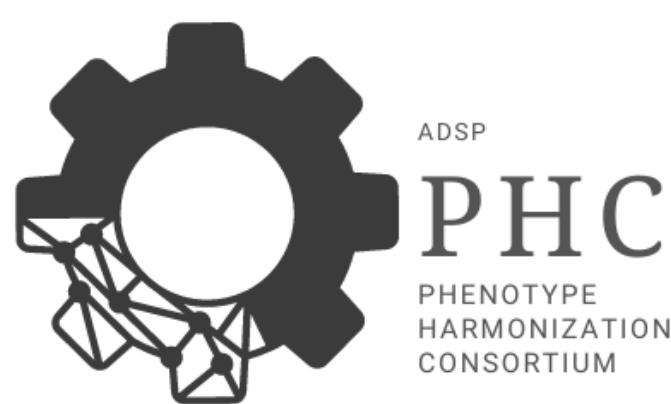




Alzheimer's Disease Sequencing Project Phenotype Harmonization Consortium

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BACKGROUND

- The AD Sequencing Project (ADSP) is a global initiative seeking to identify rare genetic variants by generating whole genome sequencing data in a diverse cohort of >100k participants.
- The ADSP Phenotype Harmonization Consortium (ADSP-PHC) was established to deepen the available endophenotypes and increase diagnostic precision in the ADSP.
- Many of the cohorts included in the ADSP have collected longitudinal cognitive, biomarker, neuroimaging, vascular risk factor, and neuropathology data.
- Our aim is to document, access, harmonize, and disseminate the rich endophenotype data as globally accessible resource to accelerate discovery.

METHODS

- Our multi-disciplinary team of world experts leverage established, peer-reviewed harmonization methods (**Figures 1-3**).
- We release all data with multiple users in mind, including both detailed and simplified phenotypes (**Table 1**).
- All data and methods are available at dss.niagads.org

Table 1. Summary of Select Endophenotype Deliverables

Domain	Deliverables
Cognition	(1) Study-Specific Availability of Cognitive Tests (2) Composite Measures of Memory, Executive Function, Language, and Visuospatial Function
Fluid Biomarkers	(1) Harmonized continuous measures of CSF AB-42, total tau, and phosphorylated tau (2) Amyloid +/-, Tau +/- Groups
Amyloid PET	(1) Normalized Images with Regional Summaries (2) Continuous Whole Brain Composite Score (3) Amyloid +/- Group
Structural MRI (T1)	(1) Regional Brain Volume and Cortical Thickness (2) Harmonized Brain Maps (3) Harmonized Images from Deep Learning
Vascular Risk Factors	(1) Summary of Vascular Risk Factors (2) Cardiovascular Risk Factor Score (3) Cardiovascular Health Score 3
Neuropathology	(1) AD Pathology (BRAAK and CERAD Stage) (2) Categorical Summaries of Concomitant Pathologies (Infarcts, Lewy Bodies, Hippocampal Sclerosis, Cerebral Amyloid Angiopathy, TDP-43)

DELIVERABLES

- We have harmonized phenotypic data from 110k+ participants, across 21 ADSP cohorts, and 413,000+ visits (**Table 2**).
- Data are released on an annual basis as we add in additional cohorts and additional phenotypes

Table 2. Harmonized Data Available via NIAGADS (ng00067.v20)

Domain	ADSP Participants	Total Participants
Autopsy	7,699	24,688
Cardiovascular Risk Factors	26,567	78,941
Cognition	35,040	104,413
Diagnosis	36,447	108,801
Fluid Biomarkers - CSF	2,876	4,807
Fluid Biomarkers - Plasma	4,999	9,361
DTI	2,960	7,646
FLAIR	9,023	22,143
T1	8,680	20,285
PET	8,044	15,753

