB58 template so that they are aligned for analysis. Next, the average FA was skeletonized and thresholded – the white matter is condensed into a

thin core to alleviate gray-white matter boundaries. This average skeleton is used to extract the core structures of individual parameter maps for voxelwise and region-of-interest analyses.

Results

First, Fig. 3 shows an example EDI from one participant as a set of slices along the z-axis in the axial view of the brain. Part of the current project was to improve MaPPeRTrac computation efficiency with the latest versions of hardwares and component softwares. Our technological efforts have reduced individual runtime from 7 hours for 930 edges to less than 10 hours for 6642 edges. With this improvement of runtime, we were able to generate a set of results consistent with the original works on EDI [3-5]. In the example, the periventricular white matter shows high edge density, especially posteriorly.
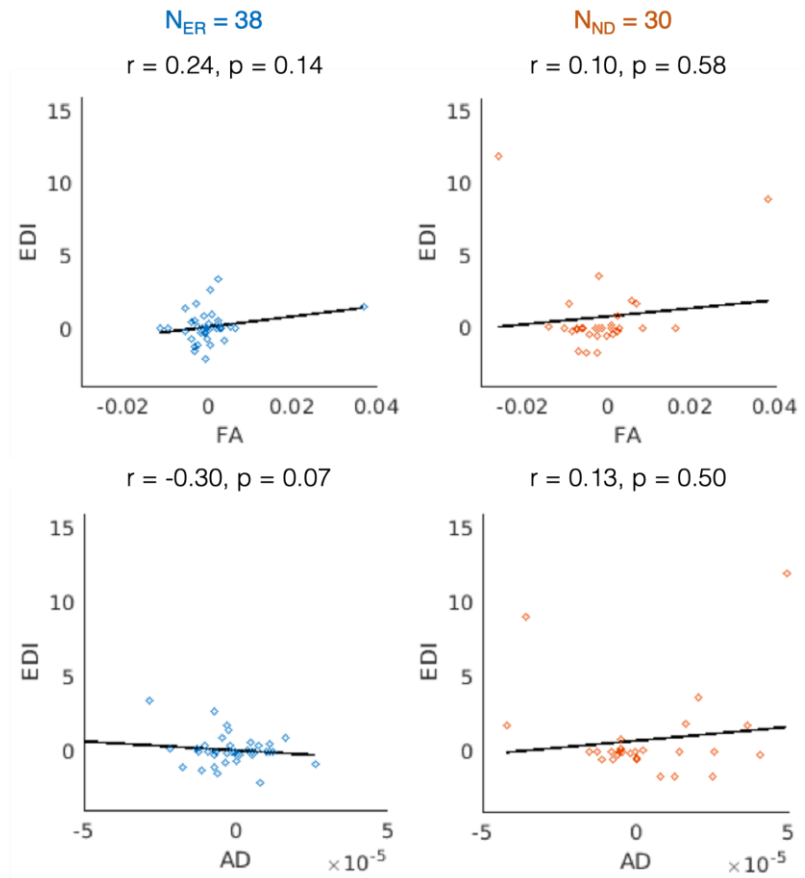

Figure 3: An example set of EDI slices.

Figure 4: Pearson correlation plots of global change in EDI vs global AD and FA respectively for the ER and ND groups between the 2 week and 6 month time points.

