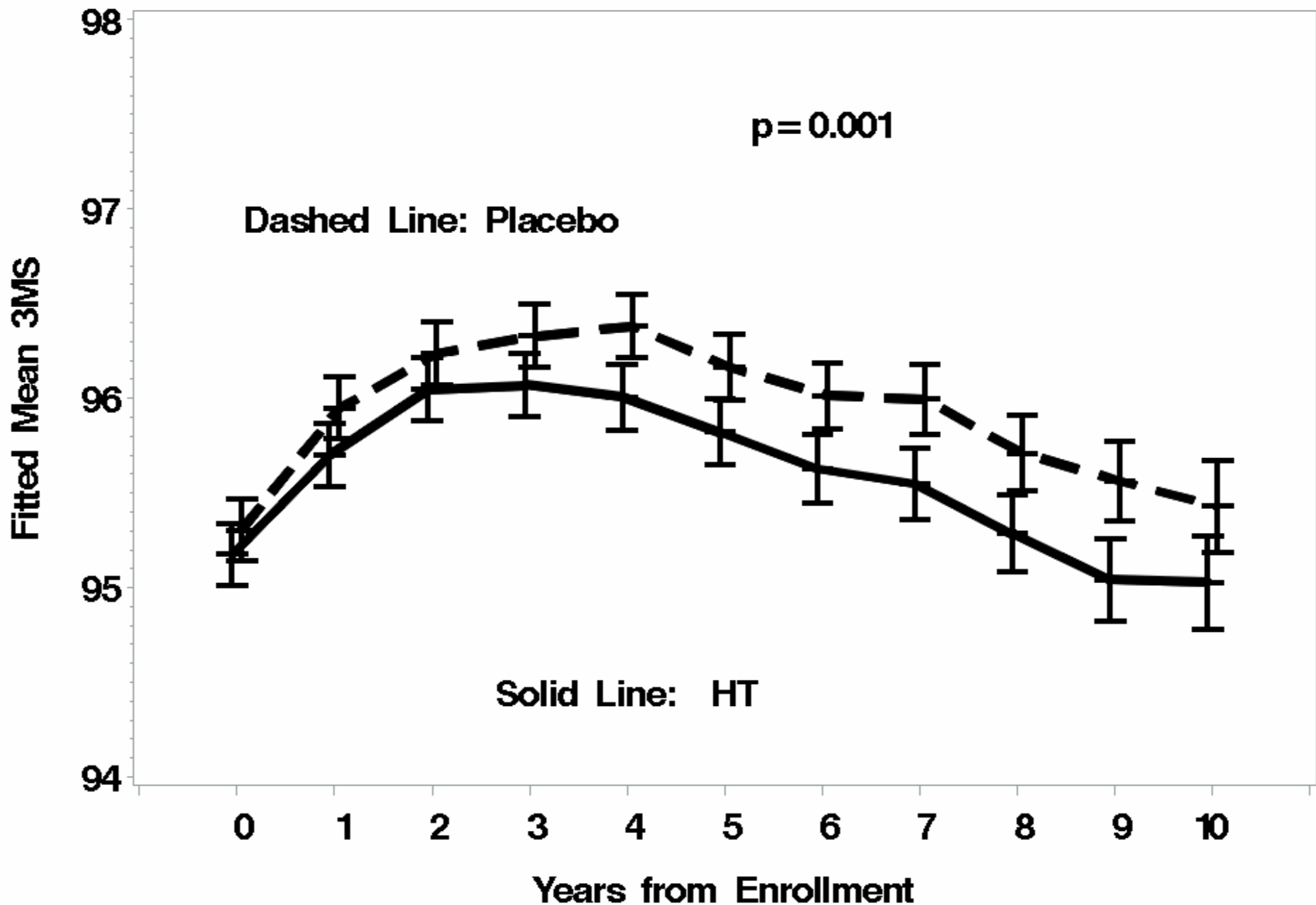


**TRAJECTORIES OF RELATIVE
PERFORMANCE ACROSS TWO MEASURES
OF GLOBAL COGNITIVE FUNCTION**

Mark A. Espeland, Jiu-Chiuan Chen, Julie Weitlauf, Kathleen M. Hayden, Stephen R. Rapp, Susan M. Resnick, Lorena Garcia, Brad Cannell, Laura D. Baker, Bonnie C. Sachs, Hilary A. Tindle, Robert Wallace, and Ramon Casanova