Figure 1. Cognitive Harmonization

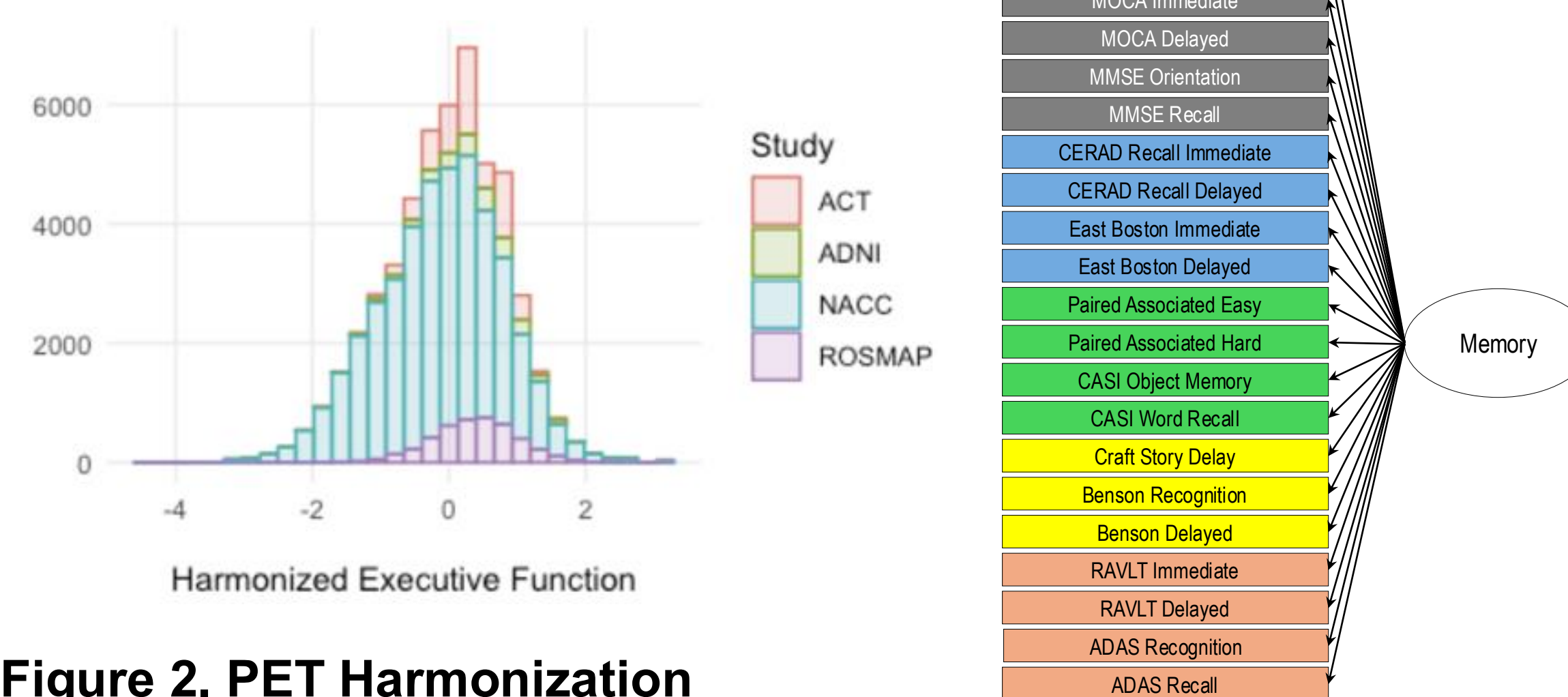


Figure 2. PET Harmonization

