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TITLE: Neuroimaging Endophenotypes and Predictors of Post-Traumatic Brain Injury Dementia in a Nationwide Cohort of Veterans

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<b>14. ABSTRACT</b> 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.					
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1. **INTRODUCTION:** 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:** 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 Officer whenever there are significant changes in the project or its direction*

- **What were the major goals of the project?**

	<b>Timeline</b>
<b>Major Task 1:</b> Obtain local and HRPO IRB approval	Months
Subtask 1: Submit document for local IRB review. <ul style="list-style-type: none"> <li>• Submitted: UCSF CHR &amp; SFVAMC R &amp; D; 07 AUG 2019</li> <li>• Approved by: UCSF CHR; 25 NOV 2019;</li> <li>• Approved by: SFVAMC R &amp; D 06 DEC 2019</li> </ul>	1-3

Subtask 2: Submit IRB approval and necessary documents for HRPO review: <ul style="list-style-type: none"> <li>Submitted: DOD HRPO; 06 DEC 2019 <ul style="list-style-type: none"> <li>Approval: 21 FEB 2020</li> </ul> </li> </ul>	3-5
<b>Milestone #1: HRPO approval</b> <ul style="list-style-type: none"> <li>DOD HRPO; Approval Achieved; 100% Complete</li> </ul>	5-6
<b>Specific Aim 1:</b>	
<b>Major Task 2:</b> To create a large, nationwide, high- quality cohort of ~200,000 TBI-exposed and un- exposed veterans with MRI imaging data.	Months
Subtask 1: Identify veterans diagnosed with TBI in the VHA system <ul style="list-style-type: none"> <li>100% Complete</li> </ul>	1-5
Subtask 2: Build MRN list for relevant neuroimages in VHA system <ul style="list-style-type: none"> <li>100% Complete</li> </ul>	5-7
Subtask 3: Retrieve MRI data via PACS-AIR <ul style="list-style-type: none"> <li>100% complete within VISN21</li> </ul>	7-9
Subtask 4: Import MRI data to research DICOM database <ul style="list-style-type: none"> <li>100% complete within VISN21</li> </ul>	9-10
Subtask 5: Sort/clean MRI data at research DICOM database <ul style="list-style-type: none"> <li>100% complete</li> </ul>	10-11
Subtask 6: Perform MRIQC rating to identify excellent and acceptable quality MRI datasets <ul style="list-style-type: none"> <li>100% complete</li> </ul>	10-12
<b>Milestone #2: Clinical and MRI Data curation completed</b> <ul style="list-style-type: none"> <li>100% complete within VISN21</li> </ul>	12
<b>Specific Aim2:</b>	
<b>Major Task 3:</b> Develop and internally validate an MRI- based algorithm for predicting 5+ year risk of post-TBI dementia N>70,000 veterans with TBI (N>33,000 with mild TBI) <ul style="list-style-type: none"> <li>In progress</li> </ul>	
Subtask 1: Robust processing of MRIs to estimate regional tissue volume metrics, following the priority ordering based on MRIQC rating and VISN <ul style="list-style-type: none"> <li>100% complete within VISN21</li> </ul>	11-24
Subtask 2: Statistical ComBat harmonization of MRI volumetric estimates, within and across the dataset subsets based on MRIQC rating and VISN <ul style="list-style-type: none"> <li>100% complete within VISN21</li> </ul>	16-24
Subtask 3: White matter hyperintensity lesions burden in T2-weighted MRIs <ul style="list-style-type: none"> <li>100% complete within VISN21</li> </ul>	15-24
Subtask 4: Machine Learning of Structural MRI Data to build prognostic models on training data, following the priority ordering based on MRIQC rating and VISN <ul style="list-style-type: none"> <li>100% complete within VISN21</li> </ul>	18-24
Subtask 5: Deep Learning of Structural MRI Data to build prognostic models on training data, following the priority ordering based on MRIQC rating and VISN <ul style="list-style-type: none"> <li>In progress</li> </ul>	22-28