Annual WHI Meetings
May 3-4, 2018
Chicago, Illinois

Fitted 3MS Scores and 95%CI Over Time From Randomization



TRANSITION TO WHIMS-ECHO

- Modified Mini Mental State Exam (3MSE)
 - 46 items: total scores range from 0-100
 - Test items measure abstract reasoning, executive function, verbal recall, naming, praxis, temporal and spatial orientation, verbal fluency, visuo-constructional abilities, and writing
- Telephone Interview for Cognitive Status-modified (TICS_m)
 - 14 items: total scores range from 0-50
 - Test items assessing abstract reasoning, executive function, verbal recall, praxis, verbal fluency, and verbal memory.

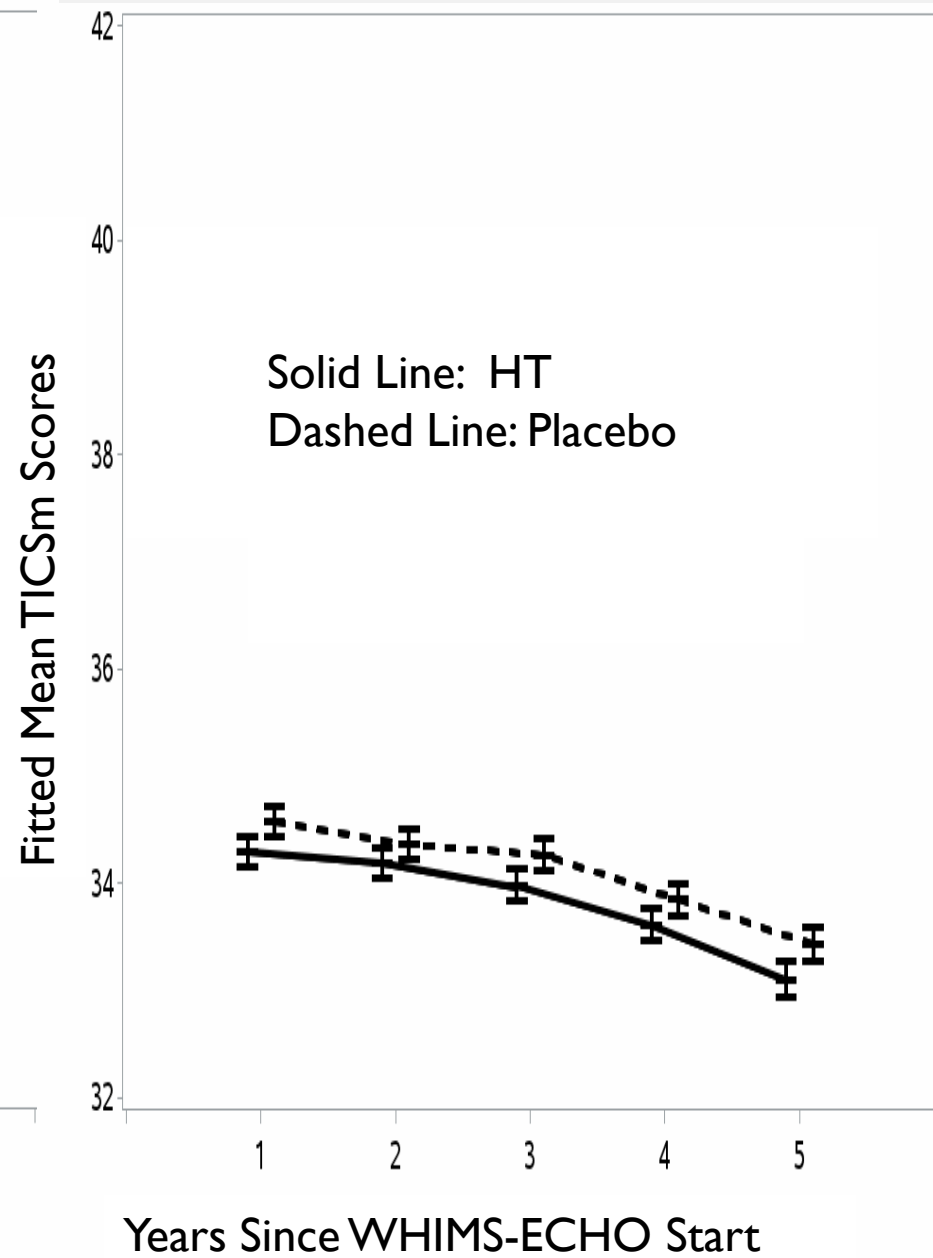
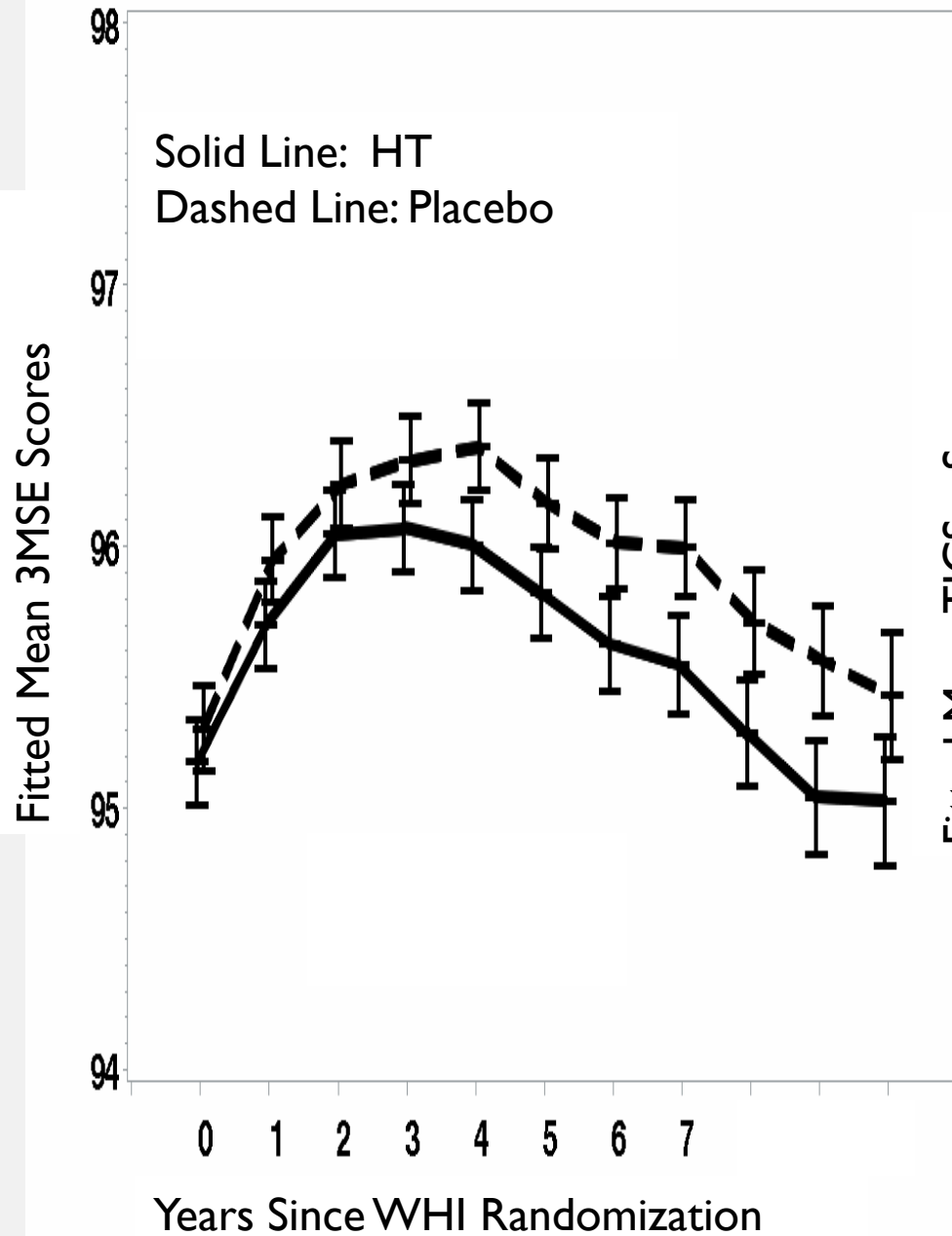
WHIMS VALIDATION ANALYSIS