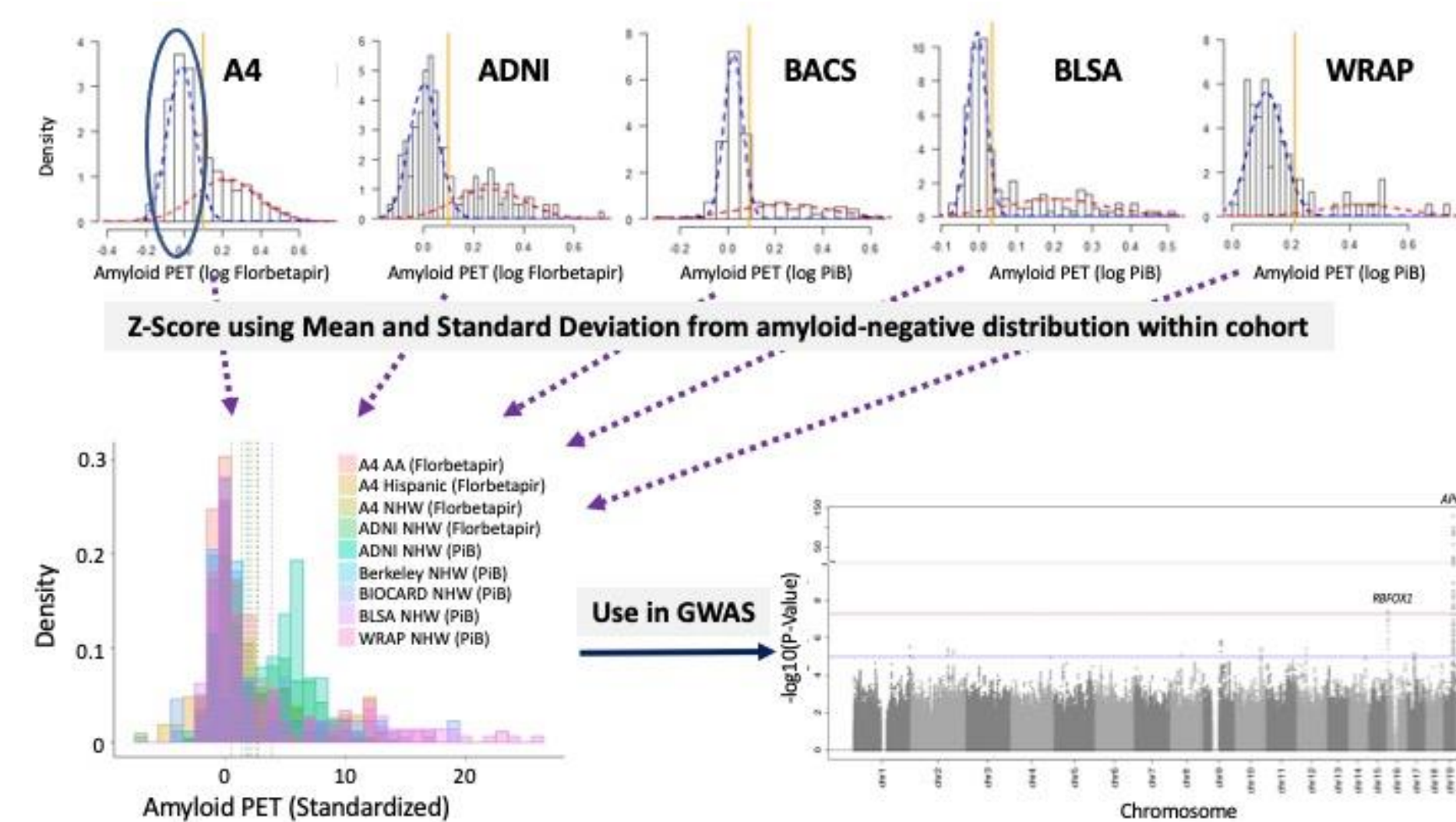
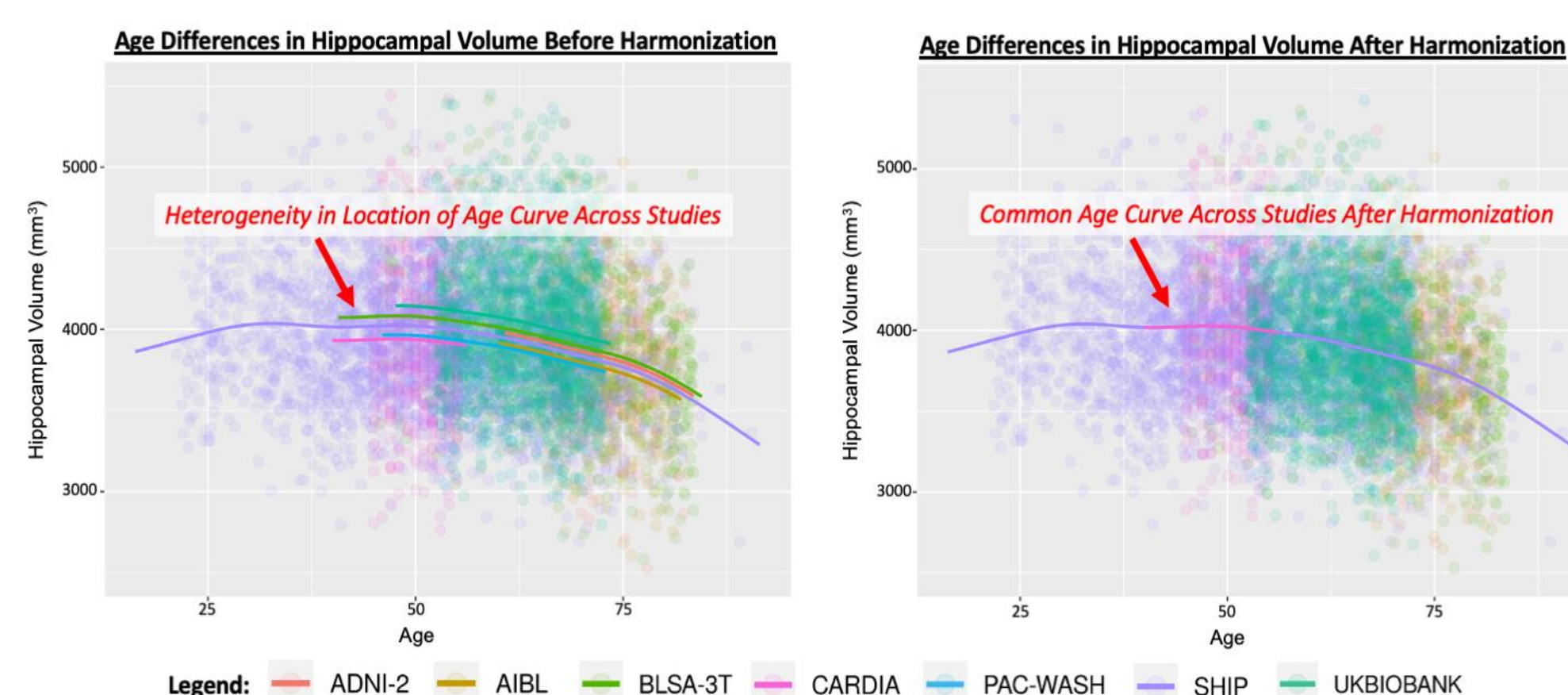