Subtask 6: Assess performance of prognostic models on independent validation data, within the dataset subsets based on MRIQC rating and VISN and the entire dataset <ul style="list-style-type: none"> <li>In progress</li> </ul>	23-25
Subtask 7: Determine whether MRI data predicts post- TBI dementia, within the dataset subsets based on MRIQC rating and VISN and the entire dataset <ul style="list-style-type: none"> <li>In progress</li> </ul>	24-27
<b>Milestone #3:</b> Developed practical prognostic model of risk for post-TBI dementia using readily available clinical MRI <ul style="list-style-type: none"> <li>In progress</li> </ul>	28
<b>Specific Aim 3:</b>	
<b>Major Task 4:</b> Build dementia phenotype relevance scores capturing individual patients' dementia MRI endophenotypes Veterans with post-TBI dementia (N=3,677) versus those with dementia without preceding TBI (N=8,435)	
Subtask 1: Create intrinsic functional connectivity map templates for 6 disease-specific NOIs <ul style="list-style-type: none"> <li>100% complete</li> </ul>	18-20
Subtask 2: Generate individual dementia atrophy signature based on voxel-based W-score estimates <ul style="list-style-type: none"> <li>100% complete within VISN21</li> </ul>	18-24
Subtask 3: Estimate dementia phenotype relevance scores <ul style="list-style-type: none"> <li>In progress</li> </ul>	24-30
<b>Milestone #4:</b> Objectively quantified NOI-based dementia-subtypes (MRI dementia endophenotyping) <ul style="list-style-type: none"> <li>In progress</li> </ul>	30
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Subtask 2: Generated W-score maps as quantitative representation of spatial distribution of white matter lesion burden <ul style="list-style-type: none"> <li>In progress</li> </ul>	28-32
Subtask 3: Bin individuals by the predominant regional pattern of white matter disease <ul style="list-style-type: none"> <li>In progress</li> </ul>	30-34
Subtask 4: Identify similarities and differences in burden/distribution of white matter lesions in TBI exposed vs. unexposed veterans with dementia <ul style="list-style-type: none"> <li>In progress</li> </ul>	30-36
<b>Milestone #5:</b> Investigated vascular contributions to post-TBI dementia <ul style="list-style-type: none"> <li>In progress</li> </ul>	36

- What was accomplished under these goals?**

A. Brief summary of progress to date: After obtaining the required local and HRPO IRB approvals, we successfully curated a data set for our initial conservative tier focusing on

images from local repository at SFVAMC, following our proposed multi-layer tier approach. This dataset has allowed us to test the hypotheses with minimal impact of imaging heterogeneity but at the same time to assess the image quality variability seen in clinical imaging compared to research quality imaging. Some noteworthy unique characteristics of this dataset are as follows: We observe a bimodal distribution of age at TBI exposure within cases without dementia, where early exposure cases clustering around age 30 and later exposure cases around age 60. Cases with dementia diagnosis had TBI exposure at age  $61.6 \pm 13.6$  years. Among cases with dementia diagnosis, 40% of them had early onset dementia (dementia diagnosis before age 65). These present a unique opportunity to study impact of TBI in isolation as late-onset individuals may have comorbid pathologies. In addition, time from TBI exposure to dementia diagnosis was  $3.9 \pm 3.1$  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  $0.9 \pm 2.1$  years of their clinical dementia diagnosis.

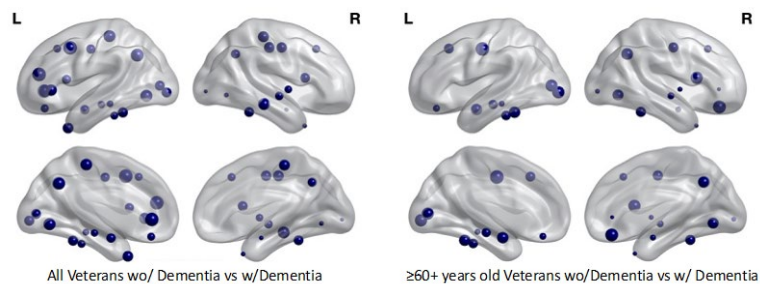
We successfully retrieved clinical brain MR images from SFVAMC Clinical PACS archives. Each image was recoded and deidentified following our secure data handling protocols. We implemented and tested an MRI quality control pipeline using MRIQC tool. We have leveraged the rich MRIQC metrics and shown that features that contribute to heterogeneity in clinical PACS data inherently has a higher dimensionality in contrast to relative one-dimensional vendor/model differences underlying the morphometry heterogeneity seen in clinical research setting. This is largely attributed to standardize and well-controlled operationalization of imaging protocols in clinical research projects. In line with this finding, we have been developing approaches to incorporate MRIQC-based clustering into the prognostic models and predictive models for harmonized interpretation of MRI morphometry measures.

