LIMBIC-CENC NEUROIMAGING CORE

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- **Main Aim**: Oversee and maintain LIMBIC-CENC neuroimaging data acquisition, QA, organization, review for abnormalities, analysis, storage, and dissemination.

- **Current Status**: All 11 PLS sites received training; imaging data collected to date reviewed for quality; analysis using central pipelines largely complete and updated; summary data disseminated for approved requests; and initial FITBIR upload complete.

- **Clinical Deliverables**: Produce high-quality conventional and advanced imaging data for models that include imaging features and relation to outcome.

- **1-year Goals**: Complete review of all LIMBIC-CENC imaging data; continue weekly audits; and update analysis.

- **End of Cycle Goal:** Creation of a durable, high-quality and well-organized dataset to allow for expanded analyses.

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NEUROIMAGING DATABASE MANAGEMENT

<u>Aim 1:</u> Maintain organized and well-characterized imaging dataset using standardized techniques of analysis

Create and manage the premiere database for military-relevant brain injury imaging data to identify indicators of neurodegeneration

NEUROIMAGING QUALITY ASSURANCE

<u>Aim 2</u>: Oversee and coordinate image procurement

Promote high-quality, accurate and consistent data collection

NEUROIMAGING DATA DISTRIBUTION

<u>Aim 3:</u> Establish procedures to receive, share, and adjudicate requests related to imaging data

Create and implement efficient logistics for data-sharing both within and outside of the consortium

NEUROIMAGING KNOWLEDGE DISSEMINATION AND PRIORITIZATION

<u>Aim 4:</u> Establish priorities, assist in generating requests, policies and procedures to assist in knowledge (clinical and research) translation and data dissemination

Facilitate interpretation of imaging data and establish priorities for data analysis and use

DATA MANAGEMENT

<u>Aim 1</u>: Maintain organized and well-characterized imaging dataset using standardized techniques of analysis

Create and manage the premiere database for military-relevant brain injury imaging data to identify indicators of neurodegeneration.

<u>Major Tasks:</u>

- Organize, transfer, archive and store imaging data
- Facilitate access to LIMBIC and other investigators

<u>In Process/Priority (ongoing through project):</u>

- Weekly meetings with Data Core
  - Report on data transferred, read, archived
- As new data is acquired, it is organized on both server (analysis) and PACS system (clinical reads)
- Monitoring of clinical reads and assistance to neuroradiologists
- Data entry of Common Data Elements to Medidata database
- Weekly cross-check audit of Medidata, PACS, Server

<u>Future:</u> (to be completed when available):

- Additional updates to software

<u>Tasks Completed:</u>

- ✓ Update and reconfigure hardware for imaging database to increase storage capacity, enhance security, permit access
- ✓ Reconfigure Core-specific PACS system that uses dicom data for neuroradiologists' clinical coding
- ✓ Enable accounts for all PLS investigators to upload data
- ✓ Update software to ensure most current versions of primary pipelines
- ✓ Reformatting imaging data to be consistent regardless of MRI manufacturer (BIDS format)
- ✓ Audit/rename CENC data to assure consistency with LIMBIC
- ✓ Initial cross-check audit of Medidata, PACS, Server

- ✓ TOTAL scans in Neuroimaging Core: 1477 PLS, 657 CENC non-PLS

QUALITY ASSURANCE

Aim 2: Oversee and coordinate image procurement

Promote high-quality, accurate and consistent data collection

Major Tasks:

- Facilitate optimal functioning of scanners
- Promote accuracy and consistency
- Minimize missing or unusable data
- Standardize performance parameters across sites (human and phantom object)
- Consistency in data collection as scanners are upgraded (hardware or software)

In Process/Priority (ongoing through project):

- Phantom testing and analysis (every two weeks, when active data acquisition resumes)
- Monitoring site performance via:
  - Quarterly self-assessment reports
    - Jan, Apr, July, Oct
  - Semiannual Core reports to each site
    - Jan, July
  - Qualitative and quantitative QA of data

Tasks Completed:

- ✓ Initial site training refreshers completed at all sites previously involved in CENC
- ✓ Updated Standard Operating Procedure manual and training slides
- ✓ Instituted new procedures:
  - ✓ site-specific report cards and course correction
  - ✓ established new quantitative QA procedures
  - ✓ new site quarterly self-assessments
  - ✓ bi-annual Core assessments
- ✓ Training all sites on completion of self assessment on Medidata
- ✓ Train new physicist, weekly QA meetings