Figure 4 depicts global EDI vs. the DTI parameters FA and AD. These values were tabulated using the TBSS average white matter skeleton mask. For ER patients, FA shows a slight positive correlation with EDI while AD shows a slight negative. Both of these do not reach significance with p values of 0.14 and 0.07 respectively. ND patients both showed a positive correlation of EDI with DTI metrics, however, p values are above 0.5 for each pairing. Some obvious outliers are present in the ND plots. ER patients show a high amount of clustering around the 0 change for EDI and FA but results are slightly more spread for EDI vs AD.
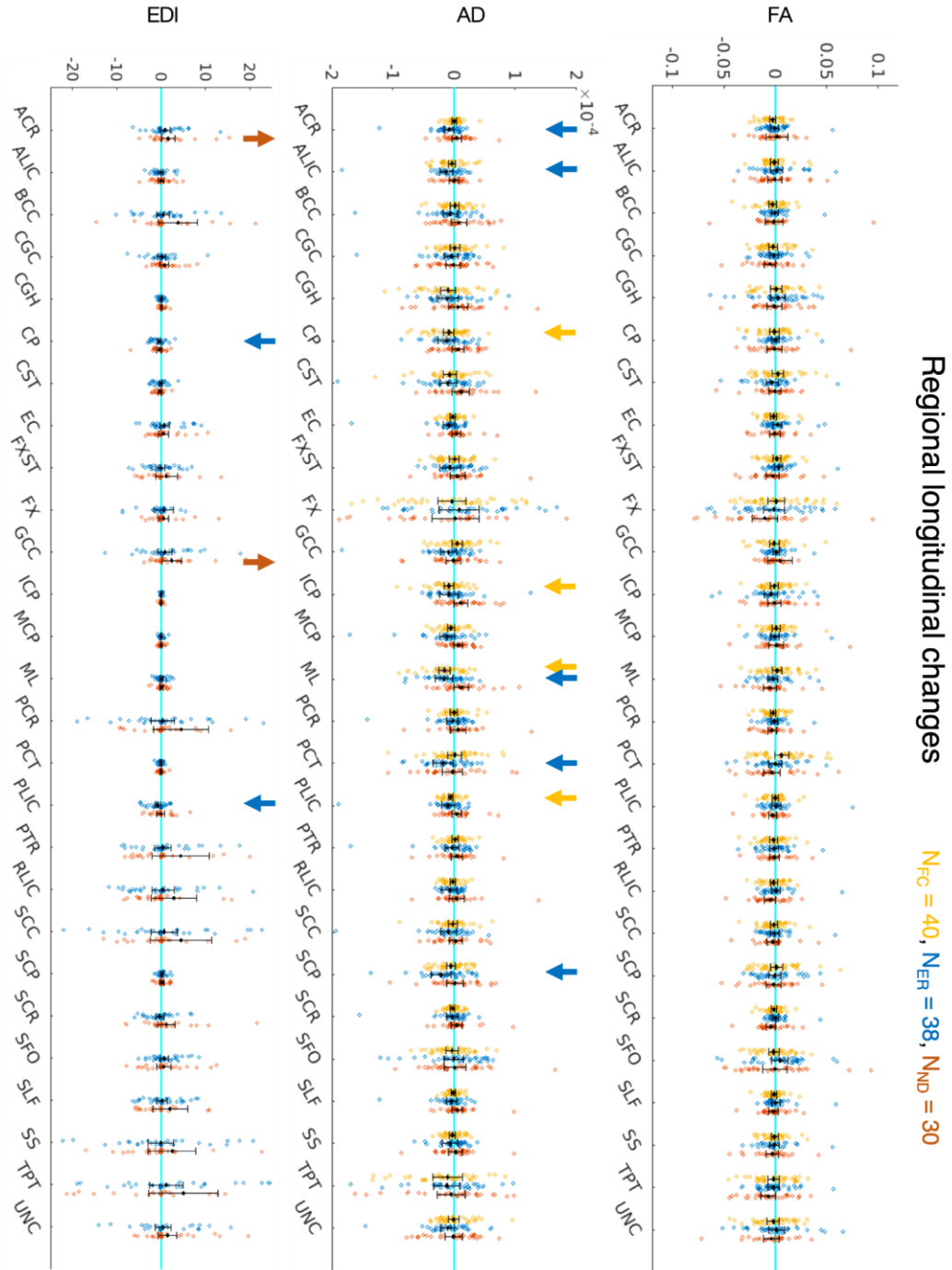
Figure 5: Regional values of FA (top), AD (middle), and EDI (bottom). The Johns Hopkins University (JHU) atlas white matter regions are labeled on the bottom abscissa. Black bars show the mean and 95% confidence intervals of each group of data. Color coded arrows show statistically significant change in the direction they are pointing. Tracts which are present bilaterally were averaged.

Figure 5 shows regional, longitudinal change in FA, AD and EDI for JHU atlas white matter regions. For FA there were no statistically significant changes in any WM tracts for each of the 3 groups. The FCs do perhaps show a tighter grouping around 0 change while ND and ER show slightly wider error bars. The fornix region for the ND cohort shows a negative change but was not statistically significant. AD change did have statistically significant changes, specifically 5 regions for ER and 4 regions for ND showed decrease in AD overtime. It does appear there are some outliers in measurements, specifically it appears one ER patient for many regions had substantial negative change in AD. The last plot shows change in regional edge density. Regions that are tightly clustered around 0 actually might be artificially low because of the region being in an exclusion mask applied for EDI measurement. 2 regions for ND patients showed a significant increase in EDI overtime and 2 regions for ER showed a decrease. EDI change is low and clustered around 0.

Longitudinal changes in the connectome matrix
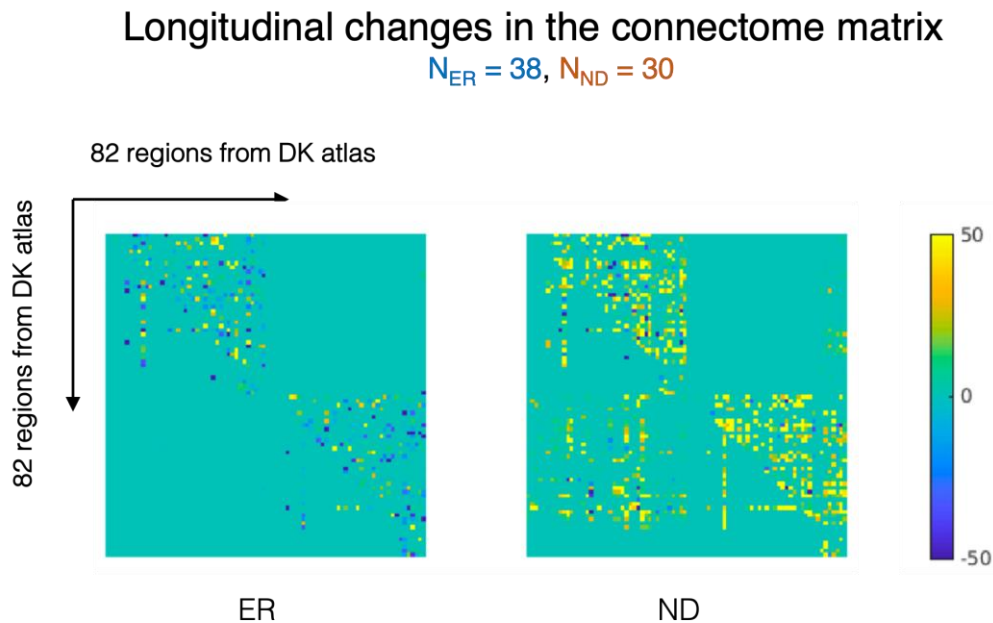### $N_{ER} = 38$, $N_{ND} = 30$

Figure 6: Longitudinal change in connectome matrix using the Desikan-Kiliany cortical and subcortical region atlas.

Figure 6 above shows the change in connectome matrix for ER and ND patients. ER patients show more of a negative change while ND patients show more of a positive trend. While differences are obvious between the two plots, it is especially evident that the lower left quadrant for the two differs substantially. ER patients in this ER show little change where ND patients have an upward trend with some negative pixels.

Discussion

The present study computed dMRI derived WM metrics including FA and AD from DTI parameters and EDI from tractography in mTBI patients who were identified with either ER or ND latent phenotypes. To adjust inter-site and inter-scanner variability, the present study has focused on the intra-subject longitudinal changes between two visits that were 6 months apart. The preliminary results show a complex pattern of longitudinal differences; however, further analysis is needed to reinforce trends and ensure proper measurements are being collected. Higher AD is often accepted as a metric depicting more intact WM microstructure and a decrease in AD would be associated with WM deterioration. One would expect ER patients to have more intact WM and there are many reasons this study may have not reflected this hypothesis. It could be due to the overall injury level being more severe for hase 2 patients. Because injuries are more severe, steps like registration and normalization for patients are more difficult due to lesions and edema. Manual QC showed significant edema in some of the ND but also ER patients. This in turn distorts some of the white matter regions and it is possible they were not properly registered during TBSS. The connectome matrices, however, show whole track differences, and thus is more of a raw datapoint. The significant differences in appearance of connectome matrices between ER and ND patients could be more representative than the global correlation plots.

Nonetheless, it is evident that some new information is being elucidated via EDI. The lack of correlation with DTI parameters shows EDI captures a separate process going on in the

brain. This could be due to differences in how DTI and EDI are modeled. For example, the DTI parameter AD is representative of the principal direction of the diffusion tensor of a given voxel. EDI, in contrast, is the number of edges passing through a voxel. EDI is more representative of the white matter connectivity where AD does not capture connection to neighboring voxels. In the region-of-interest analysis results, it perhaps goes against intuition that the ER patients should have increased edge density and stronger connectivity overtime, due to healing of neurons. The opposite being observed could point to statistical noise, or that ER patients deal better with loss of connectivity. One region where EDI is significantly higher in ND patients is the Anterior Corona Radiata (ACR). This region is associated with motor function. Bret et al. found that ER patients actually had more severe injury on average compared to ND patients [5]. Perhaps, higher ED in the ACR shows ND patients had a less severe injury to start and recovered more at a microstructural level. This diverges from the idea that more connectivity in regions yields better neurobehavioral outcomes. Furthermore, prior studies looking at the structural connectome of other neurological disorders point to an idea of phenotypes being due to network organizational differences, not simply lower connection strength [14]. Perhaps the results of this study point to a network reorganization process happening post mTBI.

Observations from the current study suggest against the hypothesis that the ER patients would show higher or increased values in AD or EDI compared to their ND counterparts. Prior work showed AD to be higher in ER patients and remain stable, whereas ND patients exhibited lower AD that reduced overtime. While these results seem conflicting, it is possible they are showing different facets of the evolving brain healing process. AD can be impacted by two things, acute neural deformation edema, or presence of extracellular fluid within patient white matter regions might be causing high AD in phase 2 ND patients. Conversely, AD may reflect axonal integrity, and higher values of AD have been associated with more robust white matter. In order to elucidate which school of thought explains a particular set of observations,

longitudinal analysis alone would not be adequate. Cross-sectional comparison of FC, ER, and ND cohorts at each time point would help to disentangle the observed AD changes. However, examination of our multi-site data set showed clustering regimes depending on where the patient acquisition was made. This suggests that in order to do worthwhile cross-sectional analysis, one would first need to harmonize dMRI data to normalize confounding site differences.

Conclusion

dMRI derived metrics including: DTI parameters and edge density imaging give insight to the damage to white matter microstructure and connectivity post mTBI. Further work is needed to unravel the complex, multidimensional problem of how WM microstructure reflects neurobehavioral symptoms. Higher ED in ND patients could be due to edema in white matter. It is possible to do NODDI measurements on these patients and separate out the free water component, giving more accurate insight to WM microstructure.

In theory when this problem is solved, clinicians might be able to flag "at risk" patients who might need extra interventions and observation to keep neuropsychiatric suffering at bay. Another possible use is to funnel patients with a phenotype of interest into a specific clinical trial looking at the treatments of mTBI. Of course, a treatment modality would be best tested on ND patients compared to ER who might heal on their own.

While this study focused on the most extreme phenotypes (ER and ND), Bret et al actually posited 2 medium phenotypes labeled cognitively resilient and cognitively impaired. Future studies probing for physiologic biomarkers might also include correlation with these two labels. EDI generated using MaPPeRTrac shows promise for being a robust way of generating structural connectomes. It surely will be a tool to parse out the complex problem of changing connectome parameters within the brain of healing mTBI patients.

Furthermore, examining ways of harmonizing data collected in the multi-site TRACK-TBI study will further elucidate better results. The analysis in this manuscript were all longitudinal, meaning the differences tabulated were specific to each patient. Cross-sectional analysis would only be possible after harmonization and could give better understanding of ER vs ND. Future plans include using the RISH (Rotation Invariant Spherical Harmonics) method for harmonizing raw dMRI data for analysis.

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