Furthermore, to better understand the differences between clinical quality and research quality MRI acquisition from quantification of imaging markers of neurodegeneration, we leveraged imaging data from another DoD funded project, namely Effects of Traumatic Brain Injury and Post-Traumatic Stress Disorder and Alzheimer's Disease on Brain Tau in Vietnam Veterans using ADNI (ADNI-DoD; W81XWH-12-2-0012), which recruited Vietnam Veterans who meet criteria for normal cognition or mild cognitive impairment with history of TBI only, PTSD only, or both TBI and PTSD or with no history of TBI and/or PTSD. We strongly believe that a comprehensive characterization of clinical versus research-quality imaging differences is crucial for clinical translation of imaging biomarkers.

Given the expected greater heterogeneity in MRI data quality in this study, we adapted a multi-atlas segmentation framework to achieve a consistent parcellation of anatomical brain structures in our MRI dataset. This approach allows us to optimally estimate regional tissue volumes in each structural MRI regardless of image acquisition parameters and quality, by imposing the consistency of segmentations, while each atlas set preserves the image intensity characteristics of the specific field strength/scanner platform/imaging protocol. When compared to data from ADNI-DoD cohort, estimated hippocampal volume distribution from clinical brain MRIs was comparable to hippocampal estimates from research MRI data ( $p=0.32$ ) despite the clinical vs research MRI quality differences, further supporting the robust application of harmonized image processing to clinical quality MRI data. Based on these robust morphometric measures, we have showed wide-spread cortical atrophy in Male Veterans with TBI+Dementia compared to ones with TBI only, after controlled for age at MRI, TBI severity at MRI, and time from Dementia diagnosis. Furthermore, when 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 to dementia in veterans with TBI. The extend of atrophy was more pronounced in temporal regions for veterans with TBI and dementia after age of 60 years. To determine network-based\_neurodegeneration sub-types of dementia while preserving the information of individual effects, we have been working on establishing a 6-dimensional dementia phenotype relevance score. The phenotype relevance score quantifies the topographic similarity between atrophy signature of each individual and networks of interest from intrinsic brain connectivity. In our Veterans cohort, the greatest association of cortical atrophy topographic patterns with post-TBI dementia was observed within executive and auditory network while association with TBI severity was strongest within the sensory network. Furthermore, frontoparietal network presented the greatest association with cortical atrophy topographic patterns and post-TBI dementia and TBI severity interaction. We are now further assessing these findings as candidate predictors for MRI-based dementia endophenotyping. We have used these observed atrophy signatures to inform the machine learning based prognostic and predictive models to test the primary hypotheses. Specifically, we have developed multi-label learning classification techniques. Multi-label classification is an important approach as each veteran's data is associated with multiple labels (e.g., exposed to TBI or not and developed dementia or not) and these are not mutually exclusive phenotypical labels. We believe that this method is closer to the clinical reality, where clinical/cognitive phenotypes are not typically independent of one another. In the context of this study, we started implementation of a multi-label random forest (MLRF) classifier. We are currently performing sensitivity analyses and an analysis to assess to what extent multi-label classifier perform better than single-label classifiers for different optimization criteria including overall accuracy, positive predictive value, and false negative rates. Further details of each accomplishment are provided below.

- B. Multilabel machine learning based phenotypical classification modeling. We have built a classifier model based on the unique anatomical signatures of TBI and dementia in veterans (Fig 1). Particularly, our recent results showed wide-spread cortical atrophy in Male Veterans with TBI+Dementia compared to ones with TBI only, after controlled for age at MRI, TBI severity at MRI, and time from Dementia diagnosis. As illustrated in the glass-brain maps shown below, predominantly frontotemporal atrophy was associated to dementia in veterans with TBI. The extend of atrophy was more pronounced in temporal regions for veterans with TBI and dementia after age of 60 years.



*Fig 1. Compared to Veterans without Dementia diagnosis, Veterans with Dementia presented with greater parietotemporal and frontal atrophy*

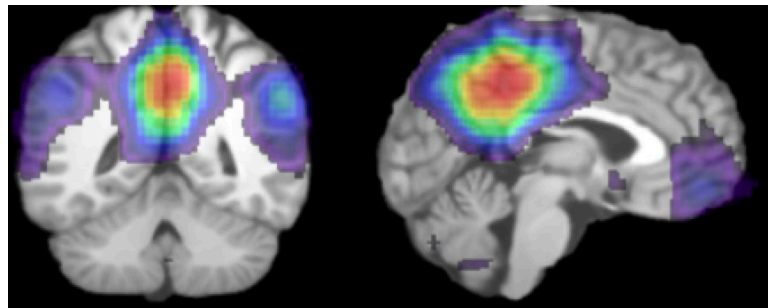
Multi-label classification is an important approach as each veteran's data is associated with multiple labels (e.g., exposed to TBI or not and developed dementia or not) and these are not mutually exclusive phenotypical labels (e.g., exposure to TBI increasing risk for development of dementia). Instead of considering each phenotypic label independently, the multi-label technique learns a single model for all phenotypical outcomes and makes a prediction at the sample level. We believe that this method is closer to the clinical reality, where clinical/cognitive phenotypes are not typically independent of one another.

In the context of this study, we started implementation of a multi-label random forest (MLRF) classifier. The RF is an ensemble method that is based on building 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.

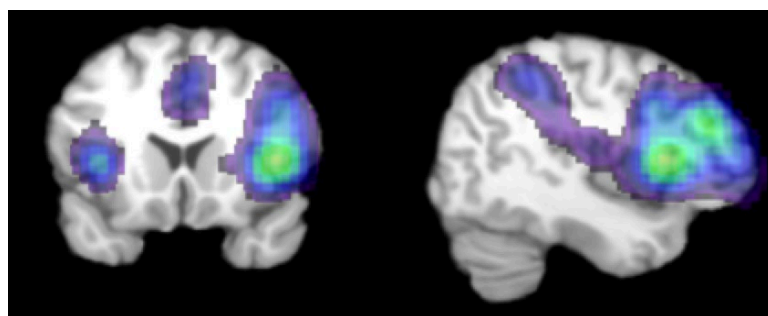
Multi-label learning is a supervised problem in which several labels are learned simultaneously. For all experiments, model construction and evaluation has been performed over 10 iterations of five-fold multi-label stratified cross-validation. Feature space includes harmonized estimates of regional atrophy measures from T1 MRIs, age at T1 MRI acquisition, and sex. The outcome phenotype labels are TBI vs no-TBI exposure and Cognitively Normal vs Dementia. Our preliminary implementation had a multi-label classification performance of  $69\% \pm 25\%$  accuracy. As mentioned below, we are currently performing sensitivity analyses and an analysis to assess to what extent multi-label classifier perform better than single-label classifiers for different optimization criteria including overall accuracy, positive predictive value, and false negative rates.

- C. Network-based neurodegeneration sub-types of dementia. To preserve the information of individual effects, a 6-dimensional dementia phenotype relevance score is computed for each Veteran. This phenotype relevance score aims to quantify topographic similarity between atrophy signature of each individual and networks of interest from intrinsic brain connectivity, including default mode network, executive network, frontoparietal network, visual network, auditory network, and motor network (Fig 2). Each of these networks of interest has been associated with distinct dementia subtypes<sup>1,2</sup>.

***Default mode network***



***Frontoparietal network***

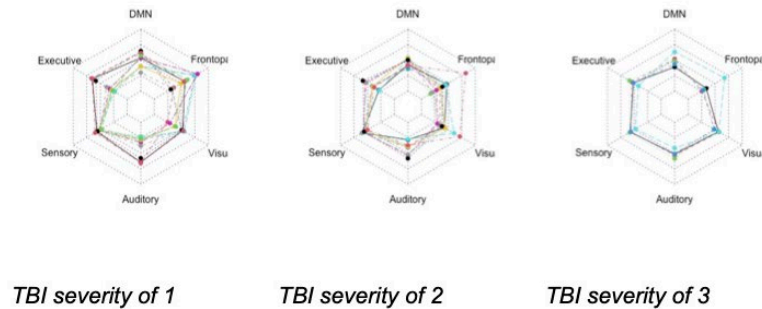


*Fig 2. Example estimated networks of interest illustrating default mode network and frontoparietal network.*

Individual atrophy signature based on harmonized MUSE parcellation has been estimated as W-scores by regressing out normal confounding effects of age and sex differences in No-TBI/No-Dementia age-matched cohort. Specifically, a W-score map provides spatial distribution where individuals' gray matter probability would fall on the normal grey matter probability distribution<sup>3</sup>. We have been developing an approach that

explicitly avoids pairwise registrations between individual brain MRIs, but instead focuses on modeling and discriminating between the 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<sup>4</sup>. 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 parcellations. W-score feature vector was normalized, yielding a W-score density vector capturing topography of atrophy signature independent of the severity of atrophy. This is important because our aim is to assign biomarker-supported dementia sub-types, 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 Fig 3, for sample individuals with post-TBI dementia diagnosis and different levels of TBI severity, capturing expected heterogeneity in atrophy patterns across individuals.

Among all networks of interest, the greatest association of cortical atrophy topographic patterns with post-TBI dementia was observed within executive and auditory network while association with TBI severity was strongest within the sensory network. Furthermore, frontoparietal network presented the greatest association with cortical atrophy topographic patterns and post-TBI dementia and TBI severity interaction. These observations will be further assessed for MRI-based dementia endophenotyping.



*Fig 3. Cortical atrophy topographic patterns within each network of interest for sample individuals with post-TBI dementia*

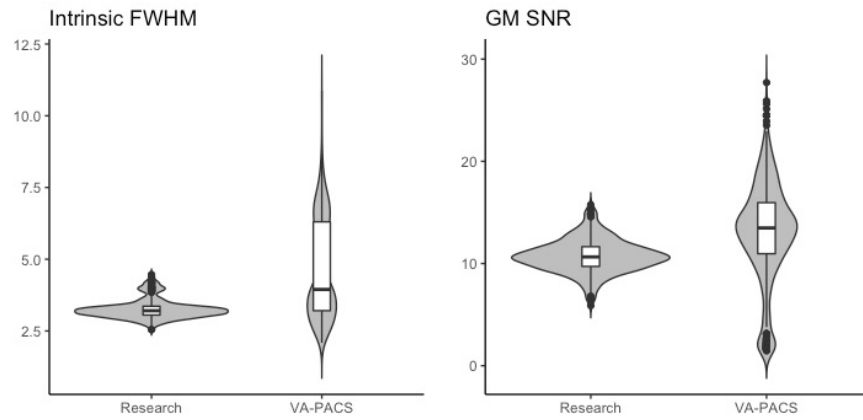
- D. MRIQC priority ordering into the prognostic models based on machine learning of structural MRI data. In clinical practice, brain MR scans are order and acquired using variability acquisition parameters following protocols approved by local clinics using clinical MR scanners. A distribution of key MR imaging parameters and scanner types that exist in VA PACS MRI dataset used in this project are summaries in Table 1. Current imaging data harmonization approaches largely focus on scanner differences based on vendor/model categorizations and magnetic field strength differences. Many of this data harmonization approaches, although shown to be effective, had limited generalizability to clinical imaging datasets. One big reason for this limited generalizability is due to the fact that even though there are heterogeneity due to scanner or magnetic field difference in clinical research datasets, across scanners and different magnetic field strength the acquisition parameters are extremely standardized. Therefore, the imaging data heterogeneity in clinical research setting is relative one dimensional and captured by a single variable coding vendor/model differences which automatically captures magnetic field strength stratification as well. As illustrated in Table 1, clinical PACS data though have inherit heterogeneity at a higher dimensionality. In this higher dimensionality, variability due to not only vendor/model or magnetic field strength difference but also

due to differences in key acquisition parameter such as slice thickness, in-plane resolution (i.e., acquisition matrix), acquisition type, and so on, should be captured.

Magnetic field strength	Acquisition matrix	Slice thickness	Vendor/model name	Acquisition type	TE	TR
1.5T	143	0.9	<u>Siemens</u>	2D	0.00137	0.00315
3T	146	1	Achieva 1	3D	-0.474	-5
	150	1.5	Avanto 2			
	152	1.6	Skyra 6			
	156	2	Symphony 7			
	160	3	Verio 8			
	162	4	NUMARIS_4 3			
	163	5				
	173		<u>GE</u>			
	179		SIGNA_EXCITE 4			
	186		Signa_HDxt 5			
	189					
	192					
	205					
	218					
	224					
	230					
	240					
	256					
	262					

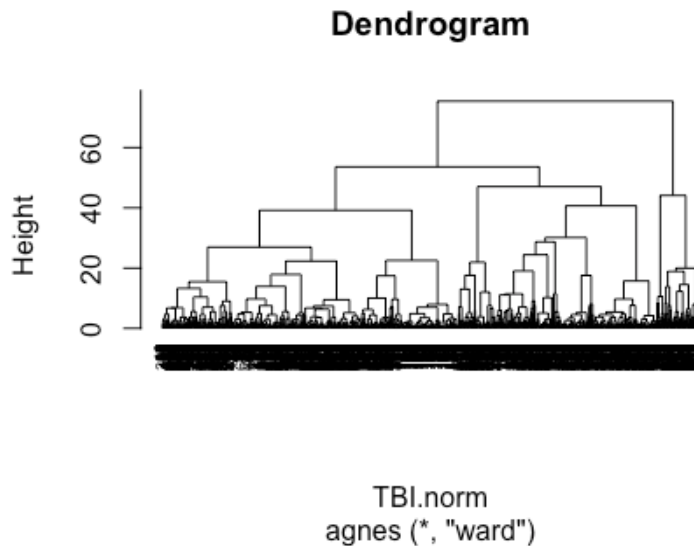
As no a priori knowledge is available on the dimensionality of the space influencing the image heterogeneity, we have been pursuing a data driven approach. In this approach, the key assumption is that heterogeneity across these dimensions affects the MR imaging morphometric measures, and these differences are quantifiably reflected in MRIQC metrics. Therefore, there should be data-driven clusters in MRIQC metric profiles we have been studying in this study.