Future:

- Annual training refresher (next will be June-August 2021)
- Prepare new Siemens Vida protocol (complete by Dec 2021)

DATA DISTRIBUTION

Aim 3: Establish procedures to receive, share, and adjudicate requests related to imaging data

Create and implement efficient logistics for data-sharing both within and outside of the consortium

Major Tasks:

- Assist in retrieving and compiling data for approved access requests
- Advise on available and most appropriate data
- Create neuroimaging composites and select variables in coordination with investigator teams
- Provide guidance on imaging-specific analysis
- Perform custom analysis, as needed

In Process/Priority (ongoing through project):

- Participation in Data Core and other subgroup calls related to imaging data (occur weekly)
- Participation in Biostatistics meetings, as required
- Assist in maintenance of data dictionary, as required
- Maintain a list of scans to exclude for QA reasons

Tasks Completed:

- ✓ Established GitHub repository
- ✓ Dr. Hannah Lindsey trained to create custom composites and assist in distributing data
- ✓ Assisted with approved requests to date involving imaging analysis
  - ✓ Richardson/Garcia
  - ✓ Newsome
  - ✓ Levin
  - ✓ Fino
  - ✓ Kenney/Gill/Werner
  - ✓ Dennis
  - ✓ Tate/Wade
  - ✓ Hodges

Future:

- Custom analysis, as required (e.g., brain stem WM tracts)

NEUROIMAGING KNOWLEDGE DISSEMINATION AND PRIORITIZATION

<u>Aim 4</u>: Establish priorities, assist in generating requests, policies and procedures to assist in knowledge (clinical and research) translation and data dissemination

Facilitate interpretation of imaging data and establish priorities for data analysis and use

<u>Major Tasks</u>

- Establish priorities for LIMBIC-CENC imaging data
- Assist investigators within and outside consortium in generating use requests
- Assist in creation of guidelines and policies around data use and sharing
- Assist in data dissemination activities (presentations/papers)
- FITBIR upload of raw imaging data

<u>In Process/Priority (ongoing through project):</u>

- Quarterly assessment of priorities (review with Hinds)
- Ongoing meetings and discussion with investigators interested in using data (incl phenotype and biomarker)
- Conference presentation and manuscript preparation
- Upload of imaging data to FITBIR (March, September)

<u>Tasks Completed:</u>

- ✓ FITBIR uploads
  - ✓ 2013-2018 CENC data
  - ✓ 2019 CENC data
  - ✓ 2020 LIMBIC data (through Sept 2020)
- ✓ Facilitated 9 requests to date:
  - ✓ Fino
  - ✓ Kenney
  - ✓ Verma
  - ✓ Dennis (ENIGMA)
  - ✓ Newsome
  - ✓ Tate
  - ✓ Dunkley
  - ✓ Digre/Katz
  - ✓ Hodges
- ✓ Manuscripts
  - ✓ 1 submitted (Wade; PTSD and hippocampal subfields)

<u>Future:</u> Submission of additional manuscripts

Selected Manuscripts

- Under Review
  - Wade et al.: *Hippocampal and amygdala subfields and PTSD symptoms*
- In Revision
  - Levin et al.: *White matter hyperintensities and relation to clinical variables*
- In Preparation
  - Wilde/Wade et al: *Imaging Harmonization*
  - Wilde/Tate et al: *Clinical and Research Lessons Learned*
  - Tate/Wade: *Bayesian and traditional analysis of diffusion data*
  - Wade/Tate/Wilde et al. *Relation between Grooved Pegboard and Imaging*
  - Richardson/Garcia: *OSA and imaging findings, including WMH*
  - Shahim/Kenney/Gill/Werner: *Diffusion imaging and NFL*
  - Dennis/Taylor: *Brain age volumetrics and outcome*

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Summary

- **Research Deliverables**:
  - Create and manage the premiere database for military-relevant brain injury imaging data to identify indicators of neurodegeneration
  - Promote high-quality, accurate and consistent data collection
  - Create and implement efficient logistics for data-sharing both within and outside of the consortium
  - Facilitate interpretation of imaging data and establish priorities for data analysis and use

