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14. ABSTRACT

The overall goal is to cost-efficiently harness the newly available wealth of nationwide clinical neuroimaging data and merge with our existing cohort of 1.6 million TBI-exposed and unexposed veterans with up to 12 years of follow-up in order to (1) create a large, nationwide, high-quality cohort of ~200,000 TBI-exposed and un-exposed veterans with MRI imaging data; (2) predict which TBI-exposed veterans will go on to develop dementia; and (3) identify prevalence of specific sub-types of dementia among TBI-exposed versus unexposed veterans. We expect that we will (1) produce the largest military-relevant MRI dataset with expertly curated TBI exposure and dementia outcome and up to 12 years of follow-up (with option of continued follow-up via VHA EMR); (2) develop a method for predicting 5+-year risk of post-TBI dementia using routinely collected clinical MRI. This work may directly inform public health planning within the DoD and VHA and generate testable hypotheses regarding underlying etiology of post-TBI dementia.

15. SUBJECT TERMS
Traumatic brain injury (TBI); veterans; dementia; magnetic resonance imaging (MRI); deep learning; brain atrophy; endophenotyping;

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1. **INTRODUCTION:** *Narrative that briefly (one paragraph) describes the subject, purpose and scope of the research.*

An estimated 10 to 20% of Veterans from the wars in Iraq and Afghanistan have suffered traumatic brain injury (TBI). Many Veterans from prior conflicts have experienced TBI as well. Some studies have reported a link between TBI and increased risk of cognitive impairment and dementia even after years of active life post injury, but few have studied Veterans. Many people with TBI do not develop dementia; however, we have no tools to predict which individuals are at highest risk and would benefit from careful follow-up and recruitment into clinical trials to prevent post-TBI dementia. Practical biomarkers for identifying patients at highest risk for dementia after TBI are desperately needed to inform individual patient management, dementia prevention strategies, and clinical trials. Furthermore, understanding the underlying etiology of post-TBI dementia (clinical dementia sub-types) could further inform clinical care and prevention for Veterans with TBI. Measures of structural brain changes rapidly measured on neuroimaging modalities, particularly structural brain magnetic resonance imaging (MRI), are well-established predictors of cognitive decline and risk for dementia in the general population. Large population-based samples of TBI-exposed veterans are needed in order to leverage advances in neuroimaging and biomarker discovery via artificial intelligence approaches to develop robust and generalizable models to predict post-TBI dementia and to discover neuroimaging biomarkers to characterize dementia subtypes among TBI-exposed individuals. The Veterans Health Administration (VHA) has recently made the nationwide VHA imaging data available to researchers; we have the unprecedented opportunity to merge this nationwide structural MRI with our existing nationwide VHA cohort of 1.6 million TBI-exposed and unexposed veterans to create the largest military-relevant TBI MRI data-set that has (to our knowledge) ever been created and directly address the major knowledge gaps described. We have assembled a team of experts in dementia, TBI, neuroimaging, and prognostic modeling with track records of successful completion of high impact research. The propose a 3-year project will cost-efficiently harness the newly available wealth of nationwide clinical neuroimaging data and merge with our existing cohort of 1.6 million TBI-exposed and unexposed veterans with up to 12 years of follow-up in order to (1) create a large, nationwide, high-quality cohort of ~200,000 TBI-exposed and un-exposed veterans with MRI imaging data; (2) predict which TBI exposed veterans will go on to develop dementia; and (3) identify prevalence of specific sub-types of dementia among TBI-exposed versus unexposed veterans. We expect that we will (1) produce the largest military relevant MRI dataset with expertly curated TBI exposure and dementia outcome and up to 12 years of follow up (with option of continued follow-up via VHA EMR); (2) develop a method for predicting 5+-year risk of post-TBI dementia using routinely collected clinical MRI. This work may directly inform clinical care of veterans and identify a high-risk subset that may be ideal for further studies of underlying mechanisms of post-TBI dementia and clinical trials for prevention; and (2) facilitate discovery of the nationwide epidemiology of neuroimaging biomarker-supported dementia sub-types in TBI-exposed versus unexposed veterans receiving care within VHA. This work may directly inform public health planning within the DoD and VHA and generate testable hypotheses regarding underlying etiology of post-TBI dementia.

2. **KEYWORDS:** *Provide a brief list of keywords (limit to 20 words).*

Traumatic brain injury (TBI); veterans; dementia; magnetic resonance imaging (MRI); deep learning; brain atrophy; endophenotyping;

3. **ACCOMPLISHMENTS:** *The PI is reminded that the recipient organization is required to obtain prior written approval from the awarding agency grants official whenever there are significant changes in the project or its direction.*

What were the major goals of the project?

List the major goals of the project as stated in the approved SOW. If the application listed milestones/target dates for important activities or phases of the project, identify these dates and show actual completion dates or the percentage of completion.

	Timeline

Major Task 1: Obtain local and HRPO IRB approval	Months
Subtask 1: Submit document for local IRB review. • Submitted: UCSF CHR & SFVAMC R & D; 07 AUG 2019 • Approved by: UCSF CHR; 25 NOV 2019; • Approved by: SFVAMC R & D 06 DEC 2019	1-3
Subtask 2: Submit IRB approval and necessary documents for HRPO review: • Submitted: DOD HRPO; 06 DEC 2019 o Approval: 21 FEB 2020	3-5
Milestone #1: HRPO approval • *DOD HRPO; Approval Achieved;*	5-6
Specific Aim 1:	
Major Task 2: To create a large, nationwide, high- quality cohort of ~200,000 TBI-exposed and un- exposed veterans with MRI imaging data.	Months
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Subtask 2: Build MRN list for relevant neuroimages in VHA system	5-7
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Specific Aim2:	
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What was accomplished under these goals?

For this reporting period describe: 1) major activities; 2) specific objectives; 3) significant results or key outcomes, including major findings, developments, or conclusions (both positive and negative); and/or 4) other achievements. Include a discussion of stated goals not met. Description shall include pertinent data and graphs in sufficient detail to explain any significant results achieved. A succinct description of the methodology used shall be provided. As the project progresses to completion, the emphasis in reporting in this section should shift from reporting activities to reporting accomplishments.

Data Curation

We successfully curated a dataset, focusing on images from the local repository at San Francisco Veterans Affairs Medical Center (SFVAMC). This dataset allowed us to test hypotheses with minimal impact of imaging heterogeneity, simultaneously assessing the variability in image quality between clinical and research imaging. Noteworthy characteristics of this dataset include a bimodal distribution of age at traumatic brain injury (TBI) exposure in cases without dementia. Early exposure cases cluster around age 30, while later exposure cases cluster around age 60. Cases with dementia diagnosis had TBI exposure at an average age of 61.6 ± 13.6 years. Intriguingly, among cases with dementia diagnosis, 40% experienced early-onset dementia (diagnosis before age 65), providing a unique opportunity to study the isolated impact of TBI, as late-onset individuals may have comorbid pathologies. The time from TBI exposure to dementia diagnosis was 3.9 ± 3.1 years (median of 3.6 years), independent of the age of TBI exposure (correlation = 0.02; p = 0.91). Furthermore, 40% of the cases had at least one clinical brain MRI within a year of TBI exposure, and cases with dementia diagnosis after TBI exposure, on average, had a clinical brain MRI within 0.9 ± 2.1 years of their clinical dementia diagnosis. These findings open new avenues for understanding the intricate relationships between TBI, age of exposure, and subsequent dementia onset. We retrieved clinical brain MR images from SFVAMC Clinical PACS archives. Each image was recoded and deidentified following our secure data handling protocols.

MRIQC priority ordering into the prognostic models based on machine learning of structural MRI data

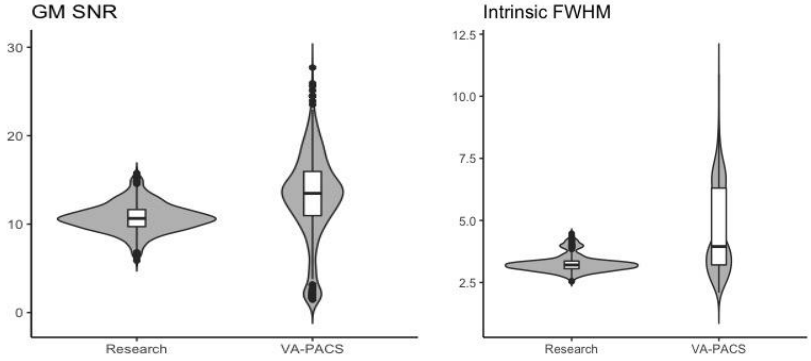
We implemented and tested an MRI quality control pipeline using the MRIQC tool. As detailed below, leveraging the rich MRIQC metrics, we demonstrated that features contributing to heterogeneity in clinical PACS data inherently have higher dimensionality compared to the relative one-dimensional vendor/model differences underlying morphometry heterogeneity in a clinical research setting. This is largely attributed to the standardized and well-controlled operationalization of imaging protocols in clinical research projects. In line with this finding, we incorporated MRIQC-based clustering into prognostic and predictive models for the harmonized interpretation of MRI morphometry measures.

The clinical brain MR scans were ordered and acquired with variable acquisition parameters following protocols approved by local clinics, using clinical MR scanners. VA PACS dataset used in this project included brain scans acquired at MRI scanners at 1.5T and 3T magnetic field strength by multiple vendors (Siemens and GE) and multiple models from these vendors (Siemens: Achieva, Avanto, Skyra, Symphony,

Verio 8, and Numaris 4; GE: Signa Excite and Signa HDxt). Furthermore, the MRI data were acquired with sequence parameters varied in acquisition type (2D versus 3D), echo time (0.00137 – 0.474s), repetition time (0.00315 – 5s), slice thickness (0.9 – 5mm), and acquisition matrix (143 – 262). Most imaging data harmonization approaches in clinical research context primarily focus on scanner differences based on vendor/model categorizations and magnetic field strength differences. While these approaches have proven effective, their generalizability to clinical imaging datasets has been limited. One significant reason for this limited generalizability is that, despite heterogeneity due to scanner or magnetic field differences in clinical research datasets, across scanners and different magnetic field strengths, the acquisition parameters are highly standardized. In another word, the imaging data heterogeneity in a clinical research setting is relatively one-dimensional, captured by a single variable coding for vendor/model differences, which automatically includes magnetic field strength stratification. However, clinical PACS data inherently exhibit heterogeneity at a higher dimensionality. In this higher dimensionality, variability arises not only from vendor/model or magnetic field strength differences but also from variations in key acquisition parameters such as slice thickness, in-plane resolution (i.e., acquisition matrix), acquisition type, and more.

As no a priori knowledge was available regarding the dimensionality influencing image heterogeneity, we adopted a data-driven approach. In this method, the key assumption was that heterogeneity across these dimensions impacts MR imaging morphometric measures, and these differences were quantifiably reflected in MRIQC metrics. Consequently, data-driven clusters in the MRIQC metric profiles we were examining should emerge in this study.

The clustering incorporated the following MRIQC metrics: coefficient of joint variation (CJV), contrast-to-noise ratio (CNR), entropy focus criterion (EFC), foreground-to-background energy ratio (FBER), full width at half maximum (FWHM; average, x, y, z), intensity nonuniformity (INU) median and range, Mortamet quality indices 1 and 2 (QI1 and QI2), signal to noise ratio for CSF, WM, GM, and total, and Dietrich's SNR for CSF, WM, GM, and total. While visualizing the multi-dimensional MRIQC metric space proved challenging, the extended heterogeneity was evident – as illustrated below for two key variables, namely intrinsic FWHM and GM SNR – in clinical PACS data when compared to a clinical research dataset—the Effects of Traumatic Brain Injury and Post-Traumatic Stress Disorder and Alzheimer's Disease on Brain Tau in Vietnam Veterans using ADNI study funded by DOD; W81XWH-14-1-0462 (PI: Weiner).

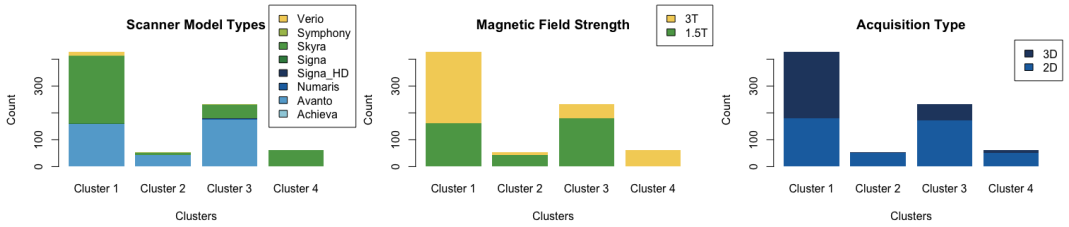


Extended heterogeneity in MR image quality in clinical PACS data compared to clinical research data, i.e., ADNI-DOD study

ADNI-DOD project recruited Vietnam Veterans meeting criteria for normal cognition or mild cognitive impairment with a history of TBI only, PTSD only, or both TBI and PTSD, or with no history of TBI and/or PTSD. To gain a deeper insight into the distinctions between clinical and research -quality MRI acquisitions for qualifying imaging markers of neurodegeneration, we leveraged imaging data from ADNI-DOD study throughout this project. This approached allowed for a comprehensive characterization of differences in clinical versus research-quality imaging as it is essential for the clinical translation of imaging biomarkers.

To perform a data-driven image quality clustering, first the Euclidean distance metric was used to compute the dissimilarity between each observation. Then, using the Ward's minimum variance method, hierarchical clustering was performed where at each step in the algorithm, two observations that are most similar are

fused into a single cluster. These steps are repeated until all observations are members of one cluster, resulting in a dendrogram, from which an optimal number of clusters were determined by implementing a cut point at the end of the longest leg of the first branch. Applying this data-driven approach, we identified four clusters (i.e., heterogeneity dimensions) in the dataset with similar MR imaging quality. The absence of a direct association of data-driven image quality clusters with scanner vendor/model types, magnetic field strength, or acquisition type, as illustrated in bar graphs below, affirmed our initial assumption. This finding underscored that the common practice of one-dimensional stratification based on these variables, typically employed in data harmonization for research datasets, was insufficient to capture the dimensions of heterogeneity in clinical PACS MRI data.

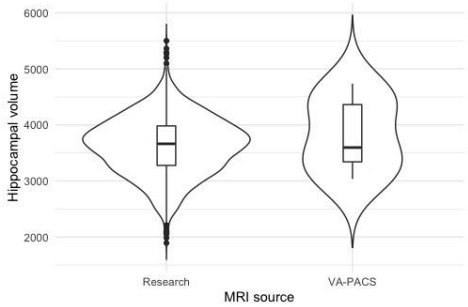


Distribution of scanner vendor/model types, magnetic field strength (1.5T vs 3T), and acquisition type (2D vs 3D) across image quality clusters

Clinical MRI as biomarker of neurodegeneration

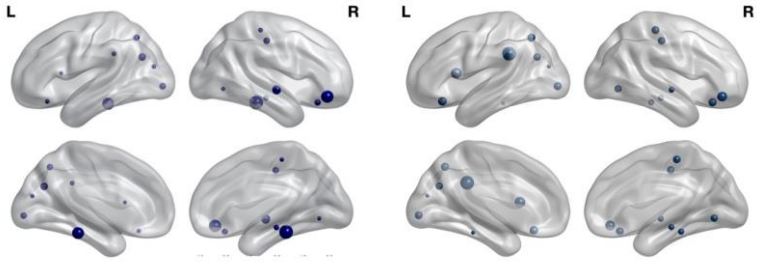
Considering the anticipated variability in MRI data quality within this project, we adopted a multi-atlas segmentation framework to ensure a consistent parcellation of anatomical brain structures in our MRI dataset. This approach enables optimal estimation of regional tissue volumes in each structural MRI, regardless of image acquisition parameters and quality, by imposing segmentation consistency. Each atlas set preserves the image intensity characteristics specific to the field strength/scanner platform/imaging protocol.

When compared to data from the ADNI-DOD cohort, the estimated hippocampal volume distribution from clinical brain MRIs proved comparable to hippocampal estimates from research MRI data (p=0.32), despite differences in clinical vs. research MRI quality. This supports the robust application of harmonized image processing to clinical-quality MRI data.



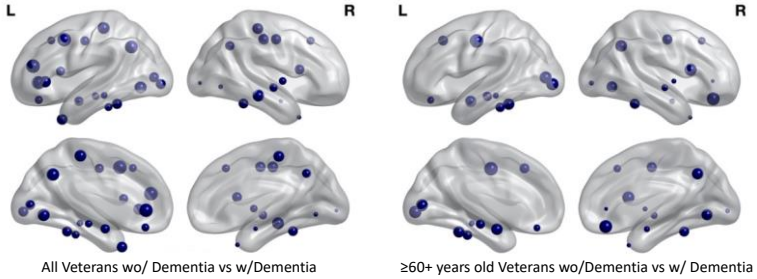
Distribution of hippocampal volume within a multicenter research imaging cohort (Research) and within clinical brain MRI cohort (VA-PACS)

Based on these robust morphometric measures, we observed widespread cortical atrophy in Male Veterans with TBI+Dementia compared to those with TBI only, controlling for age at MRI, TBI severity at MRI, and time from Dementia diagnosis. Furthermore, compared to lower TBI severity (1) cases, veterans with TBI severity of 2 and 3 presented with greater frontotemporal and parietofrontal atrophy, respectively.



Compared to lower TBI severity (1) cases, veterans with TBI severity of 2 and 3 presented with greater frontotemporal and parietofrontal atrophy, respectively

Predominantly frontotemporal atrophy was associated with dementia in veterans with TBI. The extent of atrophy was more pronounced in temporal regions for veterans with TBI and dementia after the age of 60 years.

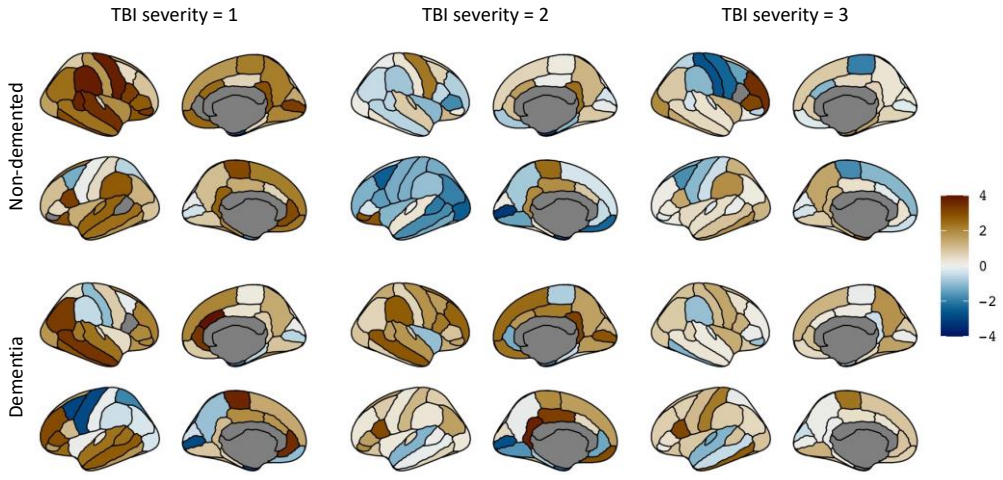


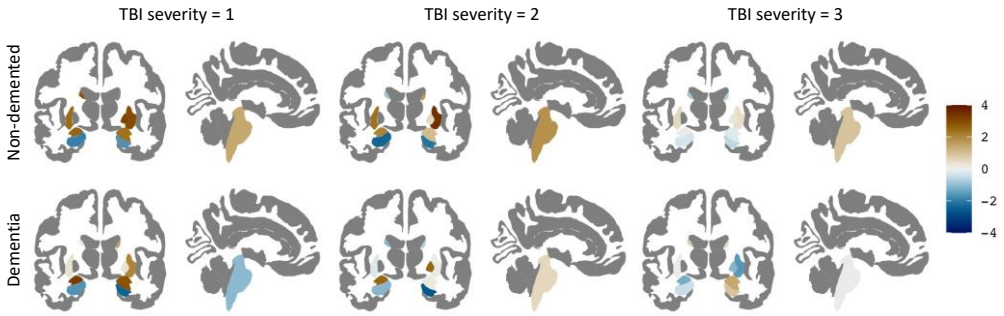
Compared to Veterans without Dementia diagnosis, Veterans with Dementia presented with greater parietotemporal and frontal atrophy

<u>Neurodegeneration patterns in intrinsic brain network-based dimensions</u>

To identify network-based neurodegeneration subtypes of dementia while preserving individual effects, we established a 6-dimensional dementia phenotype relevance score. This score quantifies the topographic similarity between the atrophy (neurodegeneration) signature of each individual from MRI and networks of interest derived from intrinsic brain connectivity, including default mode network, executive network, frontoparietal network, visual network, auditory network, and motor network. Each of these networks of interest has been associated with distinct dementia subtypes [1,2].

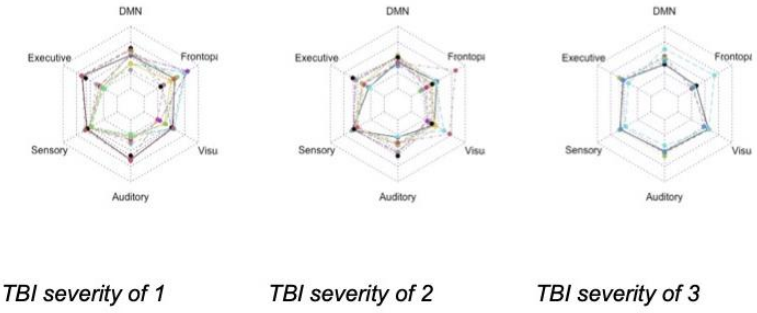
Specifically, individual atrophy signatures, based on harmonized MUSE parcellation, were estimated as W-scores by regressing out normal confounding effects of age differences in a No-TBI/No-Dementia cohort. W-score map provides a spatial distribution where individuals' gray matter probability would fall on the normal gray matter probability distribution.





The individual W-score maps in the TBI severity versus dementia captures the greater level of atrophy with greater TBI severity and dementia diagnosis. The W-score maps also allow us to capture individual spatial variability and variability due to interaction between TBI severity and dementia diagnosis.

We developed an approach that explicitly avoids pairwise registrations between individual brain MRIs but instead focuses on modeling and discriminating between cortical topographic patterns with the following computational framework. First, for each network of interest, a connectivity density vector of dimensionality equal to the number of MUSE ROI parcellations was created based on established intrinsic functional connectivity map templates. This involved estimating average functional connectivity within each MUSE ROI and vector normalization, using established intrinsic functional connectivity map templates. A ROI-based W-score feature vector was then created for each individual by averaging W-scores within each MUSE anatomical ROI parcellation. The W-score feature vector was normalized, yielding a W-score density vector capturing the topography of atrophy signatures independent of the severity of atrophy. This was important because our aim was to assign biomarker-supported dementia subtypes, regardless of the magnitude/severity of the disease.
Subject-specific cortical atrophy topographic patterns within each network of interest are illustrated using radar plots in figure below, depicting sample individuals with post-TBI dementia diagnosis and different levels of TBI severity. These plots capture the expected heterogeneity in atrophy patterns across individuals.



Cortical atrophy topographic patterns within each network of interest for sample individuals with post-TBI dementia

Within our Veterans cohort, we observed the most significant association of cortical atrophy topographic patterns with post-TBI dementia within the executive and auditory networks. Simultaneously, the association with TBI severity was most pronounced within the sensory network. Additionally, the frontoparietal network demonstrated the strongest association with cortical atrophy topographic patterns and the interaction between post-TBI dementia and TBI severity.

<u>Multilabel machine learning based phenotypical classification modeling</u>
We employed the identified atrophy signatures to guide the development of machine learning-based prognostic and predictive models to test our primary hypotheses. Specifically, we crafted multi-label learning classification techniques, acknowledging that each veteran's data was associated with multiple labels (e.g., exposed to TBI or not, and developed dementia or not), and these labels were not mutually exclusive. This approach aligned more closely with clinical reality, where clinical/cognitive phenotypes

were typically interrelated. We implemented a multi-label random forest (MLRF) classifier. The RF is an ensemble method that builds several independent decision tree classifiers on different subsets of the dataset. It considers the combination (often the average) of the output of each independent classifier to improve performance in producing overall predictions. Multi-label learning is a supervised problem in which several labels are learned simultaneously. For all experiments, model construction and evaluation were performed over 10 iterations of five-fold multi-label stratified cross-validation. The feature space includes harmonized estimates of regional atrophy measures from T1 MRIs, and age at T1 MRI acquisition. The outcome phenotype labels were TBI vs. no-TBI exposure and Cognitively Normal vs. Dementia. Our implementation showed a multi-label classification performance of 69% ± 25% accuracy.

White matter hyperintensity (WMH) segmentation and volume estimates from varying types of FLAIR sequences

Clinical FLAIR sequences varied from being absent to 2D FLAIR sequences, and 3D high-resolution FLAIR sequences. Numerous methodologies for White Matter Hyperintensities (WMH) segmentation have been developed and validated for specific MRI datasets. Consequently, we set out to explore how specific WMH segmentation methods perform when confronted with different FLAIR sequences. To achieve this, we identified a separate test dataset of 15 individuals who underwent a lower resolution FLAIR sequence compared to a high-resolution $1mm^3$ 3D FLAIR sequence within an average of 7 months from one another. We conducted comparison studies between two WMH segmentation methods: Wisconsin White Matter Hyperintensities Segmentation Toolbox (W2MHS)[5], a classical image processing framework, and Multimodal Ensemble-Based Segmentation of White Matter Lesions (Deep-WML)[6], a deep-learning segmentation model.

We compared WMH segmentation volumes and topographies. The correlation between these measurements for W2MHS was R = 0.95 with a median absolute deviation of 0.26. For Deep-WMH, the correlation was R = 0.97 with a median absolute deviation of 0.13. Consequently, the estimation of WMH volumes using classical image processing or recently developed deep-learning models was reasonably robust to harmonize significant differences between FLAIR sequences. However, Dice coefficients between the segmentations were more modest, ranging from 10% to 72% (mean 45%) for W2MHS, and ranging from 3% to 56% (mean 28%) for Deep-WML. Accordingly, topographic evaluation was more limited across different FLAIR sequences, particularly for the deep learning approach. Notably, the correlations between W2MHS and Deep-WML for low- and high-resolution FLAIR were high (R = 0.91 and 0.97, respectively).

Cerebrovascular white matter lesion burden associated with TBI and TBI severity but not clinical dementia diagnosis

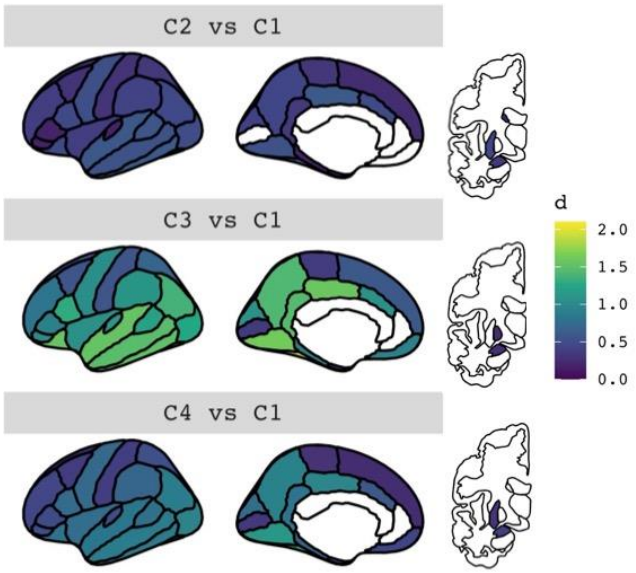
In our study, 167 Veterans, with a mean age of 61 ± 16 years at the time of MRI, underwent white matter hyperintensity segmentation to estimate cerebrovascular white matter lesion burden. Among them, 51% had a history of TBI (40% with TBI Severity = 1, 40% with TBI Severity = 2, and 20% with TBI Severity = 3). Additionally, 20% had a clinical dementia diagnosis, and 20% had both a history of TBI and a clinical dementia diagnosis.

In a nested linear regression analysis, controlling for age at MRI, total intracranial volume, education, race, age of diagnosis within Veterans diagnosed with clinical dementia, and age of TBI incidence within Veterans with a history of TBI, we observed that greater cerebrovascular white matter lesion burden was associated with age at MRI ($d=0.13$; $p<10^{-4}$), education ($d=0.14$; $p=0.02$), TBI diagnosis ($d=0.28$; $p<10^{-4}$), and age of TBI incidence ($d=0.20$; $p=0.0001$). However, it was not associated with dementia diagnosis ($d=0.09$; $p=0.14$) or age of dementia diagnosis ($d=0.08$; $p=0.06$).

Cerebrovascular white matter lesion burden clusters associated with greater parietotemporal atrophy

Four clusters of white matter lesion burden profiles were identified in the Veterans cohort. Approximately 11% exhibited low levels of white matter lesion volume, measuring at 1.8 ± 0.9 cc (Cluster 1; C1). The majority of Veterans (41%) had a white matter lesion volume of 8.3 ± 3.7 cc (Cluster 2; C2). Twenty-one percent displayed a higher white matter lesion volume, measuring at 22.6 ± 8.0 cc (Cluster 3; C3), while 27% had the greatest white matter lesion burden, measuring at 54.5 ± 17.9 cc (Cluster 4; C4). When compared to the low cerebrovascular lesion burden cluster (C1), C3 with a moderate white matter lesion burden cluster had the greatest gray matter atrophy, predominantly in parietotemporal cortical regions. This

suggests that subgroups of Veterans exhibit distinct patterns of neurodegeneration, with some presenting cerebrovascular and others cortical atrophy as dominant features underlying their dementia.



What opportunities for training and professional development has the project provided?
If the project was not intended to provide training and professional development opportunities or there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe opportunities for training and professional development provided to anyone who worked on the project or anyone who was involved in the activities supported by the project. "Training" activities are those in which individuals with advanced professional skills and experience assist others in attaining greater proficiency. Training activities may include, for example, courses or one-on-one work with a mentor. "Professional development" activities result in increased knowledge or skill in one's area of expertise and may include workshops, conferences, seminars, study groups, and individual study. Include participation in conferences, workshops, and seminars not listed under major activities.

Nothing to report.

How were the results disseminated to communities of interest?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe how the results were disseminated to communities of interest. Include any outreach activities that were undertaken to reach members of communities who are not usually aware of these project activities, for the purpose of enhancing public understanding and increasing interest in learning and careers in science, technology, and the humanities.

Nothing to report.

What do you plan to do during the next reporting period to accomplish the goals?
If this is the final report, state "Nothing to Report."

Describe briefly what you plan to do during the next reporting period to accomplish the goals and objectives.

Not applicable.

4. **IMPACT:** D*escribe distinctive contributions, major accomplishments, innovations, successes, or any change in practice or behavior that has come about as a result of the project relative to:*

What was the impact on the development of the principal discipline(s) of the project?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe how findings, results, techniques that were developed or extended, or other products from the project made an impact or are likely to make an impact on the base of knowledge, theory, and research in the principal disciplinary field(s) of the project. Summarize using language that an intelligent lay audience can understand (Scientific American style).

The project's impact on the field is substantial. In comparing data from clinical brain MRIs to a multicenter research neuroimaging cohort, the estimated distribution of cortical atrophy demonstrated consistency between clinical and research MRI data, despite variations in image quality. This aligns with the project's goal of harmonizing image processing for clinical-grade MRI data, enhancing the translational value of the methods developed.

Moreover, the project identified significant associations between cortical atrophy patterns and post-TBI dementia. The executive and auditory networks exhibited the strongest association, while TBI severity was prominently linked to the sensory network. Additionally, the frontoparietal network showed a significant association with cortical atrophy patterns and the interaction between post-TBI dementia and TBI severity. These findings are crucial for advancing our understanding of MRI-based dementia endophenotyping, providing valuable insights into the diverse neurodegenerative patterns associated with TBI.

What was the impact on other disciplines?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe how the findings, results, or techniques that were developed or improved, or other products from the project made an impact or are likely to make an impact on other disciplines.

The impact of the project extends beyond its primary discipline into various related fields. The harmonized image processing techniques developed for clinical-quality MRI data have implications for fields such as medical imaging, neurology, and cognitive neuroscience. By demonstrating the comparability of cortical atrophy distribution between clinical and research MRI data, the project contributes valuable insights that may influence practices in clinical diagnostics and research methodologies.

What was the impact on technology transfer?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe ways in which the project made an impact, or is likely to make an impact, on commercial technology or public use, including:

- *transfer of results to entities in government or industry;*
- *instances where the research has led to the initiation of a start-up company; or*
- *adoption of new practices.*

Nothing to Report.

What was the impact on society beyond science and technology?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe how results from the project made an impact, or are likely to make an impact, beyond the bounds of science, engineering, and the academic world on areas such as:

- *improving public knowledge, attitudes, skills, and abilities;*
- *changing behavior, practices, decision making, policies (including regulatory policies), or social actions; or*
- *improving social, economic, civic, or environmental conditions.*

Nothing to Report.

5. **CHANGES/PROBLEMS:** *The PD/PI is reminded that the recipient organization is required to obtain prior written approval from the awarding agency grants official whenever there are significant changes in the project or its direction. If not previously reported in writing, provide the following additional information or state, "Nothing to Report," if applicable:*

Nothing to Report.

Changes in approach and reasons for change
Describe any changes in approach during the reporting period and reasons for these changes. Remember that significant changes in objectives and scope require prior approval of the agency.

Nothing to Report.

Actual or anticipated problems or delays and actions or plans to resolve them
Describe problems or delays encountered during the reporting period and actions or plans to resolve them.

Nothing to Report.

Changes that had a significant impact on expenditures
Describe changes during the reporting period that may have had a significant impact on expenditures, for example, delays in hiring staff or favorable developments that enable meeting objectives at less cost than anticipated.

Nothing to Report.

Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents
Describe significant deviations, unexpected outcomes, or changes in approved protocols for the use or care of human subjects, vertebrate animals, biohazards, and/or select agents during the reporting period. If required, were these changes approved by the applicable institution committee (or equivalent) and reported to the agency? Also specify the applicable Institutional Review Board/Institutional Animal Care and Use Committee approval dates.

Significant changes in use or care of human subjects

Not applicable.

Significant changes in use or care of vertebrate animals

Not applicable.

Significant changes in use of biohazards and/or select agents

Not applicable.

6. **PRODUCTS:** *List any products resulting from the project during the reporting period. If there is nothing to report under a particular item, state "Nothing to Report."*

- **Publications, conference papers, and presentations**
  Report only the major publication(s) resulting from the work under this award.

  Journal publications. *List peer-reviewed articles or papers appearing in scientific, technical, or professional journals. Identify for each publication: Author(s); title; journal; volume: year; page numbers; status of publication (published; accepted, awaiting publication; submitted, under review; other); acknowledgement of federal support (yes/no).*

  Nothing to report.

  Books or other non-periodical, one-time publications. *Report any book, monograph, dissertation, abstract, or the like published as or in a separate publication, rather than a periodical or series. Include any significant publication in the proceedings of a one-time conference or in the report of a one-time study, commission, or the like. Identify for each one-time publication: author(s); title; editor; title of collection, if applicable; bibliographic information; year; type of publication (e.g., book, thesis or dissertation); status of publication (published; accepted, awaiting publication; submitted, under review; other); acknowledgement of federal support (yes/no).*

  Nothing to report.

  Other publications, conference papers and presentations. *Identify any other publications, conference papers and/or presentations not reported above. Specify the status of the publication as noted above. List presentations made during the last year (international, national, local societies, military meetings, etc.). Use an asterisk (*) if presentation produced a manuscript.*

  Nothing to report.

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

List the URL for any Internet site(s) that disseminates the results of the research activities. A short description of each site should be provided. It is not necessary to include the publications already specified above in this section.

Nothing to report.

- **Technologies or techniques**
  Identify technologies or techniques that resulted from the research activities. Describe the technologies or techniques were shared.

Nothing to report.

- **Inventions, patent applications, and/or licenses**
  Identify inventions, patent applications with date, and/or licenses that have resulted from the research. Submission of this information as part of an interim research performance progress report is not a substitute for any other invention reporting required under the terms and conditions of an award.

Nothing to report.

- **Other Products**
  Identify any other reportable outcomes that were developed under this project. Reportable outcomes are defined as a research result that is or relates to a product, scientific advance, or research tool that makes a meaningful contribution toward the understanding, prevention, diagnosis, prognosis, treatment and /or rehabilitation of a disease, injury or condition, or to improve the quality of life. Examples include:
  - *data or databases;*
  - *physical collections;*
  - *audio or video products;*
  - *software;*
  - *models;*
  - *educational aids or curricula;*
  - *instruments or equipment;*
  - *research material (e.g., Germplasm; cell lines, DNA probes, animal models);*
  - *clinical interventions;*
  - *new business creation; and*
  - *other.*

Nothing to report.

