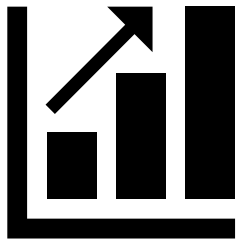
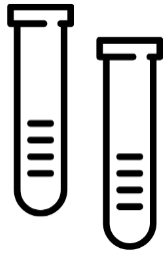
The Power of NACC Data: Genetic Drivers of Risk and Resilience

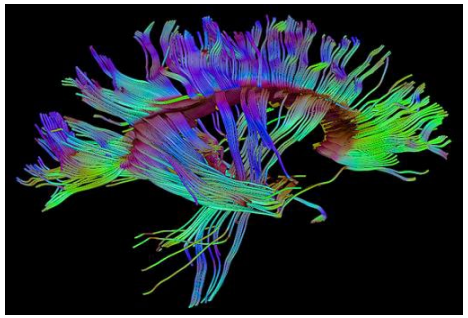
Presented by: Timothy J. Hohman, PhD

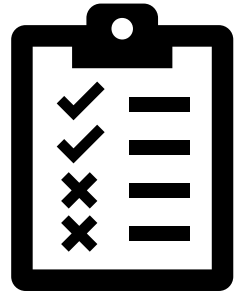
May 2, 2023 – 2023 Hybrid Spring ADRC Meeting

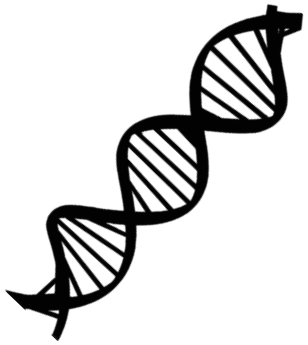
Explosion of Big Data in Alzheimer's Disease

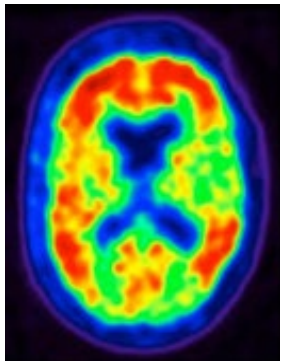


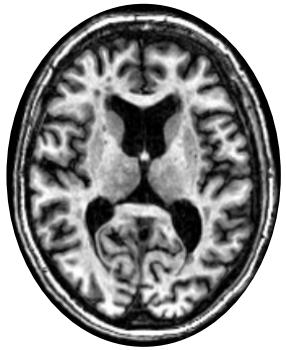






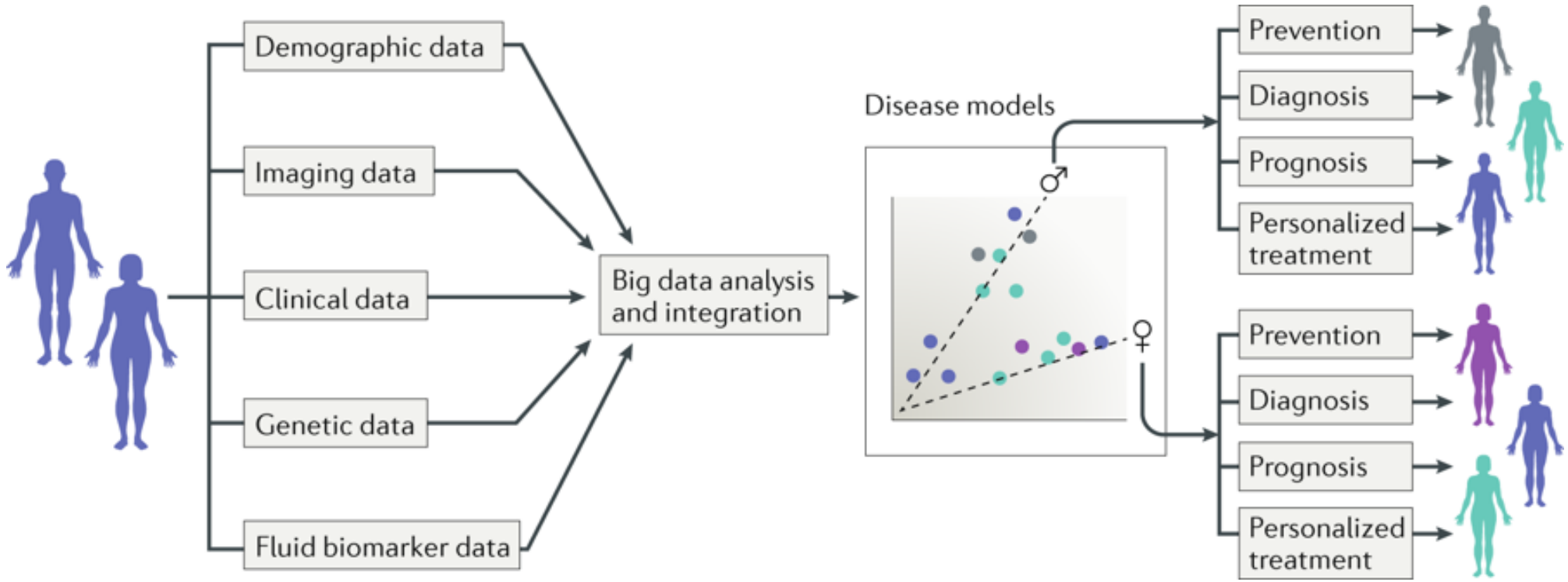






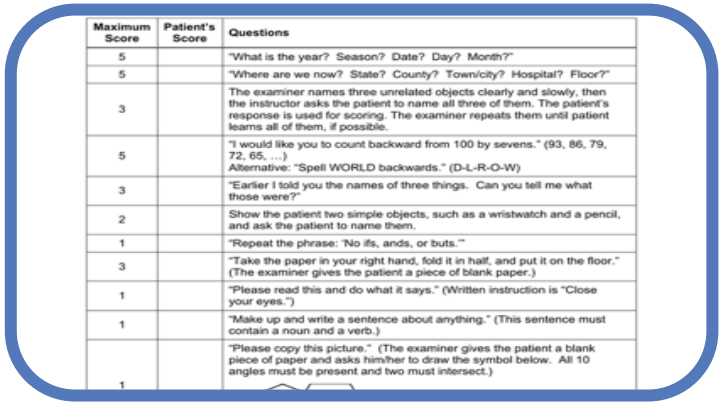
Genomics → Molecular Biomarkers → Structural Brain Imaging → Cognition

Precision Medicine in AD

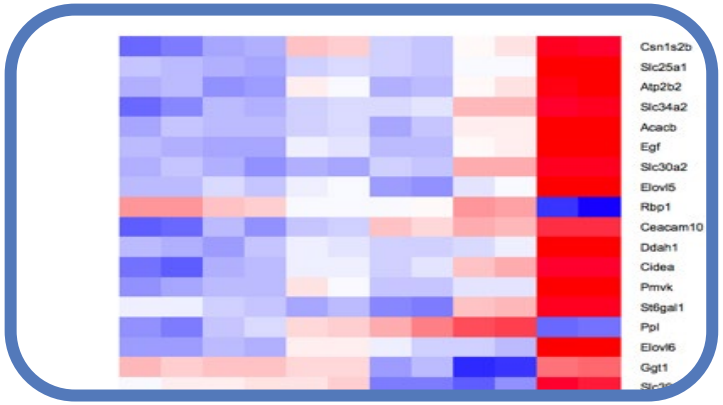


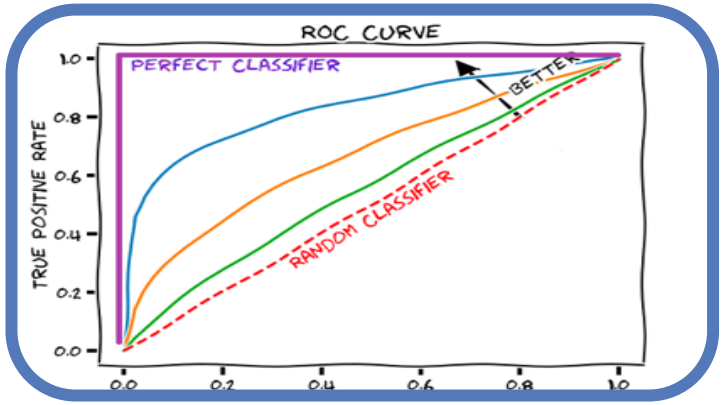
Ferretti et al., Nature Reviews Neurology, 2018

New ADSP Programs



Maximum Score	Patient's Score	Questions
5		"What is the year? Season? Date? Day? Month?"
5		"Where are we now? State? County? Town/city? Hospital? Floor?"
3		The examiner names three unrelated objects clearly and slowly, then the instructor asks the patient to name all three of them. The patient's response is used for scoring. The examiner repeats them until patient learns all of them, if possible.
5		"I would like you to count backward from 100 by sevens." (93, 86, 79, 72, 65, ...) Alternative: "Spell WORLD backwards." (D-L-R-O-W)
3		"Earlier I told you the names of three things. Can you tell me what those were?"
2		Show the patient two simple objects, such as a wristwatch and a pencil, and ask the patient to name them.
1		"Repeat the phrase: 'No ifs, ands, or buts.'"
3		"Take the paper in your right hand, fold it in half, and put it on the floor." (The examiner gives the patient a piece of blank paper.)
1		"Please read this and do what it says." (Written instruction is "Close your eyes.")
1		"Make up and write a sentence about anything." (This sentence must contain a noun and a verb.)
1		"Please copy this picture." (The examiner gives the patient a blank piece of paper and asks him/her to draw the symbol below. All 10 angles must be present and two must intersect.)

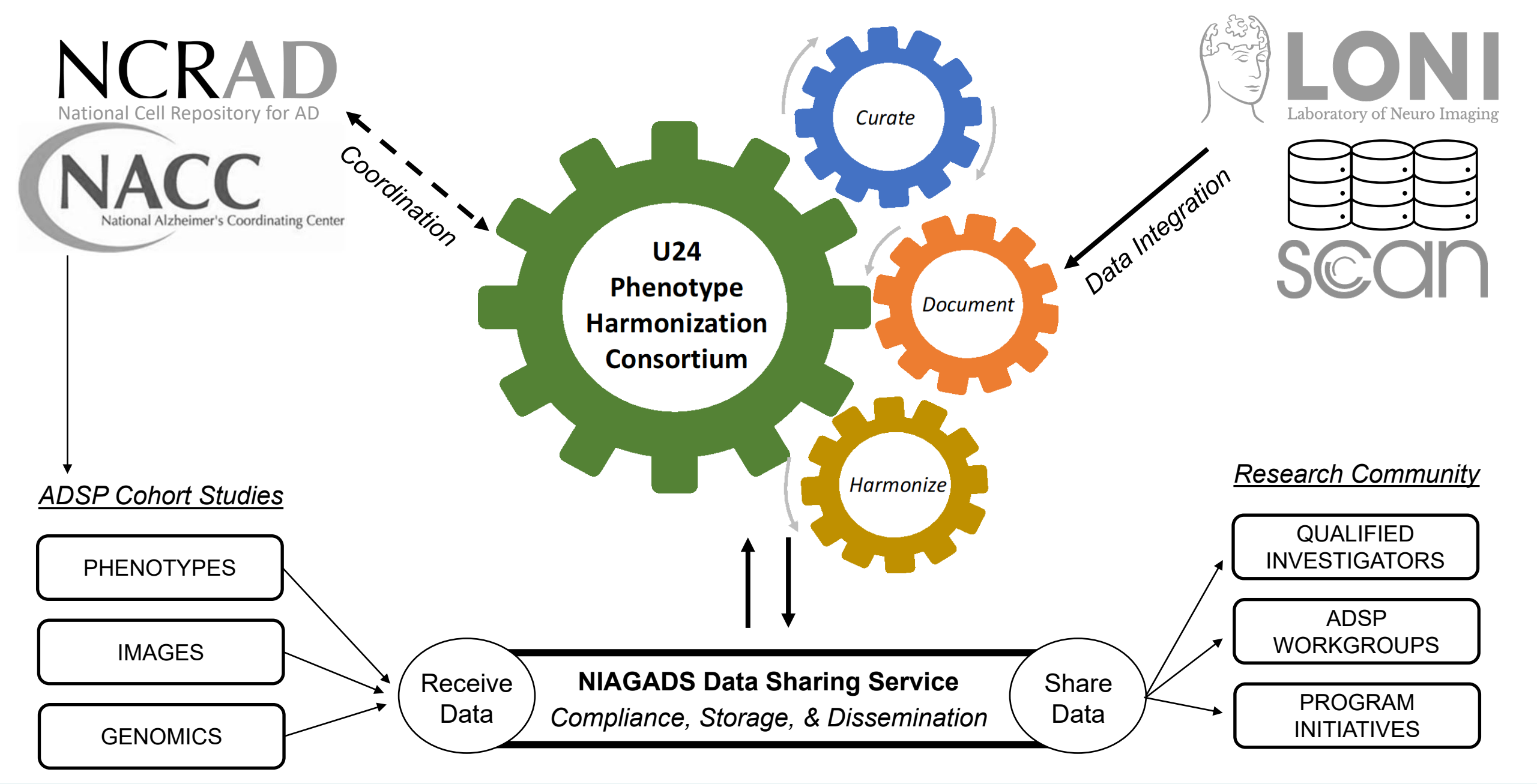




ADSP PHC
PHENOTYPE HARMONIZATION CONSORTIUM

FunGen-AD
ADSP Functional Genomics Consortium

AI4AD
GENETICS IMAGING COGNITION TREATMENT


NCRAD
National Cell Repository for AD
NACC
National Alzheimer's Coordinating Center
Coordination
Curate
U24
Phenotype
Harmonization
Consortium
Document
Harmonize
Data Integration
LONI
Laboratory of Neuro Imaging
scan
ADSP Cohort Studies
PHENOTYPES
IMAGES
GENOMICS
Receive Data
NIAGADS Data Sharing Service
Compliance, Storage, & Dissemination
Share Data
Research Community
QUALIFIED INVESTIGATORS
ADSP WORKGROUPS
PROGRAM INITIATIVES

Fluid Biomarker Harmonization

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Diffusion MRI Harmonization

Bennett Landman, PhD
Vanderbilt University

Derek Archer, PhD
Vanderbilt University Medical Center

Cognitive Harmonization

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Jesse Mez, MD, MS
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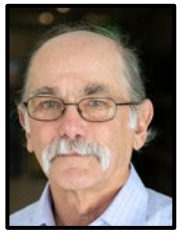
Storage & Informatics



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Vascular Harmonization

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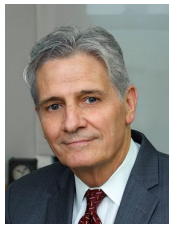

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Neuropathology Harmonization

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Gary Beecham, PhD
University of Miami

PET Harmonization

Elizabeth Mormino, PhD
Stanford University

Duygu Tosun, PhD
University of California San Francisco

NACC

Subject and cohort counts for each domain:

Cohort	Cognition	Biomarker	Neuropath
ACT	1337	0	0
ADNI	1566	1165	0
KGAD	0	64	0
MAP- Rush	639	0	538
MARS	48	0	11
NACC	10488	805	4649
NIA-LOAD	0	2	262
ROS	583	0	532
Total	14661	2036	5992

Accession Number:
NG00067.v9

Last Release Date:
October 5, 2022

Neuroimaging
Coming 2023

Vascular Risk Factors
Coming 2023

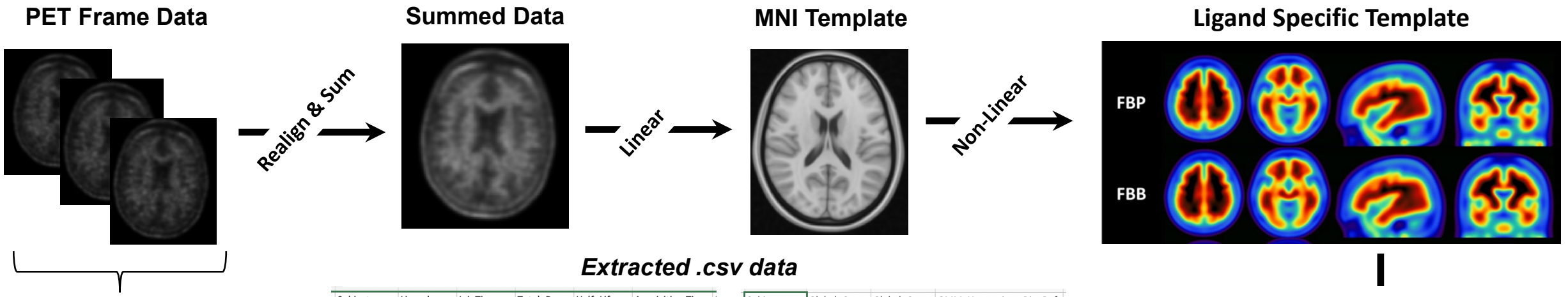
dss NIAGADS

https://dss.niagads.org/

ADSP PHC PHENOTYPE HARMONIZATION CONSORTIUM

NACC

PET Harmonization Pipeline (Landau 2022 Alz Dementia*)



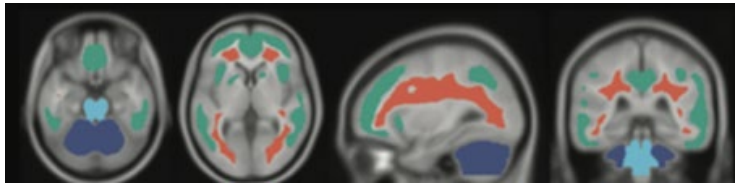
Extract Timing Info and Recon Parameters

Extracted .csv data

Subject	Ligand	Inj_Time	Total_Dose	Half_Life	Acquisition Time
NACC000531	Florbetaben	110300	307734752	6586.2002	122705
NACC000540	AV-45	123000	344100006	6586.2	131926.453
NACC000941	Neuroceq	142900	321899994	6586.2	152957.171
NACC001318	FDG--fluoroc	104400	332817216	6586.2002	113304
NACC002730	FDG--fluoroc	135500	366532512	6586.2002	145208
NACC004374	18F-AV-45FL	124600	375594528	6588	134140

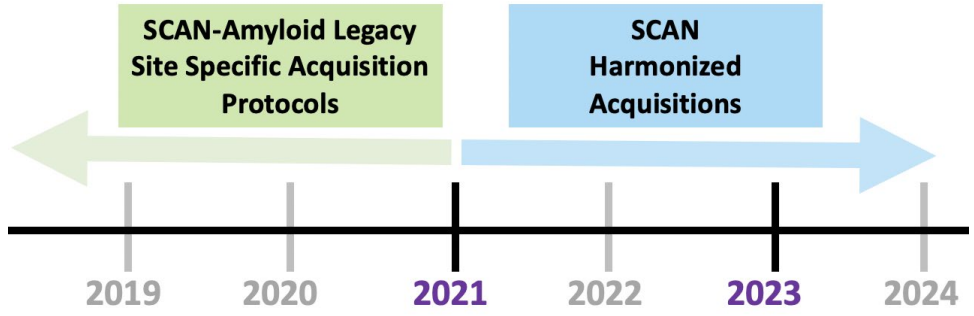
Subject	Global_Cer	Global_Comp	GMM_Uncertainty_Big_Ref
NACC000531	1.057694136	0.792113305	0.109738648
NACC000540	1.052880067	0.715220118	0
NACC000941	1.009221916	0.763438689	0
NACC001318	0.856687431	0.664103385	0
NACC002730	1.176939152	0.781881156	0.005306852
NACC004374	1.106844541	0.818670977	0.090945694

Mean Intensities Extracted
Global SUVR=
Cortical Target/Whole Cerebellum



GAAIN ROIs
Blue – Cortical Target Region
Orange - Whole Cerebellum Reference
Green+Orange - Composite Reference

*Landau 2022: Pipeline used in ADRC SCAN Project



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Neuropathology Harmonization

Strategy:

1. Create a master data dictionary
2. Map incoming data onto the dictionary
3. Generalize or simplify as needed

	Variables Harmonized		
	Primary	**Derived**	**N**
NACC	20	13	19,121
NIA-LOAD/FBS	5	4	727
ROSMAP	10	12	2,459
ACT*	13	13	532

February 2023

Thomas Montine, MD, PhD
Stanford University

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2. Mapping incoming data to the NACC Data Dictionary:

Categories	Description	VariableName	Coding	ROSMAP Coding
Amyloid deposition	CERAD (Neuritic Only)	AMY_CERAD	0 = None/No AD 1 = Sparse/Possible 2 = Moderate/Probable 3 = Definite/Frequent -9 = Missing/Not Assessed	ceradsc, 0=4 1=3 2=2 3=1 "-9" = is.na(value)
Amyloid deposition	Any amyloid (dichotomous)	AMY_ANY	0 = None 1 = Some Amyloid -9 = Missing/Not Assessed	ceradsc, 0=4 1={1,2,3} "-9"= is.na(value)
Neurofibrillary degeneration	AD Braak stage for NFT	BRAA	0 = None 1 = BRAAK Stage I 2 = BRAAK Stage II 3 = BRAAK Stage III 4 = BRAAK Stage IV 5 = BRAAK Stage V 6 = BRAAK Stage VI -9 = Missing/Not Assessed	braaksc, 0=0 1=1 2=2 3=3 4=4 5=5 6=6 "-9"= is.na(value)
Neurofibrillary degeneration	B score	B_SCORE	0 = None 1 = BRAAK Stage I-II 2 = BRAAK Stage III-IV 3 = BRAAK Stage V-VI -9 = Missing/Not Assessed	braaksc, 0=0 1={1,2} 2={3,4} 3={5,6} "-9"= is.na(value)

NACC Neuropathology Data Dictionary (2014)

Cognitive Harmonization

	NACC	ACT	ADNI	ROSMAP & MARS	**TOTAL**
Total Cog N	41459	5546	3189*	4386	**54,580**
Total ADSP N	10486	1392	1574	1575	**15,027**
Total Cog & ADSP N	8458	1340	1574	1560	**12,932**

Paul Crane, MD, MPH
University of Washington

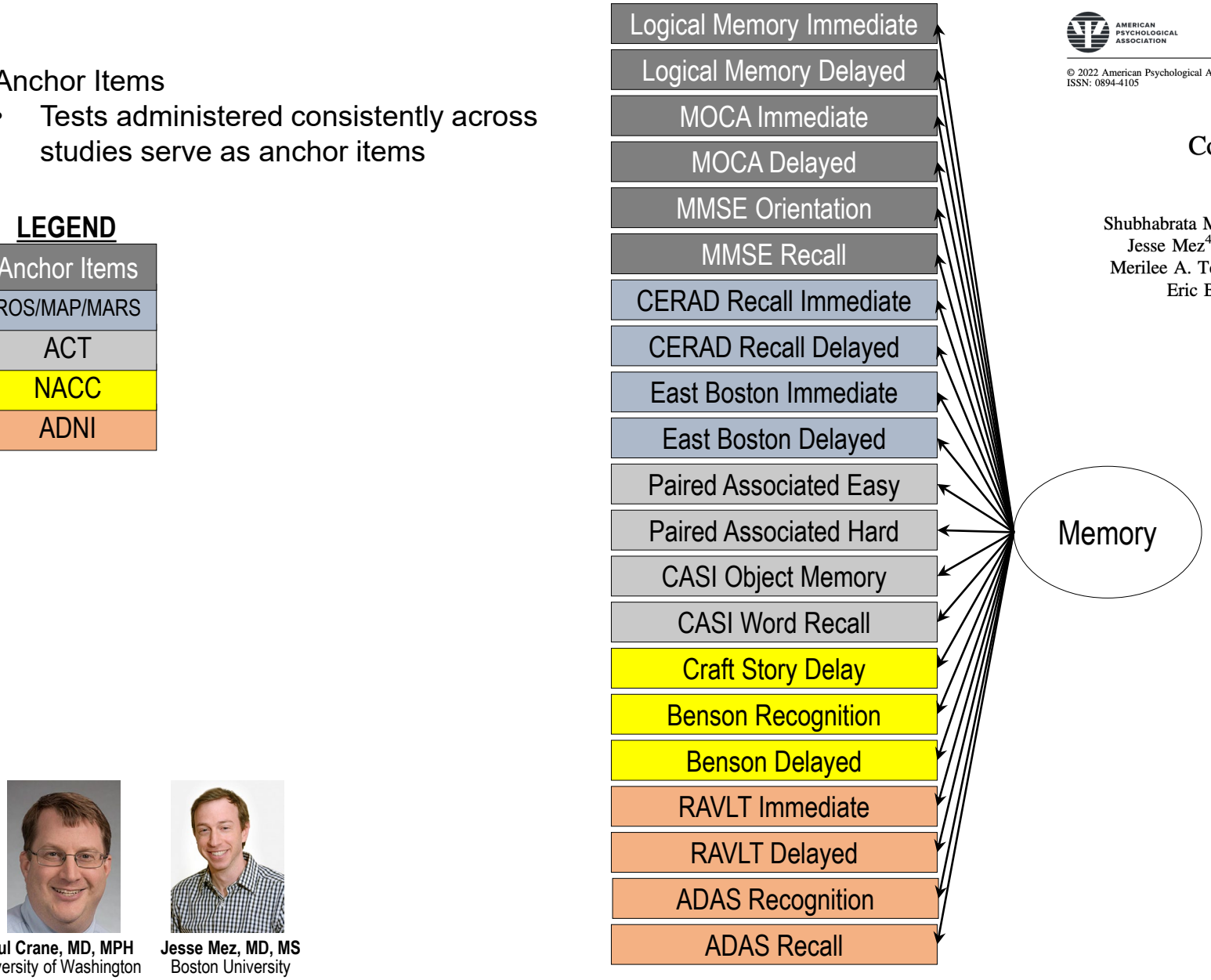
(Mukherjee et al., Neuropsychology, 2022)

Cognitive Harmonization

Anchor Items
- Tests administered consistently across studies serve as anchor items

LEGEND

Anchor Items
ROS/MAP/MARS
ACT
NACC
ADNI



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Cognitive Domain Harmonization and Cocalibration in Studies of Older Adults

Shubhabrata Mukherjee[1], Seo-Eun Choi[1], Michael L. Lee[1], Phoebe Scollard[1], Emily H. Trittschuh[2, 3], Jesse Mez[4], Andrew J. Saykin[5], Laura E. Gibbons[1], R. Elizabeth Sanders[1], Andrew F. Zaman[6], Merilee A. Teylan[7], Walter A. Kukull[7, 8], Lisa L. Barnes[9], David A. Bennett[9], Andrea Z. Lacroix[10], Eric B. Larson[11], Michael Cuccaro[6], Shannon Mercado[12, 13], Logan Dumitrescu[12, 13], Timothy J. Hohman[12, 13], and Paul K. Crane[1]

Harmonization Approach

Applied Psychometrics

- An expert panel assigns items to one of four domains:
  - Memory
  - Language
  - Executive functioning
  - Visuospatial ability

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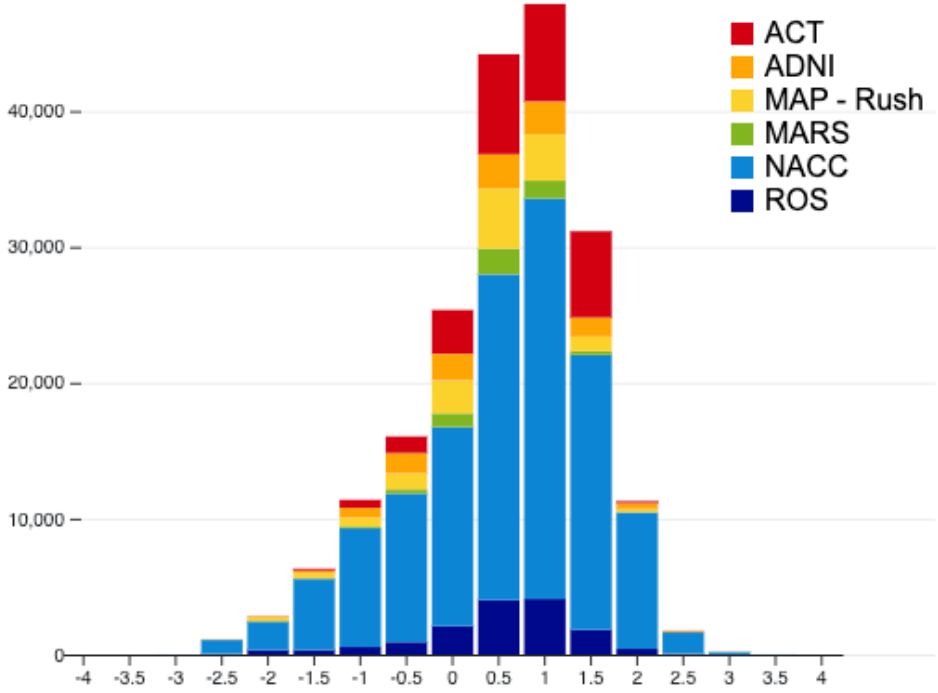
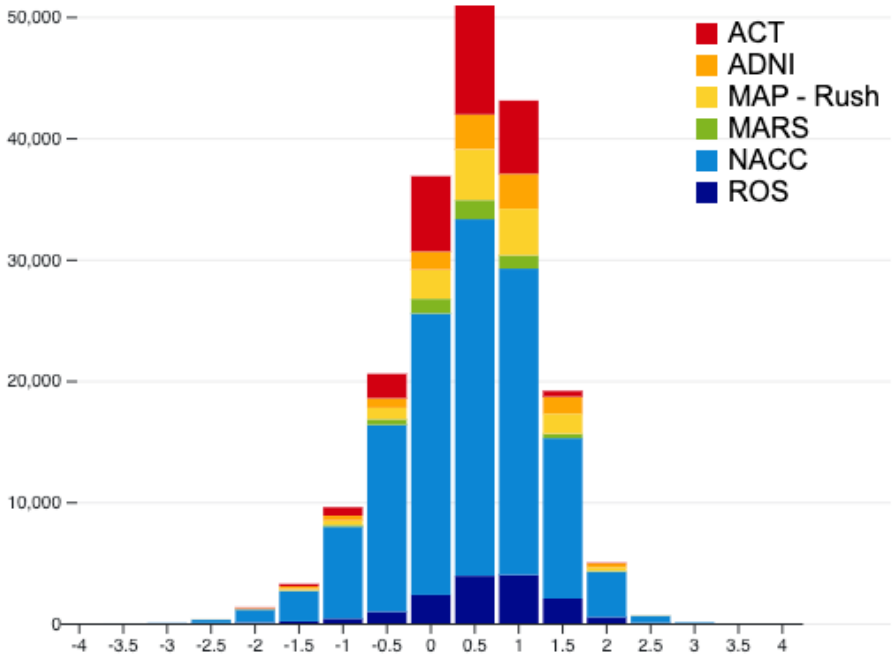
Cognitive Harmonization

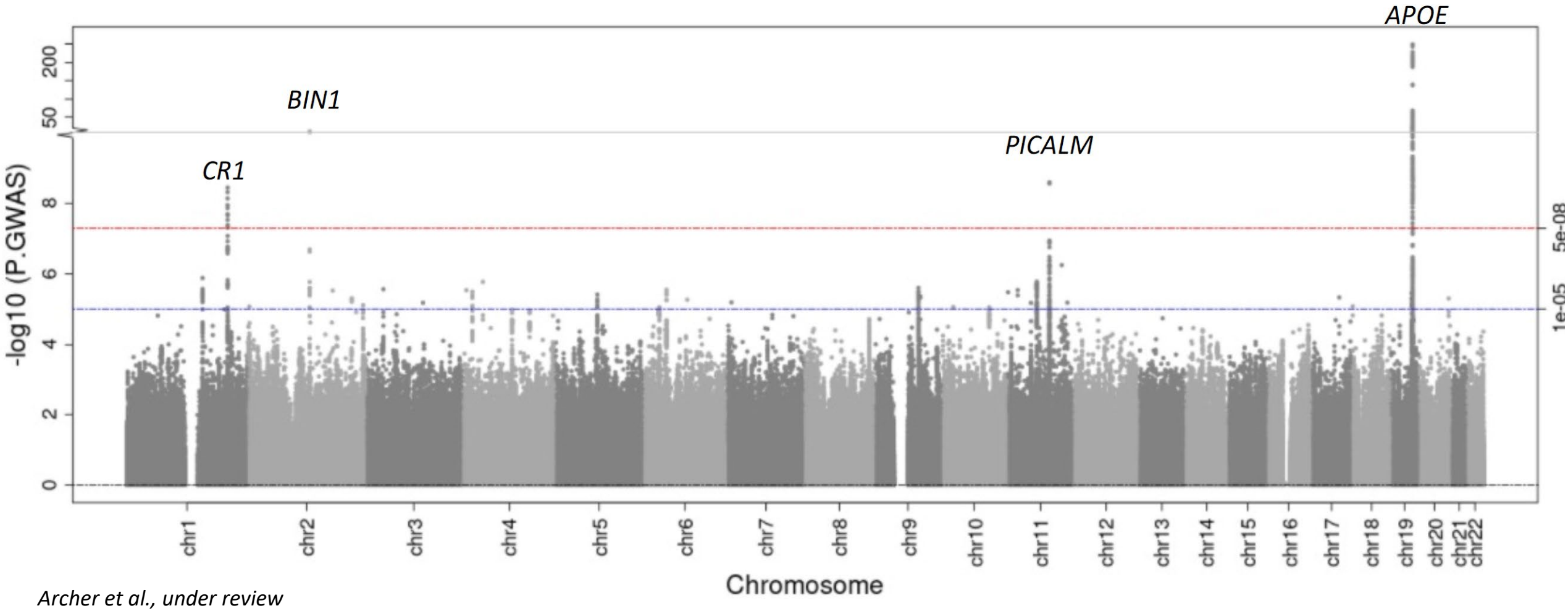


PHC_MEM -- *Harmonized Composite Memory Score*



PHC_EXF -- *Harmonized Composite Executive Function Score*

GWAS of Memory Performance



Archer et al., under review

26,633 participants over
129,201 longitudinal visits

Enabling Representative Studies of Risk and Resilience

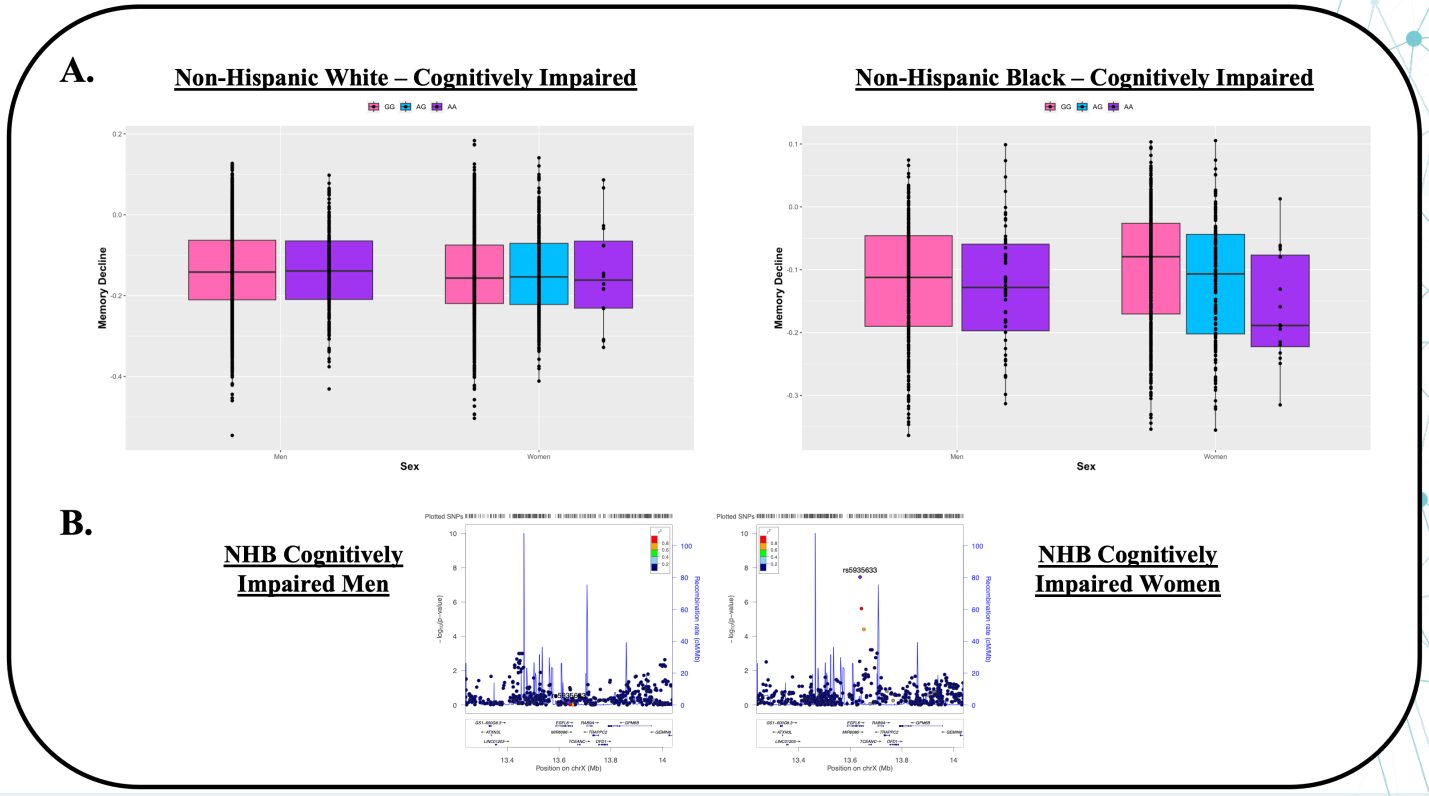
Cross-Ancestry Sex-Interaction Effects

	Memory Performance	Executive Functioning	Language Performance
APOE-ε4	↑F M	F M	↑F M
APOE-ε2	F M	F M	F M

N=32,427

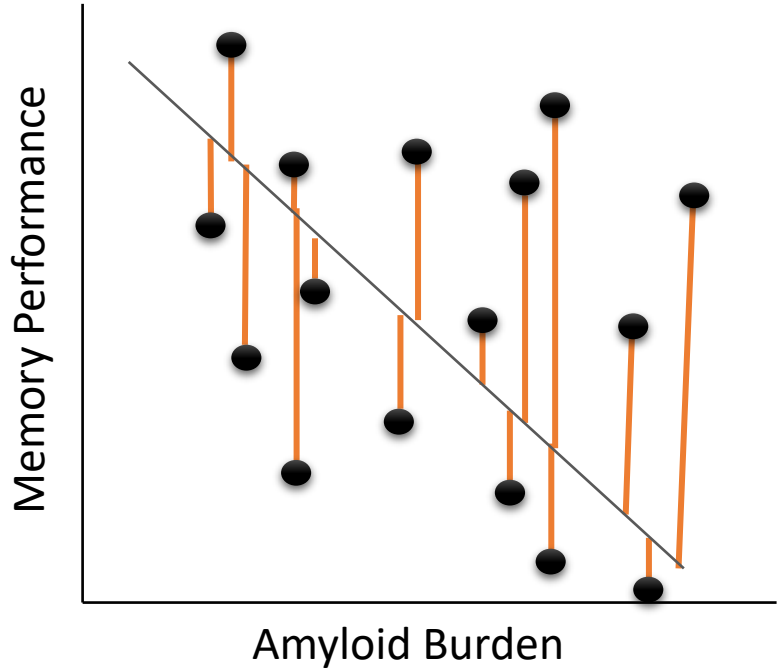
Walters et al., in press

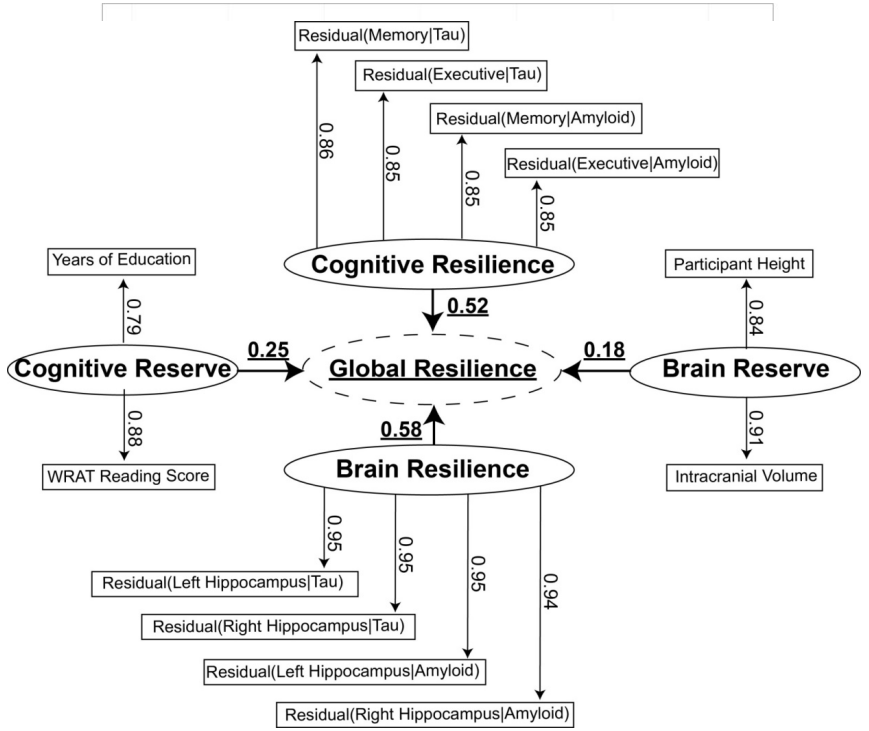
- 4,453 non-Hispanic Black



Eissman et al., under review

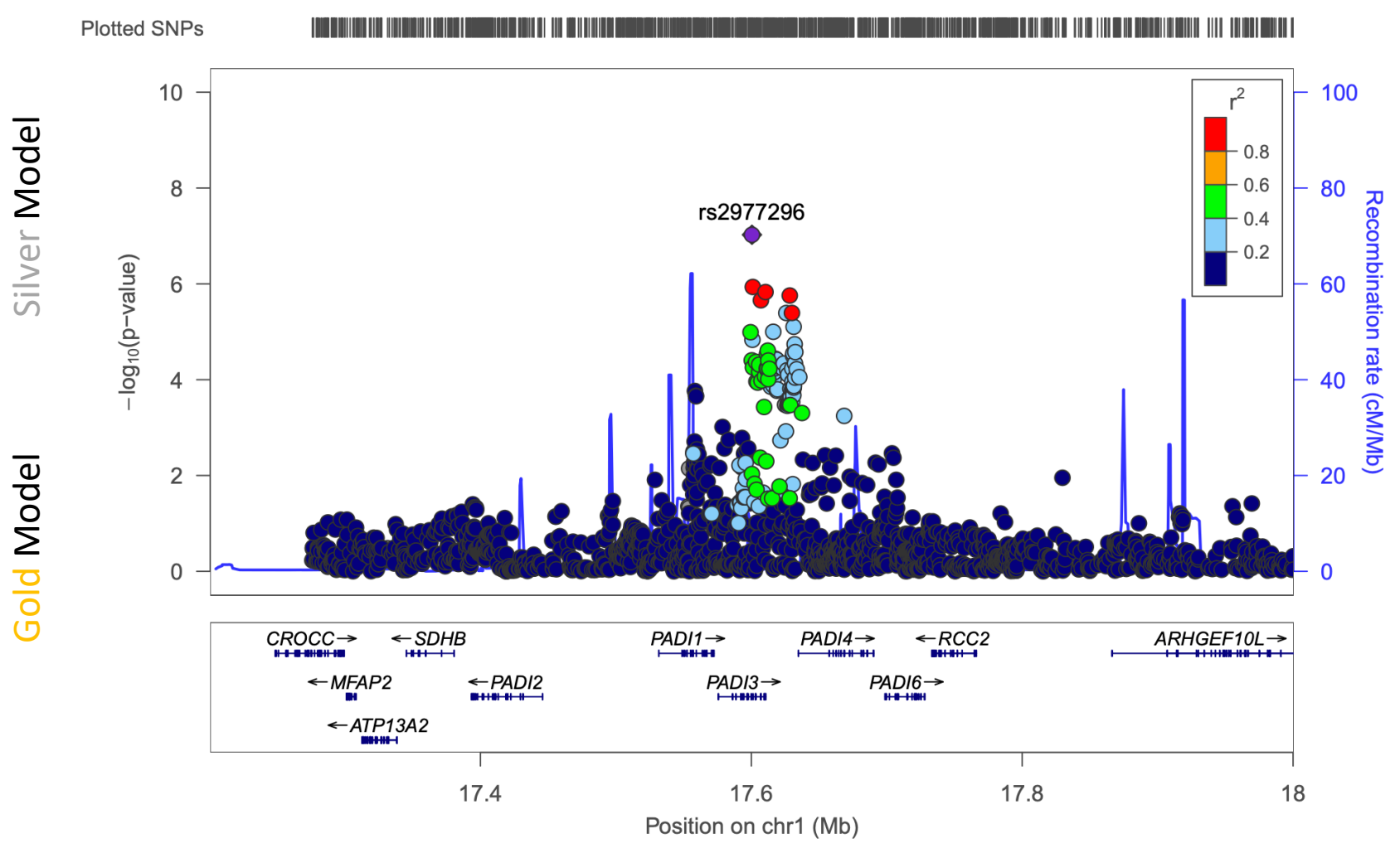
Enabling Representative Studies of Risk and Resilience





Hohman et al., *Neurology, 2016*

Enabling Representative Studies of Risk and Resilience



d Results

Thank you!

Thank you!

@timothyjhohman

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NACC