- **1-Year Goal**:
  - Up-to-date review of all LIMBIC-CENC imaging data (quality, clinical reads)
  - Up-to-date analysis using established pipelines for volumetrics, diffusion, functional connectivity, and perfusion analysis
  - Complete FITBIR submission, including supplements

- **End of Cycle Goals**:
  - Creation of a durable, high-quality and well-organized dataset to allow for expanded analyses
  - Develop and contribute to key papers identifying imaging factors associated with outcome and disease.
  - DoD, VA, NIH proposals to extend these analyses

LIMBIC-CENC NOVEL NEUROIMAGING STUDY

Elisabeth Wilde, PhD

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- **Main Aim**: Utilize neuroimaging to understand the relation between and variability in neurodegenerative disease and/or comorbidities in those with TBI, and actively investigate new and established tools for neuroimaging analysis

- **Current Status**: Assessing various methods of imaging data harmonization, and multimodal analysis

- **Clinical Deliverables**: Utilize advanced imaging data for models that include imaging features and determine and create novel imaging analysis tools and methods

- **1-year Goals**: Conduct traditional and advanced model analyses of imaging data, evaluate existing tools for harmonization

- **End of Cycle Goal:** Identify optimal analysis strategies for imaging data harmonization, multimodal analysis, and individualized analysis

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Novel Neuroimaging Project

<u>Aim 1</u>: Utilize neuroimaging to understand the relation between and variability in neurodegenerative dx and/or comorbidities in those with TBI

<u>Aim 2</u>: Actively investigate new and established tools, share methodology and compare results using different approaches

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Aim 1: Utilize neuroimaging to understand the relation between and variability in neurodegenerative dx and/or comorbidities in those with TBI

Major Tasks:

- Assess available methods for overcoming variability
  - Harmonization across sites
- Incorporate elements of advanced statistical analysis and multimodal imaging in conjunction with other injury, demographic and outcome data

In Process/Priority:

- Examine phantom-based and statistical correction for variability introduced by scanner hardware and software (COVID-restriction dependent)
- Initial, interim and final analyses of imaging data utilizing Bayesian and ML models to identify phenotypes and most salient imaging-derived components to predict risk (ongoing)
- Exploration of additional harmonization techniques (6-12 months)
- Participation in discussions with phenotype and biomarker projects (ongoing through project)

Tasks Completed:

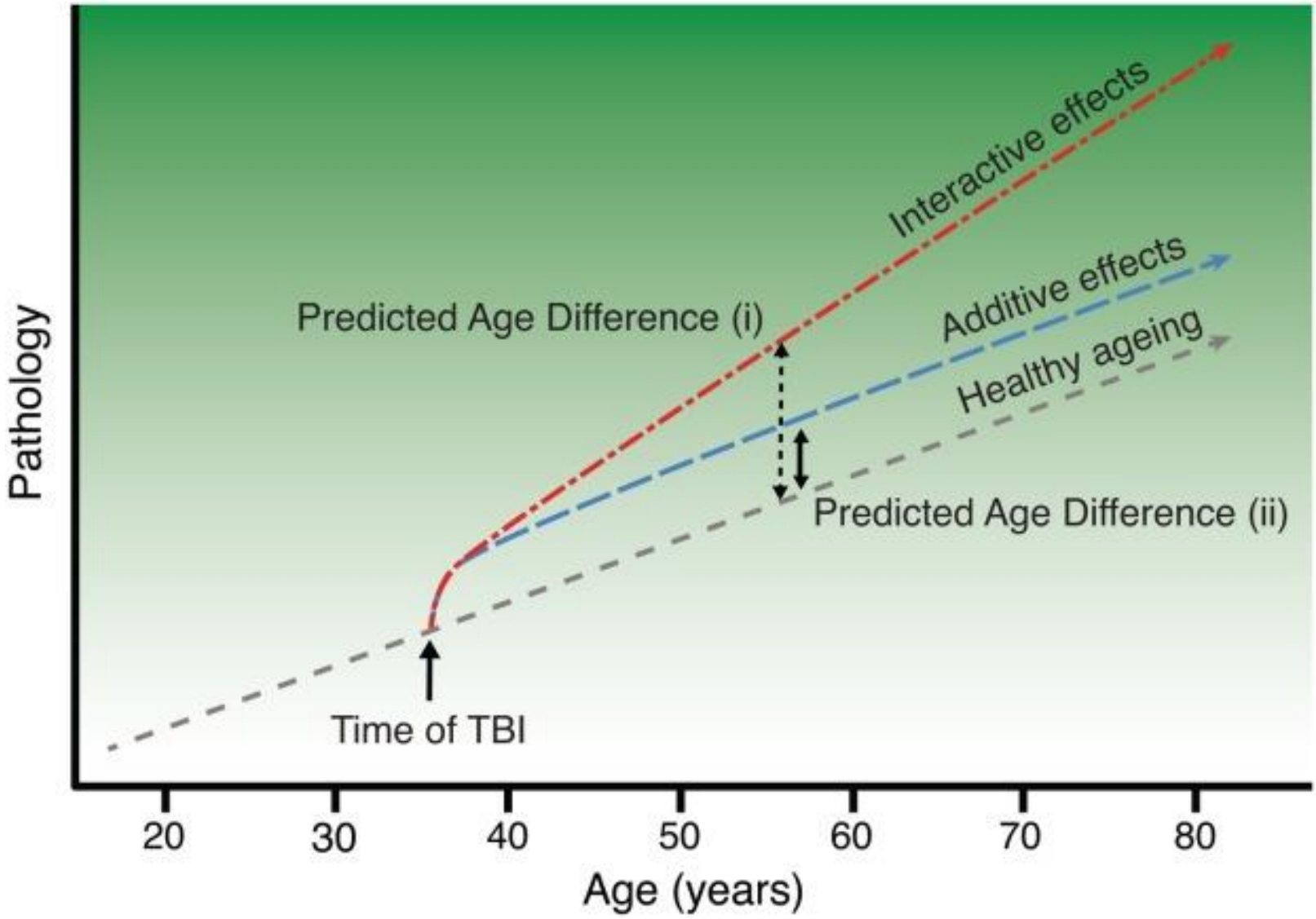
- ✓ Initial analysis of ComBat
- ✓ Bayesian analysis of imaging data
  - ✓ In relation to outcome (initial)
  - ✓ In relation to biomarkers (initial; in process of re-analysis with more data)

Future:

- Interim and final analyses of imaging data utilizing Bayesian and ML models to identify phenotypes and most salient imaging-derived components to predict risk (interim to be completed in 6-12 months)
- Development of modified ComBat (in conjunction with R66/R33 project over 3 years)

TBI and Aging

- TBI is associated with increased risk of dementia and early cognitive decline, particularly moderate/severe injuries or repetitive injuries
- Additive or interactive?
  - Cole et al., 2015 found evidence for interactive in a predominately mod/sev TBI cohort: https://onlinelibrary.wiley.com/doi/full/10.1002/ana.24367



Imaging Analysis: brainageR

- brainageR model trained on 3,377 healthy individuals from 7 datasets ages 18-100, tested on 857
  - PCA run on vectorized tissue segmentations, top 80% of variance retained

- Process
  - Input: raw T1-weighted MRIs
  - Segmented and normalized using SPM12
    - Visual QC of tissue segmentation
  - Normalized images are vectorized
  - Rotation matrix of above PCA applied to data
  - kernlab used to predict age from these

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Analysis Modules

- Cross-sectional
  - Mixed effects model
  - Response variable is ADS (age deviation score=predicted age – chronological age)
    - Negative score is “good”
  - Covariates
    - Age, sex - association between ADS and age (r=-0.33)
    - Also testing time since injury (first, index, recent), education

- Longitudinal
  - Mixed effects model → site as random effect
  - Response variable is IDS (interval deviation score=predicted interval – chronological interval)
    - Negative score is “good”
  - Covariates
    - Age, interval, sex

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Selected Preliminary Results: Males Only Cross-Sectional Analysis

Variable	T-statistic	p-value
Combat TBI hx	**2.0762**	**0.0382**
# Combat TBI exposures	1.9750	0.0731
BVMT-R Delayed Recall (Visual Memory)	**2.0593**	**0.0418**
DKEFS Category Switching (Executive Functioning)	1.9120	0.0580
TMT B-A (Executive Functioning)	1.8138	0.0735
NSI Total (Post-concussion Symptom Report)	**2.6827**	**0.0082**
PCL-5 (PTSD Symptom Report)	**3.0133**	**0.0003**
PHQ-9 (Depression Symptom Report)	**3.3858**	**0.0009**
PSQI Total (Sleep quality)	1.8038	0.0735

Greater “brain age” is positively associated with h/o combat TBI, higher number of TBI exposures, poorer cognitive performance, and greater symptom report of PTSD, depression and poor sleep quality.