Figure 3. Structural T1 MRI Harmonization



IMPACT

Harmonized Data Integration

- Data have supported 75+ manuscripts on:
 - Novel harmonization procedures and pipelines
 - Identification of novel genetic drivers of cognitive performance and neuroimaging alterations over the course of aging and dementia
 - Precision medicine applications, e.g. multi-modal disease subtyping and intersectional effects of genetic factors in the context of ancestry and biological sex.
- Support for other initiatives including CLARiTI, AI4AD, and AMP-AD



New Research Directions

- Supplemental funding supports parallel harmonization in the Million Veterans Project to support future integration.
- Future efforts will integrate blood-based biomarkers, electronic health records, and digital pathology data.

DISCUSSION

- The ADSP Phenotype Harmonization Consortium supports precise genetic studies of AD.
- These deep endophenotype data have transformed the ADSP landscape by providing information about amyloid and tau pathology, concomitant pathways of injury, neurodegeneration, and cognitive decline.
- The added depth not increases statistical power for ADSP analysis and provides an unprecedented opportunity for advanced AI applications
- All data are available to the research community!

FUTURE DIRECTIONS

- Future releases will include:
 - Vascular biomarkers
 - Digital neuropathology
 - Electronic Health Record based phenotypes

ADSP-PHC
on NIAGADS:



ADSP-PHC
Data Explorer:



Funding:

