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TITLE: TBI-Related Risk Factors for Alzheimer's Disease: Early Detection and Prognosis via Multimodal Brain Imaging and Connectomics

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14. ABSTRACT The purpose of this study is to utilize multimodal imaging to identify AD risk factors specific to the TBI population. The study scope involves (1) finding TBI-affected structural/connectomic features which are significantly associated with AD risk; and (2) imaging biomarkers which are statistically independent from other well-documented AD risk factors and which can assist with early identifying TBI survivors at risk for AD. In this reporting period, we performed automatic identification of AD/TBI pathology, calculated volumetrics, implemented connectomic/topological analyses, found TBI/AD-related connectome differences, published our results and disseminated them. Results indicate that the TBI-affected brains of older adults experience neurodegeneration on a scale which rivals that of age- and sex-matched AD patients. We also found properties of the TBI-affected brain whose characteristics are commensurate with the likelihood of TBI survivors to exhibit accelerated neurodegeneration, which may lead to the identification of early biomarkers of high AD risk.					
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1. INTRODUCTION:

Although traumatic brain injury (TBI) victims are more likely to develop Alzheimer's disease (AD), it is difficult to estimate AD risk in TBI patients. For this reason, it would be extremely useful to understand how TBI may lead to AD, and to identify new ways to predict how likely it is for a TBI victim to develop AD. The purpose of this scientific study is to utilize sophisticated imaging and connectomic methods to study the brains of older adults who are either healthy, TBI survivors, AD patients, or both.

The main hypothesis of the study is that the TBI-affected brain has certain anatomic properties which, if known, could help scientists to predict the likelihood of AD after TBI with high accuracy. The secondary hypothesis of the study is that at least some of these properties are different from those which are already known to be risk factors for AD (e.g. obesity, smoking, a history of high blood pressure, or certain inherited traits). This project thus aims to identify novel AD risk factors specific to the TBI population. The ability to accurately identify TBI victims at high risk for AD could have substantial consequences for the healthcare of such individuals; understanding the relationship between TBI and AD could advance our scientific and clinical knowledge regarding these two conditions.

2. KEYWORDS:

Traumatic brain injury, Alzheimer's disease, risk biomarkers, magnetic resonance imaging, connectomics, network theory.

3. ACCOMPLISHMENTS:

What were the major goals of the project?

The primary aim of this study is to test the hypothesis that the TBI-affected brain has structural and/or connectomic features which are significantly associated, in a statistical sense, with AD risk and which can allow TBI survivors to be stratified based on such risk. Our secondary hypothesis is that some of these biomarker-like features are specific to the TBI-affected brain, i.e. that they are statistically independent from other known and well-documented AD risk factors.

The study aims to use multimodal neuroimaging—including magnetic resonance imaging (MRI) and diffusion tensor imaging (DTI)—to understand the differences between four populations: (1) the healthy aging brain, (2) the TBI-affected brain, (3) the AD-affected brain, and (4) the brain affected by both TBI and AD. We aim to use advanced computational neuroanatomy, neural network analysis and connectomics to identify statistically significant differences between these four groups, with the goal of identifying new biomarkers which can be used to reliably estimate AD risk in TBI survivors.

We use a 2×2 factorial experimental design (factors: single mild TBI, AD) to identify and quantify the neuroanatomic and connectomic features of older adults (aged 65+) whose existence is modulated by TBI/AD interactions. Expert-validated, TBI/AD-tailored computational analyses of high-quality, multimodal MRI and DTI volumes acquired at high resolution from an adequately powered volunteer sample have allowed us to quantify brain volumetrics and morphometrics in the presence of TBI/AD-related (non-)hemorrhagic lesions. In each volunteer, MRI/DTI volume information is then used to map the macroscale connectome, its topology and to infer its network-theoretic properties, which are subsequently compared across groups.

Milestone	Timeline	Status
Project Run-in	Months	
Local IRB Approval	1	Granted by 06/11/19
HRPO Approval	1-2	Granted by 09/15/19
Maintain all IRB approvals	1-3	Approvals stand
Train research staff in all research protocols	1-2	Completed by 12/14/18
Create, revise, distribute research protocol manual	1-2	Completed by 12/14/18
Identification of AD risk factors in TBI survivors	Months	
Perform automatic identification of AD/TBI pathology	1-6	Completed by 04/14/19
Calculate volumetrics and morphometrics	1-6	Completed by 04/14/19
Implement connectomic and topological analyses	1-6	Completed by 04/14/19
Find TBI/AD-related connectome differences	7-16	Completed by 01/14/20
Internal validation of volumetrics/morphometrics	7-10	Completed by 08/14/19
Confirmation by TBI/AD clinicians	11-14, 26-28	~60% completion
Internal validation of connectomic/topological analysis	13-18	Completed by 03/14/20
Implement statistical analysis of results	19-24	Completed by 09/14/20
Reliability testing	23-26	~25% completion
Alternative hypotheses testing as needed	25-32	Planned for Y3
Revisions to methods as needed	22-34	~20% completion
Open software release via NITRC	32-36	Planned for Y3
Product: methodological manuscripts on analysis	6-18	Completed by 03/14/20
Product: software for TBI/AD connectome analysis	12	Completed by 10/15/19
Product: manuscripts on TBI/AD connectome analysis	18-24	Completed by 09/14/20
Product: manuscripts on statistical analysis	24-36	Planned for Y3
Product: presentations at national meetings	9, 21, 35	~70% completion

What was accomplished under these goals?

(I) Major activities

Throughout this annual reporting period, the following major activities were either completed or are ongoing:

- (A) performance of automatic identification of AD/TBI pathology
- (B) calculation of volumetrics and morphometrics for the subjects in the dataset
- (C) implementation of connectomic and topological analysis for the subjects in the dataset
- (D) find TBI/AD-related connectome differences
- (E) internal validation of volumetrics/morphometrics
- (F) confirmation by TBI/AD clinicians
- (G) internal validation of connectomic/topological analysis
- (H) implementation of statistical analysis for connectomic data

- (I) software reliability testing
- (J) revision to methods as needed
- (K) production of methodological manuscripts on analysis
- (L) production of software for TBI/AD connectome analysis
- (M) production of manuscripts on TBI/AD connectome analysis
- (N) presentation of results at national meetings

(2) *Specific objectives*

The specific objective of this scientific study is to identify novel AD risk factors specific to the TBI population by applying sophisticated imaging and connectomic methods to the MRI/CT brain scans of older adults who are either healthy, TBI survivors, AD patients, or both. At the end of Y2 of this project, the activities needed to meet the objective of the study are ongoing and full completion of the specific objectives is anticipated. Progress toward meeting the objectives has been adequate and in line with the stated milestones and completion deadlines of the project. All completed goals have been met.

(3) *Significant results*

Activity (A). Details on this activity completed in Y1 are in the Y1 Annual Report.

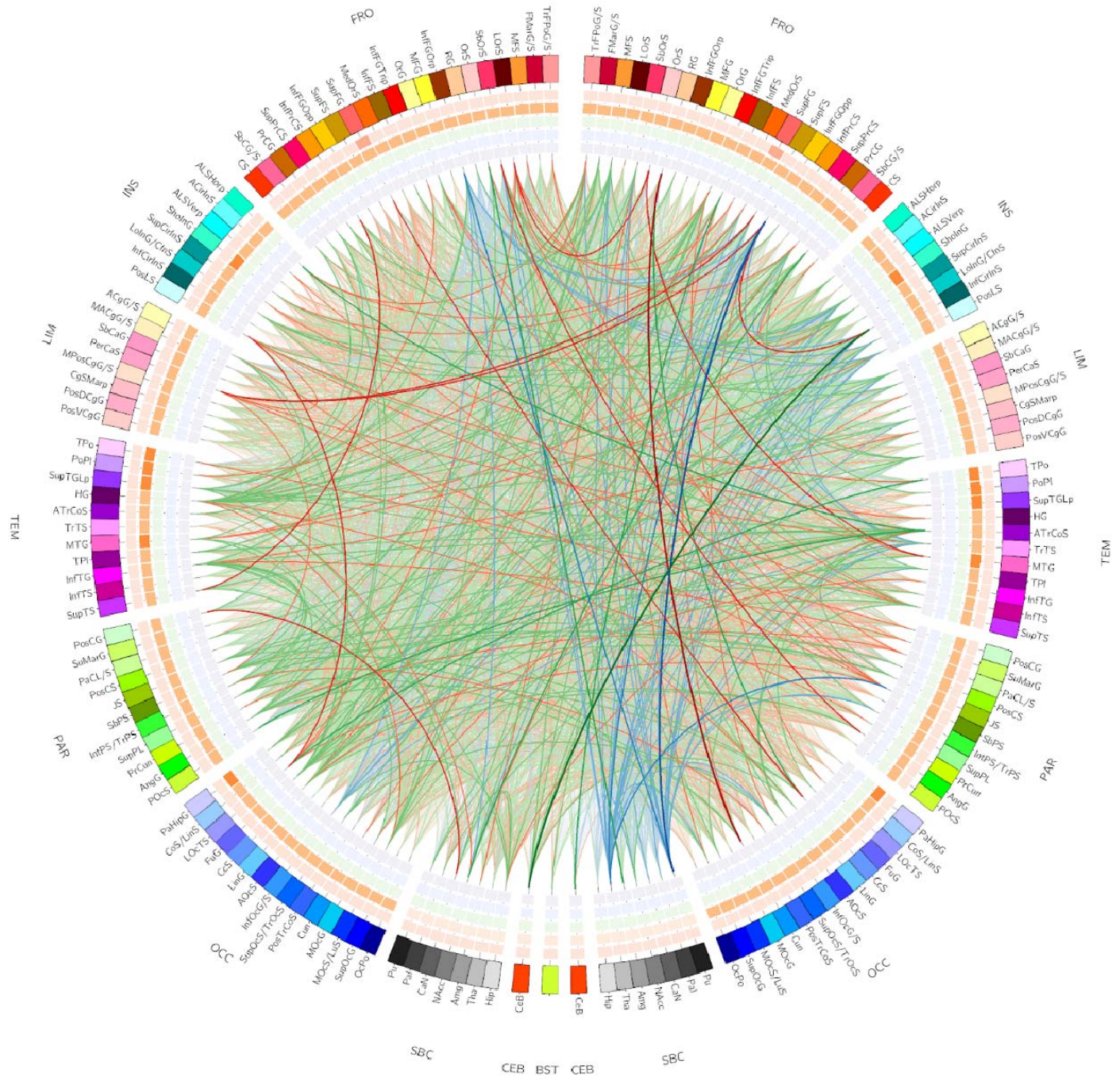
Activity (B). Details on this activity completed in Y1 are in the Y1 Annual Report.

Activity (C). Details on this activity completed in Y1 are in the Y1 Annual Report.

Activity (D). Most of the research for this activity was performed in Y1, but the activity itself was completed in Y2. Specifically, to quantify how WM atrophy translates into structural and functional connectome changes, we undertook two detailed analyses of functional and structural connectomics relating TBI to AD. The first of these analyses has been published in *GeroScience*, and the article in question is enclosed with this report in Appendix 1. This publication describes the process of identifying brain regions which become more topologically distant from the rest of the brain because of TBI and/or AD, and whose functions may degrade comparably more. This first study we wish to highlight here leverages fMRI recordings acquired from healthy controls (HCs), geriatric mTBI participants and AD patients to provide evidence that, within ~6 months post-mTBI, functional connectivity (FC) within the DMN exhibits deviations from normality whose spatiotemporal properties are statistically indistinguishable from those of similar deviations observed in AD.

A linear combination of *acute* post-traumatic cognitive scores was found to be significantly and sensitively associated with *chronic* AD-like RS DMN alterations. Additionally, a supervised machine learning (ML) classifier was found to accurately identify mTBI patients with relatively broad *chronic* abnormalities in the DMN based on *acute* cognitive performance. These findings establish a detailed functional and connectomic

relationship between mTBI-related acute cognition and AD-like DMN features, whose further characterization may facilitate the early identification of geriatric mTBI patients at relatively high risk for AD. The reader is referred to the full manuscript in Appendix 1 for additional details on methodology, results and significance.

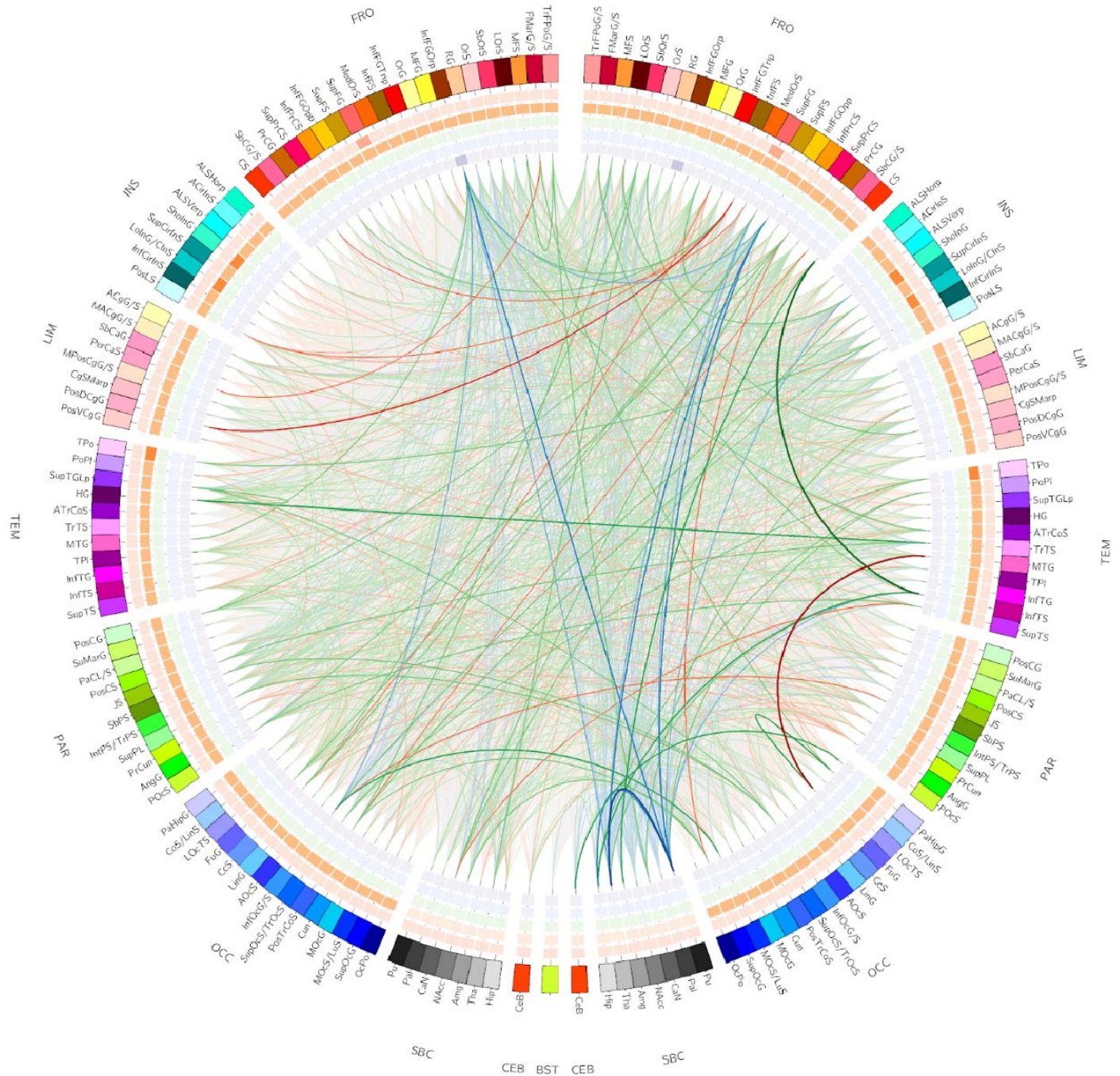


Connectogram of mTBI subjects. Links are colored in red, green, or blue. Red, green and blue links have mean fractional anisotropy (FA) values in the first, second and third terciles of the mean FA distribtioin across connectivity matrix entries. Link opacity encodes the relative fiber count of the corresponding connection. Thus, if a link is dark and is visible on top of other links, then that link is associated with relatively high connectivity density.

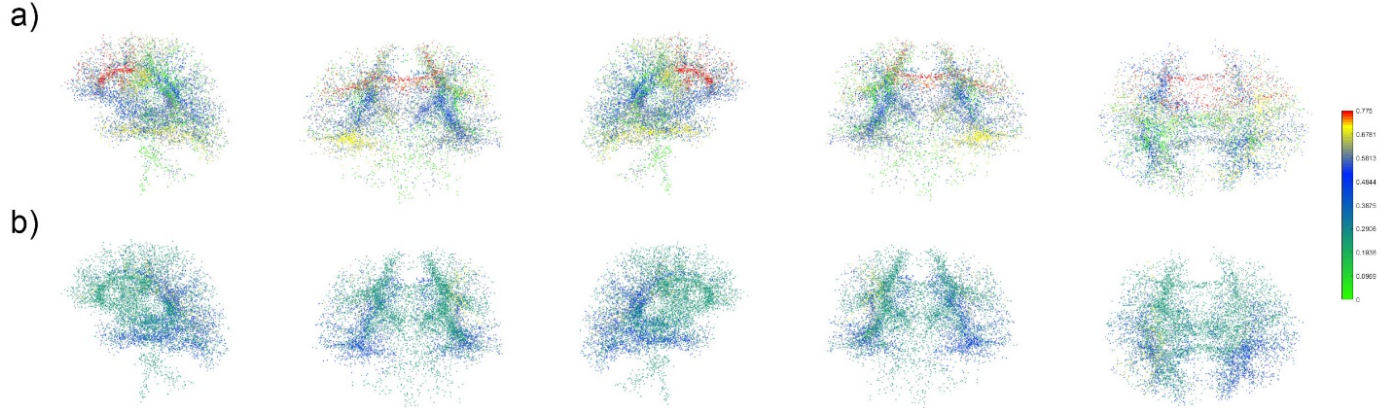
Visualization of connectivity information. In Q4, we calculated both functional and structural connectivity matrices, which can then be used to chart the strength of connections between different brain regions. By

using a combination protocol of MRI and DTI alongside automated image segmentation, connectivity matrices were generated and visualized using connectograms, as shown below.

Computed connectivity matrices depict WM connections between 165 cortical and subcortical regions of the brain. Such matrices were created for 80 healthy control (HC) subjects, 65 subjects with Alzheimer's Disease (AD), and 65 TBI subjects. Each subject has a connectivity matrix depicting the connections of her/his brain. From these matrices, three connectograms were generated; a connectogram is a circular cortical representation which is intuitive, has a high information-to-ink ratio and scales well between individuals and large groups.

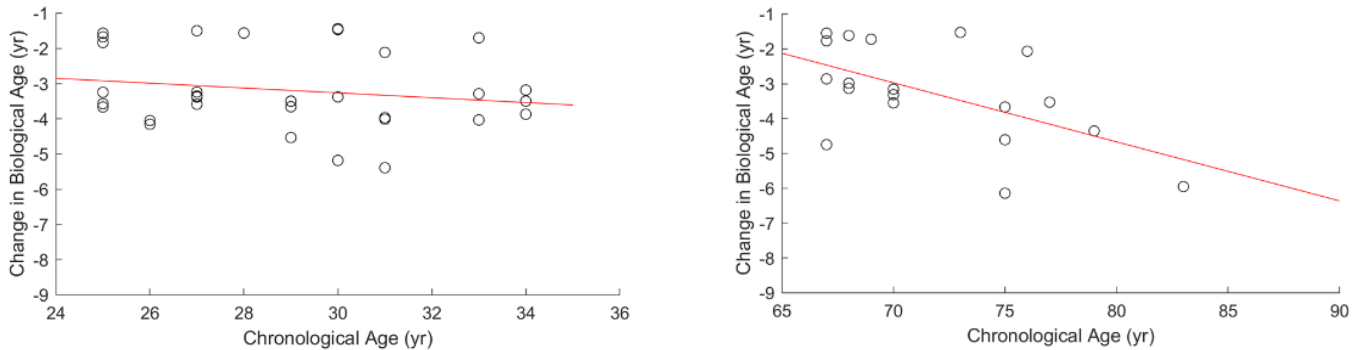


acutely and ~6 months after mTBI using DTI. T1-weighted MRI scans of 70 frontal lobe mTBI subjects ($\mu = 41.74$ years, range = 18-77 years) acquired acutely and ~6 months after mTBI. SWI was used to quantify CMB loads. Diffusion-weighted images were fitted with diffusion tensors, and FA was calculated and used as a surrogate measure of WM integrity. Dimensionality reduction of mean FA feature vectors was implemented using principal component analysis (PCA), and two prominent PCs explaining most variance were used as responses in a multivariate analysis of covariance (MANCOVA). The results identified age at injury, sex, and CMB load as predictors of WM integrity loss after TBI. The figure below identifies WM structures at high risk for degradation after TBI.



Significant white matter structures associated with PC1 (a) and PC4 (b) with varying loading scores, as shown by the various color gradient. Significantly correlated structures have loading score > 0.7 (red) and moderately correlated structures have loading score > 0.5 (blue).

In Q4, we also undertook other analyses to show the potential utility of biological brain age (BA) estimation to describe mTBI-related accelerations in brain aging trajectories and identified cortical structures that experience accelerated aging after mTBI. Using T1-weighted MRI volumes and cortical thickness, volume, surface area, and Gaussian curvature obtained using FreeSurfer software, we formulated a multivariate linear regression to determine the rate of BA increase associated with mTBI. 95 TBI patients (age in years (y): $\mu = 41$ y, $\sigma = 17$ y; range = 18 to 83) were compared to 462 healthy controls (HCs) (age: $\mu = 69$ y, $\sigma = 18$ y; range = 25 to 95) over a 6-month time period following mTBI. Across the initial ~ six months following injury, patients' BAs increased by $\sim 3.0 \pm 1.2$ years due to their mTBIs alone, i.e., above and beyond typical brain aging. The superior temporal and parahippocampal gyri, two structures involved in memory formation and retrieval, exhibited the fastest rates of TBI-related BA. In both hemispheres, the volume of the hippocampus decreased (left: $\mu=0.28\%$, $\sigma=4.40\%$; right: $\mu=0.12\%$, $\sigma=4.84\%$). These findings illustrate BA estimation techniques' potential to identify TBI patients with accelerated neurodegeneration, whose rate is strongly associated with the risk for dementia and other aging-related neurological conditions. The figure below shows the change in BA over six months vs. chronological age for TBI subjects under 35 (left) and subjects over 65 (right) to compare the rate of aging.



Changes in BA over six months of TBI subjects under 35 (left) and subjects over 65 (right). Negative values indicate an increase in BA occurred independently of natural CA increasing.

Activity (E). Details on this activity completed in Y1 are in the Y1 Annual Report.

Activity (F). In this project, both expert-labeled pathology and TBI scans where pathology has not yet been labeled were used to validate our approach and results. When assessing the reliability of pathology labeling and segmentation, validation can often be difficult due to frequent lack of reliable ground truth, and manual tracings by trained experts have traditionally been appropriate from this standpoint. When assessing segmentation error extent, it is fair to note that, although often considered to be the gold standard, even manual outlining results in moderate (3-10%) intra- and inter-operator variabilities. To address this, manual review in 3D Slicer by three operators with experience in the identification of neurotrauma was performed to edit and correct errors. The results of analyses involving this validation were published in several conference papers listed in Section 6.

Activity (G). We have completed the process of validating the topology analysis results internally. Because TBI anatomy often diverges from healthy anatomy, segmentation errors can occur, such that this type of validation is needed. Because the brains of aging adults may exhibit CMBs, particular care must be taken to identify and take these into account appropriately during analysis. The procedure for visually identifying pathology associated with cerebral micro-hemorrhages followed state-of-the-art approaches pioneered by the PI. Upon validating our topological analysis for connectome quantification, we have discovered that the extent of white matter integrity loss after TBI is associated with cognitive decline in specific cognitive domains, and that this association is driven by distinct sets of WM fasciculi. Together, these research activities have contributed to our aim to identify AD biomarkers based on MRI, as set forth in the original proposal. The results of analyses involving this validation were published in papers listed in Section 6.

Activity (H). Below we describe the most important findings of our statistical analysis pertaining to our group comparisons.

AD and HC Comparison. WM structures whose mean FA is significantly different across mTBI and AD were identified and characterized for this comparison (see submitted manuscript in Appendix 2 for complete list and for abbreviations used below). Compared to HCs, patients with AD exhibit broadest significant degeneration in the posterior thalamic radiation (PTR), cingulum, sagittal stratum (SS), and medial lemniscus (ML). In descending order, structures on the left side of the brain displaying the broadest significantly lower mean FA in the AD cohort were listed for each hemisphere (see Tables in Appendix 2 manuscript).

mTBI and HC Comparison. Table 2 in the Appendix 2 manuscript lists, in the descending order by percentage difference between groups, each structure's voxels whose mean FA differs significantly between HC and mTBI participants. In the mTBI cohort, the extent of significantly lower mean FA was broadest in the crura of the fornices (CF), anterior internal capsule (AIC), retrolenticular internal capsule (RIC), external capsule (EC), cerebral peduncle (CP), Superior cerebellar peduncle (SCbP), posterior thalamic radiation (PTR), and body of the corpus callosum (BCC). In the left hemisphere, the structures with largest differences between HC and mTBI include, in descending order by percentage, RIC, AIC, CF, EC, and PTR, on the right side these were the CF, CP, SCbP, and AIC. No streamlines in the mTBI cohort had significantly greater mean FA than the HC group.

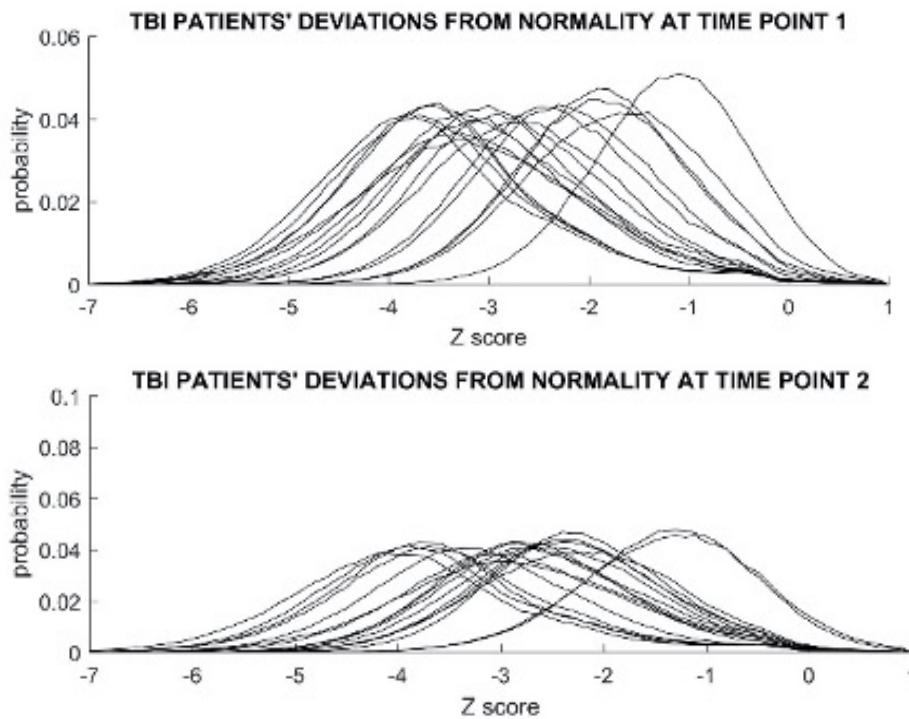
mTBI and AD Comparison. No significant differences in mean FA were revealed between mTBI and AD groups. Equivalence tests revealed significant similarities in mean FA between mTBI and AD groups throughout the brain. Table 3 in the manuscript of Appendix 2 lists a selection of WM structures and the percentages of voxels, representing significant equivalence in mean FA, within each structure. In

descending order, the structures containing the greatest number of equivalent voxels were the CF, pontine crossing tract (PCT), superior fronto-occipital fasciculus (SFOF), PTR, and ACR.

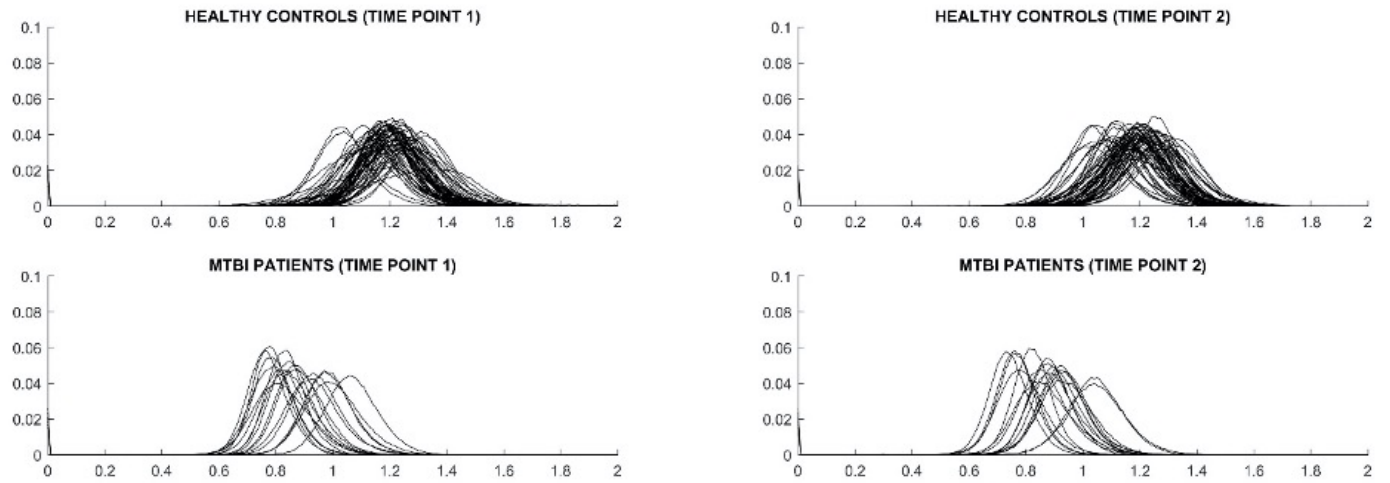
Cortical demyelination as a biomarker of AD risk after TBI. To establish TBI/AD-related connectome differences, we continued our analysis of structural T1 and T2 weighted MRI to quantify decreases in cortical myelination occurring across the first 6 months after injury. Specifically, this quarter, we processed data pertaining to the AD group and added the results to our analysis. When integrated with connectomics measures, demyelination measures can substantially add to our ability of predicting MCI risk in TBI survivors.

We are currently in the process of writing a manuscript describing these findings. This component of our statistical analysis involves the use of T1 and T2 imaging to study how myelination of the GM changes after TBI relative to AD. To establish TBI/AD-related connectome differences, we have also used structural T1 and T2 weighted MRI to quantify changes in cortical myelination occurring across the first 6 months after injury. Specifically, to better understand the relationship between mTBI and demyelination, we quantified the effect of mTBI upon the ratio R of T1-weighted to T2-weighted MRI intensities.

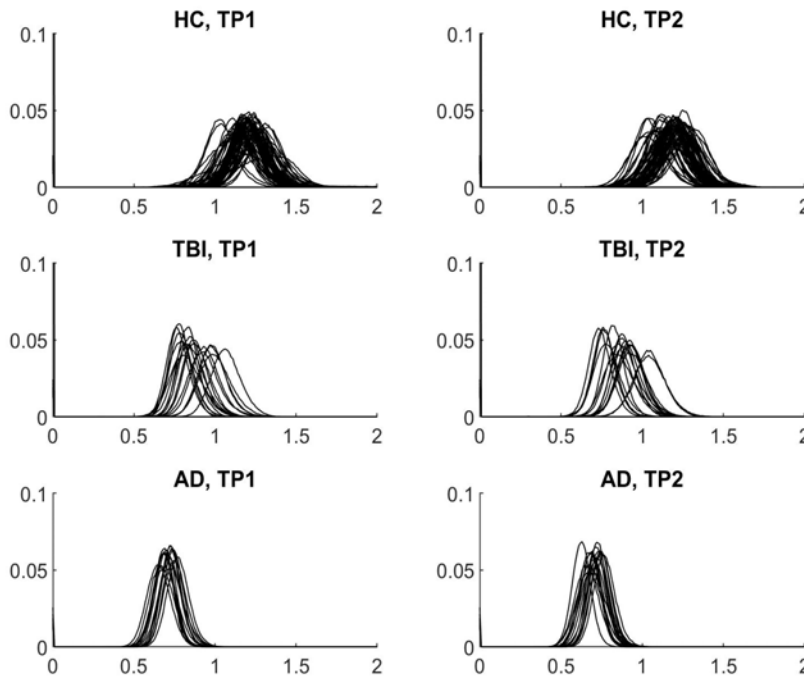
For GM, the ratio R has been shown to be a proxy measure of myelin concentration (manuscript in preparation). We studied R across two groups of age- and sex-matched participants: (A) geriatric patients with mTBI patients imaged both acutely and ~6 months post-injury, (B) HC participants whose MRIs were acquired at two time points. In the figures below, the Z scores represent TBI patients' deviations from the HC group mean R, in units of σ (HC).



TBI patients' deviations from normality at time point 1 (left) and time point 2 (right). These deviations were computed as Z scores at each vertex on the cortical surface. Specifically, with $R = T1/T2$, the TBI patients' Z scores relative to the HC population were calculated as $Z = [\mu(R(TBI)) - \mu(R(HC))] / \sigma(R(HC))$.



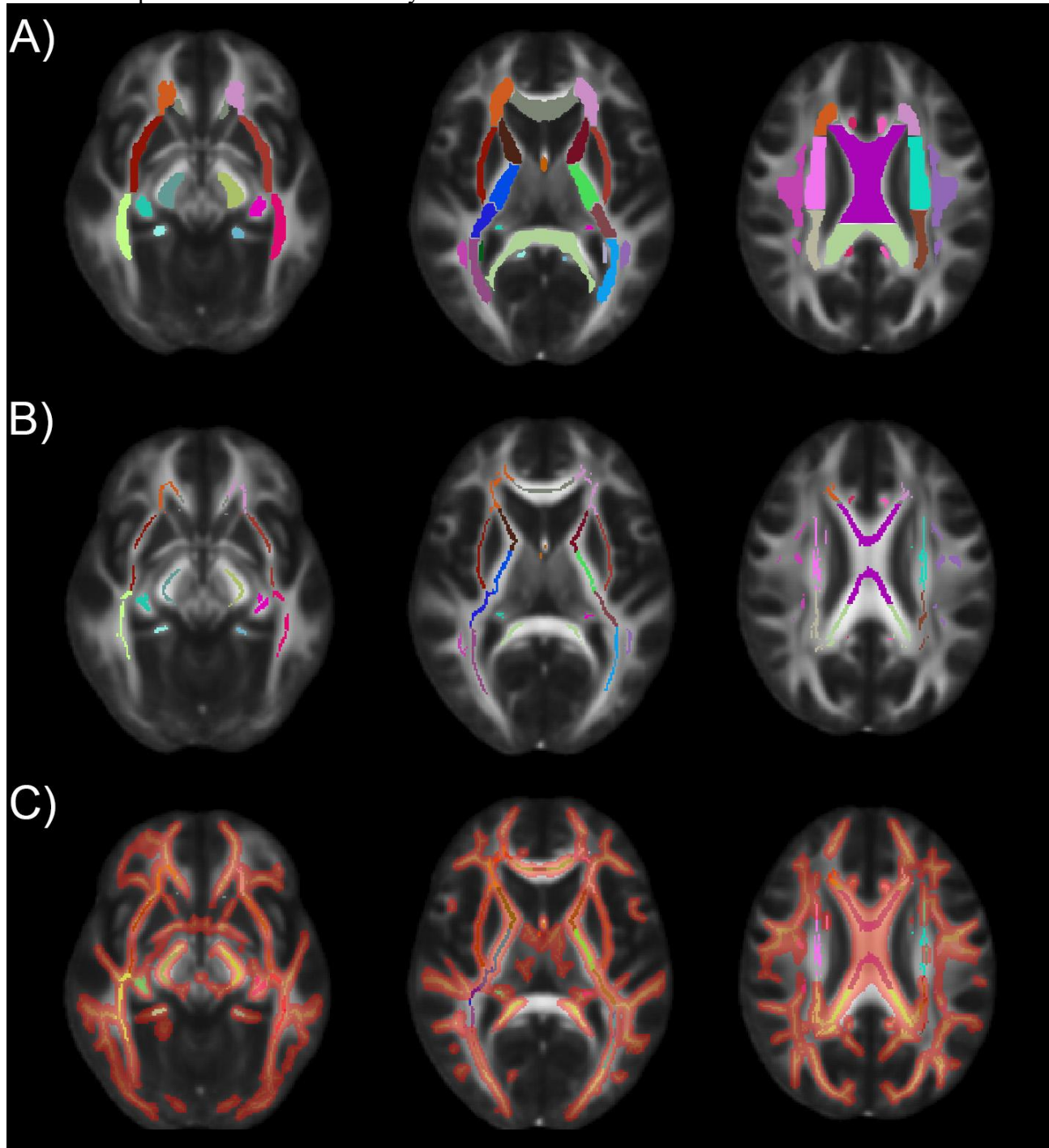
Vertex-wise distribution of myelination (i.e. T1/T2 ratios) in healthy control (top) and mTBI (bottom) groups at time point 1 (i.e. acutely, left) and time point 2 (chronically, right).



Vertex-wise distribution of T1/T2 ratios for each subject in the control (top), mTBI (middle) and AD (bottom) groups at time point 1 (TP1, left) and time point 2 (TP2, right). HCs have cortices where there is higher myelin concentration than in acute TBI patients, and that the latter group have more myelin than the AD patients. The TBI patients are on a continuum between HCs and ADs, which is also reflected in their chronic cognitive impairment.

The distributions across the cortical surface of each TBI subject's Z scores are plotted in the figures above and in that below. Note, across the two time points, both (A) the decrease of Z score means as well as (B) the broadening (increase in variance) of the Z distributions from time point 1 (TP1) to time point 2 (TP2). (A) suggest the occurrence of broad, cortex-wide demyelination across the two time points. (B) suggests that demyelination occurs at different time rates across the cortex. We are now in the process of statistically comparing these groups, in addition to AD patients imaged twice after disease onset, against one another from the standpoint of how the myelin content of their cerebral cortices changes across time. We will also describe and interpret the quantitative similarities and differences between the three groups' demyelination trajectories to establish the extent to which geriatric mTBI is associated with AD-like patterns of post-traumatic demyelination.

WM comparisons using TBSS. Thirdly, as part of our statistical analysis, we have continued our research on mapping acute functional connectivity changes in TBI patients which are predictive of AD-like cognitive impairment. In what follows, we describe our findings in detail as this pertains to the use of TBSS to quantify WM differences between groups. To investigate cerebral white matter damage between HCs, mTBI patients and AD patients, we used a tract-based spatial statistical (TBSS) approach. The following figures and tables depict the results of our analyses.



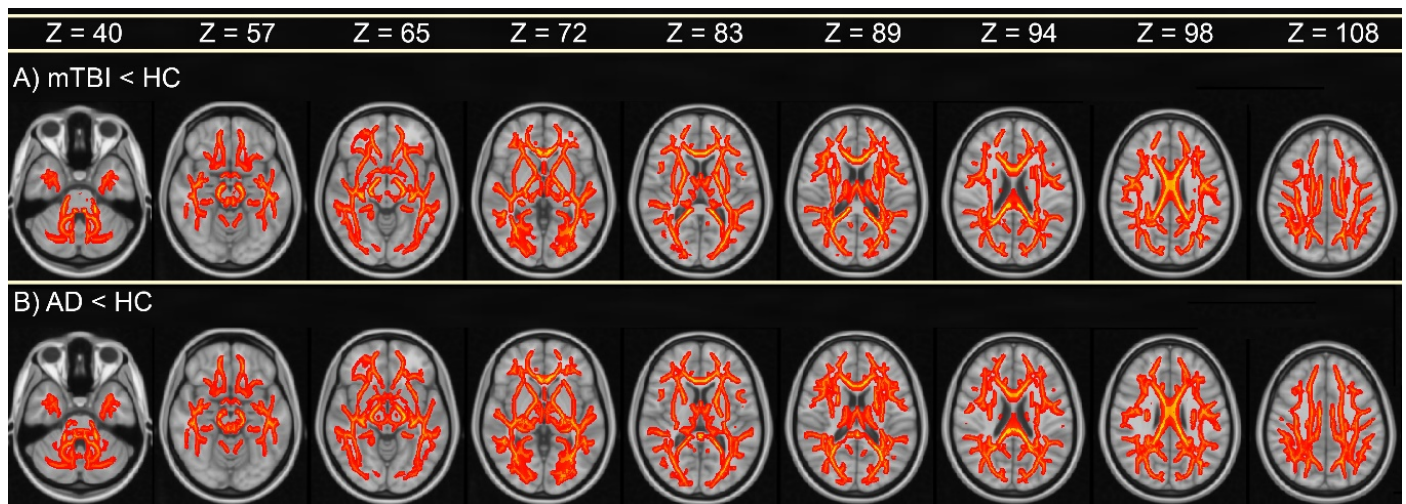
Differences between TBI and HC pertaining to WM properties. (A) WM label map of the Johns Hopkins WM Atlas. (B) skeletonized WM tract analysis based on the mean WM skeleton mask of all TBI subjects. (C) voxels in the mTBI cohort with significantly lower ($p < 0.05$) mean FA compared to the HC cohort. Overlays are superimposed on the skeletonized label map (thickened for visualization). All images were overlaid on the 1 mm x 1 mm x 1 mm FMRI B58 FA template, which is an average of the FA images of 58 healthy subjects.

In Q2, we started to statistically compare the effect of mTBI on the ratio of T1-weighted to T2-weighted grey matter MRI intensities across three groups of age- and sex-matched participants:

- (A) geriatric patients with mTBI patients imaged acutely and ~6 months post-injury
- (B) AD patients imaged twice after disease onset
- (C) healthy control (HC) participants whose MRIs were acquired at two time points

The results of this analyses revealed that the TBI patients exhibited amounts of acute cortical demyelination which were correlated with the extent of their chronic cognitive deficits. The figure below illustrates this continuum of demyelination severities.

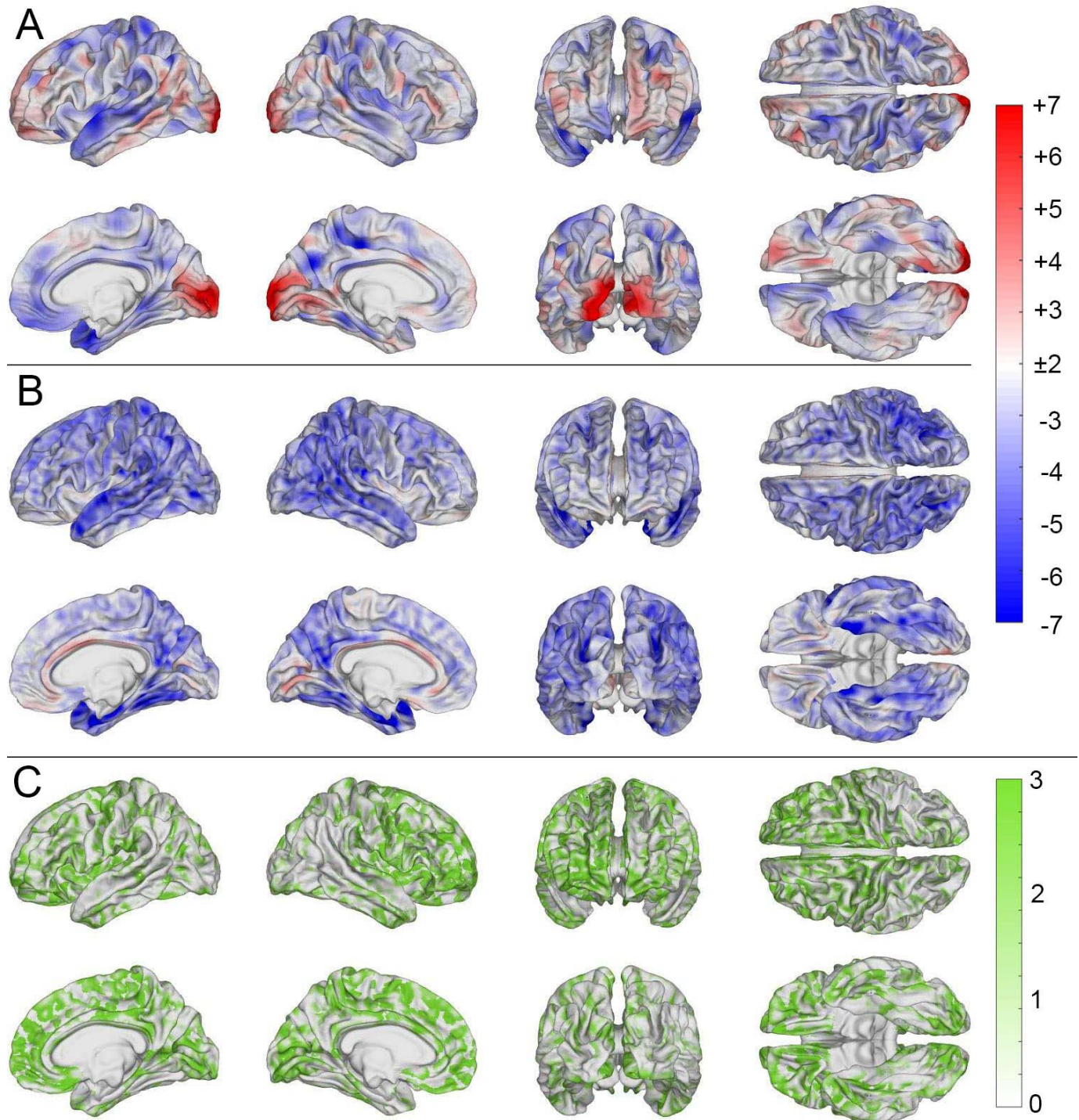
In Q4, we contrasted the patterns of neurodegeneration in geriatric mild traumatic brain injury (mTBI) (~6 months post-injury) and Alzheimer's disease (AD). Specifically, we used tract-based spatial statistics to perform a voxel-wise comparison of mean fractional anisotropy (FA) values between mTBI, AD, and healthy subjects (HC); this revealed significant differences in white matter (WM) degradation. Firstly, we find that both patient groups have significantly lower mean FA throughout the brain than HCs. For example, significantly lower mean FA was observed in the fornices, corpus callosa, and uncinate fasciculi of both mTBI and AD groups. Our analyses showed that mTBI patients did not have significantly lower mean FA anywhere in the brain than the AD group and vice versa. Voxel-wise, two one-sided t-(TOST) tests were then used to identify WM structures with significantly equivalent FA between groups. The superior frontal-occipital fasciculi and crura of the fornix display the most extensive equivalences in mean FA between mTBI and AD groups.



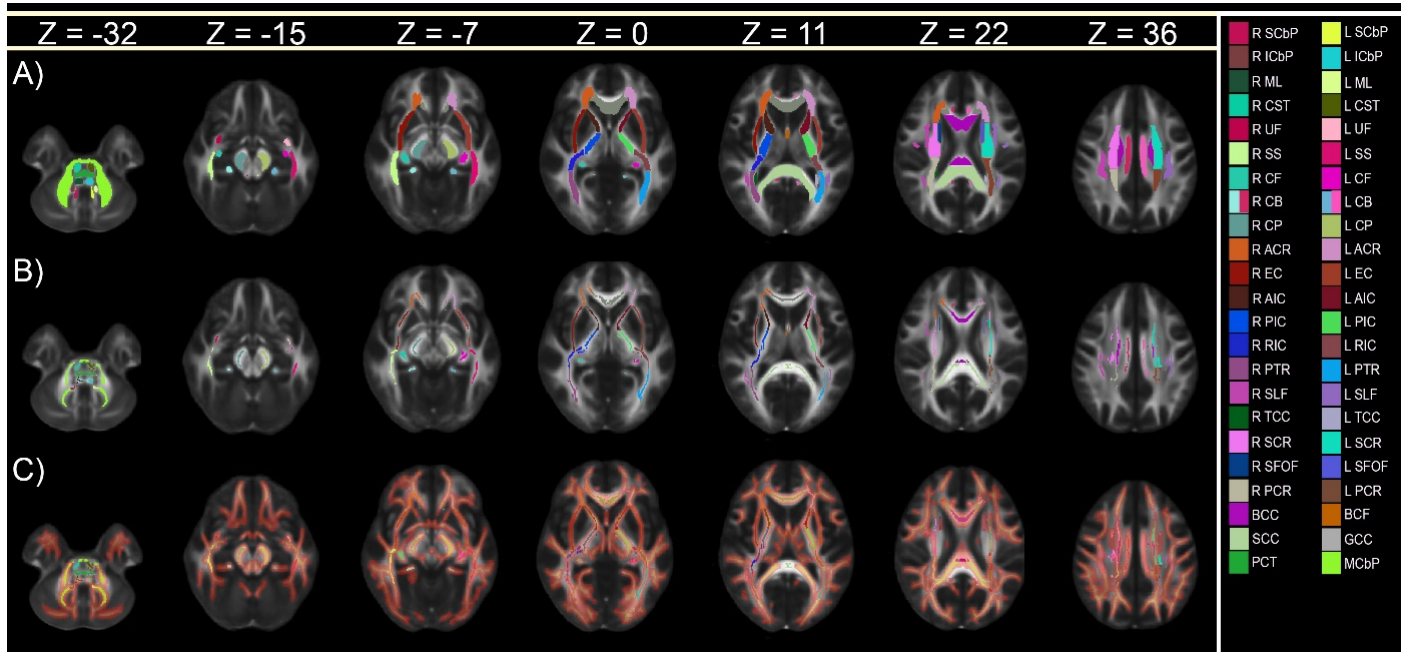
Group differences in mean FA among HCs and mTBI victims ~6 months post injury (top) and HC participants and AD subjects (bottom) as revealed by t-tests. Colors encode $-\log p$, which ranges from 2 (red) to 5 (yellow, corresponding to p-values of 0.05 (red) to ~0.0005 (yellow). P-values are displayed using an $\alpha = 0.05$, subject to multiple comparison correction. Smaller p-values are associated with lower FA values in the mTBI and AD groups compared to HC participants. Images displayed in radiological convention. The Z coordinate of each slice in MNI152 is provided.

Similar statistical methods were implemented vertex-wise to compare the cortical thickness—which can measure gray matter (GM) degradation—between mTBI, AD, and HC groups. The vertex-wise comparison of cortical thickness values between groups revealed significantly lower cortical thickness throughout temporoparietal regions in mTBI subjects when compared to HCs, and throughout the cortex in ADs when compared to HCs. A TOST test revealed significant cortical thickness equivalences throughout the frontal

and parietal lobes between ADs and mTBIs. Additionally, we used deep learning to demonstrate that acute cognitive measures such as Montréal cognitive assessment scores can predict the AD-like degeneration observed in mTBI patients. These findings illustrate our ability to early identify mTBI victims' risk for developing AD and a path that may present clinical benefits. We have submitted this manuscript to GeroScience for review and publication. The following figures depict the results of our analyses.



Regional patterns of significantly different cortical thinning between HCs and TBIs (top), HCs and ADs (middle) and statistically indistinguishable cortical thinning between mTBI and AD cohorts (bottom, $q < 0.05$). Blue indicates thinner cortex relative to HC, red indicates thicker cortex. Green indicates greater similarity between TBI and AD. Extensive similarities between TBI and AD- is observed in frontotemporal and frontoparietal regions with fewer similarities in occipital cortices.



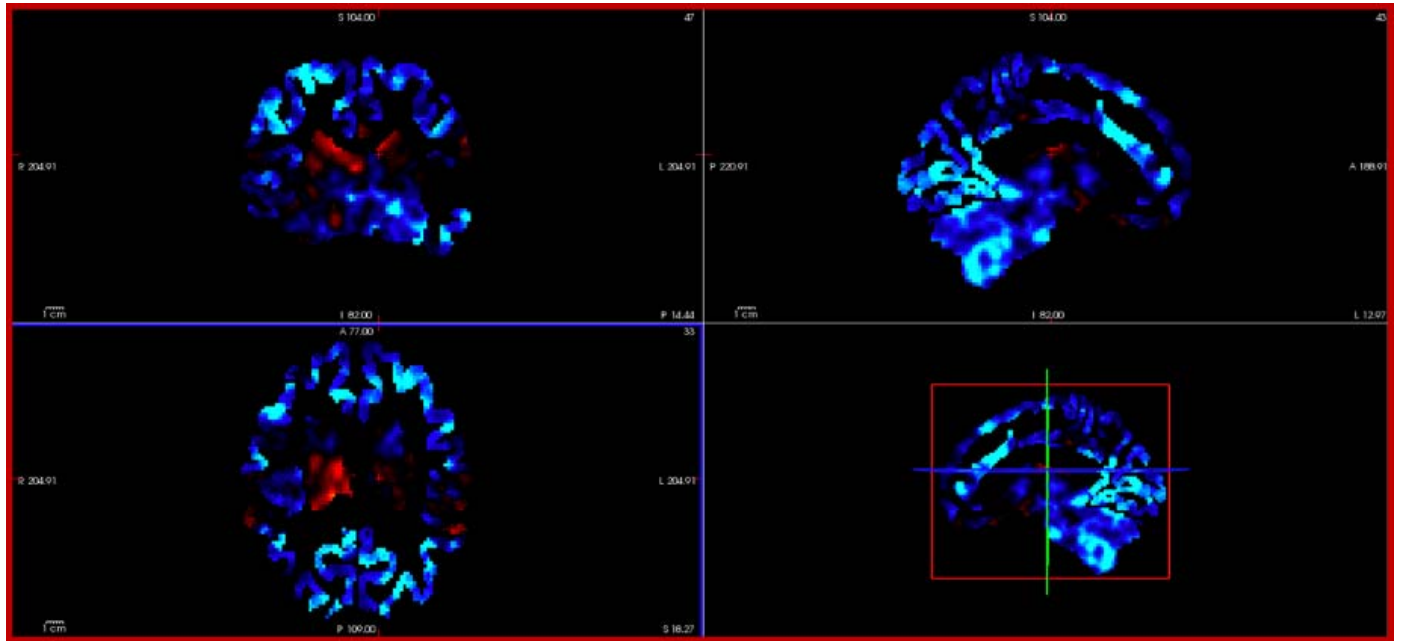
Representation for calculating the percentage of voxels associated with statistically significant findings within each neuroanatomic structure. (A) WM label map of the JHU atlas. (B) Mean WM skeleton mask of all subjects in the study. (C) Voxels where mTBI subjects exhibit mean FA values are significantly lower ($p < 0.05$) than in HCs. Colors encode WM structures (see Appendix 2).

In Q3 we also continued our investigation of similarities in cortical thinning between mTBI and AD cohorts. We have also continued to evaluate group differences in mean FA amongst HC participants and mTBI victims ~6 months post injury, HC participants and AD subjects.

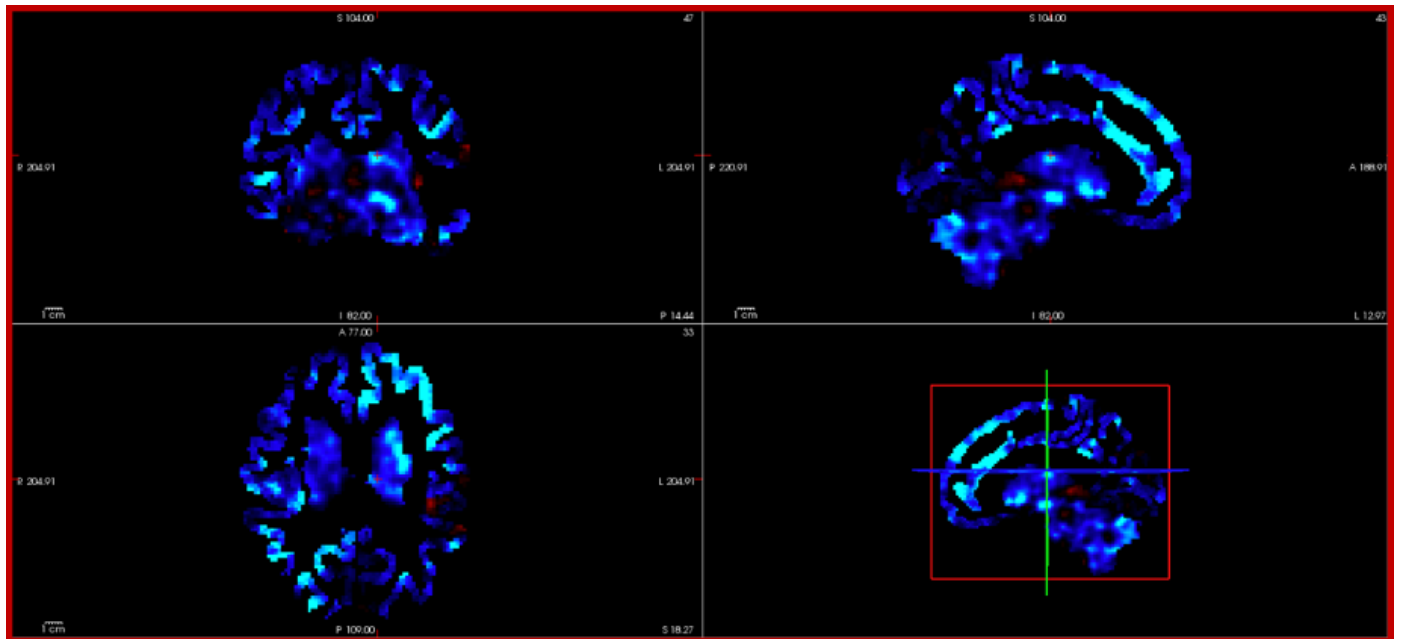
In Q3 we analyzed imaging data sets from 154 HCs and 77 mTBI subjects aged 21 and older, each with T1-weighted and diffusion weighted imaging (DWI) suitable for the analysis. These subjects were processed and added to the analysis in Q4. Our statistical analysis accounts for the presence of CMBs in the mTBI subjects, which were located and identified using an edge-based detection method designed for SWI volumes. Leveraging the intensity gradient properties of SWI to identify CMB-related hypo-intensities allowed us to investigate whether CMBs can be associated with deleterious effects upon perilesional WM in both younger and older mTBI subjects. We have also begun the process of quantifying mean FA changes within 54 known anatomical tracts, such as the arcuate fasciculus and the stratio-frontal bundle, between healthy controls and mTBI to quantify significant differences based upon our WM clustering output. Such results can provide us with knowledge of perturbations within the mTBI structural connectome that can be correlated or contrasted with known functional changes. Due to similarities in WM degeneration between mTBI and AD and to the high prevalence of CMBs in both conditions, this approach allows us to further investigate similarities between the two conditions to improve our biomarkers of CMB-based AD risk after TBI.

Functional connectomics biomarkers of AD risk after TBI. In Q2, we had started to examine the associations between alterations in the default mode network (DMN) of mTBI patients and alterations in it both in TBI and AD using fMRI connectivity seed analysis. The analysis was implemented using the Freesurfer FSFast analysis pipeline to implement a seed-based analysis comparing the resting state functional correlation (FC) patterns within the DMNs of 29 geriatric TBI patients (13 females, average age = 67, standard deviation 6 years, range 57-79). The seed-based FC analysis was implemented using default parameters for motion correction, brain masking, fMRI volume co-registration to T1-weighted volumes, surface sampling to the FS atlas, smoothing (5-mm full-width-at-half-maximum kernel), and both surfaces and volume sampling to the

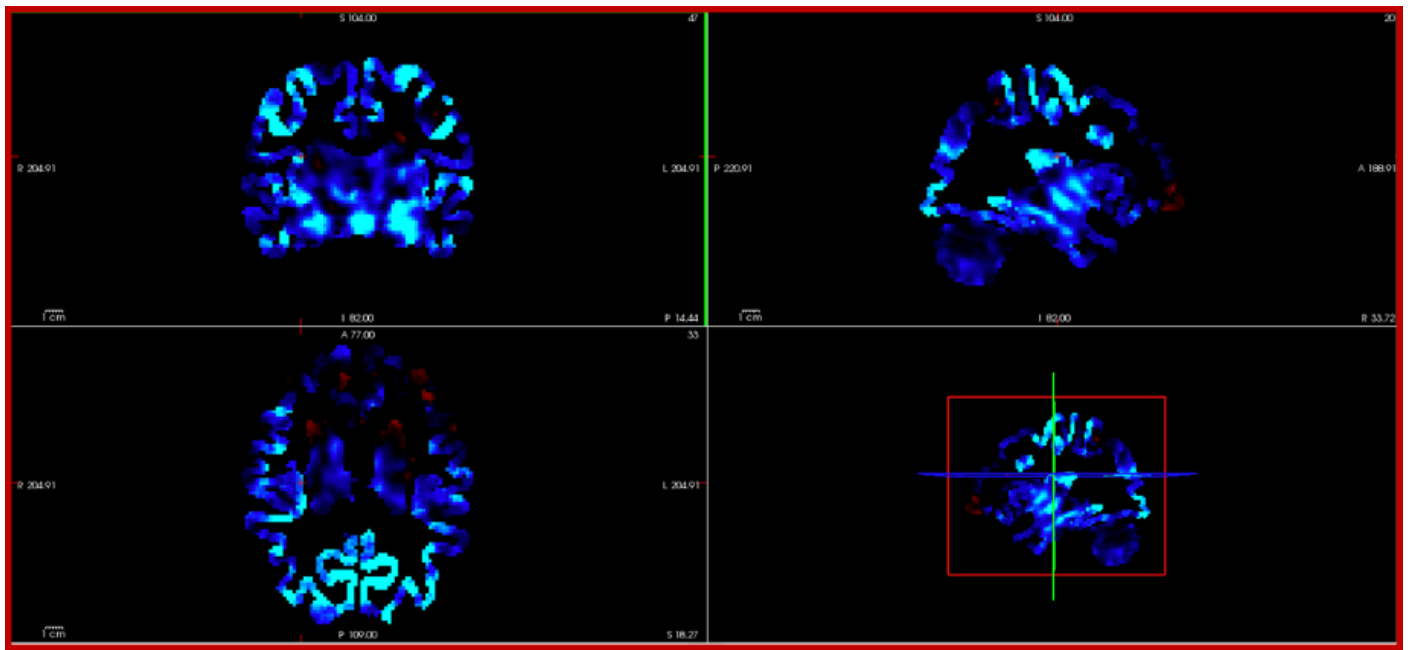
MNI305 atlas with smoothing for subcortical structure analysis. FC analysis seeds were generated from each subject's default FreeSurfer cortical parcellation anatomy. After processing, all subjects' fMRI time series were concatenated and a generalized linear model using weighted least squares was used to identify cortical areas of significant functional correlation.



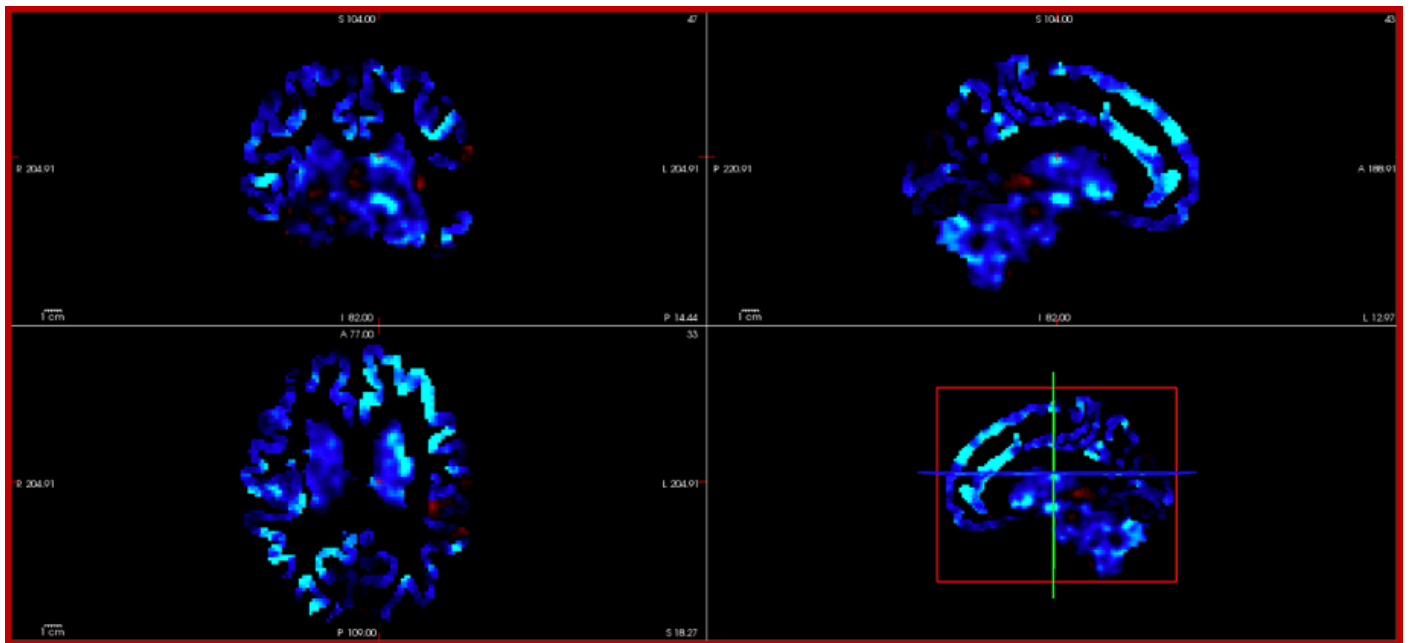
Longitudinal differences in the FC of left posterior cingulate cortex.



Like above, for the left hemisphere.



Like above, for right frontomarginal cortex.

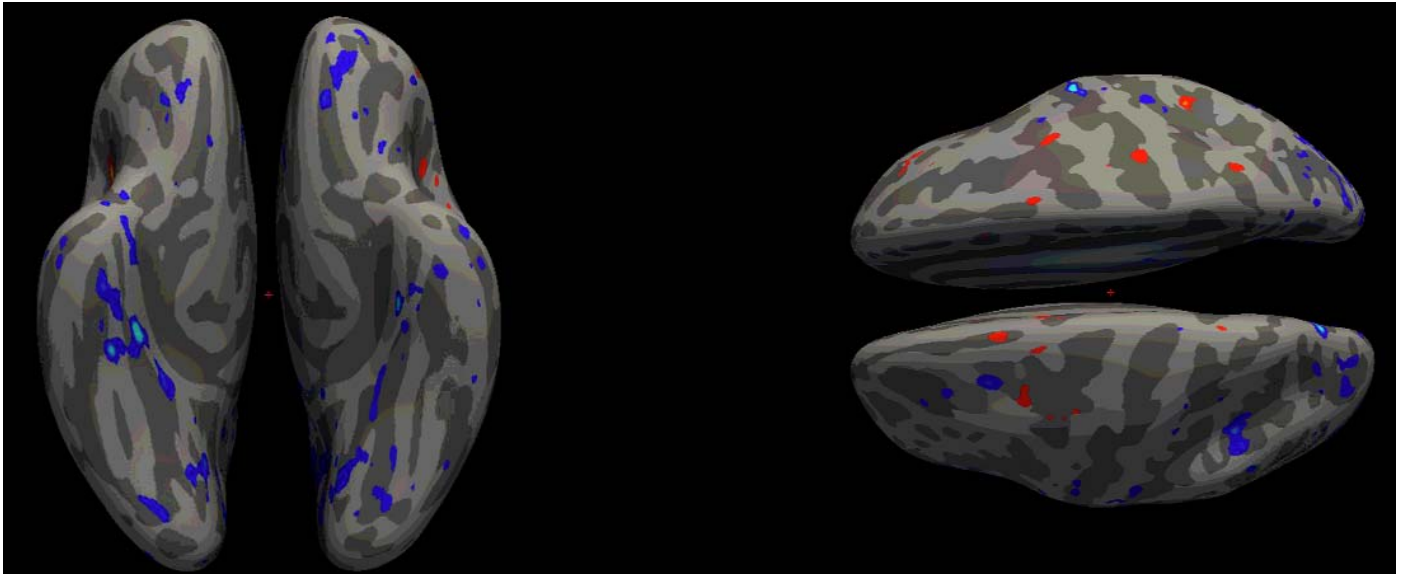


Like above, for the left hemisphere.

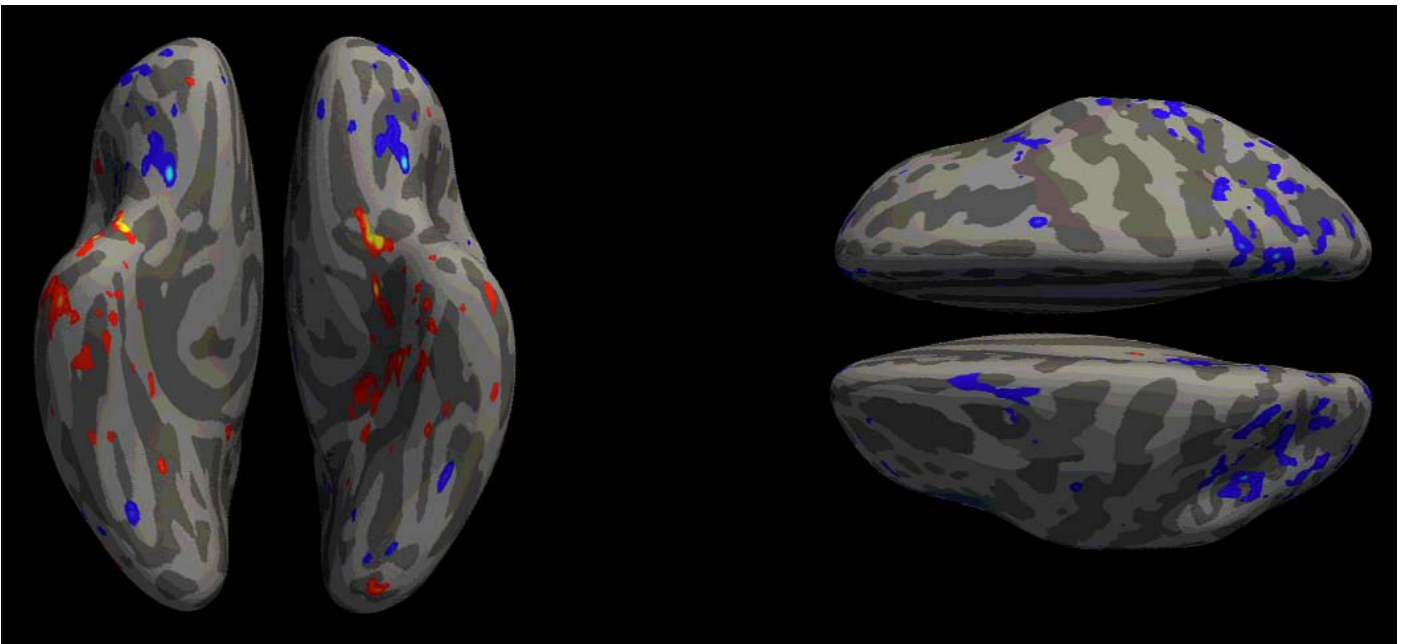
In Q4, we also continued examining the associations between alterations in the default mode network (DMN) of mTBI patients and alterations in it both in TBI and AD using fMRI connectivity seed analysis. The figures above display sample outputs from the current analysis.

The three figures below display t-statistics conveying the result of testing the hypothesis of FC statistical equivalence between the acute and chronic time points of TBI. On the heat maps, blue and red represent the $-\log p$ for the t-statistic (with range of 1.3 to 3), with brighter blue indicating areas of increased FC between the seed region and the colored region and red indicating decreased FC. The seeds used for the above three figures correspond to three regions in the 2009 Desikan-Killiany-Tourville Freesurfer atlas regions, namely

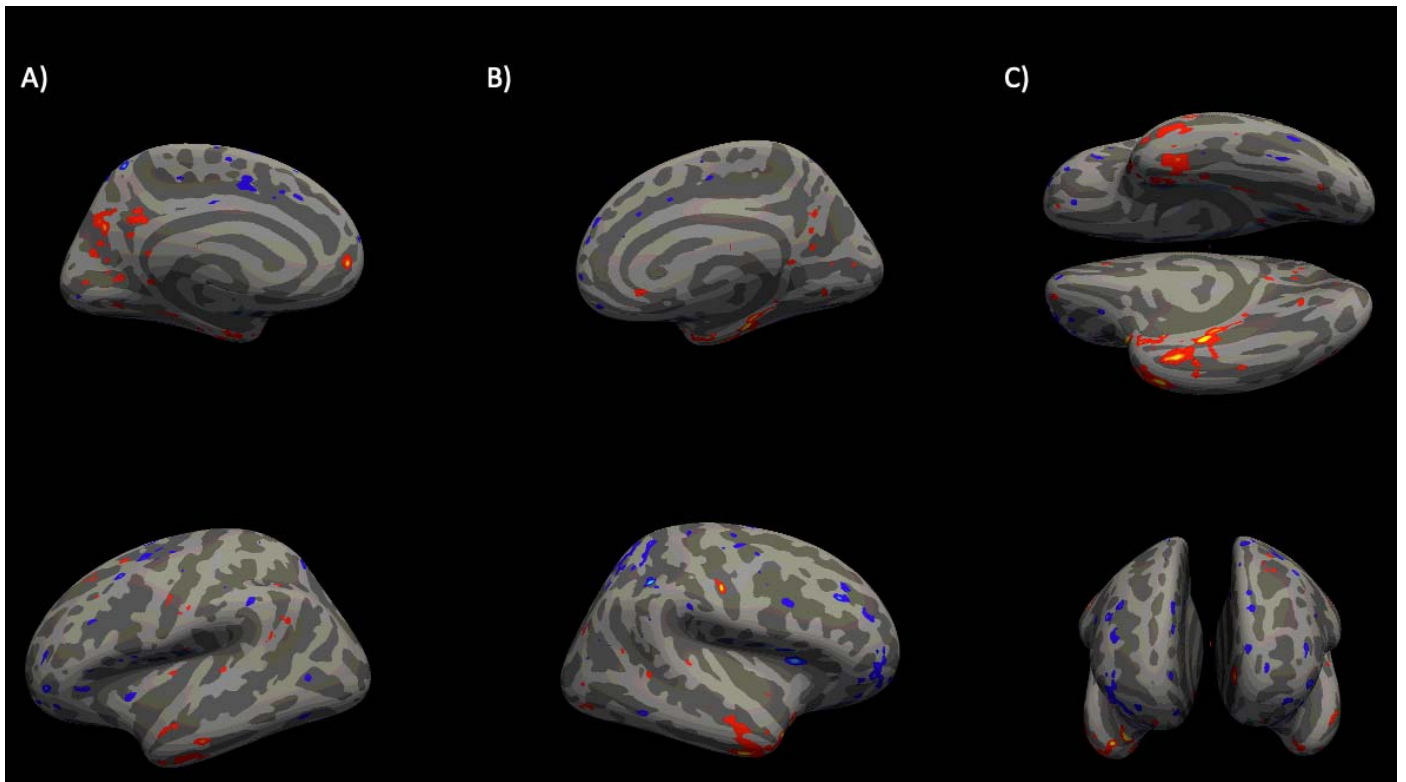
left hemisphere post dorsal cingulate cortex gyrus, left hemisphere post ventral cingulate cortex gyrus, and the left hemisphere gyrus and sulcus of the frontomarginal cortex. These three seeds show diffuse FC increase within the brain 6 months post-trauma.



Ventral (left) and superior views of both hemispheres' inflated surfaces (right). First-level analysis of younger adults (age < 39) in which the per-subject functional correlation (FC) timepoint changes were calculated between each subject's FCs computed from two scans (spaced six months apart, TP2-TP1), resulting in differences or each subject's timepoint pairs. Red indicates a positive correlation with the $-\log$ of the p -value from the t -test testing the null hypothesis of no mean FC change (i.e., TP2 has greater FC than TP1) and blue indicating anti-correlation (TP1 has greater FC than TP2). Darker hues represent a smaller value of $-\log p$ with a threshold for coloring being > 1.3 or a p -value of 0.05 and the brightest corresponding to at least a value of 3 or a p -value of .001.



Like above, for the older adults (age > 40).



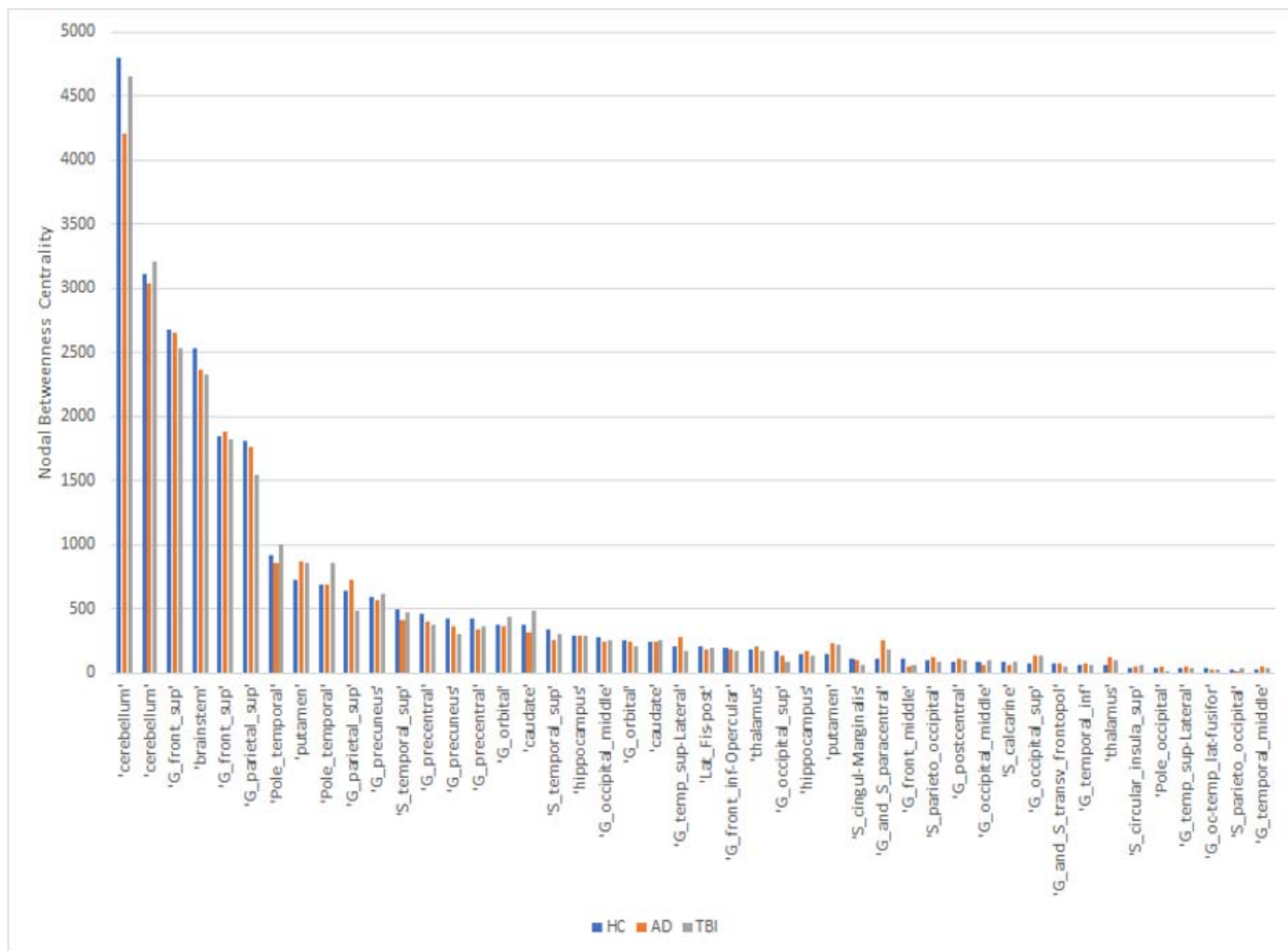
Significance map viewed on the (A) left inflated hemisphere as viewed from the longitudinal fissure side (top) and parietal side (bottom), (B) same as (A) but for the right inflated hemisphere, and (C) on both inflated hemispheres from the underside (top) and anterior (bottom). The second-level analysis explores the difference between two age groups (younger vs. older). Colors indicate correlation and anti-correlation (red and blue, respectively) values for the $-\log p$ (i.e., a red region has a value of 1.3, indicating a p -value of .05) calculated from the t -test of - (younger TBI subjects: <39 y.o., 69 subjects and older TBI subjects: >39 y.o., 68 subjects) regressing out the effect of sex and scan site. Heat map values range from 1.3 to at least three, as in the two previous figures.

Given the relatively brief period between the initial scan and the TBI incident, the 6 month recovery time is the most likely explanation for the FC increase, as seen in our previous study comparing the 6-month TBI FC network to healthy subjects (manuscript submitted). The regions colored in blue may reflect recovery of baseline FC in some brain regions. However, in the seeds that represent the main “hub” of the DMN (A and B, posterior cingulate cortex), there is FC reduction within the ipsilateral hemisphere and its corresponding region in the contralateral hemisphere as well. This supports our previous study of healthy subjects, TBI patients, and AD patients, which found lasting alterations in the DMNs of TBI patients as they recover from injury.

Activity (I). We have continued to refine and revise our methodology throughout the project period. Specifically, we refined our approach to quantify WM alterations using diffusion tensor imaging (DTI) streamlines in mTBI populations. We first performed a within-subject longitudinal matching of DTI streamlines for 22 mTBI subjects aged 55 and older. We then implemented eddy current artifact and motion corrections using the FSL library. Then, we selected the WM analysis package DTIPrep as our choice of preprocessing, and validated its utility using data of adequate quality acquired from mTBI subjects. The process was repeated for both timepoints. Tractographies were validated against those generated via TrackVis and based upon improved reconstruction of the corpus callosum. We then combined (A) automatic, atlas-informed labeling of WM streamline clusters with (B) streamline prototyping and (C) Riemannian matching of elastic curves to quantitate within-subject WM changes. After these promising results, we reprocessed the 22 subjects described above and expanded our cohort and applied our approach to an additional 37 mTBI subjects aged 25 to 55, also imaged at two timepoints approximately six months

apart. By the quarter's conclusion, we had completed the analysis for 59 mTBI subjects and begun focusing on control subjects in the analysis.

Activity (J). Our approach to generating single WM streamlines within clusters involved selecting a streamline whose path, torsion, and similar properties were most representative of the rest of the cluster according to a fiber affinity metric, as proposed in O'Donnell et al. (2007). All fibers were spectrally embedded as points, producing a point cloud whose mean would correspond to the most representative fiber trajectory. Due to the high sample size, the mean was approximated with the point closest to the mean, whose corresponding fiber was chosen as the prototype.



Betweenness centrality of 46 regions compared across three groups (HC, AD, TBI), in descending order.

We also calculated connectivity matrices, which can then be used to chart the strength of connections between different regions of the brain. The connectivity matrices in this project contain information about the lengths of fibers and about their FA properties. The matrices include information pertaining to connections between 165 different regions of the brain, including subcortical structures. These connectivity matrices were created for HC subjects, AD patients, and TBI patients. The matrices were normalized for brain size based on the intracranial volume of each subject. Using the Brain Connectivity Toolbox, several metrics were calculated to compare between the groups of subjects. These metrics include items such as density, clustering coefficient, efficiency, modularity, betweenness centrality, and more. Some of the metrics reveal information about the connection between individual areas, some of them concern all the connections to one region, and some of them are pertinent to the entire connectivity matrix.

The figure above depicts a comparison between averages values of betweenness centrality for 46 brain regions with highest values in HCs. All other brain regions contained negligible values for all three groups. Betweenness centrality is a measure of the fraction of all the shortest paths in the network that intersect a given region. A higher value means that a given region is involved in more shortest paths. A shortest path is defined as the list of regions that make up the road with the smallest possible distance between two regions. In all three groups, the largest values are found in the cerebellum.

Activity (K). Research based on funding from this award was featured in 15 journal manuscripts which are at various stages of the peer review and publication process. We have also contributed two technical book chapters as well as 11 peer-reviewed abstracts at various local, national, and international conferences. A complete list of these products is provided in Section 6 of this report.

Activity (L). the research activities conducted as part of this project resulted in the development of Matlab and Python programming code and software for the analysis of imaging data. Currently, this material is available from the PI upon request. However, we anticipate making this material available free of charge to the public at large and to the scientific community on GitHub or using a similar form of dissemination.

Activity (M). In Y2, research based on funding from this award was featured in 15 journal manuscripts which are at various stages of the peer review and publication process. These are listed in Section 6 and a few representative publications are provided in the appendix.

Activity (N). We have presented our work at the following events:

Meeting of the Gerontological Society of America (GSA '19)	Austin, TX
Meeting of the Organization for Human Brain Mapping (OHBM '20)	online
Meeting of the North American Brain Injury Society (ABI'20)	New Orleans, LA
Meeting of the American Congress of Rehabilitation Medicine (ACRM)	Chicago, IL
Meeting of the Frontiers in Traumatic Brain Injury Conference (TBI '19)	London, UK

What opportunities for training and professional development has the project provided?

Although the project was not specifically intended to provide training and professional development, the PI has been able to provide one-on-one mentorship thanks to this award. Specifically, five junior scientists (Maria Calvillo, Sean Mahoney, Van Ngo, Nikhil Chaudhari, David Robles), two graduate students (Di Fan, Alexander Maher) and seven undergraduate students (Shania Wang, Kenneth Rostowsky, Nahian Chowdhury, Hyung Jun Lee, Judy Wang, Ammar Dharani, Alex Yin, Elliot Jacobs) benefitted from the learning opportunities provided by this project. The undergraduate students contributed to methodological efforts which assisted the project as part of a USC initiative which facilitates the process of allowing undergraduate students to undertake scientific research. This is a prestigious program at USC for which only competitive students are selected. One student, Alexander Maher, was awarded the prestigious Okin Award for Quantitative Biology Research for work done as part of this project. Another, Shania Wang, was awarded a USC Provost's Research Fellowship for the Fall of 2020 to undertake research related to this project.

Aside from one-on-one training, the PI has integrated research results from this project into his lectures as part of two courses which he teaches at USC, namely a seminar course for PhD students (GER 592, Multidisciplinary Research Seminar in Gerontology), and a graduate course for master's degree students (GER 508, The Mind-Body Connection Across the Lifespan). The PI also disseminated results from this project as part of guest lectures in two PhD courses in gerontology (GER 600, GER 623), one PhD course in neuroscience and two seminar course in electrical engineering.

How were the results disseminated to communities of interest?

Research undertaken partly using funding from this contract was presented as an oral conference session of the Third Annual Conference on the Frontiers of Traumatic Brain Injury (FTBI '19) in London, UK, where the PI was awarded the first prize for best research presentation. This prestigious award was made by the Institute of Neurology of University College London and by Imperial College of Science, Technology and Medicine.

The PI was also invited to present the results of the study at several conferences, including the Gerontological Society of America (Austin TX), the 96th Conference of the American Congress of Rehabilitation Medicine (ACRM 2019, Chicago, IL), the Annual Conference of the North American Brain Injury Society (ABI '20, New Orleans, LA), the Annual Conference of the Organization for Human Brain Mapping (OHBM '20, online).

The PI undertakes public speaking engagements outside scientific circles on a regular basis. In 2020, he was invited to speak at Monash University in Melbourne, Australia as part of an invited seminar on neuroscience and neuroimaging, where he featured the results obtained using funds from this award. He also presented his work at the Brain Dynamics Electrophysiology Affinity Seminar at UCLA, where he was invited to give a presentation to clinicians and neurophysiologists.

What do you plan to do during the next reporting period to accomplish the goals?

Throughout Y3 of the project, we will finalize the task of obtaining confirmations from TBI/ADr clinicians concerning the validity and clinical utility of our findings related to connectome differences between TBI and AD inferred from structural and functional imaging data. We will also complete the reliability testing of our software, revise our methods (as needed) and test alternative hypotheses (as needed). We will share our software via NITRC and produce additional manuscripts on the statistical analysis of our findings. Finally, we will continue disseminating our work in the form of manuscripts to be submitted to peer-reviewed journals, conference presentations and other dissemination media.

4. IMPACT:

What was the impact on the development of the principal discipline(s) of the project?

The effects of mild TBI (mTBI) upon gross anatomy are typically subtler than those of moderate-to-severe TBI because the latter often changes neuroanatomy and brain circuitry to a dramatic extent. For this reason, the mTBI population studied as part of this project is substantially more homogeneous than that comprising more severe forms of TBI, which implies that mTBI is considerably more amenable to population-level studies and statistical analyses. Additionally, it has already been argued extensively within the TBI and AD research communities that moderate-to-severe TBI predisposes its victims to AD significantly, whereas the extent to which this is the case for mTBI victims is far less clear. For all these reasons, the utility of our study and its relevance are likely greatest for the welfare of mTBI victims. Nevertheless, because ~80% of all TBI victims have mild forms of this condition, this proposed research bears testimony to the substantial potential impact of our study compared to the scenario of studying only moderate-to-severe forms of TBI.

Thus far, our results indicate that the mTBI-affected brain of older adults experiences an amount of connectomic and cortical neurodegeneration which rivals that of AD patients of similar age and of the same sex. This finding is likely to be very impactful because it has also allowed to find properties of the TBI-affected brain whose characteristics are commensurate with the likelihood of TBI survivors to develop a trajectory of neurodegeneration which is more severe than that of other TBI patients, including possibly

those who will go on to develop AD. This and related findings are described in our GeroScience publication (enclosed with this report) and in our manuscript currently under review (enclosed with this report). This proposed project has identified novel AD risk factors which are specific to the TBI population can be of substantial clinical benefit. Specifically, (1) having the ability to accurately identify TBI victims at high risk for AD could have substantial consequences for the healthcare of such individuals, and (2) understanding the relationship between TBI and AD could advance our scientific and clinical knowledge regarding these two conditions.

What was the impact on other disciplines?

Outside our own discipline, the methodological innovations made as part of this project have made an impact upon the scientific field of image processing. Specifically, because our CMB identification algorithm performs better than any other methods previously proposed (sensitivity: 97%), it is likely that our approach will be useful to other researchers in the field of image processing. The task of finding CMB automatically in the brain using MRI-based analysis is important because over 40% of older adult brains exhibit CMBs, which are frequently associated with conditions like cerebral amyloid angiopathy (CAA) and cerebrovascular disease. Additional impact has been made upon the field of AD research, since we have identified not only biomarkers of AD risk in TBI patients but also novel biomarkers of early AD neurodegeneration.

What was the impact on technology transfer?

Nothing to report.

What was the impact on society beyond science and technology?

The results of this project will likely make an impact upon public perceptions of mTBI severity in older adults. Our work indicates that mTBI affects the aging brain substantially more than it affects other age groups, particularly from the standpoint of connectome degradation and cortical thinning. Our finding that AD and mTBI share significant patterns of connectivity losses will likely assist in improving public knowledge of seniors' vulnerability to AD after suffering concussions. The PI will continue to expend effort in the direction of increasing public awareness of these findings so that older adults are granted an adequate amount of attention from public policy makers and from governmental and non-governmental entities seeking to improve the healthcare of our aging population.

5. CHANGES/PROBLEMS:

Nothing to report.

Changes in approach and reasons for change

Nothing to report.

Actual or anticipated problems or delays and actions or plans to resolve them

Nothing to report.

Changes that had a significant impact on expenditures

Nothing to report.

Significant changes in use/care of human subjects, vertebrate animals, biohazards, or select agents

Significant changes in use or care of human subjects

Nothing to report.

Significant changes in use or care of vertebrate animals

Not applicable (no use or care of vertebrate animals).

Significant changes in use of biohazards and/or select agents

Not applicable (no biohazards and/or select agents).

6. PRODUCTS:

• Publications, conference papers, and presentations

Journal publications.

A Irimia & JD van Horn (2020) Mapping the rest of the human connectome: atlas of the spinal cord and peripheral nervous system *NeuroImage* (accepted; *acknowledgment of federal support: yes*)

KA Rostowsky & **A Irimia** for the Alzheimer's Disease Neuroimaging Initiative (2020) Acute cognitive impairment after traumatic brain injury predicts the occurrence of brain atrophy patterns observed in Alzheimer's disease (under review; *acknowledgment of federal support: yes*)

H Akrami, RM Leahy, **A Irimia**, PE Kim, CN Heck & AA Joshi (2020) Neuroanatomic prediction of post-traumatic epilepsy using magnetic resonance imaging and machine learning (under review; *acknowledgment of federal support: yes*)

JA Holguin, JL Margetis, A Narayan, GM Yoneoka & **A Irimia** (2020) Vascular cognitive impairment after mild stroke: connectomic insights, neuroimaging and knowledge translation (under review; *acknowledgment of federal support: yes*)

Andrei Irimia*, Alexander S Maher*, Nikhil N Chaudhari, Nahian F Chowdhury & Elliot B Jacobs for the Alzheimer's Disease Neuroimaging Initiative [*these authors contributed equally] (2020) Acute cognitive deficits after traumatic brain injury predict Alzheimer's disease-like degradation of the human default mode network *GeroScience* vol. 42, pp. 1411–1429 (*acknowledgment of federal support: yes*)

Di Fan, Nikhil N. Chaudhari, Maria Calvillo, Sean K. Lee, Nahian F. Chowdhury, Kenneth A. Rostowsky, Fan Zhang, Lauren J. O'Donnell and **Andrei Irimia** (2019) Post-traumatic cerebral microhemorrhages and their effects upon white matter connectivity in the aging human brain *IEEE Engineering in Medicine and Biology*, volume 40, pages 198-203. (*acknowledgment of federal support: yes*)

Andrei Irimia (2020) Cross-sectional volumes and trajectories of the human brain, gray matter, white matter and cerebrospinal fluid in 9,473 typically aging adults *Neuroinformatics*, online first (*acknowledgment of federal support: yes*)

- M Calvillo & **Andrei Irimia** (2020) Neuroimaging and psychometric assessment of mild cognitive impairment after traumatic brain injury *Frontiers in Psychology* vol. 11, article 1423, 26 pp (acknowledgment of federal support: yes)
- Andrei Irimia**, Di Fan, Nikhil N. Chaudhari, Van Ngo, Fan Zhang, Shantanu H. Joshi and Lauren J. O'Donnell (2019) Mapping cerebral connectivity changes after mild traumatic brain injury in older adults using diffusion tensor imaging and Riemannian matching of elastic curves *IEEE Proceedings in Biomedical Engineering*, vol. 2020, pp. 1690-1693 (acknowledgment of federal support: yes)
- Alexander Olsen, Talin Babikian, Erin Bigler, Karen Caeyenberghs, Virginia Conde, Kristen Dams-O'Connor, Ekaterina Dobryakova, Helen Genova, Jordan Grafman, Asta K Håberg, Ingrid Heggland, Torgeir Hellstrøm, Cooper B. Hodges, **Andrei Irimia**, Ruchira M. Jha, Paula K. Johnson, Harvey Levin, Lucia M. Li, Hannah M. Lindsey, Abigail Livny, Marianne Løvstad, John Medaglia, David Menon, Stefania Mondello, Martin M. Monti, Virginia F. J. Newcombe, Agustin Petroni, Jennie Ponsford, David Sharp, Gershon Spitz, Lars T. Westlye, Paul M. Thompson, Emily L. Dennis, David F. Tate, Elisabeth A. Wilde, Frank G. Hillary (2019) Toward a global and reproducible science for brain imaging in neurotrauma: The ENIGMA adult moderate/severe traumatic brain injury working group (Brain Imaging & Behavior -- accepted; acknowledgment of federal support: yes)
- Avnish Bhattarai, **Andrei Irimia** and John D. Van Horn (2019) Neuroimaging and cellular biomarkers of traumatic brain injury in military veterans *Journal of Clinical Neuroscience* (vol. 70, pp. 1-10; acknowledgment of federal support: yes)
- IK Koerte, CL Esopenko, SR Hinds, ME Shenton, EM Bonke, JJ Bazarian, KC Bickart, ED Bigler, S Bouix, TA Buckley, MC Choe, PS Echlin, GM Jessica, CC Giza, J Hayes, CB Hodges, **A Irimia**, PK Johnson, K Kenney, HS Levin, AP Lin, HM Lindsey, MLLipton, JE Max, AR Mayer, TB Meier, K Merchant-Borna, T Merkeley, BD Mills, MR Newsome, T Porfido, JA Stephens, RD Zafonte, MM Zeineh, PM Thompson, DFTate, EL Dennis, EA Wilde & D Baron for the ENIGMA-TBI Consortium (2020) The ENIGMA sports injury working group: an international collaboration to further our understanding of sports-related brain injury *Brain Imaging & Behavior* (accepted; acknowledgment of federal support: yes)
- C Esopenko, J Meyer, EA Wilde, AD Marshall, DF Tate, AP Lin, IK Koerte, KB Werner, EL Dennis, AL Ware, NL de Souza, DS Menefee, Kristen Dams-O'Connor, DJ Stein, ED Bigler, ME Shenton, K Chiou, JL Postmus, K Monahan, B Eagan-Johnson, P van Donkelaar, T Merkley, C Valez, C Hodges, H Lindsey, P Johnson, **A Irimia**, M Spruiell, E Bennett, A Bridwell, G Ziemann & FG Hillary for the ENIGMA-TBI Consortium (2020) A global collaboration to study intimate partner violence-related head trauma: the ENIGMA Consortium IPV Working Group *Brain Imaging & Behavior* (accepted; acknowledgment of federal support: yes)
- DF Tate, EL Dennis, JT Adams, MM Adamson, HG Belanger, ED Bigler, HC Bouchard, AL Clark, LM Delano-Wood, SG Disner, BC Eapen, CE Franz, E Geuze, NJ Goodrich-Hunsaker, K Han, JP Hayes, SR Hinds II, CB Hodges, ES Hovenden, **A Irimia**, K Kenney, IK Koerte, WS Kremen, HS Levin, HM Lindsey, RA Morey, MR Newsome, J Ollinger, MJ Pugh, RS Scheibel, ME Shenton, DR Sullivan, BA Taylor, M Troyanskaya, C Velez, BSC Wade, X Wang, AL Ware, RD Zafonte, PM Thompson & EA Wilde for the ENIGMA-TBI Consortium (2020) Coordinating global multi-site studies of military-relevant traumatic brain injury: opportunities, challenges and harmonization guidelines *Brain Imaging & Behavior* (accepted; acknowledgment of federal support: yes)
- EL Dennis, K Caeyenberghs, KR Hoskinson, TL Merkley, SJ Suskauer, RF Asarnow, T Babikian, B Bartnik-Olson, K Bickart, ED Bigler, A Figaji, CC Giza, CB Hodges, NJ Goodrich Hunsaker, **A Irimia**, M Königs, HS Levin, JE Max, MR Newsome, A Olsen, NP Ryan, AT Schmidt, MS Spruiell, AL Ware, KO

Yeates, BA Zielinski, P Kochunov, N Jahanshad, PM Thompson, DF Tate & EA Wilde for the ENIGMA-TBI Consortium (2020) White matter disruption after pediatric traumatic brain injury: results from ENIGMA pediatric msTBI (*under review; acknowledgment of federal support: yes*)

Books or other non-periodical, one-time publications.

Maria Calvillo, Di Fan and **Andrei Irimia** (2019) Multimodal imaging of cerebral microhemorrhages and white matter degradation in geriatric patients with mild traumatic brain injury (*Methods in Molecular Biology for Aging: Methods and Protocols*, vol. 2144, pp. 223-236; *acknowledgement of federal support: yes*)

A Irimia, KA Rostowsky, EM Law & HC Chui (2020) Cerebral hemorrhages in traumatic brain injury *The Neuroscience of Traumatic Brain Injury* (book chapter accepted; book is in press; *acknowledgement of federal support: yes*)

Alexander S. Maher, Nikhil N. Chaudhari, Elliot B. Jacobs, Sean O. Mahoney, Van Ngo and **Andrei Irimia** (2020) Statistical equivalence of resting-state functional correlation patterns in the default mode networks of patients with Alzheimer's disease vs. geriatric victims of mild traumatic brain injury *Fourteenth Symposium of the International Neurotrauma Society (INTS '20)*, March 29-April 2, 2020, Melbourne, Australia (accepted; conference postponed due to pandemic)

Kenneth A. Rostowsky, Nikhil N. Chaudhari and **Andrei Irimia** (2020) Statistically equivalent distribution of cortical thinning and white matter degradation in geriatric patients with mild traumatic brain injury relative to Alzheimer's disease *Fourteenth Symposium of the International Neurotrauma Society (INTS '20)*, March 29-April 2, 2020, Melbourne, Australia (accepted; conference postponed due to pandemic)

HC Bouchard, D Sun, EL Dennis, SG Disner, JA Elman, AM Silva, C Velez, M Newsome, ND Davenport, **A Irimia**, M Troyanskaya, SR Sponheim, RS Scheibel, BSC Wade, CE Franz, WS Kremen, MJ Coleman, W Williams, HS Levin, E Geuze, IK Koerte, MM Adamson, R Coimbra, GA Grant, LA Shutter, MS George, R Zafonte, TW McAllister, ME Shenton, MB Stein, EA Wilde, DF Tate, PM Thompson, A Sotiras & RA Morey (2020) White matter abnormalities in military traumatic brain injury: results from ENIGMA Brain Injury *26th Annual Meeting of the Organization on Human Brain Mapping (OHBM '20)*, June 26-30, 2020, Montréal, Canada

V Ngo, HJ Lee, SO Mahoney & **A Irimia** (2020) Estimation of biological brain aging acceleration after mild traumatic brain injury *26th Annual Meeting of the Organization on Human Brain Mapping (OHBM '20)*, June 26-30, 2020, Montréal, Canada

KA Rostowsky, NN Chaudhari, M Calvillo & **A Irimia** (2020) Similarities in cerebral neurodegeneration between geriatric patients with mild traumatic brain injury and patients with Alzheimer's disease *26th Annual Meeting of the Organization on Human Brain Mapping (OHBM '20)*, June 26-30, 2020, Montréal, Canada

AS Maher, NN Chaudhari, EB Jacobs, SO Mahoney & **A Irimia** (2020) Default mode network dysfunction in geriatric mild traumatic brain injury vs. Alzheimer's disease *26th Annual Meeting of the Organization on Human Brain Mapping (OHBM '20)*, June 26-30, 2020, Montréal, Canada.

SO Mahoney, NN Chaudhari & **A Irimia** (2020) Neuroimaging measures of cortical demyelination after mild traumatic brain injury in older adults *26th Annual Meeting of the Organization on Human Brain Mapping (OHBM '20)*, June 26-30, 2020, Montréal, Canada.

Alexander S. Maher, Elliot B. Jacobs, Nikhil N. Chaudhari and **Andrei Irimia** (2020) Default mode network differences between geriatric mild traumatic brain injury and Alzheimer's disease *Fifteenth Annual Conference of the North American Brain Injury Society (ABI '20)*, February 26-29, 2020, New Orleans, Louisiana, USA.

Andrei Irimia, Kenneth A. Rostowsky, Nikhil N. Chaudhari, Maria Calvillo, Sean K. Lee (2019) Geriatric traumatic brain injury and Alzheimer's disease share similar patterns of white matter degradation *Annual Scientific Meeting of the Gerontological Society of America (GSA '19)*, November 13-17, 2019, Austin, Texas, USA.

A Irimia, AS Maher, KA Rostowsky & NN Chaudhari (2019) Personalized connectome profiling for the rehabilitation of patients with neural injury and neurodegenerative disorder *96th Conference of the American Congress of Rehabilitation Medicine (ACRM'19)*, November 3-8, 2019, Chicago, IL

D Fan, NN Chaudhari, KA Rostowsky, M Calvillo, SK Lee, NF Chowdhury, F Zhang, LJ O'Donnell & **A Irimia** (2019) White matter integrity following post-traumatic cerebral micro-hemorrhages in the aging human brain *3rd Annual Conference on the Frontiers of Traumatic Brain Injury (FTBI '19)*, September 16, 2019, Institute of Neurology, University College & Imperial College, London, UK

Other publications, conference papers and presentations.

H Akrami, **A Irimia**, AA Joshi & RM Leahy (2020) Prediction of post-traumatic epilepsy using machine learning (under review)

Di Fan, Nikhil N. Chaudhari, Kenneth A. Rostowsky, Maria Calvillo, Sean K. Lee, Nahian F. Chowdhury, Fan Zhang, Lauren J. O'Donnell and **Andrei Irimia** (2019) White matter integrity following post-traumatic cerebral micro-hemorrhages in the aging human brain *Presentation at the Third Annual Conference on the Frontiers of Traumatic Brain Injury (Frontiers of TBI '19)*, September 16, 2019, Institute of Neurology, University College London and Imperial College London, UK.

A Irimia, D Fan, NN Chaudhari, V Ngo, F Zhang, SH Joshi & LJ O'Donnell (2019) Mapping cerebral connectivity changes after mild traumatic brain injury in older adults using diffusion tensor imaging and Riemannian matching of elastic curves *IEEE Proceedings on Biomedical Imaging*, vol. 2020, pp. 1690-1693

- **Website(s) or other Internet site(s)**

Journal papers, conference publications and main results are disseminated online via the PI's official webpage on the website of the USC Leonard Davis School of Gerontology (www.gero.usc.edu) as well as through the PI's personal website (www.andrei-irimia.com), which is a mirror site of the official university webpage.

- **Technologies or techniques**

A novel algorithm for the automatic segmentation of cerebral microbleeds (CMBs) from SWI MRI was designed as part of this project. The algorithm steps have been published in a peer-reviewed publication.

- **Inventions, patent applications, and/or licenses**

Nothing to report.

- **Other Products**

The research activities resulted in the development of Matlab and Python programming code and software for the analysis of imaging data. This material is available from the PI upon request and will be made available to the public on GitHub or in a similar venue when the software product is mature.

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

Name:	Andrei Irimia, PhD
Project Role:	Principal Investigator
Researcher Identifier:	0000-0002-9254-9388
Nearest person month worked:	1
Contribution to Project:	Dr. Irimia oversees all aspects of the project and ensures regulatory compliance. He carries out and/or supervises all data analyses, publication efforts and dissemination activities.

Name:	Sean Mahoney
Project Role:	project scientist
Researcher Identifier:	Not available
Nearest person month worked:	12
Contribution to Project:	Mr. Mahoney contributed to the analysis of post-traumatic demyelination, as well as to the implementation of GM comparisons between TBI, AD and HC groups. He also contributed to the quantitative analysis, to the refinement and development of methods for image segmentation and to the interpretation of results.

Name:	Nahian Chowdhury
Project Role:	project scientist
Researcher Identifier:	Not available
Nearest person month worked:	4
Contribution to Project:	Mr. Chowdhury contributed to the assessment of white matter integrity from DTI data, to the quantitative analysis, to the refinement and development of methods for image segmentation and to the interpretation of results. He also assisted with data curation, and with the execution of computer programs. He was primarily responsible for structural connectomics analysis and visualization using connectograms.

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?

Nothing to report.

What other organizations were involved as partners?

Organization Name:	Harvard Medical School
Location of organization:	Cambridge, MA

Partner's contribution to the project:	Our collaborators at Harvard Medical School provided expertise and advice with our use of their freely available software for image analysis. This expertise was
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provided at no cost to our team. The Harvard team also contributed to the interpretation of our results and to our publication efforts.

Organization Name: University of California
Location of organization: Los Angeles, CA

Partner's contribution to the project: Our collaborators at UCLA provided expertise and advice with our use of their freely available software for Riemannian curve matching. This expertise was provided at no cost to our team. The UCLA team also contributed to the interpretation of our results and to our publication efforts.

8. SPECIAL REPORTING REQUIREMENTS

COLLABORATIVE AWARDS: Not applicable (this is not a collaborative award).

QUAD CHARTS: The updated quad chard is attached to this progress report.

9. APPENDICES:

A selection of the peer-reviewed papers which have been submitted, accepted and/or published in Y2 are included on the subsequent pages of this progress report.

TBI-related risk factors for Alzheimer's disease

AZ170072

W81XWH-18-1-0413



PI: Andrei Irimia, PhD

Org: University of Southern California

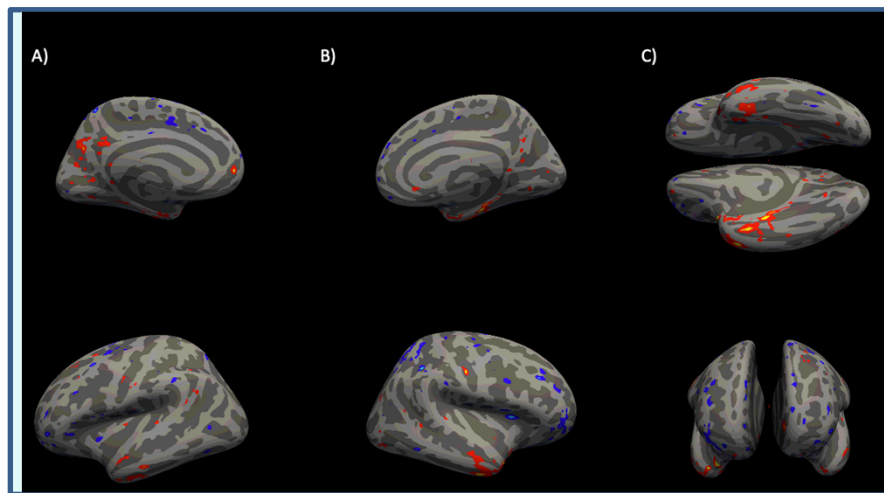
Award Amount: \$371,250.00

Study/Product Aim(s)

Aim: to understand the differences between (1) the healthy aging brain, (2) the TBI-affected brain, (3) the AD- affected brain, and (4) the brain affected by both TBI and AD.

Approach

TBI/AD-tailored computational analyses of magnetic resonance imaging (MRI) and diffusion tensor imaging (DTI) volumes will provide volumetrics, morphometrics, connectomics, network topology and network-theoretic properties. Longitudinal differences in the trajectories of brain structure and connectomics in TBI-/AD- (i.e. healthy control), TBI+/AD-, TBI-/AD+ and TBI+/AD+ volunteers. A general linear model (GLMs) will be implemented to identify volumetric, morphometric and connectomic signatures present only in the brains of TBI survivors and whose properties are significantly correlated with the severity of their AD-like cognitive impairment and, potentially, with the likelihood of TBI survivors to develop this condition.



Functional correlation (FC) differences after TBI across younger vs. older adults. Colors indicate (anti)correlations (red and blue, respectively) associated with testing that younger TBI subjects' FCs are equal to those of older subjects. Sex and scan sites are regressed out..

Timeline and Cost

Activities	CY	18	19	20	21
Segmentation & connectomics					
Topological analysis & validation					
Statistical & reliability analysis					
Identification of AD biomarkers					
Estimated Budget (\$K)		\$21.9	\$75.0	\$75.0	\$53.1

Updated: 10/15/20

Goals/Milestones

CY18 Goal – Segmentation & connectomics

☒ Pathology identification ☒ Volumetrics & morphometrics

CY19 Goals – Topological analysis & validation

☒ Connectomics & topology analysis ☒ Connectomic differences between groups ☒ Validation ☒ Confirmation by clinicians

CY20 Goal – Statistical & reliability analysis

☒ Statistical analysis ☒ Reliability testing ☒ Revisions to methods ☒ Biomarker identification ☒ Internal validation of biomarker analysis

CY21 Goal – Identification of AD biomarkers

☒ Testing alternative hypotheses ☒ Manuscript redaction & publication

Budget Expenditure to Date

Projected Expenditure: \$247,500.00

Actual Expenditure: \$255,578.91



Acute cognitive deficits after traumatic brain injury predict Alzheimer's disease-like degradation of the human default mode network

Andrei Irimia · Alexander S. Maher ·
Nikhil N. Chaudhari · Nahian F. Chowdhury ·
Elliot B. Jacobs ·
the Alzheimer's Disease Neuroimaging Initiative

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Abstract Traumatic brain injury (TBI) and Alzheimer's disease (AD) are prominent neurological conditions whose neural and cognitive commonalities are poorly understood. The extent of TBI-related neurophysiological abnormalities has been hypothesized to reflect AD-like neurodegeneration because TBI can increase vulnerability to AD. However, it remains challenging to prognosticate AD risk partly because the functional relationship between acute posttraumatic sequelae and chronic AD-like degradation remains elusive. Here, functional magnetic resonance imaging (fMRI), network theory, and machine learning (ML)

are leveraged to study the extent to which geriatric mild TBI (mTBI) can lead to AD-like alteration of resting-state activity in the default mode network (DMN). This network is found to contain modules whose extent of AD-like, posttraumatic degradation can be accurately prognosticated based on the acute cognitive deficits of geriatric mTBI patients with cerebral microbleeds. Aside from establishing a predictive physiological association between geriatric mTBI, cognitive impairment, and AD-like functional degradation, these findings advance the goal of acutely forecasting mTBI patients' chronic deviations from normality along AD-like functional trajectories. The association of geriatric mTBI with AD-like changes in functional brain connectivity as early as ~6 months post-injury carries substantial implications for public health because TBI has relatively high prevalence in the elderly.

Andrei Irimia and Alexander S. Maher contributed equally to this work.

Data used in preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). As such, the investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in the analysis or writing of this report. A complete listing of ADNI investigators can be found at: http://adni.loni.usc.edu/wp-content/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf

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Keywords Alzheimer's disease · Traumatic brain injury · Default mode network · Resting state · Geriatrics · Functional connectome

Introduction

Traumatic brain injury (TBI) can result in functional brain alterations causing neural and cognitive deficits [1, 2]. Even after mild TBI (mTBI), any cognitive domain can be affected by such deficits [3], whose manifestation may accelerate the onset of mild cognitive impairment (MCI) [4, 5], particularly in geriatric patients [6]. Although neurotrauma increases the risk for

Alzheimer's disease (AD) [7], there is little knowledge on how TBI affects functional trajectories and gives rise to neuropathophysiology. Furthermore, the relationship between TBI severity and AD-like brain dysfunction is poorly understood, and the mechanisms whereby TBI can elicit functional abnormalities which increase AD risk remains unclear. One hypothesis is that posttraumatic functional changes exhibit patterns which progressively resemble those of AD [5, 8, 9]; if this is the case, characterizing AD-like brain alterations after TBI could assist in improving AD risk assessment and the early identification of TBI patients at higher risk for this disease.

The default mode network (DMN) is a large-scale brain network which is most commonly active when a person is at wakeful rest [10]. In this resting state (RS), individuals lie quietly awake without performing tasks or being exposed to stimuli, and their DMN activity can be recorded using techniques like functional magnetic resonance imaging (fMRI). RS fMRI recordings only require passive participation from study participants, such that the prospect of isolating AD prognosticators from such data is logistically and clinically appealing. Although DMN alterations have been quantified in both AD and TBI [11–13], whether and how posttraumatic DMN abnormalities reflect AD-like functional degradation remains unknown. Because the DMN includes some of the longest white matter tracts in the brain (including tracts which integrate brain activity across the corpus callosum) [14], this network is particularly vulnerable to diffuse axonal injury after trauma [15]. Thus, studying TBI-related alterations in the DMN of subjects with cerebral microbleeds (CMBs, which are biomarkers of non-focal axonal injury [16])—as opposed to changes in other, less broadly distributed networks—is attractive. To identify posttraumatic biomarkers of AD risk, focusing on mTBI is appealing because the mTBI population is considerably larger, more homogeneous, and logistically easier to study than that of patients with moderate-to-severe TBI. Additionally, geriatric TBI is a promising setting for studying how this condition can lead to AD-like neural degradation because the comparison of AD patients to young or middle-aged TBI patients is confounded by aging effects.

This study leverages fMRI recordings acquired from healthy controls (HCs), geriatric mTBI participants with CMBs, and AD patients to provide evidence that, within ~ 6 months post-mTBI, functional connectivity (FC) within the DMN exhibits deviations from normality

whose spatiotemporal properties are statistically indistinguishable from those of similar deviations observed in AD. A linear combination of *acute* posttraumatic cognitive scores is found to be significantly and sensitively associated with *chronic* AD-like RS DMN alterations. Additionally, a supervised machine learning (ML) classifier is found to accurately identify mTBI patients with relatively broad *chronic* abnormalities in the DMN based on *acute* cognitive performance. These findings establish a detailed functional and connectomic relationship between mTBI-related acute cognition and AD-like DMN features, whose further characterization may facilitate the early identification of geriatric mTBI patients with CMBs at relatively high risk for AD.

Methods

Participants

This study was conducted with the Institutional Review Board approval. Included were one HC group ($N_1 = 48$, 22 females; age: $\mu = 69$ y, $\sigma = 5$ y, range: 58–79 y) and two study groups: geriatric mTBI ($N_2 = 29$, 13 females; age: $\mu = 68$ y, $\sigma = 6$ y; range: 57–79 y) and AD ($N_3 = 37$, 19 females; age: $\mu = 70$ y, $\sigma = 8$ y; range: 55–84 y). HC and AD subjects were selected from the AD Neuroimaging Initiative (ADNI) cohort, whose eligibility criteria are described elsewhere [17]. A total of 15 HC volunteers (31%), 9 TBI participants (38%), and 17 AD patients (46%) were hypertensive. Some ADNI participants were receiving hormonal treatment (HC: $N = 14$ or 29%; AD: $N = 9$ or 24%); some were taking medications for neurological and/or psychiatric disease (HC: $N = 20$ or 42%; TBI: $N = 18$ or 62%; AD: $N = 36$ or 97%), vascular disease (HC: $N = 29$ or 60%; TBI: $N = 19$ or 65%; AD: $N = 22$ or 59%), or metabolic disease (HC: $N = 6$ or 13%; TBI: $N = 3$ or 10%; AD: $N = 5$ or 14%). To be included, all participants had to have Montreal Cognitive Assessment (MoCA) scores and a complete session of RS fMRI data. HC participants had been clinically evaluated as having normal cognition; their MoCA scores ranged from 22 to 29 ($\mu = 26$, $\sigma = 2$). AD patients' scores ranged from 6 to 25 ($\mu = 17$, $\sigma = 5$), and all had a clinical AD diagnosis; TBI participants' scores were acquired within 48 h post-injury and were between 20 and 29 ($\mu = 23$, $\sigma = 2$). The Mini-Mental State Examination (MMSE) scores were available for both HC ($\mu = 29$, $\sigma = 1$; range: 26 to 30), TBI volunteers ($\mu = 22$,

$\sigma = 7$; range: 13 to 29), and AD participants ($\mu = 20$, $\sigma = 5$; range: 9 to 28). AD patients had Clinical Dementia Rating (CDR) sub-scores between 2 and 17 ($\mu = 6$, $\sigma = 4$), while HCs had CDR sub-scores between 0 and 2 ($\mu = 1$, $\sigma = 0.7$); CDR scores were not available for TBI participants. For HCs, the number of apolipoprotein E (ApoE) $\epsilon 4$ alleles was zero for 54% of the sample, one for 31%, and two for 15%. For AD patients, 24% had no $\epsilon 4$ alleles, 46% had one, and 30% had two. No ApoE allele information was available for TBI participants. TBI volunteers had fMRI recordings acquired ~ 6 months post-injury ($\mu = 5.6$ months, $\sigma = 0.5$ months) at 3 T, i.e., the same scanner field strength as the HC and AD participants. They had to have (a) a TBI due to a fall, (b) no clinical findings on acute T_1/T_2 -weighted MRI, (c) no clinical findings other than CMBs on susceptibility-weighted imaging (SWI), (d) an acute Glasgow Coma Scale score greater than 12 ($\mu = 13.7$, $\sigma = 0.5$) upon initial medical examination, (e) loss of consciousness of fewer than 30 min ($\mu \approx 4$ min, $\sigma \approx 8$ min), (f) posttraumatic amnesia of fewer than 24 h ($\mu \approx 3.5$ h, $\sigma \approx 3.2$ h), and (g) a lack of clinical history involving pre-traumatic neurological disease, psychiatric disorder, or drug/alcohol abuse. CMBs were identified in each subject using an automatic algorithm for CMB segmentation [18] and the validity of the findings were confirmed by two human experts with training in CMB identification from SWI, who had been blinded to automatic segmentation results. Disagreements between these experts were resolved by a third one (AI). Null hypotheses of group differences in age and cognition were tested using Welch's two-tailed t test for samples with unequal variances. The null hypothesis of independence between sex and group membership was tested using Pearson's χ^2 test. Effect sizes were quantified using Cohen's d for Welch's t test and the ϕ coefficient for Pearson's χ^2 test.

Neuroimaging

HC and AD participant data used in the preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (<http://adni.loni.usc.edu>). ADNI was launched in 2003 as a public-private partnership, led by Principal Investigator Michael W. Weiner, MD. The primary goal of ADNI has been to test whether serial MRI, positron emission tomography (PET), other biological markers, and clinical and neuropsychological assessment can be combined to

measure the progression of MCI and early AD. For up-to-date information, see www.adni-info.org. fMRI volumes were acquired at 3 T using the ADNI acquisition protocol [19]. An average of 140 fMRI volumes was obtained using the following parameters: $T_R = 3$ s; $T_E = 30$ ms; flip angle = 80° ; slice thickness ≈ 3.3 mm; 48 slices). TBI subjects' fMRI data were acquired in a Siemens Trio TIM 3 T scanner using an acquisition protocol very similar to the ADNI protocol.

Preprocessing

fMRI analysis was implemented using the FreeSurfer (FS) Functional Analysis Stream (FS-FAST, <https://surfer.nmr.mgh.harvard.edu/fswiki/FsFast>) with default parameters for (a) motion correction, (b) frame censoring, (c) frequency filtering, (d) brain masking, (e) intensity normalization, (f) co-registration of fMRI volumes to T_1 -weighted volumes, (g) surface sampling to the FS atlas, (h) smoothing (kernel with full width of 5 mm at half maximum), (i) surface and volume sampling to the Montreal Neurological Institute (MNI) atlas containing 305 subjects, and (j) smoothing for subcortical structure analysis. The first four volumes in each fMRI time series were discarded to preserve signal equilibrium and to account for each participant's adaptation to the sequence; the rest were used for analysis [20]. Nuisance variables (cerebrospinal fluid, white matter, and motion correction parameters) were accounted for using FS-FAST.

fMRI seeds

Seeds were derived in a two-step process. In the first step, the cortical delineation of the DMN defined by Yeo et al. [14] was used to parcel the cortex. This delineation includes the following cortical regions: (a) *frontal* (prefrontal cortex, precentral ventral cortex, anterior cingulate cortex, etc.), (b) *medial temporal/retrosplenial* (the parahippocampal complex), (c) *lateral temporal* (the inferior temporal gyrus and superior temporal sulcus), (d) *lateral parietal* (inferior parietal, intraparietal regions, etc.), and (e) *medial parietal/posterior cingulate* (posterior cingulate cortex and part of the precuneus). In the second step, Yeo regions were divided into gyral/sulcal parcels based on the intersection of the Yeo regions with the cortical parcellation scheme of Destrieux et al. [21]. In other words, the final

set of fMRI seeds consisted of all the regions which resulted from the intersection of the Yeo and Destrieux schemes. This was deemed to provide greater spatial detail to the analysis, particularly for DMN regions with substantial cortical coverage (e.g., the frontal DMN, which includes a large contiguous portion of cerebral cortex). The intersection of the Destrieux and Yeo schemes led to the delineation of 46 DMN regions (22 cortical regions and the hippocampus for each hemisphere; see caption to Fig. 1).

FC analysis

Both within each subject's space and within MNI space, individual fMRI time series s were consolidated using `isxconcat-sess`. A weighted least-squares (WLS) general linear model (GLM) was implemented using `mri_glmfit` to identify pairs of anatomic regions (i, j) whose fMRI signals s_i and s_j had a statistically significant partial correlation ρ_{ij} . For each DMN seed parcel i , a subject-level, voxel-wise analysis was implemented to identify spatially contiguous clusters in target region j ($i \neq j$) within which ρ_{ij} is significant. How ρ_{ij} differed in each study group (TBI or AD) relative to HC was investigated using the same GLM. Effect sizes were quantified using Cohen's f^2 .

Equivalence testing

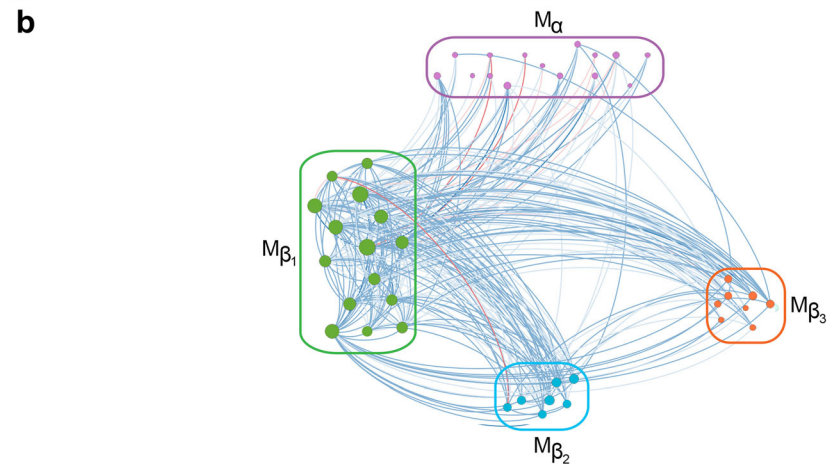
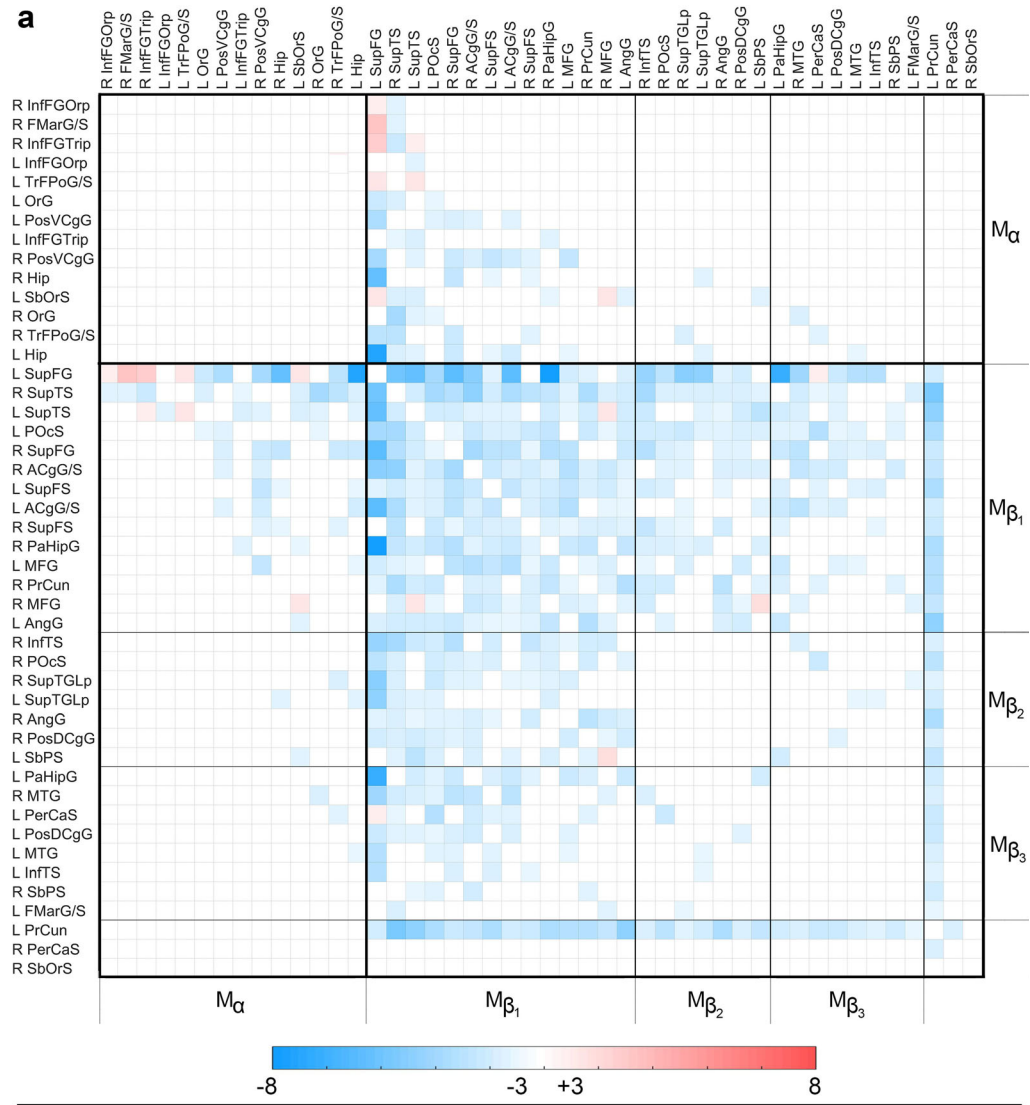
One key premise of this study is that brain features which are both (a) significantly different from HCs in both TBI and AD and (b) significantly similar across TBI and AD can be said to be *AD-like*. Thus, a brain feature observed in TBI patients can be said to be AD-like if the feature in question differs from HCs in both TBI and AD and is also significantly similar across both TBI and AD. If ρ_{ij} differs significantly from HCs in both TBI and AD, a null hypothesis of *statistical equivalence* can be tested to determine whether ρ_{ij} is AD-like. Formally, for two samples A and B , a null hypothesis of equivalence can be stated as $\mu_A(\rho_{ij}) \neq \mu_B(\rho_{ij})$ rather than as the conventional null hypothesis $\mu_A(\rho_{ij}) = \mu_B(\rho_{ij})$. The null hypothesis of equivalence fails to be accepted if the two means fall within the interval $(-\delta, \delta)$, where δ is the equivalence margin of the test [22]. In statistical parlance, equivalence implies that the correlations $\rho_{ij}(A)$ and $\rho_{ij}(B)$ are sufficiently close that neither can be considered greater or smaller than the other [23]. Equivalence hypotheses can be tested using the two one-sided t tests (TOSTs) [24]; in this study, δ is assigned a

conservative value equal to 0.2 times the width of the 95% confidence interval for the difference $\mu_A(\rho_{ij}) - \mu_B(\rho_{ij})$. To identify TBI and AD participants' correlations which deviate appreciably from normality (i.e., from the HC group) in both former groups, the null hypothesis of equivalence is only tested if both $\mu_{TBI}(\rho_{ij})$ and $\mu_{AD}(\rho_{ij})$ differ significantly from $\mu_{HC}(\rho_{ij})$. Effect sizes were quantified using Cohen's f^2 . Multiple comparison corrections using 300 permutations and a cluster-wise p -value threshold of 0.05 were implemented for all statistical tests. Equivalence testing was implemented using the freely available MATLAB software (<https://www.mathworks.com/matlabcentral/fileexchange/63204>).

(Dis)similarity matrices

Two *dissimilarity matrices* $D(TBI, HC)$ and $D(AD, HC)$ were assembled to describe mean differences in ρ_{ij} between HCs and each of the study groups (TBI and AD), respectively. Each matrix element $D_{ij}(TBI, HC)$ is set to the value of the t statistic for the test of the null

Fig. 1 (A) The dissimilarity matrix $D(HC, TBI)$ displays significant differences in the FC ρ between the HC and mTBI groups. Each cell $D_{ij}(HC, TBI)$ encodes the result of testing the null hypothesis of no mean difference in ρ_{ij} between groups. Cells corresponding to region pairs for which the null hypothesis fails to be rejected are drawn in white. Elsewhere, the color-coded quantity is a t statistic with 75 df. If $\rho_{ij}(TBI) > \rho_{ij}(HC)$, t is positive and D_{ij} is drawn in red; otherwise, t is negative and D_{ij} is drawn in blue. Boundaries between M_α and M_β are delineated by thick black lines; boundaries between the submodules of M_β are delineated by thinner lines. Regions are labeled using the connectogram abbreviations of Irimia et al. [64]. Frontal regions are the FMarG/S, InfFGOrp, InfFGTrip, MFG, OrG, SbOrS, SupFG, SupFS, and TrFPoG/S; limbic regions are the ACgG/S, PerCaS, PosDCgG, and PosVCgG; temporal regions are the InfTS, PaHipG, SupTGLp, and SupTS; parietal regions are the AngG, POcS, PrCun, and SbPS. (B) Graph representation of $D(HC, TBI)$. Nodes are color-coded and grouped by module. Edge colors encode t score values, according to the color bar in (A). Abbreviations: R, right; L, left; Hip, hippocampus. Cortical region abbreviations: ACgG/S, anterior cingulate gyrus and sulcus; AngG, angular gyrus; FMarG/S, frontomarginal gyrus and sulcus; InfFGOrp, inferior frontal gyrus, orbital part; InfFGTrip, inferior frontal gyrus, triangular part; InfTS, inferior temporal sulcus; MFG, middle frontal gyrus; OrG, orbital gyrus; PaHipG, parahippocampal gyrus; PerCaS, pericallosal sulcus; POcS, parieto-occipital sulcus; PosDCgG, posterior dorsal cingulate gyrus; PosVCgG, posterior ventral cingulate gyrus; PrCun, precuneus; SbOrS, suborbital sulcus; SbPS, subparietal sulcus; SupFG, superior frontal gyrus; SupFS, superior frontal sulcus; SupTGLp, superior temporal gyrus, lateral part; SupTS, superior temporal sulcus; TrFPoG/S, transverse frontopolar gyrus and sulcus



hypothesis $\rho_{ij}(TBI) - \rho_{ij}(HC) = 0$, and a similar procedure is used for $D_{ij}(AD, HC)$. A *similarity matrix* $S(TBI, AD)$ was also calculated to describe significant statistical equivalences of ρ_{ij} across study groups. Each matrix element S_{ij} is set to the TOST t statistic which had the smallest magnitude.

Network analysis

To investigate DMN-related commonalities and differences between TBI and AD, three analyses were carried out. The first two involved studying $D(HC, TBI)$ and $D(HC, AD)$ to group DMN nodes based on how TBI modulated their correlation differences relative to HCs and ADs, respectively. The third one examined $S(TBI, AD)$ to identify DMN nodes affected equivalently in both TBI and AD. To identify network modules, the Louvain algorithm for community detection [25] was applied 100 times for each matrix to identify module partitions. The symmetric reverse Cuthill-McKee (RCM) ordering [26] of each module was then calculated to rearrange nodes within each module. This method permutes the rows and columns of a symmetric sparse matrix to form a band matrix with minimal bandwidth, i.e., whose nonzero elements are optimally close to the diagonal. The algorithm identifies a pseudo-peripheral vertex of the network, and then utilizes a breadth-first search to order vertices by decreasing distance from the pseudo-peripheral vertex. When applied to each module of S , such blocks are arranged along the main diagonal and produce a visual representation which facilitates module inspection and analysis. Network analysis was implemented using the freely available Brain Connectivity Toolbox (sites.google.com/site/bctnet).

Network randomization

To determine whether modules' node memberships were dependent upon the DMN parcellation scheme used in the study, the DMN was reparcelled randomly 100 times to generate alternative parcellations which had the same number of nodes as the original DMN but different cortical patches corresponding to each node. An approach similar to those of Gordon et al. [27] and Irimia and Van Horn [28] was used to obtain randomized parcellations of the DMN. Briefly, random points within the cortical coverage of the DMN were selected. From these seeds, parcels were simultaneously expanded outward on the cortical mesh until they met

either other parcels or the boundary of the DMN. The procedure for identifying network modules was implemented for each randomized parcellation, and the modularity structure of the network was found each time by applying the Louvain algorithm 100 times to each matrix. The spatial overlap between each original module and the randomized modules was quantified using the Sorensen-Dice coefficient [29].

Acute cognitive impairment vs. chronic brain function

A multivariate regression analysis was implemented to study the relationship between TBI patients' *acute* MoCA scores and the number of their *chronic* FCs which were statistically equivalent to those of AD patients. The latter involved region pairs with the largest absolute values of S_{ij} (highest similarity across TBI and AD): (a) the right superior temporal sulcus and the right anterior cingulate gyrus/sulcus, (b) the left and right superior frontal gyri, (c) the left hippocampus and superior temporal sulcus, and (d) the left middle frontal gyrus and the ventral part of the posterior cingulate gyrus. The predictor variables were the entries in S associated with these region pairs, and the response variable was the MoCA score. Sex, age at MRI acquisition, and educational attainment were included as covariates. Cohen's f^2 was used as a measure of effect size and the null hypothesis of overall regression was tested using Fisher's F test [30]. To confirm and to broaden regression findings, a support vector machine (SVM) was implemented in MATLAB (<http://mathworks.com>) with default parameters and using the iterative single data algorithm (ISDA), a linear kernel function, and a heuristically assigned kernel scale parameter. The SVM was trained and cross-validated tenfold to distinguish (a) TBIs with relatively *moderate* AD-like DMN deviations from normality (i.e., with 7 or fewer statistical equivalences across TBI and AD) from other TBIs and also (b) TBIs with relatively *extensive* abnormalities (i.e., with at least 15 equivalences) from other TBIs. Let N_E be the number of significant equivalences identified ($N_E = 22$ here, see Fig. 3). Then the threshold values of 7 and 15 correspond to $\lfloor N_E/3 \rfloor$ and $\lceil 2N_E/3 \rceil$, respectively (Fig. 3). For the SVM, the number of true negatives (TNs), true positives (TPs), false negatives (FNs), and false positives (FPs) was computed, as were the true positive rate (TPR, or sensitivity), true negative rate (TNR, or specificity), positive prediction value (PPV, or precision) and Matthews' correlation coefficient

(MCC) [31]. Regression and SVM analyses were implemented in MATLAB using the `glmfit`, `fitcsvm`, and `predict` functions.

Visualization

Matrices were visualized to identify and examine DMN modules (Fig. 1, Fig. 2, and Fig. 3). Matrix entries were thresholded by statistical significance; for example, if ρ_{ij} does not differ significantly between the groups compared, the cell for D_{ij} is drawn in white. Similarly, if ρ_{ij} does not differ significantly between TBI and AD, and the cell for S_{ij} is also drawn in white. For statistically significant results, dissimilarity matrix cells are drawn in either red or blue, depending on their sign (see the caption to Fig. 3). To facilitate inspection, the cortical regions within each module were drawn on an average atlas representation of the brain. Graph representations of each functional correlation matrix were also generated using Gephi software (<http://gephi.org>). In these, each region's node was depicted as a circle whose diameter was proportional to the number of cortical regions to which the region represented by the node was functionally connected. Similarly, edges were colored using shades of blue or red to reflect the t score of lowest magnitude associated with the TOSTs for statistical equivalence testing.

Results

Demographics

Three cohorts were studied: HC participants (48 subjects, 22 females; age $\mu \pm \sigma = 69 \pm 5$ years (y)), geriatric mTBI subjects with CMBs (29 subjects, 13 females; 68 ± 6 y), and AD patients (37 subjects, 18 females; 74 ± 8 y). Further demographic descriptors are provided in the “Methods” section. CMB counts were found to range from 0 to 43 ($\mu \pm \sigma = 13 \pm 9$) in HCs, from 0 to 89 ($\mu \pm \sigma = 17 \pm 14$) in mTBI volunteers, and from 0 to 6 ($\mu \pm \sigma = 1.0 \pm 1.7$) in AD patients. No significant differences in mean age were found between HC and TBI participants ($t = 0.52$, $df = 47$, $p = 0.60$, Cohen's $d = 0.36$), between HC and AD volunteers ($t = -0.95$, $df = 55$, $p = 0.17$, Cohen's $d = 0.16$), or between TBI and AD patients ($t = -1.24$, $df = 64$, $p = 0.11$, Cohen's $d = 0.46$). No significant differences in sex ratios were found

across groups ($\chi^2 = 0.22$, $df = 1$, $p = 0.90$, $\phi = 0.09$). Significant differences in MoCA scores were found between HC and acute TBI participants ($t = 5.7$, $df = 50$, $p < 0.001$, Cohen's $d = 1.50$), between HC and AD participants ($t = 9.0$, $df = 44$, $p < 0.001$, Cohen's $d = 2.36$), but not between acute TBI participants and AD patients ($t = 0.4$, $df = 61$, $p = 0.65$, Cohen's $d = 1.58$). Similarly, significant differences in MMSE scores were found between HC and acute TBI participants (Welch's $t = 5.4$, $df \approx 28.7$, $p < 0.001$, Cohen's $d = 1.2$), between HC and AD participants (Welch's $t = 10.8$, $df \approx 37.2$, $p < 0.001$, Cohen's $d = 2.7$), but not between acute TBI participants and AD patients (Welch's $t = 1.3$, $df \approx 48.7$, $p = 0.1$, Cohen's $d = 0.3$).

(Dis)similarity matrices and modularity

Participants' DMNs were delineated and then parcellated into gyri and sulci based on the morphometric boundaries between cortical structures, as previously described. For each pair of regions i and j , clusters of significant functional correlations ρ_{ij} were then identified. Two *dissimilarity matrices* $D(TBI, HC)$ and $D(AD, HC)$ were computed to quantify significant mean differences in ρ_{ij} between HC and each of the study groups (TBI and AD, respectively). A *similarity matrix* $S(TBI, AD)$ was also calculated to describe significant statistical equivalences of ρ_{ij} across TBI and AD. Both similarity and dissimilarity were quantified using Student's t scores (see Methods).

To determine which brain regions are similarly vulnerable to TBI- and to AD-related deviations from normality (i.e., from HCs), network modules were identified within each (dis)similarity matrix. For reproducibility, the dependence of module composition upon the anatomy-based parcellation scheme was also explored. This was done by repartitioning the DMN randomly and repeatedly to create alternative parcellations which had the same number of nodes—but different spatial configurations—as the original, anatomy-based parcellation. The process of identifying network modules was then repeated for each of these randomized parcellations. At every iteration, DMN modules were identified in each dissimilarity matrix; the number N_R of randomized modules ($\mu \pm \sigma = 2.01 \pm 0.3$) was not found to differ significantly from the number of modules N_A obtained using the anatomic parcellation ($N_A = 2$; Student's $t > 0.37$, $df = 99$, Cohen's $d = 0.03$). Furthermore, the original and randomized modules overlapped spatially with high consistency across the 100

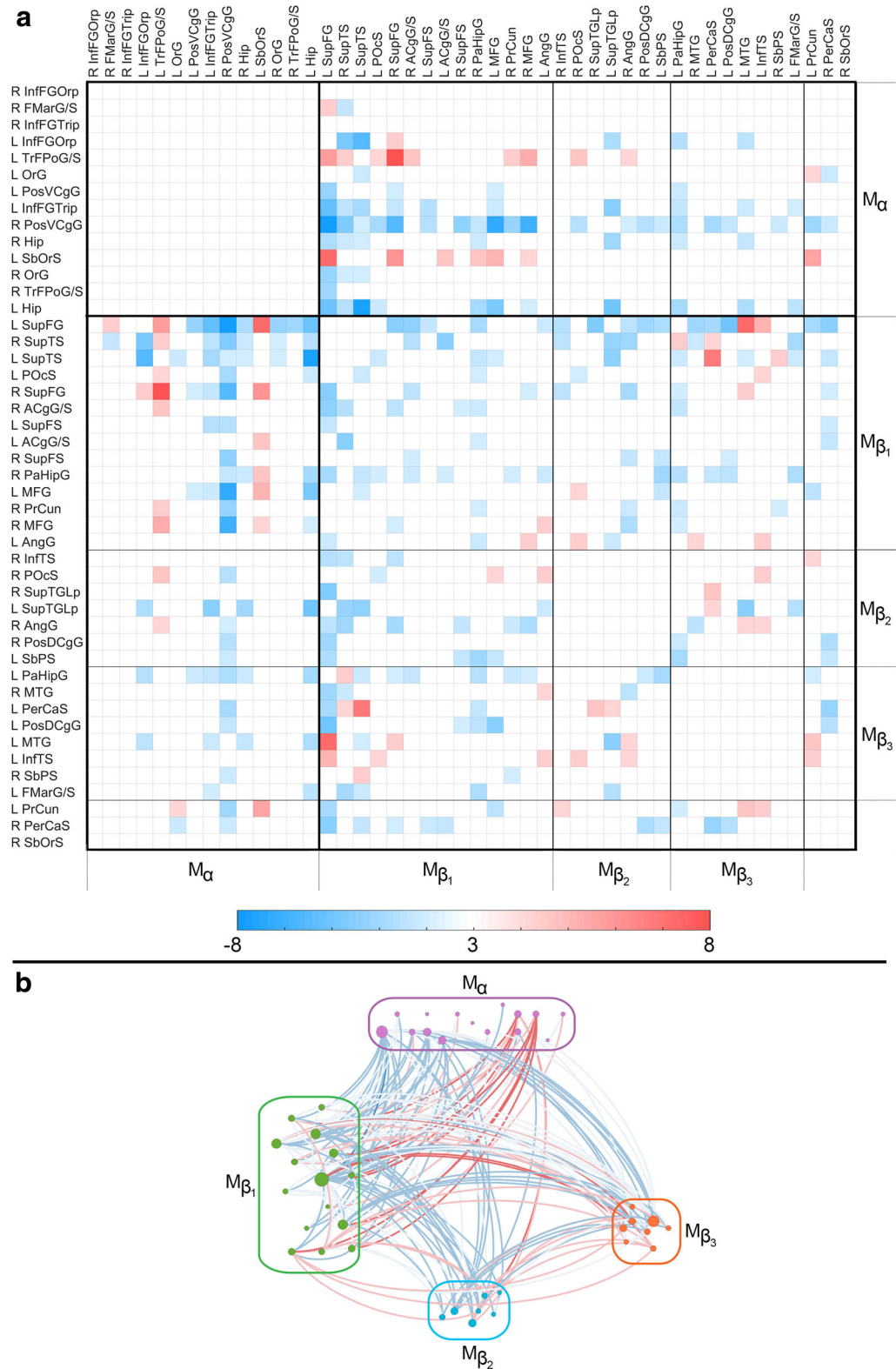


Fig. 2 Like Fig. 1, for $D(HC, AD)$. The color-coded quantity is a t statistic with 82 df . See the caption of Fig. 1 for abbreviations

randomizations (Sørensen-Dice coefficient $\mu \pm \sigma = 0.94 \pm 0.06$; 95% CI = [92.89, 95.10]). Thus, the randomized modules' nodal memberships and spatial coverages agreed with those of the original modules.

DMN modules in mTBI versus HC

RCM orderings [26] were used to display modules along the main diagonal of each (dis)similarity matrix. The RCM-ordered modules of $D(HC, TBI)$ and $D(HC, AD)$ are displayed in Fig. 1 and Fig. 2, respectively, as are the graph representations of the corresponding dissimilarity matrices. M_α , the first module common to both $D(HC, TBI)$ and $D(HC, AD)$, includes (a) the hippocampus, (b) ventral and dorsal prefrontal cortex, and (c) the ventral aspect of the posterior cingulate gyrus. Significant functional correlations between nodes within M_α do not differ significantly across TBI and HC (Fig. 1); this may indicate that, on average, the geriatric mTBI patients did not experience substantial FC alterations within brain areas covered by M_α within the first ~ 6 months post-injury. M_β , the second module along the diagonal of $D(HC, TBI)$, contains all the DMN regions outside M_α . Within M_β , correlations are consistently weaker in mTBI participants relative to HCs. Furthermore, the superior frontal gyrus and precuneus are found to be the two structures whose TBI-related FC deviations from normality are the broadest across the DMN. FC differences between TBI and HC involve relatively few pathways connecting M_α and M_β . Thus, although M_α connections are considerably less affected by TBI compared with M_β , some pathways between these modules are not.

DMN modules in AD versus HC

Whereas FC is typically weaker in TBI than in HC (Fig. 1), AD patients' FC deviations from normality vary considerably (Fig. 2). These deviations can be grouped into five modules which occur bilaterally; the first is identical to M_α and the rest are subdivisions of M_β (M_{β_1} through M_{β_4}). Across AD and TBI, M_α , M_{β_3} , and M_{β_4} are similar in that their intramodular FCs do not differ significantly from those of HC participants. M_{β_1} is a frontotemporal module with relatively few intramodular FC differences between AD and HC but with considerably more differences of this kind involving intermodular connections. M_{β_2} contains broadly distributed frontal, limbic, and parietal regions; comparing the HC and AD groups from the standpoint

of correlations within M_{β_2} reveals sparse group differences involving both intra- and intermodular connections. Like in the case of M_α , AD patients' M_{β_3} and M_{β_4} modules do not have intramodular correlations which differ significantly from HC, although both subunits exhibit numerous such differences involving intermodular connections.

DMN modules in TBI versus AD

Figure 3 displays the similarity matrix $S(TBI, AD)$ and its graph representation to identify regions with statistical equivalences across study groups. Regions exhibiting such similarities involve the dorsolateral prefrontal cortex, the lateral temporal lobe, and the ventral aspect of the posterior cingulate gyrus. The hippocampus is topologically proximal to the latter two areas; furthermore, hippocampo-cortical correlations are substantially affected in both TBI and AD. Nevertheless, only few hippocampo-cortical correlations are statistically equivalent across these conditions. The strongest similarities between TBI and AD involve connectivity between the lateral temporal lobe and anterior cingulate cortex, as well as between dorsolateral prefrontal cortex and each of the following three structures: the hippocampus, the lateral temporal lobe, and the posterior cingulate cortex.

Acute cognition versus chronic DMN in TBI

Upon testing the association between MoCA scores and the number of FC similarities (i.e., pairwise statistical equivalences) between TBI and AD, the null hypothesis of the test for overall multivariate regression was rejected ($F = 1.6$, $df_1 = 5$, $df_2 = 111$, $p < 0.0034$, Cohen's $f^2 = 0.39$). In other words, this test rejected the null hypothesis according to which there was no multivariate correlation between (a) MoCA scores and (b) the number of FC similarities involving TBI and AD. To study further the relationship between acute cognition and chronic DMN dysfunction, two support vector machines (SVM) were used. The first one was trained on 50% of each cohort to distinguish TBI participants with relatively *moderate* AD-like DMN deviations from normality (i.e., with 7 or fewer statistical equivalences across TBI and AD) from other TBI participants. Another SVM was trained on 50% of each sample to distinguish TBI participants with relatively *extensive* abnormalities (i.e., with 15 or more equivalences) from the rest of the TBI participants. The means and standard deviations for the number of TNs, TPs, FNs,

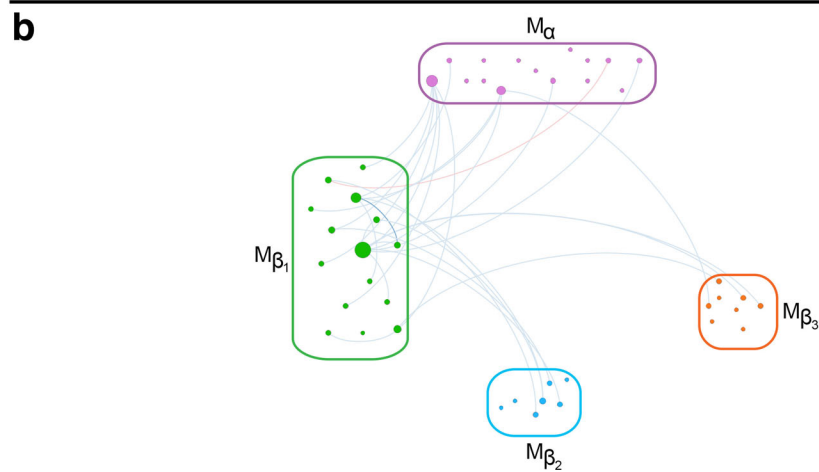
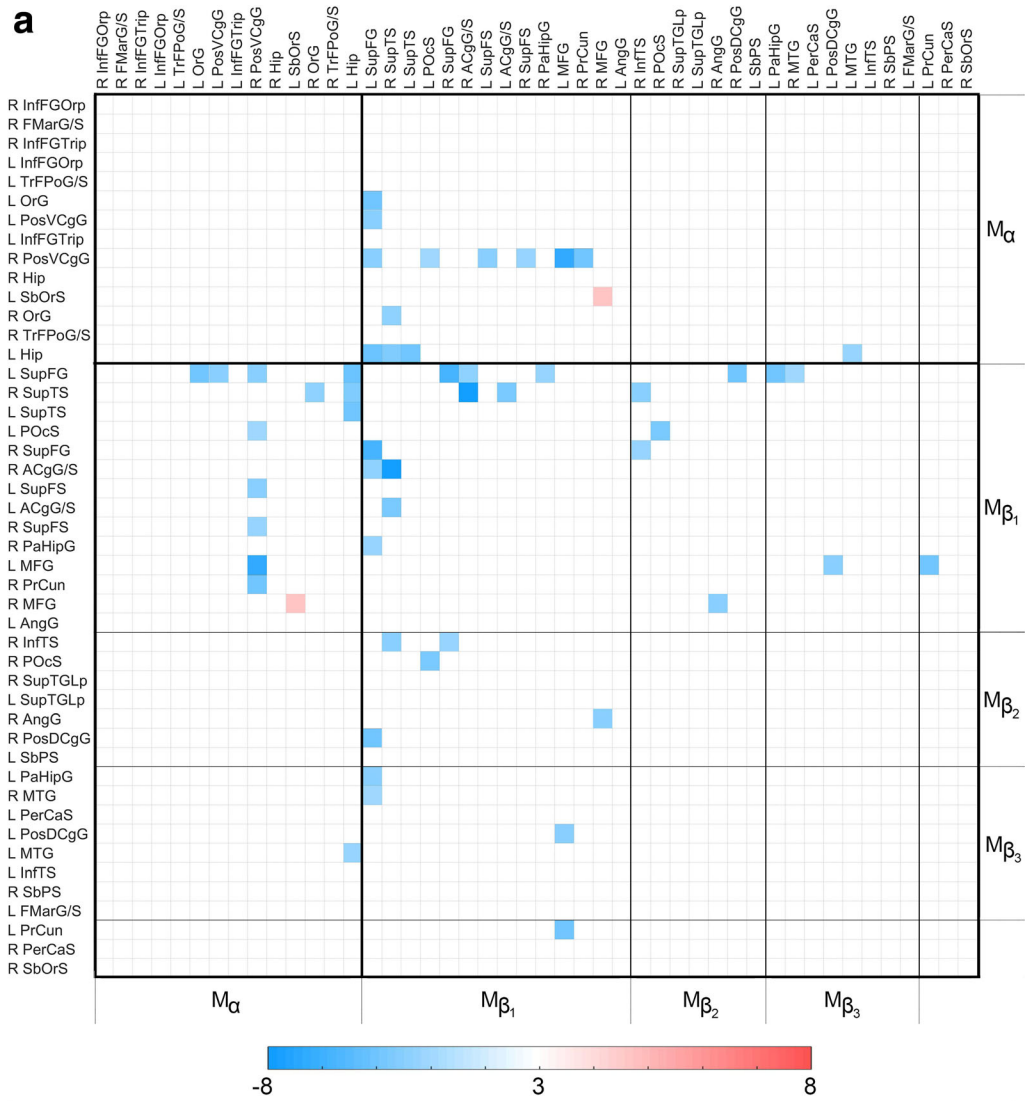


Fig. 3 The similarity matrix $S(TBI, AD)$ displays statistically significant equivalences of functional correlation ρ between the TBI and AD groups. Each cell S_{ij} encodes the result of testing the null hypothesis of equivalence in ρ_{ij} across these two groups. This null hypothesis is only tested if both TBI and AD differ significantly from HC. In other words, if there is no significant mean difference in ρ between either (a) HC and TBI and/or (b) HC and AD, S_{ij} is drawn in white. If both study groups differ from the HC group but no significant statistical equivalence is found across TBI and AD, S_{ij} is also drawn in white. Elsewhere, the color-coded quantity is the value of the TOST procedure's t statistic with the smallest magnitude. The color-coded quantity is a t statistic with 63 df . If a statistical equivalence is associated with a relatively stronger correlation in both TBI and AD relative to HC, t is positive and S_{ij} is drawn in red; if the correlation is weaker relative to HC, t is negative and S_{ij} is drawn in blue. Boundaries between M_α and M_β are delineated by thick black lines; boundaries between the submodules of M_β are delineated by thinner lines. See the caption of Fig. 1 for abbreviations. (B) Graph representation of $S(TBI, AD)$. Nodes are color-coded and grouped by module. Edge colors encode t score values, according to the color bar in (A)

and FPs were computed, as were their TPRs (i.e., sensitivities), TNRs (i.e., specificities), PPVs (i.e., precisions), and MCCs. Across 100 scenarios, the SVM trained to identify TBI patients whose similarities to AD were relatively modest (7 or fewer equivalences) achieved the following means and standard deviations: $TN = 18.0 \pm 0.8$; $TP = 9.0 \pm 0.6$; $FN = 1.0 \pm 0.6$; $FP = 1.0 \pm 1.0$; $TPR = 0.90 \pm 0.06$; $TNR = 0.95 \pm 0.06$; $PPV = 0.91 \pm 0.1$; and $MCC = 0.85 \pm 0.1$. The SVM trained to predict which TBI patients' similarities to AD were relatively broad (15 or more equivalences) yielded the following results: $TN = 17.1 \pm 0.7$; $TP = 10.0 \pm 0.7$; $FN = 0.9 \pm 0.7$; $FP = 1.1 \pm 1.0$; $TPR = 0.9 \pm 0.1$; $TNR = 0.95 \pm 0.1$; $PPV = 0.9 \pm 0.1$; and $MCC = 0.86 \pm 0.1$. Figure 4A displays cortical maps of M_α and M_β on the surface of an average brain atlas, contrasting the fact that M_α includes primarily frontal regions whereas M_β includes the rest of the DMN. Figure 4B displays DMN parcels whose *chronic* DMN similarities across TBI and AD were accurately predicted from *acute* MoCA scores using the two SVMs. These regions include areas of the dorsolateral prefrontal, lateral temporal, posterior cingulate, and parahippocampal cortices.

Discussion

Significance

mTBI patients with relatively high rates of neural degradation may be at commensurately high risk for AD,

and the estimation of such risk can be assisted by knowledge of how TBI modifies brain function along AD-like trajectories. Thus, an important indication of this study is that the DMNs of geriatric mTBI patients can exhibit distinct patterns of AD-like RS FC as early as ~ 6 months post-injury. If this is the case, our finding highlights older adults' substantial vulnerability to TBI [32] and may be unsurprising given that the highest incidence of TBI is in older adults [5], where even injuries of mild severity can increase AD risk [8]. An alternative, more general interpretation is that geriatric mTBI patients exhibit RS FC patterns which may occur in several neurodegenerative diseases among which AD can be counted.

The outcome of the test of overall regression indicates a significant, inverse association between TBI patients' *acute* MoCA scores and the extent of their *chronic* DMN similarities to AD. This outcome is confirmed by the SVM classifications, which achieved sensitivities and specificities which compare favorably with those for blood and imaging biomarkers of AD [33]. Our results may be useful for predicting the risk of AD-like functional degradation after TBI because mTBI patients' acute cognitive scores are predictive of their AD-like DMN features. Thus, our study is significant in three distinct ways. Firstly, it identifies a set of functional DMN features which are common to both geriatric mTBI and AD. Secondly, it demonstrates that the analysis of RS FC in the DMN using the present approach can reveal the extent to which mTBI-affected function may transition onto AD-like trajectories. Thirdly, it suggests that, if AD-like abnormalities are indeed commensurate to mTBI patients' AD risk, the DMN features described here can be used to improve AD risk estimation. An alternative and potentially broader implication is that our results can be used to improve risk estimation not only in AD but also in other neurodegenerative conditions whose brain degradation patterns resemble those of AD in their early stages.

Connectomic pathophysiology

Although DMN subdivisions have been mapped with high stability across health and disease [14], such subunits' relative vulnerability to TBI is not well understood. An intriguing finding of this study is that the node memberships of M_α , M_{β_2} , and M_{β_4} are consistently similar across the TBI and AD groups (Fig. 1 and

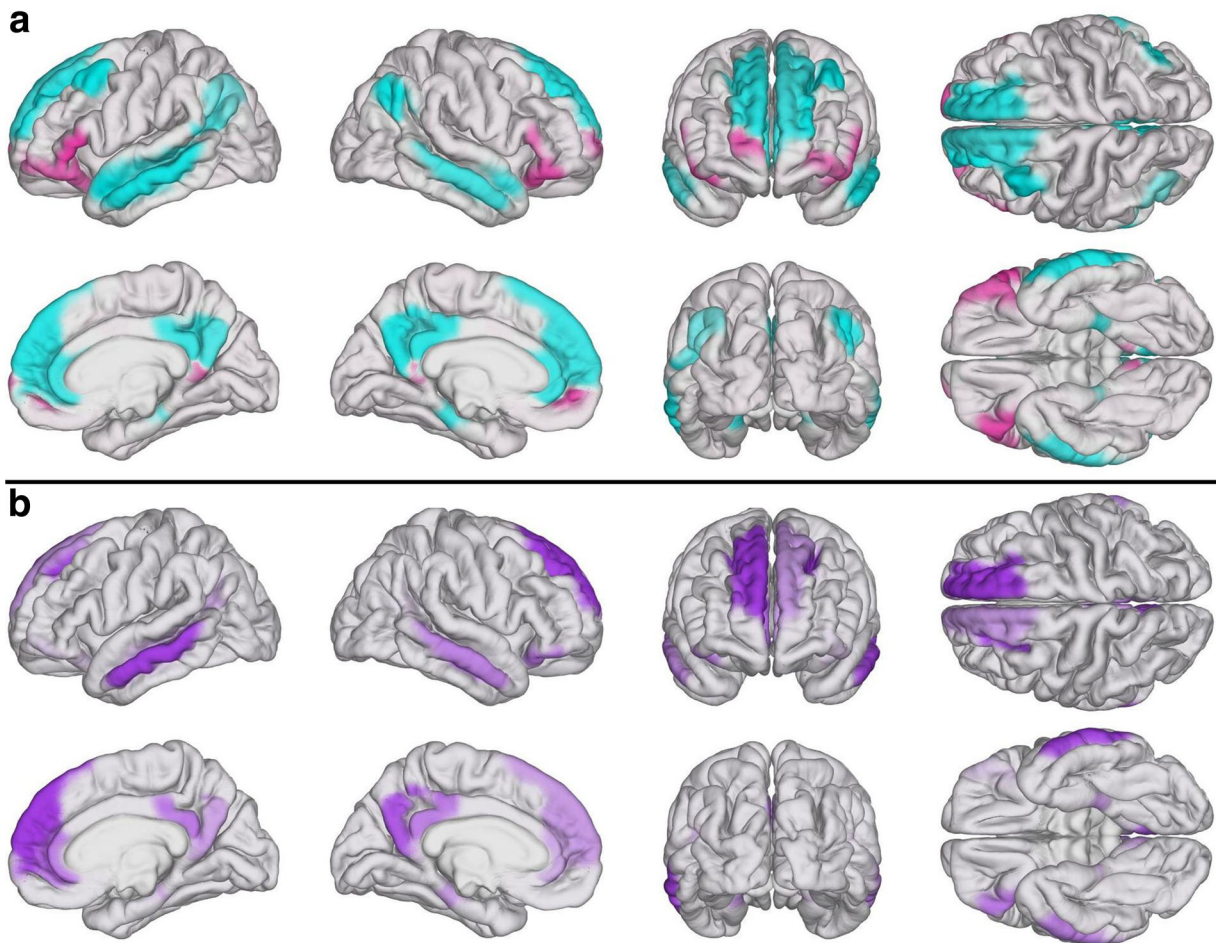


Fig. 4 Cortical maps of DMN modules. (A) M_α (magenta) and M_β (cyan) mapped on the surface of an average brain atlas. (B) TBI-affected brain regions in $S(TBI, AD)$ (see Fig. 3) whose *chronic* similarity to AD was predicted based on *acute* cognitive scores using SVMs

Fig. 2). The probability of such an occurrence being due to chance is low given the results of our randomization analysis and the fact that the modules of each dissimilarity matrix were identified independently of one another. Instead, it is more likely that this likeness of modularity could be due to intrinsic properties of the DMN which modulate their susceptibility to TBI and AD, and perhaps even to neurodegenerative processes in general.

M_α contains primarily fronto-hippocampo-limbic connections. For this reason, the existence of modular structure resemblances between TBI and AD may imply that both conditions impact intermodular connections within M_α , M_{β_2} , and M_{β_4} in ways which are substantially different from how they affect the rest of the DMN. Since the three modules are distinct, however,

their existence may also indicate that, although FC within DMN subunits can be robust to geriatric mTBI, such robustness can manifest itself in distinct ways via mechanisms which are yet to be determined. Although appealing, the task of exploring such network-theoretic differences between DMN subunits could not be undertaken adequately here due to the small effect sizes implied by such differences. More specifically, such minute effect sizes require commensurately large samples to avoid high probabilities for errors of type I and/or II when contrasting module properties across groups. Thus, future research should aim further to study DMN similarities between TBI and AD.

The properties of the M_α module summarized in Fig. 1 and Fig. 2 suggest that geriatric mTBI affects certain FCs between frontal, limbic, and

hippocampal areas in ways which differ from those pertaining to other DMN regions. This is perhaps unsurprising given that many frontal areas experience atrophy as early as middle age [34] and that the frontal lobe appears to exhibit distinct trajectories in TBI compared with AD [35–37]. On the other hand, although FC involving the hippocampus and cingulate areas is sensitive to both TBI and AD from the early stages of both conditions [38–40], their interactions within the RS DMN remain poorly understood and require further research. Interestingly, only very few hippocampocortical connectivity alterations were found to be statistically similar across AD and mTBI (Fig. 3), despite such connections being significantly affected by both conditions. This may suggest that geriatric mTBI and AD affect this connectivity ensemble in different ways and that the functional abnormalities observed in this study might be associated with dissimilar functional trajectories within DMN modules during posttraumatic neurodegeneration. Here it is important to remind the reader of the aphorism according to which “absence of evidence is not evidence of absence.” In our context, this means that the absence of a statistical similarity finding between TBI and AD—as represented by blank connectivity matrix cells in Fig. 3—does not imply evidence for the absence of such similarities. Instead, there are at least two possible scenarios. The first of these involves the situation where a similarity exists but its effect size is not large enough for its adequately powered detection to be possible in this sample. In the second scenario, although the FCs of both TBI participants and AD patients differ significantly from the FCs of HCs, the former two are not significantly equivalent. To provide an example of this, consider the scenario where the mean FC between two regions is 0 in HC, 0.8 in TBI, and -0.8 in AD, and the standard deviation of each measure is 0.01. Clearly, the FCs of the TBI group (0.8) and that of the AD group (-0.8) are both significantly different from that of HCs (0); nevertheless, the FCs of the TBI and AD groups differ substantially from each other (0.8 vs. -0.8), such that these FCs are not statistically equivalent. This simple example highlights the need to interpret statistical equivalent findings carefully.

In this study, the most prominent common feature of M_α , M_{β_3} , and M_{β_4} is the extent to which the intermodular connections of these three modules deviate from normality in both mTBI and AD. Furthermore, none of these modules exhibits intramodular connectivity which differs significantly from HCs in either clinical condition. These findings suggest, at the very least, that posttraumatic functional connections can be grouped according to their relative vulnerability to injury-related neurodegeneration. This is analogous to the similar task of grouping structural connections based on their vulnerability to injury, which entails mapping the structural scaffold of the human connectome [41]. Nevertheless, findings like ours may be difficult to interpret further in the absence of connectome-wide characterizations of connectivity between the DMN and the rest of the brain. Thus, future studies should aim to clarify how DMN subdivisions differ from the standpoint of their response to TBI or AD.

There are relatively few statistical similarities between TBI and AD (Fig. 3), despite the much greater number of significant differences between HC and TBI, as well as between HC and AD (Fig. 1 and Fig. 2). To contextualize this, it is important to note that the statistical similarities observed in this study between TBI and AD were detected only ~ 6 months after geriatric TBI of mild severity. Presumably, injuries of greater severity can be associated with additional significant similarities, and future research should test this hypothesis. For example, the severity of TBI- and AD-related digestive disturbances may be associated with connectomic disruptions which affect similar cortical areas and which may be associated with injury/disease severity [42–45].

It is not unlikely that the pathophysiological processes giving rise to the relatively few observed similarities between TBI and AD continue to affect the aging brain long after injury. Thus, the number of DMN-related similarities between TBI and AD may be proportional to how late after injury such similarities are measured and quantified. Specifically, if the neuropathological processes initiated by TBI continue to affect the DMN long after injury, it is possible that TBI and AD patients' DMNs start to resemble each other more and more as the time since injury increases. If this is the case, the number of statistical similarities observed here may provide a lower bound on the number of similarities between geriatric mTBI and AD. In such a scenario, the later fMRI recordings are acquired post-injury, the

greater DMN degradation there should be along AD trajectories. Whether this conjecture is valid should be investigated by future studies.

Neurovascular pathophysiology

The occurrence of CMBs in geriatric mTBI patients is relevant to the spatial profile and severity of posttraumatic WM alterations [16, 32, 46]. Previously, we showed that the trajectories and integrities of WM fasciculi passing through the vicinity (penumbrae) of post-traumatic CMBs can be altered in ways which persist for at least 6 months post-injury [47, 48]. Furthermore, other studies have found that CMB count is associated with network alterations in patients with early AD as well [49]. Since CMBs are associated with structural connectivity changes in both TBI and AD, these manifestations of blood-brain barrier breakdown may also modulate functional connectivity patterns shared by TBI and AD. In the present study, however, AD patients' CMB counts were quite low, which suggests that CMB-related network changes previously observed in AD are relatively unlikely to drive the RS FC similarities between mTBI participants and AD patients described here. One could argue that, in ideal circumstances, (dis)similarities between HCs, mTBI patients, and AD participants should be studied in the absence of CMBs; this, however, is particularly challenging in older adults. For example, in geriatric TBI patients, posttraumatic CMBs are frequently co-morbid with CMBs of hypertensive etiology, as well as with CMBs due to cerebral amyloid angiopathy (CAA), which is also a risk factor for AD. Because of the relatively high combined prevalence of neurovascular disease, CAA, and hypertension in older adults [46], studying TBI-related brain network alterations in the absence of CMBs may be either logistically impractical or of limited relevance to the pathophysiological processes of the average person's aging brain. In other words, studying functional network alterations in CMB-free older individuals may limit the utility of the insights gained from such studies to a relatively minor subset of the aging adult population. Although elucidating how CMBs modulate the extent of AD-like FC patterns in the mTBI-affected brain is beyond our scope, this study's inclusion of individuals with a wide range of CMB counts assists in resolving AD-like FC trajectories in a sample whose neurovascular profile reflects, at least to some extent, the radiological findings of aging adults with TBI and/or

AD. Future research should aim to clarify the extent to which CMBs modulate the extent and severity of AD-like FC deviations from normality in geriatric mTBI patients.

Comparison to prior studies

Arguably, the statistical similarities between study groups (TBI and AD) are of greatest interest in this study. Nevertheless, differences between HC and TBI and between HC and AD are also relevant because they underlie key comparisons between TBI and AD [50]. Fortunately, the comparison of our results to those of previous studies strengthen the case for our own analysis and broadens the scientific consensus on DMN differences between (a) HC vs. TBI and (B) HC vs. AD.

Our findings are in broad agreement with those of important previous studies on DMN abnormalities after TBI. For instance, Mayer et al. [13] reported that, compared with mTBI, HC subjects have stronger FC between the (a) anterior and posterior cingulate cortices, (b) anterior cingulate cortex and the superior frontal gyrus, (c) anterior cingulate cortex and the supramarginal gyrus, (d) the inferior parietal lobule and posterior parietal cortex, (e) the inferior parietal lobule and the middle frontal gyrus, (f) prefrontal cortex and the superior parietal lobule, and between (g) prefrontal cortex and the superior frontal gyrus. Our findings are in remarkable agreement with those of Mayer et al. (Figure 1). Furthermore, like in the present study, Johnson et al. [11] identified stronger FC in HC participants compared with TBI volunteers between posterior cingulate cortex and the hippocampal formation. These authors also found that (a) the lateral parietal lobes have significantly more bilateral RS FCs to the dorsolateral prefrontal cortex in HCs, that (b) mTBIs show only ipsilateral connections between these regions, and that (c) RS FCs between medial prefrontal and lateral parietal cortices are primarily observed in mTBI. These three sets of findings are replicated by our own study (Figure 1).

Influential prior results on DMN differences between HC and AD are confirmed by ours. For example, as we did, Greicius et al. [51] found that AD patients exhibit deficient activity involving the hippocampus and posterior cingulate cortex. In AD patients, Damoiseaux et al. found stronger FCs between (a) the frontal poles and other anterior frontal regions, (b) the left superior frontal gyrus and other frontal regions, and between (c) the

precuneus and the frontal poles, but weaker FCs involving regions like the superior and middle frontal gyri. Our results confirm the findings of Greicius et al. (Fig. 2) as well as those of Zhang et al. [52], who found reduced RS FCs between (a) posterior cingulate cortex and the hippocampus, (b) posterior cingulate cortex and the precuneus, and between (c) dorsolateral prefrontal cortex and middle temporal areas. Additionally, as we did, Zhang et al. found stronger RS FCs between the precuneus and many dorsolateral prefrontal regions.

Equivalence testing

This study uses equivalence testing, which originates in pharmacokinetics [53]. There, marketing new drugs requires testing whether their effectiveness is undistinguishable from that of older and more expensive competitors. Here, testing whether TBI-related DMN alterations are equivalent to AD-related alterations assists in illustrating how TBI and AD can result in statistically indistinguishable patterns of DMN deviations from normality (i.e., from HCs). Using equivalence testing in studies like ours is key because attempting to establish equivalence using statistical tests of conventional null hypotheses (e.g., $\mu_1 = \mu_2$) frequently leads to incorrect conclusions. Specifically, a significant result after such a test establishes a difference, whereas a non-significant one simply implies that equivalence cannot be ruled out. Thus, the risk of wrongly inferring equivalence can be very high, such that proper equivalence testing is needed instead [23]. In the current context, it is important to emphasize that equivalence testing was implemented here only for pairs of regions whose partial correlations ρ_{ij} differed significantly from HCs in *both* AD and mTBI. If this constraint had not been imposed, distinguishing normal from abnormal statistical equivalence patterns would not have been possible within this statistical inference framework.

Modularity structure

Here, DMN modules were identified from dissimilarity matrices rather than from FC matrices, as typical of functional connectomics studies [54]. Thus, the modules found in this study should be interpreted as groups of nodes whose FCs deviate from normality in similar ways, rather than as sets of nodes which are similarly connected to one another. The concept of deriving modularity properties from dissimilarity matrices is not new

and is, in fact, the basis of multidimensional scaling (MDS)—an ordination technique for information visualization and dimensionality reduction which has been used widely for decades [55]. In MDS, like here, dissimilarity matrices can be conceptualized as distance matrices whose entries are calculated using a distance function whose definition can be conveniently assigned depending on the nature of the data. In this study, the distance in question is a t score, which is a proper statistical metric defined as the standardized difference between two group means. This framework is univariate and therefore accommodates only one measure at a time, i.e., functional correlation in our case. However, should additional connectivity measures (e.g., Granger causality, phase locking value) or functional modalities (e.g., electro- or magnetoencephalography) be available [56–58], this formalism could be extended to an arbitrary number of dimensions using the (multivariate) Mahalanobis distance and/or non-Euclidian metrics, like in generalized MDS [59].

Replicability

Our findings should be replicated in larger cohorts for confirmation and improvement of statistical estimates. Although the samples used in this study were of moderate size, the effects reported here reflect relatively large mean differences between cohorts. This is perhaps unsurprising because, across a variety of studies and methodologies, even TBI of *mild* severity has been associated consistently with large statistical effects related to anatomical and physiological measures [60]. Furthermore, the mTBI participants studied here did not have clinical findings on MRI except for sporadic, SWI-detectable CMBs; this is rare in TBI studies. Thus, the present study facilitates the comparison of TBI to AD partly due to the uniquely suitable profile of the geriatric TBI sample involved, whose MRI profile is relatively rare; this lends strength and uniqueness to the present study. Specifically, the effect sizes characterized here are more likely to be due to functional—rather than to structural—pathology because the structural MRI findings of these geriatric mTBI patients are minimal. For this reason, the large statistical effects of TBI upon the DMN are quite likely responsible for the large effect sizes reported. This contrasts with many other neurological conditions, where FC metrics often exhibit relatively smaller effect sizes, such that considerably larger samples are often required to detect effects of interest

with adequate statistical power. It also contrasts with most other TBI studies, where gross TBI pathology on MRI findings is the norm. Nevertheless, despite the unique characteristics of our sample, further research in a larger cohort remains necessary for replication. This observation also pertains to our SVM findings, which may not be applicable to TBI cohorts of greater severity, even if only due to the greater heterogeneity of moderate-to-severe TBI relative to mTBI. Thus, our findings should not be interpreted as being broadly applicable to TBIs of any severity. Furthermore, the predictive value of our SVM relies heavily on acute MoCAs, whose values do not convey well the rich subtleties of posttraumatic cognitive impairment [61]. Thus, future studies should aim to utilize more detailed descriptors, preferably across all cognitive domains [62], to take better advantage of SVMs' potential for functional outcome prediction. Finally, it should be mentioned that replication of our findings using electrophysiological techniques like electro- and magnetoencephalography (EEG and MEG, respectively) [56, 63] would be very helpful in establishing the spatiotemporal parameters of the (dis)similarities observed here.

Limitations

It is important to acknowledge the possibility that the similarities between mTBI and AD described here may also be shared by mTBI with other neurodegenerative conditions. Although exploring whether this is the case is outside the scope of this study, future research should attempt to clarify whether the similarity patterns identified are representative not only of mTBI similarities to AD but also of the relationship between mTBI and other neurodegenerative conditions like Parkinson's disease, for which TBI is also a risk factor. Furthermore, because many participants were on medications for neurological, psychiatric, vascular, and/or metabolic disease when scans were acquired, the extent to which comorbidities affect the results of this study is unclear. Fortunately, the proportion of volunteers on medications for vascular and metabolic disease was approximately equal for the mTBI and AD groups, such that confounds due to these treatments are likely to be less severe than in the scenario where large discrepancies between groups existed. By contrast, the proportion of subjects undergoing treatment involving medications for neurological/psychiatric disease was much higher for the AD group (97%) than in the mTBI group (62%), mostly because almost all AD

patients were taking cognition-enhancing medications. The effects of comorbidities upon AD-like FC trajectories in mTBI patients are worthy of further study.

One potential limitation of FC studies like ours is that results can be affected by how the DMN is defined and by the cortical parcellation used for fMRI seed analysis. Here, the DMN was defined based on the Yeo delineation and parcelled based on the intersection of this delineation with the Destrieux parcellation scheme. Nevertheless, the use of other parcellation schemes of similar spatial resolution may not alter conclusions substantially because the randomization analysis undertaken yielded network modules whose anatomic coverage was consistent. Last but not least, the equivalence margin used in this study was 0.2, which is considered to be relatively conservative [23]; as the margin becomes narrower and narrower, however, more and more hypotheses of equivalence are rejected. Unfortunately, there is currently no consensus-based standard for the "ideal" equivalence margin which life scientists should utilize.

Conclusion

This study provides evidence that geriatric mTBI is associated with DMN deviations from normality which are statistically indistinguishable from those observed in AD. The DMN regions affected can be grouped into modules based on their vulnerability, with striking similarities in the composition and properties of these modules across the two neurological conditions. Multivariate regression analysis identified a clear relationship between acute cognitive deficits and chronic DMN alterations. Furthermore, SVM classifications suggested that DMN features may be useful for early prognostication of the extent and severity associated with posttraumatic neuropathophysiology. Nevertheless, the neurodegenerative processes of TBI and AD differ substantially despite their potential commonalities. Thus, the similarities in DMN alteration trajectories shared by these conditions and reported here may not be driven by similar trends toward functional reorganization. Because the methodological limitations of functional neuroimaging prevent us from a mechanistic exploration of this hypothesis, future research should study the pathophysiological mechanisms shared by TBI and AD in further detail.

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Computer code availability The computer code used in this study is freely available. FreeSurfer and FS-FAST are freely available (<https://surfer.nmr.mgh.harvard.edu>). Equivalence testing was implemented using freely available MATLAB software (<https://www.mathworks.com/matlabcentral/fileexchange/63204>). Network analysis was implemented using the freely available Brain Connectivity Toolbox (<https://sites.google.com/site/bctnet/>). Network visualizations were generated using Gephi (<http://gephi.org>). Regression and SVM analyses were implemented in MATLAB (<http://mathworks.com>) using the `glmfit`, `fitcsvm`, and `predict` functions.

Authors' contributions A.I. contributed to the study design, data analysis, and result interpretation and wrote the manuscript. A.S.M., N.N.C., N.F.C., and E.B.J. contributed to the study design, data analysis, and result interpretation.

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Compliance with ethical standards

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Acute cognitive impairment after traumatic brain injury predicts the occurrence of brain atrophy patterns similar to those observed in Alzheimer's disease

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Abstract:	Traumatic brain injuries (TBIs) are often followed by persistent structural brain alterations and by cognitive sequelae, including memory deficits, reduced neural processing speed, impaired social function, and decision-making difficulties. Although mild TBI (mTBI) is a risk factor for Alzheimer's disease (AD), the extent to which these conditions share patterns of macroscale neurodegeneration has not been quantified. Comparing such patterns can not only reveal how the neurodegenerative trajectories of TBI and AD are similar, but may also identify brain atrophy features which can be leveraged to prognosticate AD risk after TBI. The primary aim of this study is to systematically map how TBI affects white matter (WM) and gray matter (GM) properties in AD-analogous patterns. Our findings identify substantial similarities in the regional macroscale neurodegeneration patterns associated with mTBI and AD. In cerebral GM, such similarities are most extensive in brain areas involved in memory and executive function, such as the temporal poles and orbitofrontal cortices, respectively. Our results indicate that the spatial pattern of cerebral WM degradation observed in AD is broadly similar to the pattern of diffuse axonal injury observed in TBI, which frequently affects WM structures like the fornix, corpus callosum, and corona radiata. Using machine learning, we find that the severity of AD-like brain changes observed during the chronic stage of mTBI can be accurately prognosticated based on acute assessments of post-traumatic mild cognitive impairment. These findings suggest that acute post-traumatic cognitive impairment predicts the magnitude of AD-like brain atrophy, which is itself associated with AD risk.	

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Acute cognitive impairment after traumatic brain injury predicts the occurrence
of brain atrophy patterns similar to those observed in Alzheimer's disease

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Abstract

Traumatic brain injuries (TBIs) are often followed by persistent structural brain alterations and by cognitive sequelae, including memory deficits, reduced neural processing speed, impaired social function, and decision-making difficulties. Although mild TBI (mTBI) is a risk factor for Alzheimer's disease (AD), the extent to which these conditions share patterns of macroscale neurodegeneration has not been quantified. Comparing such patterns can not only reveal how the neurodegenerative trajectories of TBI and AD are similar, but may also identify brain atrophy features which can be leveraged to prognosticate AD risk after TBI. The primary aim of this study is to systematically map how TBI affects white matter (WM) and gray matter (GM) properties in AD-analogous patterns. Our findings identify substantial similarities in the regional macroscale neurodegeneration patterns associated with mTBI and AD. In cerebral GM, such similarities are most extensive in brain areas involved in memory and executive function, such as the temporal poles and orbitofrontal cortices, respectively. Our results indicate that the spatial pattern of cerebral WM degradation observed in AD is broadly similar to the pattern of diffuse axonal injury observed in TBI, which frequently affects WM structures like the fornix, corpus callosum, and corona radiata. Using machine learning, we find that the severity of AD-like brain changes observed during the chronic stage of mTBI can be accurately prognosticated based on acute assessments of post-traumatic mild cognitive impairment. These findings suggest that acute post-traumatic cognitive impairment predicts the magnitude of AD-like brain atrophy, which is itself associated with AD risk.

Keywords: traumatic brain injury, Alzheimer's disease, mild cognitive impairment, neuroimaging, neurodegeneration

Abbreviations

ACR	anterior corona radiata
AD	Alzheimer's disease
ADNI	Alzheimer's Disease Neuroimaging Initiative
AIC	anterior internal capsule
ApoE	Apolipoprotein E
A β	amyloid beta
BCC	body of the corpus callosum
BCF	body and column of the fornix
CB	cingulum bundle
CC	corpus callosum
CDR	clinical dementia rating
CDR-SB	clinical dementia rating sum of boxes
CF	crus of the fornix
CI	confidence interval
CMB	cerebral microbleed
CP	cerebral peduncle
CST	corticospinal tract
CT	computed tomography
DAI	diffuse axonal injury
DL	deep learning
DMN	default mode network
dMRI	diffusion magnetic resonance imaging
DTI	diffusion tensor imaging
DWI	diffusion weighted imaging
EC	external capsule
FA	fractional anisotropy
FLAIR	fluid-attenuated inversion recovery
FSL	FMRIB software library
FWER	family-wise error rate
GCC	genu of the corpus callosum
GCS	Glasgow Coma Scale
GLM	general linear model

1		
2		
3	GM	gray matter
4		
5	GRE	gradient-recalled echo
6		
7	HC	healthy control
8		
9	ICbP	inferior cerebellar peduncle
10	ICBM	International Consortium of Brain Mapping
11		
12	IFG	inferior frontal gyrus
13		
14	IFOF	inferior fronto-occipital fasciculus
15		
16	JHU	Johns Hopkins University
17		
18	LOC	loss of consciousness
19		
20	MCI	mild cognitive impairment
21		
22	ML	medial lemniscus
23		
24	MMSE	mini mental state examination
25		
26	MNI	Montreal Neurological Institute
27		
28	MoCA	Montreal cognitive assessment
29		
30	MP-RAGE	magnetization-prepared rapid acquisition gradient echo
31		
32	MRI	magnetic resonance imaging
33		
34	mTBI	mild traumatic brain injury
35		
36	MTG	medial temporal gyrus
37		
38	NFT	neurofibrillary tangles
39		
40	OFC	orbitofrontal cortex
41		
42	PCR	posterior corona radiata
43		
44	PCT	pontine crossing tract
45		
46	PET	positron emission tomography
47		
48	PFC	prefrontal cortex
49		
50	PIC	posterior internal capsule
51		
52	PS	processing speed
53		
54	PTR	posterior thalamic radiation
55		
56	RIC	retrolenticular internal capsule
57		
58	ROI	region of interest
59		
60	SCC	splenium of the corpus callosum
61		
62	SCbP	superior cerebellar peduncle
63		
64	SCR	superior corona radiata
65		
	SFOF	superior fronto-occipital fasciculus
	SLR	superior longitudinal fasciculus

1		
2		
3	SS	sagittal stratum
4		
5	STG	superior temporal gyrus
6		
7	SWI	susceptibility weighted imaging
8		
9	TBI	traumatic brain injury
10		
11	TBSS	tract-based spatial statistics
12		
13	TCC	tapetum of the corpus callosum
14	TFCE	threshold-free cluster enhancement
15		
16	TOST	two one-sided t test
17		
18	UF	uncinate fasciculus
19		
20	VBM	voxel-based morphometry
21	vmPFC	ventromedial prefrontal cortex
22		
23	WM	white matter
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25	3D	three-dimensional
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Introduction

The chronic effects of traumatic brain injury (TBI) on cognitive function can share similarities with those of Alzheimer's disease (AD) [1, 2]. These effects may be particularly severe in older individuals, who are ~3 times more likely to sustain a TBI than those in any other age group [3, 4]. Such greater vulnerability is partly due to a higher risk for physical injuries (like falls) and to a higher likelihood of pre-existing conditions at the time of injury, resulting in poorer clinical outcomes [3]. Within the Glasgow Coma Scale (GCS), TBIs can be classified as mild, moderate, or severe based on neurological measures which include loss of consciousness (LOC) duration. In the United States, mild TBI (mTBI) affects nearly two million residents annually and accounts for ~80% of all TBI cases [5]. Nevertheless, the potential relationship between TBI and AD remains underexplored despite the epidemiological significance of both conditions. Repeated mTBIs are particularly associated with AD risk [6-8], and *post mortem* studies of mTBI effects on brain microstructure have identified both Amyloid β ($A\beta$) plaques and neurofibrillary tangles (NFTs) of τ protein which resemble those observed in AD [7]. At the macroscale, however, few studies have investigated whether TBI-affected brain structure can change along AD-analogous trajectories, particularly at older ages.

Brain morphometry studies often utilize magnetic resonance imaging (MRI) and computed tomography (CT) [9] to provide noninvasive *in vivo* mapping, visualization and quantification of the brain after TBI. Diffusion MRI (dMRI) can be used to quantify the fractional anisotropy (FA) and other properties of water diffusion along white matter (WM) fibers in the TBI-affected brain to identify abnormalities [10]. For example, independent investigations comparing the FAs of healthy controls (HCs) to those of AD patients and acute mTBI victims found significantly lower FA [10, 11], which is indicative of damage, along WM tracts projecting to the hippocampi and to temporal regions in the brains of AD and mTBI patients [12, 13]. Researchers have also utilized cortical thickness as a measure of gray matter (GM) atrophy and have independently observed similar spatial patterns of cortical thinning in AD and mTBI patients compared to HCs [14-16]. Despite such similarities of findings comparing mTBI and AD to HCs, hardly any studies have combined GM and WM measurements in a longitudinal design to examine whether subacute neurodegeneration after mTBI can occur along AD-analogous trajectories.

Previously, our laboratory showed that the *acute* cognitive deficits of mTBI patients predict *chronic* functional alterations after TBI which resemble those observed in AD to a statistically significant extent [17]. To complement these previous findings, the present investigation implements a statistical comparison of *structural* GM and WM changes occurring in AD, geriatric mTBI, and HCs by integrating MRI-based WM analysis with GM morphometry. Given that previous studies suggested similarities between the two conditions, our aim is to extend this evaluation by further mapping the statistical similarities of WM degradation and GM

atrophy between TBI and AD relative to HCs. We identify GM regions and WM structures whose neuroanatomic properties (cortical thickness and FA, respectively) exhibit significant statistical equivalences across the two groups. Furthermore, we provide insight into the commonalities between TBI and AD which complement those in our previous investigation. Importantly, the present study finds that acute post-traumatic cognitive measures can be used as input for a deep learning (DL) model to predict accurately the extent and magnitude of statistical similarities between mTBI and AD. This illustrates our ability to early identify mTBI patients at high risk for AD-analogous neurodegeneration and suggests an avenue for the early estimation of AD risk after mTBI, with substantial potential benefits to medical science.

Methods

Participants. This study was conducted with the approval of the Institutional Review Board at the University of Southern California and was carried out in accordance with the Declaration of Helsinki and with the U.S. Code of Federal Regulations (45 C.F.R. 46). Three volunteer groups were studied: one with AD ($N = 66$; 26 females; age $\mu = 75.6$ y, $\sigma = 8.9$ y, range = 55–92 y), one with mTBI ($N = 33$; 15 females; age $\mu = 62.7$ y, $\sigma = 10.6$ y, range = 47–83 y) and one consisting of HCs ($N = 81$; 59 females; age $\mu = 68.7$, $\sigma = 7.0$ y, range = 55–87 y). The statistical significance of differences in age means between the three groups was evaluated using two-tailed Welch's t -tests. The significance of group differences in sex composition was tested using a χ^2 test. HC and AD subjects were selected from the AD Neuroimaging Initiative (ADNI) cohort, whose eligibility criteria are described elsewhere [18]. To be included, all participants had to have Montréal Cognitive Assessment (MoCA) scores. If available, AD patients' cognitive assessments were made within 0 to 394 days after imaging ($N = 61$, $\mu = 32$ days, $\sigma = 62$ days). HC volunteers' cognitive scores were acquired within 0 to 302 days after imaging ($N = 72$, $\mu = 29$ days, $\sigma = 42$ days). HC participants had been clinically evaluated as having normal cognition; their MoCA scores ranged from 20 to 30 ($N = 72$, $\mu = 26$, $\sigma = 3$). AD patients' scores ranged from 2 to 28 ($N = 61$, $\mu = 15$, $\sigma = 5$), and all had a clinical AD diagnosis. TBI participants' scores were acquired within 48 hours post-injury and were between 23 and 30 ($N = 33$, $\mu = 26$, $\sigma = 5$). Mini Mental State Examination (MMSE) scores were available for HCs ($N = 72$, $\mu = 29$, $\sigma = 1$; range: 22–30), TBI volunteers ($N = 33$, $\mu = 25$, $\sigma = 3$; range: 23–30) and AD participants ($N = 61$, $\mu = 22$, $\sigma = 3$; range: 11–29). AD patients had global Clinical Dementia Rating (CDR) sum of boxes (CDR-SB) scores between 1 and 14 ($N = 61$, $\mu = 5.35$, $\sigma = 2.34$), whilst HCs had global CDR-SB scores between 0 and 2 ($N = 72$, $\mu = 0.05$, $\sigma = 0.25$); CDR scores were not available for TBI participants. For HCs whose Apolipoprotein E (ApoE) genotype had been determined ($N = 68$), the number of ApoE- $\epsilon 4$ alleles was zero for 63% of the sample, one for 34% and two for 3%. For AD patients with ApoE genotyping ($N = 60$), 30% had no $\epsilon 4$ alleles, 50% had one and 20% had two. No ApoE allele information was available for TBI participants.

TBI participant inclusion criteria. TBI volunteers had no clinical history of neurological or psychiatric disorder prior to their injuries, which were their first ones. They had MRI recordings acquired ~6 months post-injury at 3 T, i.e. the same scanner field strength as the HC and AD participants. They had to have (a) a TBI due to a fall, (b) no clinical findings on acute T_1/T_2 -weighted MRI, (c) no clinical findings other than cerebral microbleeds (CMBs) on susceptibility weighted imaging (SWI), (d) an acute GCS score greater than 12 ($\mu = 14.1$, $\sigma = 0.7$) upon initial medical evaluation, (e) LOC of fewer than 30 minutes ($\mu \approx 14$ minutes, $\sigma \approx 3$ minutes), (f) post-traumatic amnesia of fewer than 24 hours ($\mu \approx 5.5$ hours, $\sigma \approx 3.2$ hours), and (g) a lack of clinical history involving pre-traumatic neurological disease, psychiatric disorder or drug/alcohol abuse. CMBs were identified in each subject using an automatic algorithm for CMB segmentation [19] and the validity of the findings were

confirmed by a human expert with training in CMB identification from SWI, who had been blinded to automatic segmentation results.

Data acquisition. HC and AD participant data used for the preparation of this article were obtained from the ADNI database (<http://adni.loni.usc.edu>). ADNI was launched in 2003 as a public-private partnership, led by Principal Investigator Michael W. Weiner, MD. The primary goal of ADNI has been to test whether serial MRI, positron emission tomography (PET), other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of mild cognitive impairment (MCI) and early AD. For up-to-date information, see www.adni-info.org. TBI imaging data were acquired at 3 T using the Prisma MAGNETOM Trio TIM MRI scanner model (20-channel head coil, Siemens Corporation, Erlangen, Germany). Data included T_1 - and T_2 -weighted, fluid-attenuated inversion recovery (FLAIR), gradient recalled echo (GRE)/SWI and dMRI volumes. T_1 -weighted images were acquired using a three-dimensional (3D), magnetization-prepared rapid acquisition gradient echo (MP-RAGE) sequence [repetition time (T_R) = 1,950 ms; echo time (T_E) = 2.98 ms; inversion time (T_I) = 900 ms; voxel size = 1.0 mm $\times$ 1.0 mm $\times$ 1.0 mm]. T_2 -weighted images were acquired using a 3D sequence (T_R = 2,500 ms; T_E = 360 ms; voxel size = 1.0 mm $\times$ 1.0 mm $\times$ 1.0 mm) [4]. Flow-compensated GRE/SWI volumes were acquired axially (T_R = 30 ms; T_E = 20 ms; voxel size = 1.33 mm $\times$ 1.33 mm $\times$ 1.6 mm). dMRI volumes were acquired axially in 64 gradient directions (T_R = 8,300 ms; T_E = 72 ms; voxel size = 2.7 mm $\times$ 2.7 mm $\times$ 2 mm). One volume with b = 0 s/mm² and another with b = 1,000 s/mm² were also acquired, where b is the diffusion-weighting constant of diffusion weighted imaging (DWI). All acquired data were anonymized and de-linked prior to archiving and analysis.

Preprocessing. DWI volumes were corrected for susceptibility-induced artifacts, subject motion, and eddy currents using software in the FMRIB Software Library (FSL). Based on a pair of images with opposite phase encoding directions, susceptibility-induced artifacts were estimated [20]. Subsequently, a brain mask was created, and susceptibility corrections were implemented, followed by eddy current and patient motion corrections, resulting in output containing the artifact-corrected, skull-stripped brain volume. Then, the B vectors of each volume were rotated such that any inadequate rotations caused by patient motion were accounted for. DWI volumes were further processed in FSL by fitting tensors to corrected DWI volumes to perform diffusion tensor imaging (DTI). These latter volumes were then used for voxel-wise FA calculation such that FA maps could be generated for each volume. T_1 -weighted volumes underwent intensity normalization, bias field correction and motion correction as part of the FreeSurfer 6.0 processing workflow (<http://surfer.nmr.mgh.harvard.edu>).

Cortical reconstruction. The segmentation of subcortical structures, cerebral WM and cortical GM was based on T_1 -weighted volumes and was implemented in FreeSurfer 6.0 with default execution parameters, as

described elsewhere [21, 22]. Briefly, this process includes (1) the removal of non-cerebral voxels using a hybrid watershed/surface deformation procedure, (2) an automated transformation to Talairach space, (3) voxel intensity normalization, (4) segmentation of cortical and subcortical GM, (5) tessellation of the GM/WM boundary, and (6) automated surface topology correction. The reader is referred elsewhere [21, 22] for comprehensive details on each of these steps. Each hemisphere was divided into 74 regions by segmenting subcortical structures and by parceling the cortex into gyri and sulci using the Desikan-Killiany atlas nomenclature [23]. For each subject, cortical thickness was estimated at each cortical location and then resampled onto a seventh-order icosahedral mesh for inter-subject comparison.

Regional labeling and atlas. WM voxels were mapped onto WM structures in Montreal Neurological Institute (MNI) MNI₁₅₂ space using FSL version 6.0.1 and the Johns Hopkins University (JHU) International Consortium of Brain Mapping (ICBM) DTI₈₁ WM labeling scheme. First, the mean FA skeleton mask was co-registered onto the JHU label map, thereby creating a skeletonized version of the latter. Images were then binarized such that voxels corresponding to statistical significance ($p < 0.05$) were set to 1, whereas remaining voxels were set to 0; these binarized images were then projected onto the skeletonized label map. The total number of significant voxels in the volume associated with each label was divided by the total number of voxels pertaining to that label so as to calculate the percentage volume of voxels associated with statistical significance and located in each structure. Results were represented graphically for visual interpretation. For cortical thickness calculations, after binarizing each subject's cortical surface overlay based on statistical significance (1 = significant; 0 = not significant), the resulting binary map was registered onto the average cortical surface in the Desikan-Killiany atlas. Then, a similar procedure was used to calculate the percentage of cortical surface area within each cortical region which contained vertices associated with statistical significance. **Fig. 1** illustrates a conceptual representation of this process.

Tract-based spatial statistics (TBSS). A TBSS approach was used for the voxel-wise statistical analysis of mean WM FA differences between groups. In contrast to algorithms involving regions of interest (ROIs) or voxel-based morphometry (VBM) approaches, TBSS utilizes a nonlinear registration algorithm to co-register FA maps, resulting in alignment errors which are substantially smaller than those produced by traditional linear registration algorithms [24]. Moreover, TBSS facilitates the calculation of brain-wide statistics such that both global and local differences in FA can be quantified. First, FA volumes had their end slices set to zero to remove outliers which may have been introduced by fitting diffusion tensors to DWI volume data. After this step, nonlinear transforms to FMRIB₅₈ FA standard space were calculated and applied. The FMRIB₅₈ FA space was then affinely aligned to the MNI₁₅₂ space and the resulting transform was applied to each subject's FA volume such that all volumes could be aligned to the 1 mm × 1 mm × 1 mm MNI₁₅₂ space. FA maps were then averaged across subjects to generate a mean FA volume which was skeletonized to reveal FA values along the

trajectories of major WM structures. The mean FA skeleton was thresholded to remove values below a default threshold of 0.2, below which the low signal-to-noise ratio results in relatively inaccurate FA measurements.

Statistical testing of group differences. Group differences in mean FA were calculated between (A) AD and mTBI, (B) AD and HCs, and (C) mTBI and HCs. The null hypothesis H_0 , according to which each pair of groups' mean FA values are equal, was tested using Welch's t -test. Using a general linear model (GLM), the confounding effects of sex and age on FA values [25, 26] were regressed out and a nonparametric two-sided t -test with 500 permutations and with threshold-based free-cluster enhancement (TFCE) was implemented. This revealed clusters of WM voxels whose mean FA differed significantly between groups. All p -values were corrected for multiple comparisons using 500 nonparametric permutations with TFCE, while controlling for the family-wise error rate (FWER) [27, 28].

Statistical testing of group similarities. A premise of this study is that a brain feature f which is both (a) significantly different from HCs in both TBI and AD, *and* (b) significantly similar across TBI and AD, can be said to be *AD-analogous*. Thus, a brain feature f observed in TBI patients can be said to be AD-analogous if f differs from HCs in both TBI and AD, *and* is also significantly similar across *both* TBI and AD. If f differs significantly from HCs in both TBI *and* AD, a null hypothesis of *statistical equivalence* can be tested to determine whether f is AD-analogous. Thus, for samples A and B , a null hypothesis of equivalence is stated as $\mu_A(f) \neq \mu_B(f)$, i.e. as the complement of the typical null hypothesis $\mu_A(f) = \mu_B(f)$. A null hypothesis of equivalence fails to be accepted if the two means fall within an interval $(-\delta, +\delta)$, where δ is known as the *equivalence margin* of the test [29]. In a statistical sense, equivalence implies that the values of the empirical estimates of the features $f(A)$ and $f(B)$ are so close that neither estimate can safely be considered to be greater or smaller than the other [30]. In this study, δ is assigned a conservative value equal to 0.2 multiplied by the width of the 95% confidence interval (CI) for the difference $\mu_A(f) - \mu_B(f)$. Equivalence hypotheses were tested using two one-sided t tests (TOSTs) [31]. Specifically, the TOSTs were used to quantify the statistical equivalence of FA means between AD and mTBI cohorts. TOSTs are commonly used to test hypotheses of statistical equivalence [17], which can be interpreted as a measure of statistical similarity between groups.

To identify WM tracts whose FA means were statistically equivalent (i.e. statistically similar) across mTBI and AD, the null hypothesis H_0 of equivalence was only tested at locations where the mean FA differed significantly from the mean FA for HCs in both the AD and the TBI group. This restriction was necessary to ensure that any identified statistical equivalences between AD and TBI were associated with deviations from normality (i.e. from HCs). For GM, like for WM, TOSTs were implemented vertex-wise to determine whether the cortical thickness means of the AD and mTBI groups were statistically equivalent. As in the case of the WM analysis, testing for the statistical equivalence of mean cortical thickness in the AD and mTBI groups was only

implemented at locations where each of these groups had been found to differ significantly from HCs. Cortical maps of statistical equivalence between AD and mTBI were generated for display and smoothed across using five iterations of nearest-neighbor interpolation. Equivalence testing was implemented using freely available MATLAB software (<https://www.mathworks.com/matlabcentral/fileexchange/63204>).

Cognitive impairment vs. brain connectivity alterations. Two support vector machines (SVMs) were designed in MATLAB using the `glmfit`, `fitcsvm` and `predict` functions with default parameters, the iterative single data algorithm (ISDA), a linear kernel function, and heuristic kernel scale parameters. The SVMs were trained and cross-validated ten-fold to distinguish TBI participants whose AD-like mean FA deviations from normality (i.e. equivalences across TBI and AD) were either relatively *moderate* or relatively *extensive*, respectively. Such deviations were defined as *moderate* or *extensive* depending on whether they belonged to the lowest or highest terciles, respectively, of the TOST statistics' empirical distribution. The number of true negatives (TNs), true positives (TPs), false negatives (FNs) and false positives (FPs) were computed, as were the true positive rate (TPR, or sensitivity), true negative rate (TNR, or specificity), positive prediction value (PPV, or precision) and Matthews' correlation coefficient (MCC) [32].

Results

Participants. No significant group differences of sex composition were identified [$\chi^2 = 2.22$, degrees of freedom (df) = 1, $p = 0.136$]. Welch's t -test found significant differences in mean age between AD and mTBI (Welch's $t = 6.38$, $df = 97$, $p = 6.31 \times 10^{-4}$) AD and HCs (Welch's $t = 5.28$, $df = 145$, $p = 4.57 \times 10^{-7}$), and mTBI and HCs (Welch's $t = -3.52$, $df = 112$, $p = 6.03 \times 10^{-9}$). CMB counts were found to range from 0 to 2 ($\mu \pm \sigma = 0.27 \pm 0.65$) in HCs, from 4 to 46 ($\mu \pm \sigma = 24.95 \pm 11.11$) in mTBI volunteers, and from 0 to 25 ($\mu \pm \sigma = 1.66 \pm 4.49$) in AD patients. Significant differences in MMSE scores were found between HC and mTBI participants (Welch's $t = -7.49$, $df \approx 35$, $p = 4.53 \times 10^{-9}$), between HC and AD participants (Welch's $t = 17.01$, $df \approx 131$, $p < 0.001$) but not between mTBI participants and AD patients (Welch's $t = 4.69$, $df = 64$, $p = 0.99$). Significant differences in MoCA scores were found between HC and AD participants (Welch's $t = 17.26$, $df \approx 131$, $p = 9.33 \times 10^{-39}$), between acute mTBI participants and AD patients (Welch's $t = 10.65$, $df \approx 59$, $p = 1.04 \times 10^{-15}$), but not between HC and acute TBI participants (Welch's $t = -0.29$, $df \approx 42$, $p = 0.39$).

WM comparison between HC and mTBI. **Fig. 2 (A)** depicts regions where mTBI subjects had significantly lower mean FA than HCs ($p < 0.05$). In the mTBI group, these regions include the genu and body of the corpus callosum (GCC, and BCC, respectively), body and column of the fornix (BCF), as well as crura of the fornix (CF). **Table 1** lists WM structures in the descending order of the percentage of voxels within each structure where mean FA is significantly lower in mTBI participants than in HCs. In other words, the percentage of voxels quantifies the proportion of each structure's volume which exhibits significant mean FA differences between the two groups. In the mTBI cohort, the structures whose volumes' mean FAs differ most between groups are the tapeta of the CC (TCC), the uncinate fasciculi (UF), the anterior and posterior internal capsules (AICs and PICs, respectively), the external capsules (ECs), cingulum bundle (CB), superior cerebellar peduncles (SCbPs), BCF, GCC and BCC. WM structures which (A) are more affected by mTBI in the right hemisphere and which (B) differ to the greatest extent in mTBI compared to HCs include, in descending order, the AIC, SCbP, sagittal stratum (SS), cerebral peduncle (CP), posterior corona radiata (PCR), medial lemniscus (ML), and corticospinal tract (CST). Structures which are more affected in the left hemisphere are the EC, UF, CB, PIC, CF, inferior cerebellar peduncle (ICbP), superior longitudinal fasciculus (SLF), retrolenticular internal capsule (RIC), posterior thalamic radiation (PTR), anterior corona radiata (ACR), superior fronto-occipital fasciculus (SFOF), and superior corona radiata (SCR). No WM fascicles in the mTBI cohort were found to have significantly higher mean FA than in HCs.

WM comparison between HC and AD. **Fig. 2 (B)** depicts significant differences in mean FA between the HC and AD cohorts. In AD, mean FA values were significantly lower along commissural fibers like the (A) splenium of the corpus callosum (SCC), the BCC, GCC, BCF, and CF. **Table 2** lists WM structures in the descending order of

the percentage of each structure's voxels where mean FA is significantly lower in AD participants than in HCs. Thus, compared to HCs, AD patients' mean FAs differ from those of HCs most extensively in the BCC, BCF, CF, UF, CB, GCC, TCC, EC, SS and SFOF. In descending order according to the same criterion, fasciculi which are more affected in the right hemisphere and which differ most in AD compared to HCs are the CB, TCC, EC, SS, ACR, CP, ML and PCR. For the left hemisphere, these are the SFOF, PTR, SCbP, AIC, SLF, ICbP, RIC, PIC, SCR, and CST. No WM structures in the AD cohort were found to have significantly greater mean FA than the HC group.

WM comparison between AD and mTBI. No significant differences in mean FA were revealed between mTBI and AD groups. Equivalence testing comparing mTBI to AD revealed significant statistical similarities of mean FA throughout the brain. **Table 3** lists the WM structures in the descending order of the percentage of each structure's voxels for which mean FAs are statistically equivalent in AD and mTBI participants. In descending order according to the same criterion, these structures included the SFOF, CF, pontine crossing tract (PCT), ACR, BCF, and SCR.

GM comparison between HC and mTBI. **Fig. 3 (A)** displays significant differences in cortical thickness between the HC and mTBI cohorts. In the latter, significantly thinner cortex (blue) is observed in the lateral superior portion of the left temporal lobe, in parietal and in frontal regions. Significantly lower cortical thickness in the HC group (red) is observed diffusely across the cortex. Such cortical thickening after TBI is relatively ubiquitous and has been hypothesized to be associated with chronic inflammation of the GM [33, 16, 34, 35].

GM comparison between HC and AD. **Fig. 3 (B)** displays significant differences in cortical thickness between the HC and AD cohorts. In the latter, significantly thinner cortex (blue) is found in the lateral and medial parts of the temporal and frontal lobes. In the HC group, significantly thinner cortex (red) is observed at very few locations on the medial surface of the brain, particularly in the cingulate gyri.

GM comparison between mTBI and AD. **Fig. 3 (C)** displays regions where cortical thinning was statistically indistinguishable between (i.e. significantly equivalent across) mTBI and AD cohorts. Extensive areas of statistical similarity are observed in frontotemporal and frontoparietal regions and, more sparsely, in occipital areas. **Table 4** lists gyri and sulci in descending order of each structure's percentage (i.e. proportion) of cortical area exhibiting an amount of cortical thinning which was statistically indistinguishable between mTBI and AD. The parcels whose cortical thinning was most statistically similar across mTBI and AD include the superior part of the precentral sulcus, the short insular gyri, the horizontal ramus of the anterior lateral sulcus, the marginal cingulate sulcus, and the orbital gyri. There are few regions whose statistical similarities were largely restricted to a single hemisphere across the AD and mTBI cohorts, including lateral occipital regions, the supramarginal gyri, anterior transverse marginal gyri, inferior partial lobules, and superior temporal gyri (STG).

Cognitive impairment vs. brain connectivity alterations. Across 100 scenarios, the SVM trained to identify TBI patients whose WM similarities to AD were relatively modest (bottom tercile of equivalence statistic distribution) achieved the following means and standard deviations: TN = 20.0 $\pm$ 1.1; TP = 10.0 $\pm$ 0.8; FN = 1.6 $\pm$ 0.3; FP = 1.4 $\pm$ 0.2; TPR = 0.87 $\pm$ 0.09; TNR = 0.93 $\pm$ 0.09; PPV = 0.88 $\pm$ 0.2; MCC = 0.80 $\pm$ 0.2. The SVM trained to predict which TBI patients' similarities to AD were relatively extensive (top tercile of equivalence statistic distribution) yielded the following results: TN = 19.2 $\pm$ 0.5; TP = 9.1 $\pm$ 0.9; FN = 1.1 $\pm$ 0.3; FP = 1.9 $\pm$ 0.9; TPR = 0.83 $\pm$ 0.6; TNR = 0.95 $\pm$ 0.5; PPV = 0.83 $\pm$ 0.3; MCC = 0.79 $\pm$ 0.4.

Discussion

This study investigated cortical thickness and FA changes associated with geriatric mTBI and compared these changes to those observed in AD. The analysis demonstrated (i) broad, significant similarities in cortical thinning between mTBI and AD, primarily in frontal and temporal regions but also in the occipital lobe; (ii) bilateral patterns of significant similarities in mean FA across mTBI and AD; (iii) significantly lower mean FA and thinner cortex in both mTBI and AD compared to HCs.

Translational significance. The high prevalence of geriatric mTBI and its subsequent risk for AD underscore the need to predict the latter. Studies have identified significant correlations between certain cognitive measures—like CDR-SB scores—and neural tissue integrity metrics, in that higher CDR-SB scores are indicative of lower integrity [36, 37]. Our findings of significant similarities between AD and mTBI pertaining to cortical thickness, mean FA and cognitive test scores provide clinical insight to identify individuals at high AD risk. Such information can be combined with cognitive test scores (e.g. CDR-SB scores), demographics and ApoE genotype information to predict the extent and pattern of cortical degeneration experienced by geriatric mTBI patients. Thus, our study can assist the prognostication of geriatric mTBI patients in terms of their AD risk. Adding to our ability to make such prognostications is the fact that our SVM classification results suggest that the severity of acute cognitive deficits observed in TBI patients can be leveraged *acutely* to predict, with high sensitivities and specificities, the *future* extent and breadth of their AD-like brain atrophy patterns.

Structural neurodegeneration in TBI vs. AD. **Table 1** lists WM structures with significantly lower average FA values in mTBI patients compared to HCs. The structures with the greatest differences in mean FA include the TCC, EC, UF, BCC, and GCC. Diffuse axonal injury (DAI) accompanies TBI often and commonly affects large WM structures (like the corpus callosum (CC)) as well as fasciculi innervating temporal or frontal regions, like the UF [38-40]. Our findings agree with these previous studies because the UF—which projects to the temporal lobe—is found here to exhibit extensive lower mean FA in mTBI subjects. Structures listed in **Table 1** exhibit similar extents of damage across hemispheres; this may be partly attributable to contrecoup injuries that can cause contusions and edema, which affect FA [41]. Thus, the listing of WM structures in **Table 1** is consistent with the set of WM fiber bundles that are commonly reported as being affected by TBI-related DAI.

Table 2 lists the BCC, BCF, CF, UF, and CB as exhibiting significantly lower mean FAs in AD subjects. Two prominent scenarios for AD-related WM degeneration involve Wallerian degeneration and retrogenesis. In Wallerian degeneration, AD-related damage initiated in the GM extends to WM tracts connected to these degenerating GM areas [42]. By contrast, retrogenesis postulates that WM fibers undergoing myelogenesis latest during development are the first to degenerate [43]. Many researchers conceptualize AD neurodegeneration as being due to several competing mechanisms and, thus, as being the product of both

phenomena. In **Table 2**, the structure with the fewest voxels exhibiting lower mean FA in AD is the CST. This agrees with the retrogenesis model, since the CST consists of long, motor-projecting fibers which are among the first to myelinate (and thus among the last to degrade, according to the retrogenesis model). Importantly, our findings of significantly lower mean FA in AD subjects in the BCC, BCF, CF, UF, and CB agree with studies suggesting that frontally- and temporally-projecting fibers are more susceptible to AD neurodegeneration [44-47]. **Figs. 3A** and **3B** depict cortical thinning in the temporal lobes of both mTBI and AD subjects, respectively. Previous studies suggest that such thinning is characteristic of AD and that it precedes the Wallerian degeneration of fibers projecting to these regions. Our study agrees with these findings because **Tables 1 and 2** show both mTBI and AD victims as exhibiting significantly lower mean FA than HCs in temporally-projecting fibers like the CB, BCF, and CF. Thus, our findings agree with previous studies of AD-related WM neurodegeneration and may reflect the competing effects of several neurodegenerative mechanisms.

Table 3 illustrates how mTBI and AD are similar from the standpoint of mean FA decreases within major WM fasciculi. Studies have identified WM fibers proximal to the brain stem as being commonly affected by DAI following TBI [40, 48-51]; however, fibers like the PCT and CST are listed here as being relatively spared by both mTBI (**Table 1**) and AD (**Table 2**). Instead of appearing to be affected by TBI, these tracts exhibit damage resembling that observed in AD (**Table 3**). This may reflect similar neurodegeneration mechanisms following TBI and AD [52], and is consistent with the retrogenesis model as these structures are among the first to be myelinated during development [53-55].

Functional neurodegeneration in TBI vs. AD. At the microscale, parallels between TBI and AD have been identified by neuropathology studies [7, 56, 57]. Similarly, in neuropsychological and cognitive studies, neural correlates of cognitive deficits observed after TBI and AD have been found to share commonalities [2, 58]. Nevertheless, few studies have compared the effects of TBI and AD upon brain architecture at the macroscale. The present study found significant similarities between mTBI and AD subjects pertaining to the cortical thinning in the ACC, PCC, and temporal poles (**Table 4**). Our findings are consistent with those of previous studies [59-62, 10], which independently examined neurodegeneration after the two conditions. Such comparisons of cognitive symptoms across TBI and AD have identified similar deficits in processing speed, cognitive flexibility, attention, and memory [63]. The ACC and PCC are part of the default mode network, which may be hypoactive after mTBI, resulting in deficits of divided attention [64]. Similarly, AD studies of attention suggest that the ACC is involved in divided attention deficits [65]. Simultaneously, TBI-related damage to the ACC and temporal lobes has been implicated in poor self-awareness due to bilateral hyperactivity within these regions. Other studies have found strong involvement of the ACC and temporal poles in functional deficits

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3 pertaining to memory and perceptual ability [66, 67]. In what follows, we discuss potential relationships
4 between deficits within specific cognitive domains and both AD- and TBI-related neurodegeneration patterns.
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8 *Social function deficits.* Social function has been studied in the context of concepts like the *social brain* and the
9 multi-faceted *social network*, which includes the orbitofrontal cortex (OFC), superior aspect of the lateral
10 temporal lobe, the medial prefrontal cortex (PFC), ACC, and the amygdala [68]. The amount of cortical thinning
11 identified by our investigation in the OFC was found to be statistically indistinguishable across the mTBI and
12 AD cohorts (**Table 4**), which is consistent with studies identifying the OFC as modulating social function.
13 Specifically, in TBI, the OFC has been cited as being involved in social function (e.g. emotion recognition), and
14 prominent mTBI-related deficits pertain to social function [69-71]. This type of deficit has also been identified
15 in AD, where social withdrawal and dysfunction are typical manifestations of the disease [72, 68, 73]. Thus,
16 our findings suggest that TBI and AD share social function deficits which may be due to similar spatial
17 neurodegeneration patterns.
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21 *Decision-making deficits.* This study found that damage to the PIC, UF, orbital gyri, and orbital sulci is common
22 in both mTBI and AD (**Tables 3 and 4**). Typically, decision-making after TBI is significantly poorer than in HCs, a
23 phenomenon which often persists up to five years post injury [74]. There are, however, conflicting findings on
24 how lesion location impacts decision-making. In mice, for example, spatially non-specific associations have
25 been found between unilateral parietal and bilateral frontal lesions, on the one hand, and riskier decision-
26 making and increased impulsivity, on the other hand [75, 76]. By contrast, however, human studies indicate
27 that decision-making deficits are not limited to cases involving frontal lesions [77]. Thus, dMRI studies of
28 patients with mild-to-moderate blast TBIs have revealed that the compromised integrities of the right UF, right
29 inferior fronto-occipital fasciculus (IFOF), and right PIC are associated with decision-making deficits [78]. Aside
30 from TBI, such deficits are also observed in AD, where structural changes within ventromedial PFC (vmPFC) are
31 correlated with measurable deficits [79]. Thus, our findings are consistent with those of prior studies on
32 decision-making and identify commonalities between decision making deficits and the neurodegenerative
33 patterns of TBI and AD.
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37 *PS deficits.* This study identified similar patterns of WM degradation across mTBI and AD in the left AIC, UF, CB,
38 ACR, and GCC (**Table 3**). Such findings are consistent with those of previous dMRI studies that revealed
39 correlations between reduced WM integrity in these areas and relatively low PS [80-83]. In mTBI, lower PS has
40 been reported as early as one-month post-injury and has been documented to persist for up to six years post-
41 injury [84-87]. Commonly, lower PS is coexistent with other mTBI-related symptoms like fatigue, anxiety, and
42 attention deficits. In particular, reports of fatigue following mTBI are exceedingly common and may be
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3 explained by the *coping hypothesis*, which states that compensatory recruitment of areas increases cognitive
4 load, resulting in fatigue which lowers PS [88-91]. Similar PS reductions have been observed in AD, as quantified
5 by pause and reaction times [92, 93]. Thus, our findings agree with those of previous studies which identified
6 neuroanatomic structure correlates of PS deficits in TBI and AD.
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11 *Verbal fluency deficits.* Our study reports similarities between mTBI and AD pertaining to global reductions in
12 cortical thickness (**Table 4**). Some of these affected structures and regions (e.g. the left ascending fibers in the
13 CC, the frontal lobes, the left inferior frontal gyrus (IFG), the left middle temporal gyrus (MTG), and the left
14 STG have been identified as being responsible for reduced verbal fluency [94-96] . Verbal fluency can be
15 broadly classified as phonemic or semantic, and deficits in both are frequent after TBI, with estimated
16 prevalences of ~70% and ~87%, respectively, and with comparable magnitudes for each [97, 98]. Whereas
17 other deficits following TBI can recover relatively well, verbal fluency deficits have been suggested to recover
18 relatively poorly and slowly, since they persist for more than six weeks post-injury [99, 100]. In AD, deficits in
19 both phonemic and semantic fluency have been observed. Importantly, the latter is reported as being
20 significantly more impaired than the former [101]. Such differences in severity have been proposed to reflect
21 the increased susceptibility of temporal regions—which have a role in semantic memory—to
22 neurodegeneration following AD [102, 103]. **Fig. 2B** displays reduced cortical thickness in the temporal regions
23 of AD subjects, in agreement with previous studies [15, 104]. Thus, the degradation of brain regions reported
24 here is consistent with the findings of previous studies reporting relatively slow recovery of verbal fluency after
25 TBI. Together, our findings indicate that TBI and AD share neuroanatomic patterns of brain degradation which
26 underlie verbal fluency deficits.
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42 *Executive function (EF) deficits.* EF is greatly impacted by both mTBI and AD [105-108]. Here we identified
43 relatively low mean FA in the ACCs, GCCs, SCCs and PICs of both mTBI and AD patients compared to HCs (**Tables**
44 **1** and **2**). Reduced integrity in these WM structures is correlated with impaired planning abilities [109, 65],
45 although such findings are not unanimous across studies [110]. This may suggest that planning deficits are
46 modulated by injury severity, particularly since some authors [111] did not identify planning deficits associated
47 with WM damage. By contrast, AD patients' planning deficits have been documented extensively and there is
48 substantial consensus on their profiles [112-114, 65]. Thus, our findings of similarly reduced WM integrity in
49 the CCs of mTBI and AD subjects are consistent with previous studies tying these areas to EF deficits [115, 116].
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58 *Cognitive flexibility deficits.* Reductions in cognitive flexibility are often noted after mTBI and have been
59 documented both acutely and up to two months after injury. Our study revealed reduced WM integrity
60 throughout the CCs of mTBI and AD patients, in agreement with investigations of these areas' involvement in
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EF. Inflexibility affects multiple facets of cognition, including the ability to integrate new information, to adapt one's behavior in response to stimuli, and to switch attention fluidly. Cognitive flexibility is intimately related to EF, which recruits frontal cortex and frontally-projecting fibers [106]. Because of this, similar methods like task switching have been used to reveal that reduced GM integrity—particularly in the superior frontal gyrus (SFG), PFC, precuneus, ACC, and in the fusiform gyrus—affects cognitive flexibility [117, 118]. In our mTBI and AD cohorts, reduced cortical thickness was observed in the superior FG, in the PFC, precuneus, ACC, and in the fusiform gyrus (**Table 4**). Thus, our findings support the hypothesis according to which AD and TBI patients share a previously documented neuroanatomic substrate of cognitive inflexibility.

Limitations. One limitation of this study is that the JHU WM atlas includes only 25 WM structures and omits some functionally prominent fascicles. For example, superficial WM streamlines—described as typically short cortical association fibers near the surface of the cortex [119]—are excluded here. Such connections are more difficult to segment and more poorly documented than larger WM structures, and since the JHU WM atlas does not include them, neither does our study. Future studies should use atlases that map more WM structures; in our case, this was beyond the scope of the study as our primary interest was in the largest and best-mapped WM structures in the brain. Another limitation is the fact that MRI data used in the study were acquired at distinct sites using different scanners. This is known to confound measurements of both cortical thickness and WM properties [120, 121], such that harmonization protocols like ComBat can be useful [122, 121, 120]. Nevertheless, because our MRI acquisition protocol parameters were very similar across sites and scanners, such confounds may not be substantial in this study.

Although age-related effects were regressed out in our statistical analyses, the groups included here did exhibit significant mean differences of age. These differences are partly due to the fact that the subjects included in this study were selected from retrospective samples of convenience, such that age matching across groups was possible to a very limited extent. Furthermore, because this is a longitudinal study involving both structural MRI and dMRI of individuals with very specific eligibility criteria, only a relatively small subsample of the ADNI cohort was useful for our purposes. This also limited our ability to match subjects by age. Finally, AD occurs relatively rarely before the age of 65, whereas TBIs can occur at any age. This implies that comparing AD patients to TBI victims can be problematic if the latter are relatively young compared to the former. Thus, to some extent, the confound of age in studies like ours is unavoidable if young or middle-aged TBI patients are to be compared to AD patients. Nevertheless, because TBI patients younger than 65 may still be vulnerable to AD-analogous neurodegeneration (as suggested, in fact, by our study), the inability to match TBI and AD patients by age may be unavoidable in studies like ours, particularly if relatively young TBI patients are studied.

Conclusion

Upon comparing AD patients to mTBI participants imaged ~6 months post injury, this study identified statistical similarities between these groups pertaining to both WM and GM neurodegeneration, as evidenced by both mean FA and cortical thickness measurements. Whereas other studies explored the effects of TBI and AD on the brain without reference to each other, we directly compare such effects. Furthermore, this study focuses on chronic mTBI findings rather than on acute mTBI, thereby providing insight into the medium-to-long-term effects of mTBI upon macroscale brain structure. Our findings agree with those of previous studies of functional and structural correlates in these conditions, and additionally reveal AD-analogous patterns of neurodegeneration after mTBI, which may be proportional to AD risk. Thus, our findings are relevant to ongoing efforts to identify mTBI patients at high risk for AD. Future studies should quantitatively compare the neurological and neuropsychological consequences of mTBI and AD to further elucidate their relationship.

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Conflicts of interests/competing interests

The authors declare that this research was conducted with no commercial or financial relationships that could be construed as a potential conflict of interest statement.

Ethics approval

This study was conducted with the approval of the Institutional Review Board at the University of Southern California and was carried out in accordance with the Declaration of Helsinki and with the U.S. Code of Federal Regulations (45 C.F.R. 46).

Consent to participate

All subjects provided written informed consent.

Consent for publication

Both authors approved the final version of the manuscript for publication.

Availability of data and material

MRI data acquired from HC and AD participants are publicly available from the ADNI database (<http://adni.loni.usc.edu>). For TBI participants, primary data generated during and/or analyzed during the current study are available subject to a data transfer agreement. At the request of some participants, their written permission is additionally required in some cases.

Code availability

The computer code used in this study is freely available. FreeSurfer (<https://surfer.nmr.mgh.harvard.edu>) and the FMRIB Software Library (<https://fsl.fmrib.ox.ac.uk>) are freely available. Equivalence testing was implemented using freely available MATLAB software (<https://www.mathworks.com/matlabcentral/fileexchange/63204>). Regression and SVM analyses were implemented in MATLAB (<http://mathworks.com>) using the glmfit, fitcsvm and predict functions.

Authors' contributions

K.A.R. and A.I. contributed to study design, data analysis, result interpretation and to manuscript redaction.

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Figure Legends

Fig. 1. Conceptual representation of the process for calculating the percentage of voxels associated with statistically significant findings within each neuroanatomic structure. (A) WM label map of the JHU atlas. (B) Mean WM skeleton mask of all subjects in the study. (C) Voxels where mTBI subjects exhibit mean FA values which are significantly lower ($p < 0.05$) than in HCs. The voxel map is overlaid on the skeletonized label map of the atlas, which is thickened for easier visualization. All images are overlaid on the $1\text{ mm} \times 1\text{ mm} \times 1\text{ mm}$ FMRIB₅₈ FA template, which is an average of FA maps across 58 healthy subjects. Colors encode various WM structures (see **Tables 1-3** for abbreviations).

Fig. 2. Statistically significant differences in mean FA between (A) HCs and mTBI patients, and between (B) HCs and AD patients. Color encodes $-\log_{10} p$, ranging from 2 (red) to 5 (yellow), corresponding to p -values between 0.05 (red) and ~ 0.0005 (yellow). p -values are for t tests using a significance threshold $\alpha = 0.05$, subject to multiple comparison correction. Smaller p -values are associated with higher values of $-\log_{10} p$ and with greater differences in mean FA between the groups compared. Images are displayed in radiologic convention. The z coordinate of each slice in MNI₁₅₂ atlas space is provided.

Fig. 3. Statistically significant differences in cortical thickness between (A) mTBI and HCs, (B) AD and HCs, and (C) mTBI and AD patients. Color encodes $-\log_{10} q$, where q is a p -value adjusted for the false discovery rate (FDR). Cortical overlays were smoothed using a Gaussian kernel with a full width at half maximum (FWHM) of 5 mm. In (A) and (B), blue regions represent areas where mTBI and AD subjects, respectively, have significantly thinner cortex compared to HCs. Regions colored in red represent areas where HCs have significantly thinner cortex. In (C), areas colored in green represent regions whose mean cortical thickness is statistically indistinguishable across mTBI and AD participants.

Tables

Table 1. WM structures listed, in descending numerical order, according to the percentage of voxels associated with FA averages which are significantly lower ($p < 0.05$), for each structure, in the mTBI cohort compared to HCs. Values are reported for the left and right hemispheres, except for structures which straddle both; in this latter case, only one value is reported halfway between the columns for the left and right hemispheres.

abbrev.	structure	part	%	
			left	right
TCC	corpus callosum	tapetum	100	100
EC	external capsule	—	100	99
UF	uncinate fasciculus	—	100	99
BCC	corpus callosum	body	98	
GCC	corpus callosum	genu	97	
CB	cingulum bundle	—	97	96
AIC	internal capsule	anterior	94	97
BCF	fornix	body	95	
SCbP	cerebellar peduncle	superior	91	95
PIC	internal capsule	posterior	91	90
SS	sagittal stratum	—	85	94
CP	cerebral peduncle	—	87	90
CF	fornix	cres	90	87
ICbP	cerebellar peduncle	inferior	87	86
SCC	corpus callosum	splenium	84	
SLF	longitudinal fasciculus	superior	83	82
RIC	internal capsule	retrolenticular	92	72
PTR	thalamic radiation	posterior	90	74
ACR	corona radiata	anterior	83	73
MCbP	cerebellar peduncle	middle	78	
SFOF	fronto-occipital fasciculus	superior	85	64
PCR	corona radiata	posterior	68	79
ML	medial lemniscus	—	56	68
SCR	corona radiata	superior	60	48
CST	corticospinal tract	—	18	23
PCT	pontine crossing tract	—	9	

Table 2. Like **Table 1**, comparing AD patients to HCs.

abbrev.	structure	part	%	
			left	right
BCC	corpus callosum	body	100	
BCF	fornix	body	100	
CF	fornix	cres	100	100
UF	uncinate fasciculus	—	100	100
CB	cingulum bundle	—	99	100
GCC	corpus callosum	genu	99	
TCC	corpus callosum	tapetum	97	100
SS	sagittal stratum	—	94	100
EC	external capsule	—	96	97
SFOF	fronto-occipital fasciculus	superior	98	95
PTR	thalamic radiation	posterior	99	88
ACR	corona radiata	anterior	85	91
SCbP	cerebellar peduncle	superior	90	82
SCC	corpus callosum	splenium	85	
AIC	internal capsule	anterior	93	77
SLF	longitudinal fasciculus	superior	88	80
ICbP	cerebellar peduncle	inferior	84	79
MCbP	cerebellar peduncle	middle	78	
RIC	internal capsule	retrolenticular	88	62
CP	cerebral peduncle	—	73	75
ML	medial lemniscus	—	72	73
PCR	corona radiata	posterior	63	66
PCT	pontine crossing tract	—	63	
PIC	internal capsule	posterior	69	43
SCR	corona radiata	superior	54	47
CST	corticospinal tract	—	15	6

Table 3. WM structures listed, in descending numerical order, according to the percentage of voxels associated with FA means which are statistically equivalent ($p < 0.05$), for each structure, across the mTBI and AD cohorts while also different from HCs to a statistically significant extent ($p < 0.05$). Values are reported for the left and right hemispheres, except for structures which straddle both; in this latter case, only one value is reported halfway between the columns for the left and right hemispheres.

abbrev.	structure	part	%	
			left	right
SFOF	fronto-occipital fasciculus	superior	91	95
CF	fornix	cres	65	80
PCT	pontine crossing tract	—	69	
ACR	corona radiata	anterior	58	53
BCF	fornix	body	49	
SCR	corona radiata	superior	45	52
PTR	thalamic radiation	posterior	59	38
PCR	corona radiata	posterior	46	45
MCbP	cerebellar peduncle	middle	44	
CST	corticospinal tract	—	36	35
BCC	corpus callosum	body	35	
ICbP	cerebellar peduncle	inferior	33	33
SLF	longitudinal fasciculus	superior	33	27
RIC	internal capsule	retrolenticular	28	31
TCC	corpus callosum	tapetum	9	43
ML	medial lemniscus	—	22	30
GCC	corpus callosum	genu	23	
CB	cingulum bundle	—	29	15
SS	sagittal stratum	—	19	23
SCbP	cerebellar peduncle	superior	19	21
PIC	internal capsule	posterior	16	23
SCC	corpus callosum	splenium	16	
CP	cerebral peduncle	—	11	13
AIC	internal capsule	anterior	13	9
EC	external capsule	—	4	12
UF	uncinate fasciculus	—	0	7

Table 4. GM structures listed, in descending numerical order, according to the percentage of cortical mesh vertices associated with FA means which are statistically equivalent ($p < 0.05$), for each structure, across the mTBI and AD cohorts while also different from HCs in a statistically significant way.

structure	part/segment	%	
		left	right
part of the precentral sulcus	superior	91	100
of the lateral sulcus	horizontal/anterior	75	86
short insular gyri	—	71	83
orbital gyri	—	76	74
cingulate sulcus	marginal branch	78	71
frontomarginal gyrus & sulcus	—	66	79
insular long gyrus & central sulcus	—	76	64
of the lateral sulcus	vertical anterior	72	65
straight gyrus	—	74	55
inferior frontal gyrus	triangular	63	65
inferior frontal gyrus	opercular	59	67
olfactory sulcus	—	57	68
inferior frontal gyrus	orbital	55	67
cingulate gyrus	posterior/ventral	56	65
transverse frontopolar gyri & sulci	—	52	69
subcentral gyrus & sulci	—	65	53
superior frontal gyrus	—	54	62
cuneus	—	53	63
cingulate gyrus & sulcus	anterior	62	50
cingulate gyrus & sulcus	middle/anterior	47	64
lateral orbital sulcus	—	40	69
cingulate gyrus & sulcus	middle/posterior	45	62
circular sulcus of the insula	superior	53	49
inferior temporal gyrus	—	55	47
paracentral lobule & sulcus	—	58	39
precentral gyrus	—	34	61
parieto-occipital sulcus	—	47	47
inferior frontal sulcus	—	28	66
lingual gyrus	—	46	47
middle frontal gyrus	—	35	58
calcarine sulcus	—	47	44
subcallosal area & gyrus	—	55	35
cingulate gyrus	posterior/dorsal	35	54
Heschl's gyrus	—	54	33
collateral & lingual sulci	—	31	55
temporal pole	—	49	36
central sulcus	—	27	57
circular sulcus of the insula	inferior	44	39
posterior transverse collateral sulcus	—	38	38
occipital pole	—	37	38
precuneus	—	35	38
suborbital sulcus	—	33	37
superior occipital gyrus	—	39	29

precentral sulcus	inferior	32	35
postcentral gyrus	—	32	32
supramarginal gyrus	—	36	25
fusiform gyrus	—	28	32
inferior occipital gyrus & sulcus	—	31	29
anterior occipital sulcus	—	23	34
parahippocampal gyrus	—	28	27
postcentral sulcus	—	25	29
middle temporal gyrus	—	24	27
superior temporal gyrus	lateral	13	35
middle frontal sulcus	—	18	29
anterior transverse collateral sulcus	—	6	39
superior parietal lobule	—	15	29
superior & transverse occipital sulci	—	34	9
superior temporal gyrus	polar plane	32	11
circular sulcus of the insula	anterior	23	19
orbital sulci	—	17	24
subparietal sulcus	—	16	20
middle occipital gyrus	—	19	16
lateral sulcus	posterior	16	16
pericallosal sulcus	—	17	13
lateral occipito-temporal sulcus	—	18	12
Jensen's sulcus	—	12	13
superior temporal gyrus	temporal plane	13	12
inferior temporal sulcus	—	13	8
angular gyrus	—	14	1
superior temporal sulcus	—	0	14
superior frontal sulcus	—	13	1
middle occipital & lunati sulci	—	7	4
intraparietal & transverse parietal sulci	—	3	7

Figure 1