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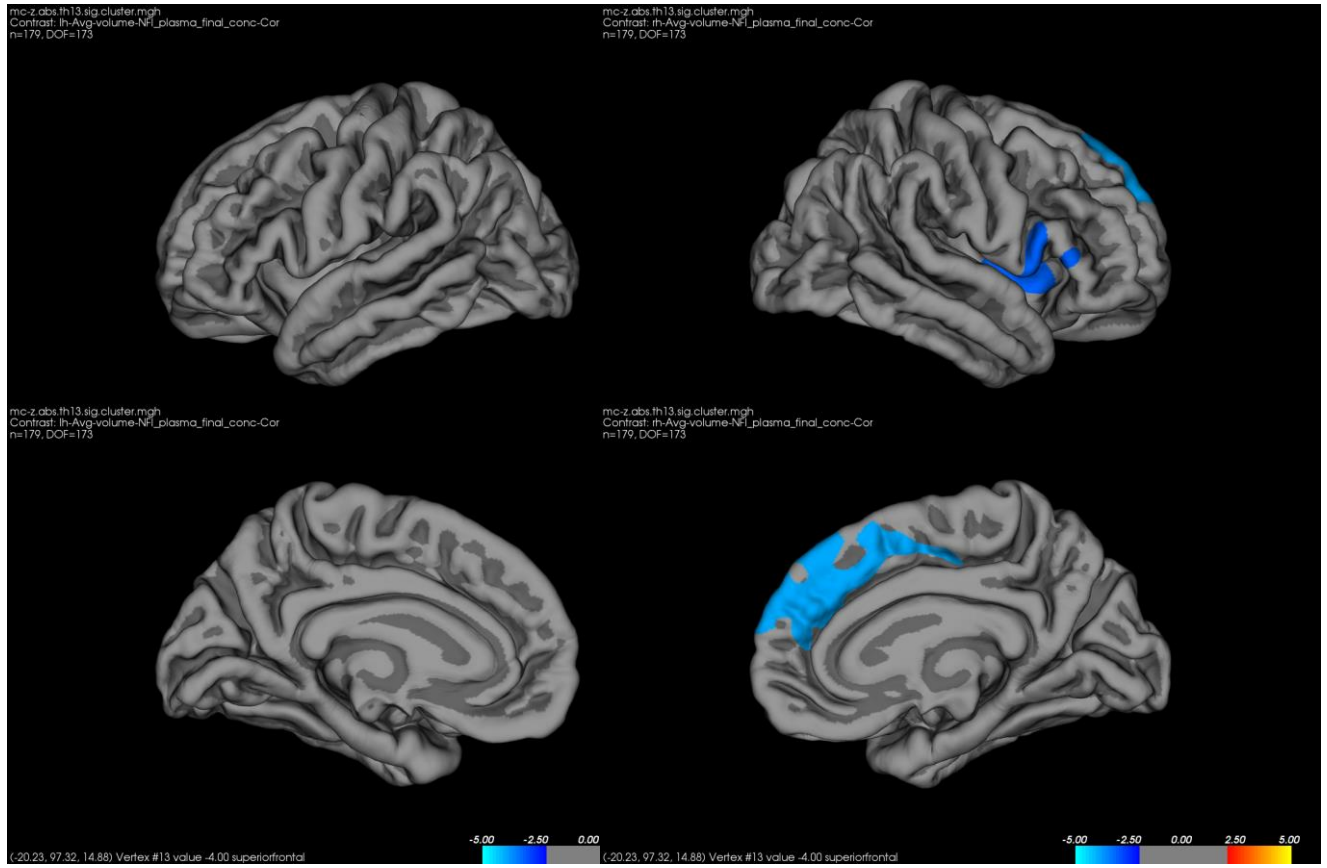
Cortical Volume and NFL Plasma Concentration



Correlation between NFL plasma and cortical volume, accounting for sex (NV=age); N=179 (initial snapshot)
Threshold p=0.05 (MC-simulation, abs)

Comments:

- In chronic injury, NFL may reflect ongoing degenerative process
- In previous studies (AD) NFL predicts cortical gray matter volume loss, as well as cognitive impairment.
- Blue areas indicate that higher NFL is associated with lower cortical volume

Next Steps:

- Biomarker data now available on much larger sample; analyses will be re-run
- Examine within TBI groupings
- Examine in relation to cognitive measures

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Aim 2: Actively investigate new and established tools, share methodology and compare results using different approaches

Major Tasks:

- Critically examine and compare strengths and limitations of analysis methods
- Evolve existing analytic pipelines
- Create novel analytic approaches where gaps exist
- Share data with external investigators

Tasks Completed:

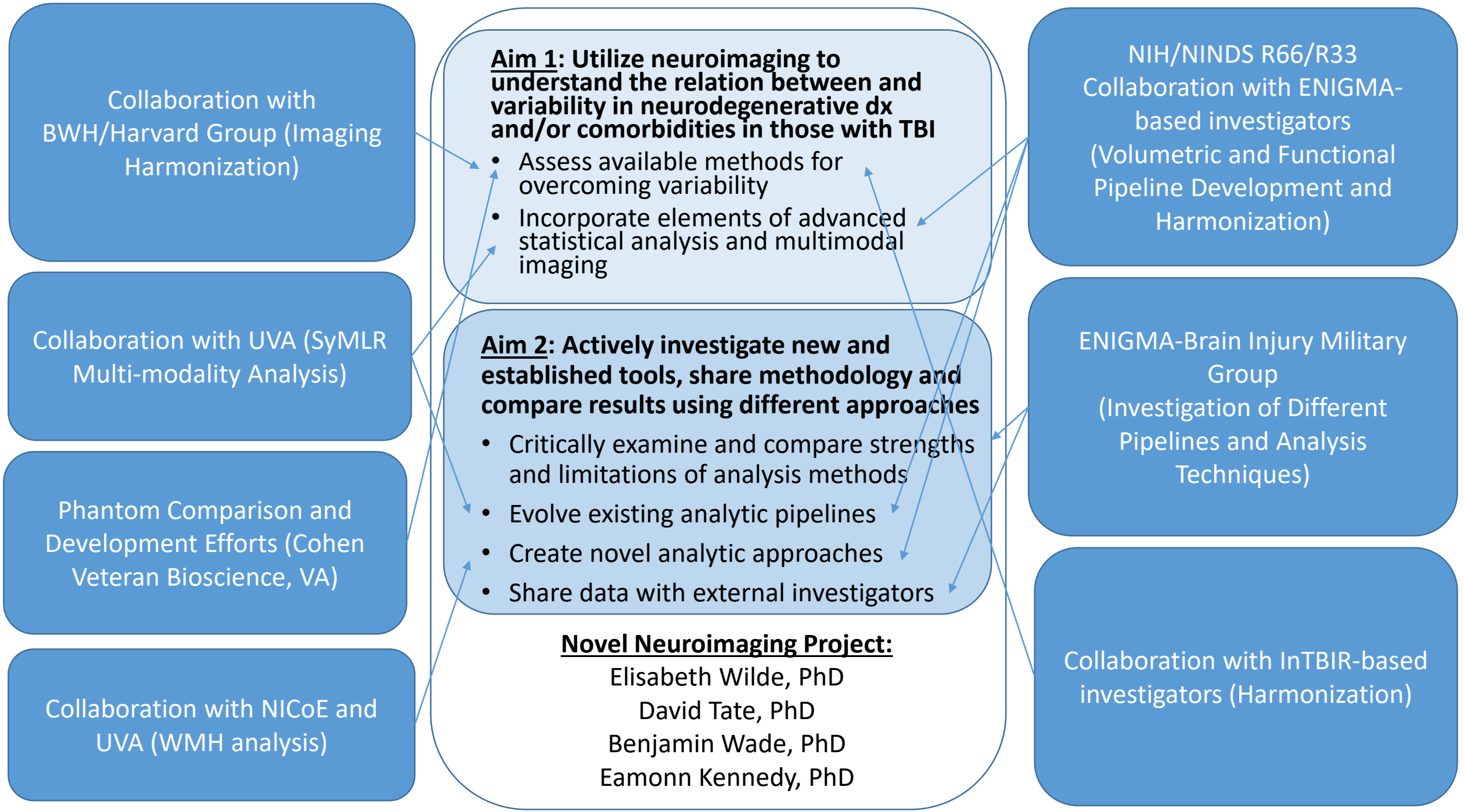
- ✓ Initial analysis of SyMLR in conjunction with UVA
- ✓ Identification of test data set
- ✓ Successful (awarded) R61/R33 grant submission in conjunction with ENIGMA; began 2021

In Process/Priority (ongoing through project):

- Critically examine pre-processing approaches to enhance accuracy and consistency
- Systematic examination of processing steps to determine differences
- Further refine CENC pipelines, including WMH, volumetric, diffusion and fcMRI

Future:

- Complete work on WMH pipeline (6-12 months)
- Complete work on rs-fMRI pipeline (24 months)
- Manuscripts:
  - Comparisons of analysis pipelines (6 months)
  - Harmonization review and considerations using LIMBIC data (3 months)
- Critical review and testing of methods that target "individual" analysis to determine clinical utility for dx, tx planning and evaluation of tx response (later half of project).


Collaboration with BWH/Harvard Group (Imaging Harmonization)
Collaboration with UVA (SyMLR Multi-modality Analysis)
Phantom Comparison and Development Efforts (Cohen Veteran Bioscience, VA)
Collaboration with NICoE and UVA (WMH analysis)
Aim 1: Utilize neuroimaging to understand the relation between and variability in neurodegenerative dx and/or comorbidities in those with TBI
Assess available methods for overcoming variability
Incorporate elements of advanced statistical analysis and multimodal imaging
Aim 2: Actively investigate new and established tools, share methodology and compare results using different approaches
Critically examine and compare strengths and limitations of analysis methods
Evolve existing analytic pipelines
Create novel analytic approaches
Share data with external investigators
Novel Neuroimaging Project:
Elisabeth Wilde, PhD
David Tate, PhD
Benjamin Wade, PhD
Eamonn Kennedy, PhD
NIH/NINDS R66/R33 Collaboration with ENIGMA-based investigators (Volumetric and Functional Pipeline Development and Harmonization)
ENIGMA-Brain Injury Military Group (Investigation of Different Pipelines and Analysis Techniques)
Collaboration with InTBIR-based investigators (Harmonization)

Summary

- **Research Deliverables**:
  - Utilize neuroimaging to understand the relation between and variability in neurodegenerative disease and/or comorbidities in those with TBI
  - Actively investigate new and established tools for neuroimaging analysis

- **1-Year Goal**:
  - Papers submitted regarding Bayesian analysis, subfield analysis, and harmonization
  - Re-analysis of WMH using updated pipeline
  - Through collaboration with other groups, further refine and implement HALF-PIPE for connectivity analysis

- **End of Cycle Goals**:
  - **Identify optimal analysis strategies for imaging data harmonization, multimodal analysis, and individualized analysis**
  - Creation and evolution of pipelines for resting state analysis and WMH
  - Additional DoD, VA, NIH proposals to extend these analyses

Questions

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Definitions

- “harmonization”: methods of reducing site variability introduced by scanner-specific differences; transforming points into one cohesive data set
- “pipeline”: post-acquisition imaging analysis procedures that includes steps for improving data quality (e.g., motion correction) as well as performing analysis
- “qualitative”: relating to, measuring, or measured by the quality of something rather than its quantity; in this case, used as the visual inspection of data by trained personnel
- “quantitative”: data in the form of counts or numbers where each dataset has an numerical value; in this case, used to quantitatively establish parameters of data accuracy
- SyMLR: Symmetric Multiview Linear Reconstruction
- WMH: white matter hyperintensity
- ComBat: derived from “combining batch effects when combining batches”
- ENIGMA: Enhancing Neuroimaging and Genetics through Meta-analysis (global imaging consortium)
- InTBIR: International Initiative For Traumatic Brain Injury Research (global imaging consortium)
- PACS: Picture Archiving and Communication System (imaging visualization system widely used in radiology)
- NFL: Neurofilament light (serum biomarker)

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