The following MRIQC metrics were included in the clustering: 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. Although it is difficult to visualize the multi-dimensional MRIQC metric space, the extended heterogeneity in two key variables, i.e., intrinsic FWHM and GM SNR, in clinical PACS data is illustrated in comparison to a clinical research dataset, namely 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).



*Figure 4: Extended heterogeneity in MR image quality in clinical PACS data compared to clinical research data, i.e., ADNI-DOD study*

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 (Figure 5). The optimal number of clusters were determined by implementing a cut point at the end of the longest leg of the first branch. Analyses were conducted in R with the factoextra and cluster packages.



*Figure 5: Data-driven clustering of image quality profiles in clinical VA PACS MRI dataset*

Using this data-driven approach, four clusters (i.e., heterogeneity dimensions) were identified in the dataset with similar MR imaging quality. The lack of direct association of data-driven image quality clusters with scanner vendor/model types, magnetic field strength, or acquisition type as illustrated in Figures 6-8, confirms our original assumption that one dimensional stratification based on these variables – which is the common practice in data harmonization in research datasets – is insufficient to capture dimensions of heterogeneity in clinical PACS MRI data.

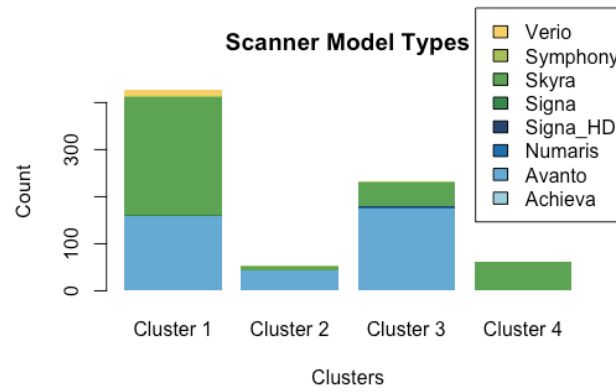


Figure 6: Distribution of scanner vendor/model types across image quality clusters

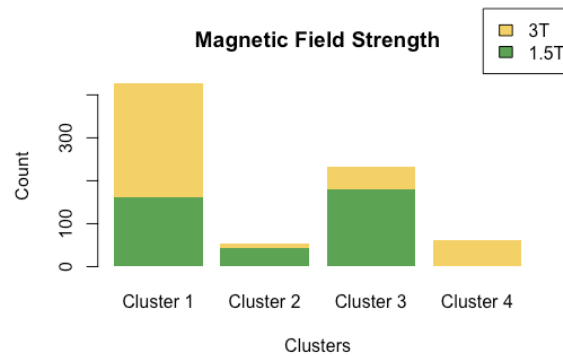


Figure 7: Distribution of magnetic field strength (1.5T vs 3T) across image quality clusters

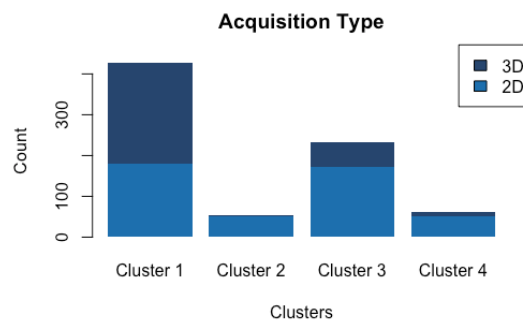


Figure 8: Distribution of acquisition type (2D vs 3D) across image quality clusters

In contrast, when the VA PACS dataset was assessed for clusters of homogenous image quality, compared to Cluster 1,

- Cluster 2 had significantly higher CJV, lower CNR, higher FWHM (avg, x, y) lower FWHM z, lower INU (med and range), lower QI 2, higher SNR CSF and WM, lower SNR GM, and higher SNRD-GM
- Cluster 3 had significantly lower CNR, higher FWHM (avg, x, y, z), lower INU (med and range), higher QI1, lower QI2, higher SNR GM and total

- Cluster 4 had significantly higher CJV, lower CNR, higher FBER, higher FWHM (avg, x, y, z), lower INU med, higher INU range, higher QI1, higher SNR CSF and GM, lower SNR WM, higher SNRD (CSF, GM, Total, WM)

In the context of this study, we aim to incorporate MRIQC clustering into the prognostic models for harmonized interpretation of MRI morphometry measures and predictive models. We recently pulled the EHR information on the reason for ordering these clinical MRIs. We will be testing the influence of clinical MRI order reason on the image quality and our ability to quantify imaging biomarkers. One question we want to tackle is the reason for ordering different sequence and if the reasoning is random or bias by the ordering physician's clinical impression of the patient. We recently gained access the radiology order forms via VA VINCI system.