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?
Provide the following information for: (1) PDs/PIs; and (2) each person who has worked at least one person month per year on the project during the reporting period, regardless of the source of compensation (a person month equals approximately 160 hours of effort). If information is unchanged from a previous submission, provide the name only and indicate "no change".

Name:	Duygu Tosun-Turgut
Project Role:	PI
Researcher Identifier (e.g. ORCID ID):	ORCID ID 0000-0001-8644-7724
Nearest person month worked:	0.93
Contribution to Project:	Dr. Tosun-Turgut is the contact Principal Investigator and oversees all aspects of the project.

Name:	W. John Boscardin
Project Role:	*Co-Investigator*
Researcher Identifier (e.g. ORCID ID):	N/A
Nearest person month worked:	0.6
Contribution to Project:	Dr. Boscardin is Co-Investigator. In coordination with Dr. Tosun-Turgut, provides scientific leadership and input on the analyses and interpretation of results

Name:	Alison Myoraku
Project Role:	Staff Research Associate
Researcher Identifier (e.g. ORCID ID):	N/A
Nearest person month worked:	5.7
Contribution to Project:	Ms. Myoraku works on dataset creation and management.
Name:	Alison Myoraku

Name:	Eliana Philips
Project Role:	Imaging Programmer
Researcher Identifier (e.g. ORCID ID):	N/A
Nearest person month worked:	3.0
Contribution to Project:	Responsible for management of all VHA imaging data.

Name:	Tamar Schaap
Project Role:	Biostatistician
Researcher Identifier (e.g. ORCID ID):	N/A

Nearest person month worked:	4.7
Contribution to Project:	Responsible for implementation and validation of all statistical modeling.

Name:	Feng Xia
Project Role:	Epidemiology Programmer
Researcher Identifier (e.g. ORCID ID):	N/A
Nearest person month worked:	1.0
Contribution to Project:	Responsible for management of all VHA statistical non-imaging.

Name:	Stephanie R. Chen
Project Role:	Project Manager
Researcher Identifier (e.g. ORCID ID):	N/A
Nearest person month worked:	1.5
Contribution to Project:	Serves as the project coordinator

Name:	Mark Choe
Project Role:	Research Associate
Researcher Identifier (e.g. ORCID ID):	N/A
Nearest person month worked:	1.8
Contribution to Project:	Serves as the imaging research associate

Name:	Zachary Hausle
Project Role:	Biostatistician
Researcher Identifier (e.g. ORCID ID):	N/A
Nearest person month worked:	3.5
Contribution to Project:	Leads the biostatistical analysis

Name:	Marta Mila Aloma
Project Role:	Post Doc

Researcher Identifier (e.g. ORCID ID):	N/A
Nearest person month worked:	9.5
Contribution to Project:	Serve as the scientific researcher

Name:	Jiaxiuxiu Zhang
Project Role:	Research Associate
Researcher Identifier (e.g. ORCID ID):	N/A
Nearest person month worked:	5.6
Contribution to Project:	Responsible for multimodal image processing

Name:	Pamela Zobel-Thropp
Project Role:	Project Manager
Researcher Identifier (e.g. ORCID ID):	N/A
Nearest person month worked:	4.6
Contribution to Project:	Serves as the lead project manager

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

If the active support has changed for the PD/PI(s) or senior/key personnel, then describe what the change has been. Changes may occur, for example, if a previously active grant has closed and/or if a previously pending grant is now active. Annotate this information so it is clear what has changed from the previous submission. Submission of other support information is not necessary for pending changes or for changes in the level of effort for active support reported previously. The awarding agency may require prior written approval if a change in active other support significantly impacts the effort on the project that is the subject of the project report.

Nothing to report.

What other organizations were involved as partners?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe partner organizations – academic institutions, other nonprofits, industrial or commercial firms, state or local governments, schools or school systems, or other organizations (foreign or domestic) – that were involved with the project. Partner organizations may have provided financial or in-kind support, supplied facilities or equipment, collaborated in the research, exchanged personnel, or otherwise contributed.

Provide the following information for each partnership:
Organization Name:

Location of Organization: (if foreign location list country)
Partner's contribution to the project (identify one or more)

- *Financial support;*
- *In-kind support (e.g., partner makes software, computers, equipment, etc., available to project staff);*
- *Facilities (e.g., project staff use the partner's facilities for project activities);*
- *Collaboration (e.g., partner's staff work with project staff on the project);*
- *Personnel exchanges (e.g., project staff and/or partner's staff use each other's facilities, work at each other's site); and*
- *Other.*

Nothing to report.

8. SPECIAL REPORTING REQUIREMENTS

COLLABORATIVE AWARDS: *For collaborative awards, independent reports are required from BOTH the Initiating Principal Investigator (PI) and the Collaborating/Partnering PI. A duplicative report is acceptable; however, tasks shall be clearly marked with the responsible PI and research site. A report shall be submitted to* ***https://ebrap.org/eBRAP/public/index.htm*** *for each unique award.*

QUAD CHARTS: *If applicable, the Quad Chart (available on https://www.usamraa.army.mil/Pages/Resources.aspx) should be updated and submitted with attachments.*

9. APPENDICES: *Attach all appendices that contain information that supplements, clarifies or supports the text. Examples include original copies of journal articles, reprints of manuscripts and abstracts, a curriculum vitae, patent applications, study questionnaires, and surveys, etc.*