Baseline Measure	Face-To-Face N=52	Telephone N=53	P-value
TICS-m	29.0 (1.91)	28.8 (2.60)	0.71
Verbal Fluency Animals	18.9 (5.0)	17.4 (5.3)	0.14

Change in 6 Months	Face-To-Face N=52	Telephone N=53	P-value
TICS-m	0.20 (0.13)	0.01 (0.13)	0.09
Verbal Fluency Animals	-0.22 (0.12)	0.28 (0.12)	0.01

Correlation Between 6 Month Measures	Face-To-Face to Telephone N=52	Telephone to Telephone
TICS-m	r=0.09 (p=0.69)	r=0.70 (p<0.001)
Verbal Fluency Animals	r=0.71 (p<0.001)	r=0.88 (p<0.001)

HOW TO BRIDGE WHIMS AND WHIMS-ECHO?



Raw Scores Over Time

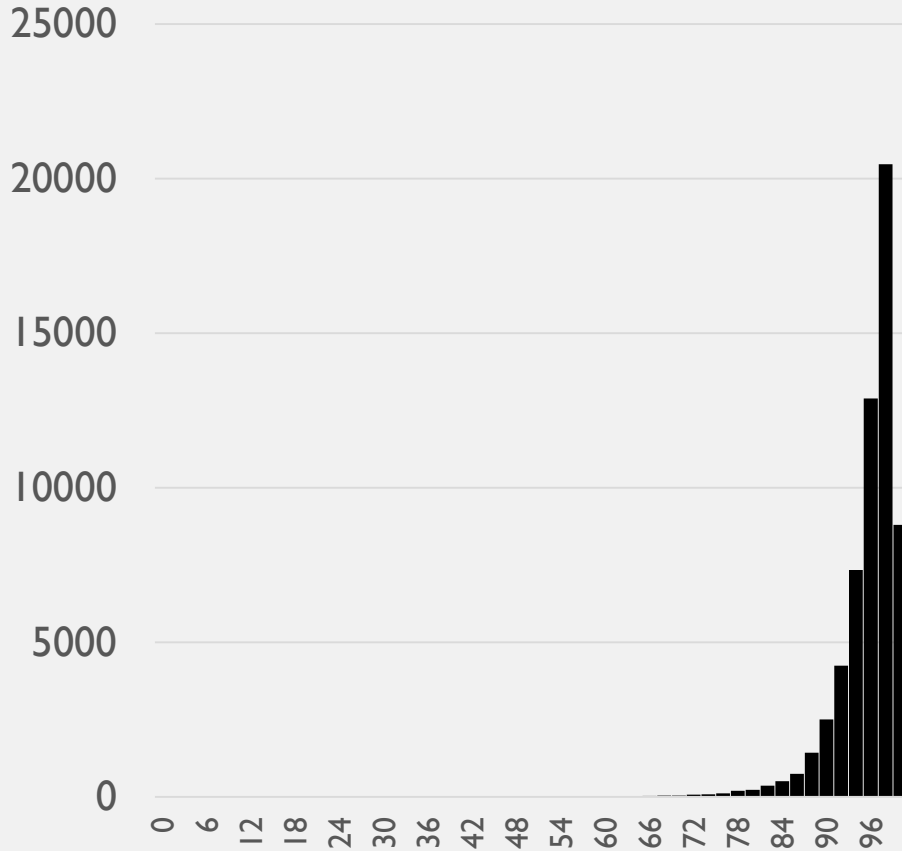
Years From Transition	3MSE		TICS _m	
	N	Score (SD)	N	Score (SD)
-5	2498	97.4 (2.9)	0	
-4	2495	97.4 (2.8)	0	
-3	2080	97.3 (3.0)	0	
-2	2155	97.0 (3.2)	0	
-1	2423	97.0 (3.2)	0	
0	273	96.7 (4.3)	0	
1	0		1846	34.9 (5.1)
2	0		2194	34.9 (5.1)
3	0		2222	34.6 (5.3)
4	0		2025	34.7 (5.3)
5	0		1782	34.7 (5.4)

APPROACH

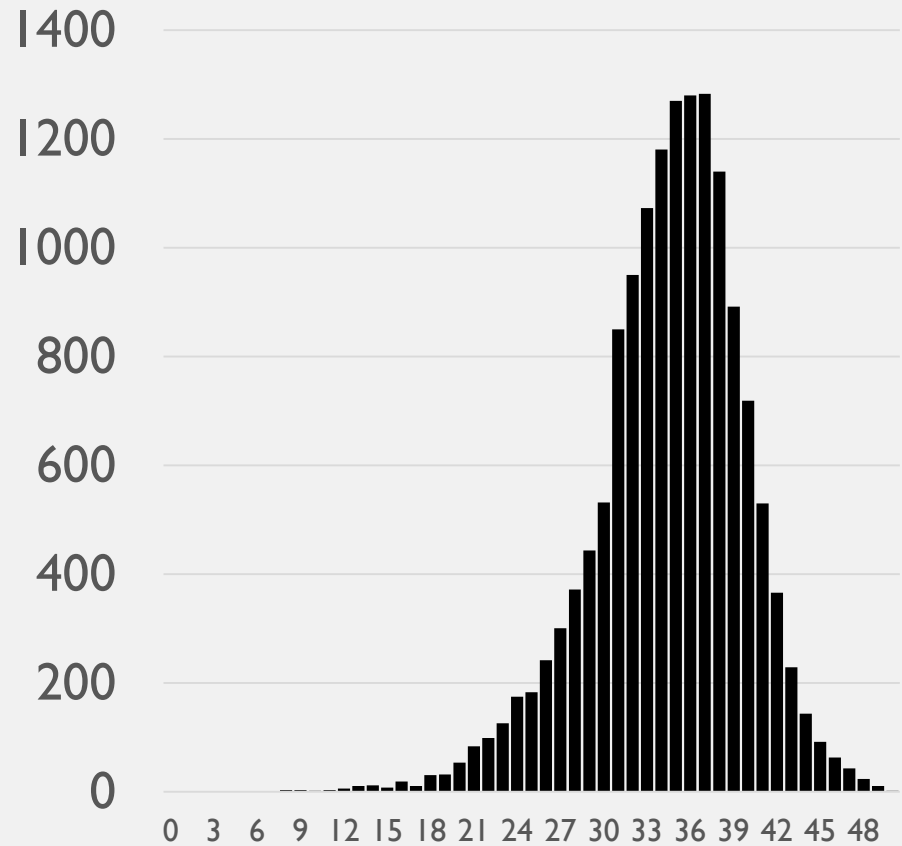
- Align scores onto a common metric
- Examine trajectories over time
 - Discontinuities when methods change?
 - Reasonable patterns?
- Are clusters of trajectories internally valid?
 - Expected risk factor relationships?

DISTRIBUTIONS OF TEST SCORES

3MSE



TICS_m

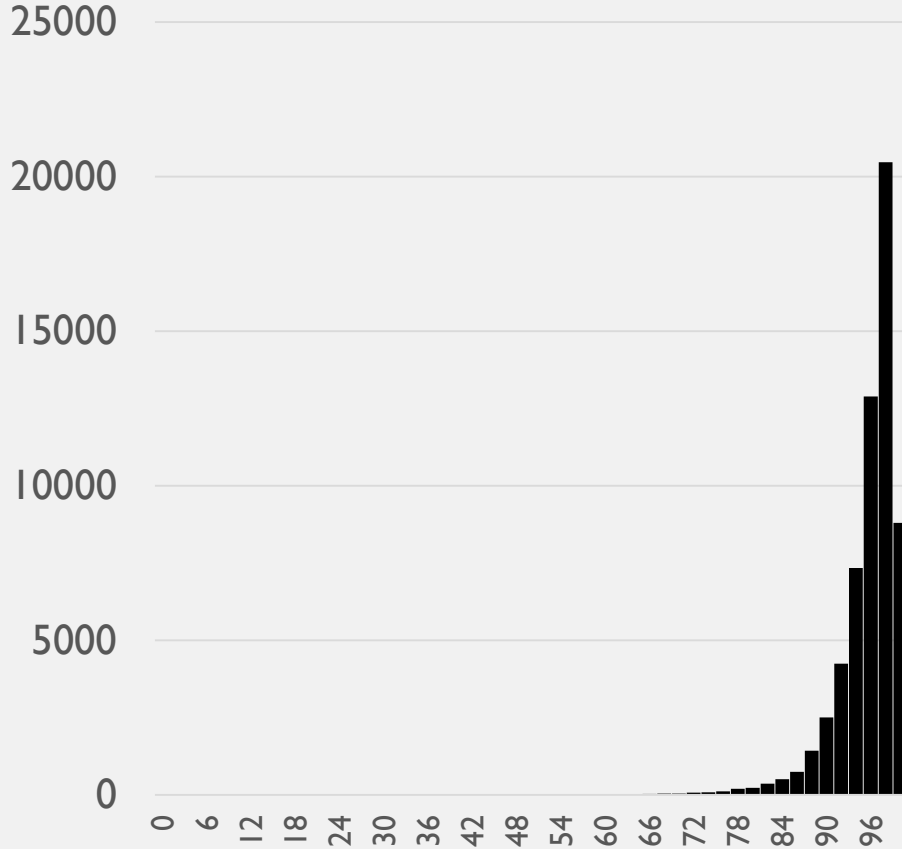


POTENTIAL APPROACHES

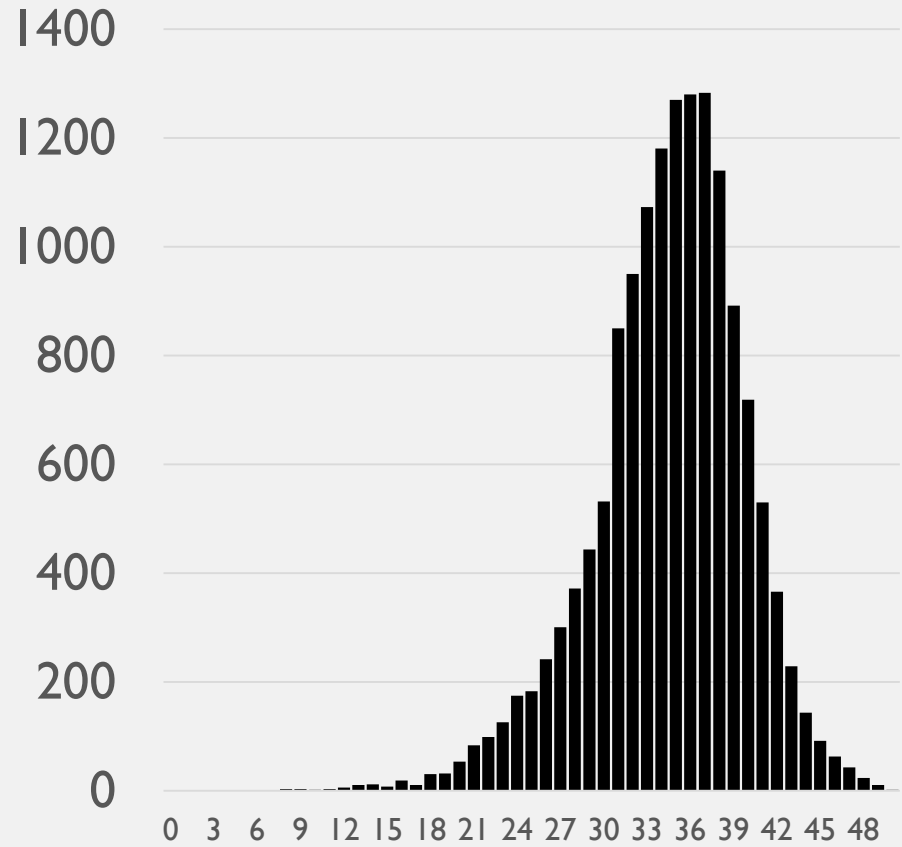
- Map similar individual responses to questions?
- Principal components?
- Z-scores?