- E. White matter hyperintensity (WMH) segmentation and volume estimates from varying types of FLAIR sequences. Currently FLAIR sequences vary from being absent, to 2D FLAIR sequences, to 3D high resolution FLAIR sequences. Many WMH segmentation methodologies have been developed and validated for specific MRI datasets. Accordingly, we have set out to explore how well particular WMH segmentation methods compare when faced with different FLAIR sequences. In order to accomplish this, we identified a separate test dataset of 15 individuals who underwent a lower resolution FLAIR sequence compared to a high resolution 1mm<sup>3</sup> 3D FLAIR sequence within an average of 7 months from one another. We have been running comparison studies between two WMH segmentation methods: Wisconsin White Matter Hyperintensities Segmentation Toolbox (W2MHS) <sup>5</sup>, a classical image processing framework, and Multimodal Ensemble-Based Segmentation of White Matter Lesions (Deep-WML) <sup>6</sup>, a deep-learning segmentation model. WMH segmentation volumes and topographies were both compared. The correlation between these measurements for W2MHS was R = 0.95 with a median absolute deviation of 0.26. For Deep-WML, the correlation was R = 0.97 with a median absolute deviation of 0.13. Thus, estimation of WMH volumes using classical image processing or recently developed deep-learning models is 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 versus ranging from 3% to 56% (mean 28%) for Deep-WML. Accordingly, topographic evaluation is more limited across different FLAIR sequences, particularly for the deep learning approach. Of note, the correlations between W2MHS and Deep-WML for low- and high-resolution FLAIR were high (R = 0.91 and 0.97, respectively).

We are currently building pipelines to additionally test the MarkVCID recommended WMH segmentation algorithm (UCD/UCLA/UCSF collaboration). We plan to implement one of the automated algorithms for all FLAIR sequences in this project to calculate WMH volumes. We will evaluate the value of implementing another algorithm on high resolution FLAIR sequences only for topographic evaluation.

1. Seeley WW, Crawford RK, Zhou J, Miller BL, Greicius MD. Neurodegenerative diseases target large-scale human brain networks. *Neuron*. 2009;62(1):42-52
2. Gardner RC, Boxer AL, Trujillo A, et al. Intrinsic connectivity network disruption in progressive supranuclear palsy. *Annals of neurology*. 2013;73(5):603-616.3732833
3. Suk HI, Lee SW, Shen D. Hierarchical feature representation and multimodal fusion with deep learning for AD/MCI diagnosis. *Neuroimage*. 2014;101:569-582.PMC4165842
4. Smith SM, Fox PT, Miller KL, et al. Correspondence of the brain's functional architecture during activation and rest. *Proceedings of the National Academy of Sciences*. 2009;106(31):13040-13045

5. Soh SS, Tan TS, Alang TAIT, Supriyanto E. White matter hyperintensity segmentation on T2 FLAIR brain images using supervised segmentation method. Paper presented at: 2016 International Conference on Robotics, Automation and Sciences (ICORAS); 5-6 Nov. 2016, 2016.
6. Rathore S, Niazi T, Iftikhar MA, et al. Multimodal Ensemble-Based Segmentation of White Matter Lesions and Analysis of Their Differential Characteristics across Major Brain Regions. *Applied Sciences*. 2020;10(6):1903

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

- *Invited lecture on "Advanced neuroimaging analytic methods: Beyond voxel-based analysis, and a little bit towards the dark side...", at Dementia Workshop by Ageing Epidemiology (AGE) Research Unit of the Imperial School of Public Health, Imperial College, UK*

- **How were the results disseminated to communities of interest?**

- *Invited presentation on "Impact of AI and advanced imaging on neurodegenerative diseases," at COBRA 2022: Bay Area Nuclear Imaging Conference at University of California Davis, Davis, CA*

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

- We plan to direct our efforts in four areas as follows:

1. Deep Learning of Structural MRI Data to build prognostic models on training data;
2. Developed practical prognostic model of risk for post-TBI dementia using readily available clinical MRI
3. Objectively quantified NOI-based dementia-subtypes (MRI dementia endophenotyping)
4. Investigated vascular contributions to post-TBI dementia
5. Establish an automated WML segmentation framework robust to acquisition variability in VA PACS FLAIR MRI data.

- The primary goal is to use machine-learning to develop and internally validate an MRI-based algorithm for predicting 5+ year risk of post-TBI dementia.

4. **IMPACT:** *Describe 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?**

- When compared to data from a multicenter research neuroimaging cohort of ADNI-DoD, estimated cortical atrophy distribution from clinical brain MRIs was comparable to estimates from research MRI data despite the clinical vs research MRI quality differences as reported above. This finding has a significant impact on clinical translational value of methods developed in this project, further supporting the robust application of harmonized image processing to clinical quality MRI data.

- Among all networks of interest, the greatest association of cortical atrophy topographic patterns with post-TBI dementia was observed within executive and auditory network while association with TBI severity was strongest within the sensory network. Furthermore, frontoparietal network presented the greatest association with cortical atrophy topographic patterns and post-TBI dementia and TBI severity interaction. These observations will be further assessed for MRI-based dementia endophenotyping.

- **What was the impact on other disciplines?**

- *Nothing to Report.*

- **What was the impact on technology transfer?**

- *Nothing to Report.*

- **What was the impact on society beyond science and technology?**

- *"Nothing to Report."*

## 5. CHANGES/PROBLEMS:

- **Changes in approach and reasons for change**

- *Nothing to Report.*

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

- Shelter-in-place order due to Covid-19 pandemic has been in effect in San Francisco since March 13th 2020. Since then, the research team has been practicing social distancing and working remotely from home via VPN and Citrix connections. We expect that the pandemic is likely to have effects on research team members' academic performance and productivity during this period and upcoming months. We also recognize that the disruptions of shelter-in-place ordinances, both direct (e.g., an inability to access laboratories, etc.) and indirect (e.g., childcare issues, a need to devote time to adjust to remote work), will have an impact on our productivity. Although, we have been working on this project as outlined in the approved SOW table, the extend of the disruptions remains unclear.

- **Changes that had a significant impact on expenditures**

- Shortly after initiation of our study, Covid-19 shelter-in-place was declared. As our project heavily relies on access to VA clinical data and use of databases and computational resources within VA network, shelter-in-place followed by strict remote work restrictions by VA significantly affected our ability to access the data and work with the data. Extended hiring freeze during shelter-in-place also affected our ability to hire and retain qualified employees particularly with data analytics skills.

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

- Not applicable.

- **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.** Nothing to Report.
  - **Books or other non-periodical, one-time publications.** Nothing to Report.
  - **Other publications, conference papers, and presentations.** Nothing to Report.
- **Website(s) or other Internet site(s)**
  - *Nothing to Report.*
- **Technologies or techniques.**
  - Nothing to Report.
- **Inventions, patent applications, and/or licenses**
  - Nothing to Report.
- **Other Products**
  - Nothing to Report.

7. **PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS**

- **What individuals have worked on the project?**

Name:	Duygu Tosun-Turgut
Project Role:	PI
Researcher Identifier (e.g. ORCID ID):	ORCID ID 0000-0001-8644-7724
Nearest person month worked:	0.9
Contribution to Project:	Dr. Tosun-Turgut is the contact Principal Investigator and oversees all aspects of the project.

Name:	Raquel Gardner
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Project Role:	<i>PI</i>
Researcher Identifier (e.g. ORCID ID):	ORCID ID 0000-0003-4028-440X
Nearest person month worked:	1.6
Contribution to Project:	Dr. Gardner is Co-Principal Investigator. In coordination with Dr. Tosun-Turgut, provides scientific leadership and input on the analyses and interpretation of results

Name:	W. John Boscardin
Project Role:	<i>Co-Investigator</i>
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:	7.2
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:	1.98
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:	0.23
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:	1.20
Contribution to Project:	Responsible for management of all VHA statistical non-imaging.

- **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?**
  - *"Nothing to Report."*

#### 8. SPECIAL REPORTING REQUIREMENTS

- **COLLABORATIVE AWARDS:** *For collaborative awards, independent reports are required from **BOTH** the Initiating 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> for each unique award.*
- **QUAD CHARTS:** *If applicable, the Quad Chart (available on <https://www.usamraa.army.mil>) should be updated and submitted with attachments.*

#### 9. APPENDICES:

- None