DISTRIBUTIONS OF TEST SCORES

3MSE



TICS_m



RANK-BASED APPROACH

- Regress raw scores on age, sequence, and race/ethnicity
- Rank residuals (e.g. percentiles) for each year of age to obtain adjusted relative standing
- Examine trajectories of adjusted ranks over time to assess whether these exhibit inflection points and have expected risk factor relationships
 - Demography/SES: Education
 - Metabolism: Diabetes
 - Genetics: APOE-e4
 - Brain structure: Alzheimer's Disease Probability Scores (AD-PS)



Regional Neurotoxicity and Early Biomarkers of Air Pollution Effects on Brain Aging (NIA R21) The investigation of connections between air pollution and brain function and structure is an emerging field. We will combine sophisticated machine learning methods with traditional analyses techniques to uncover associations of air pollution with brain structure and Alzheimer's disease (AD).

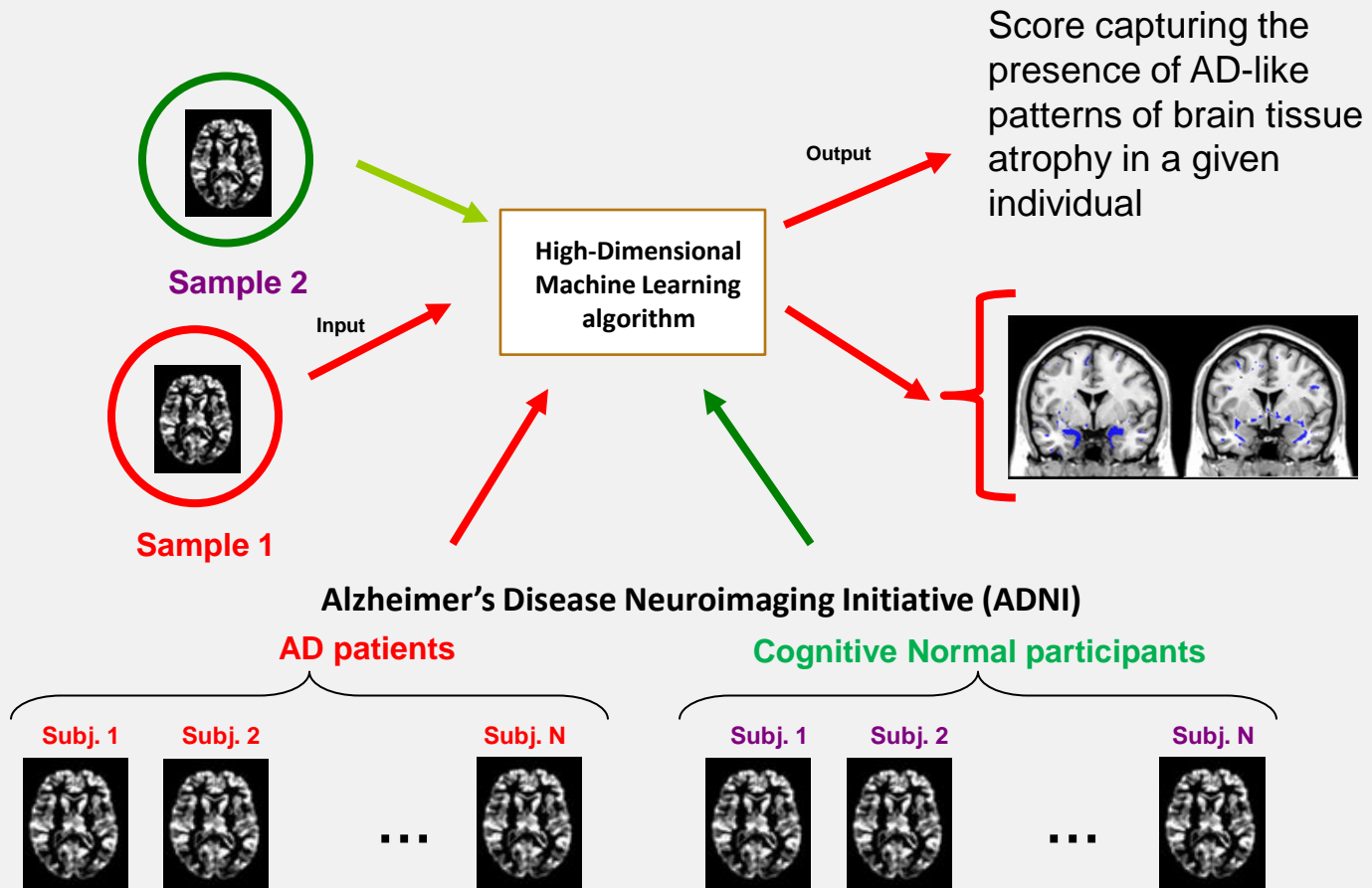


Ramon Casanova, PhD

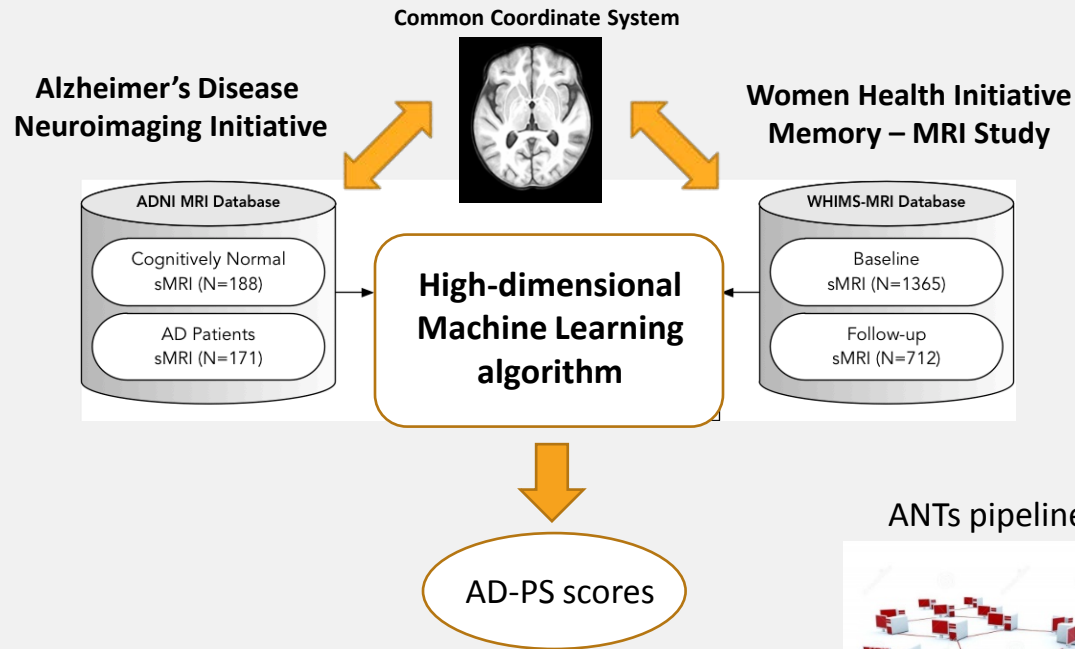


Jiu-Chiuan Chen, MD, PhD

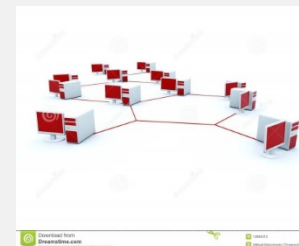
AD Pattern Similarity Scores (AD-PS)



Estimating WHIMS-MRI AD-PS Scores



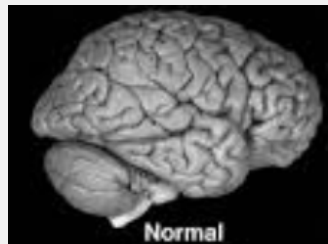
ANTs pipeline



WHIMS-MRI study

Designed to investigate impact of hormone therapies on brain structure

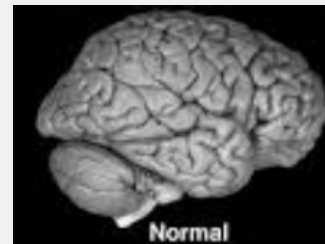
Scan 1 – 2005-2006



N=1365



Scan 2 – 2009-2010



N = 730

PRELIMINARY FINDINGS

- AD-PS scores are associated with:
 - Risk for dementia and MCI; White matter ischemic lesion volume and progression (Casanova, et al., under review)
 - Cognitive decline (Espeland, et al., in press JAGS, 2018)
 - Airborne particulate matter (Younans*, et al.)
 - Depression / Cognitive reserve (Petkus,* et al.)

*USC early career investigator

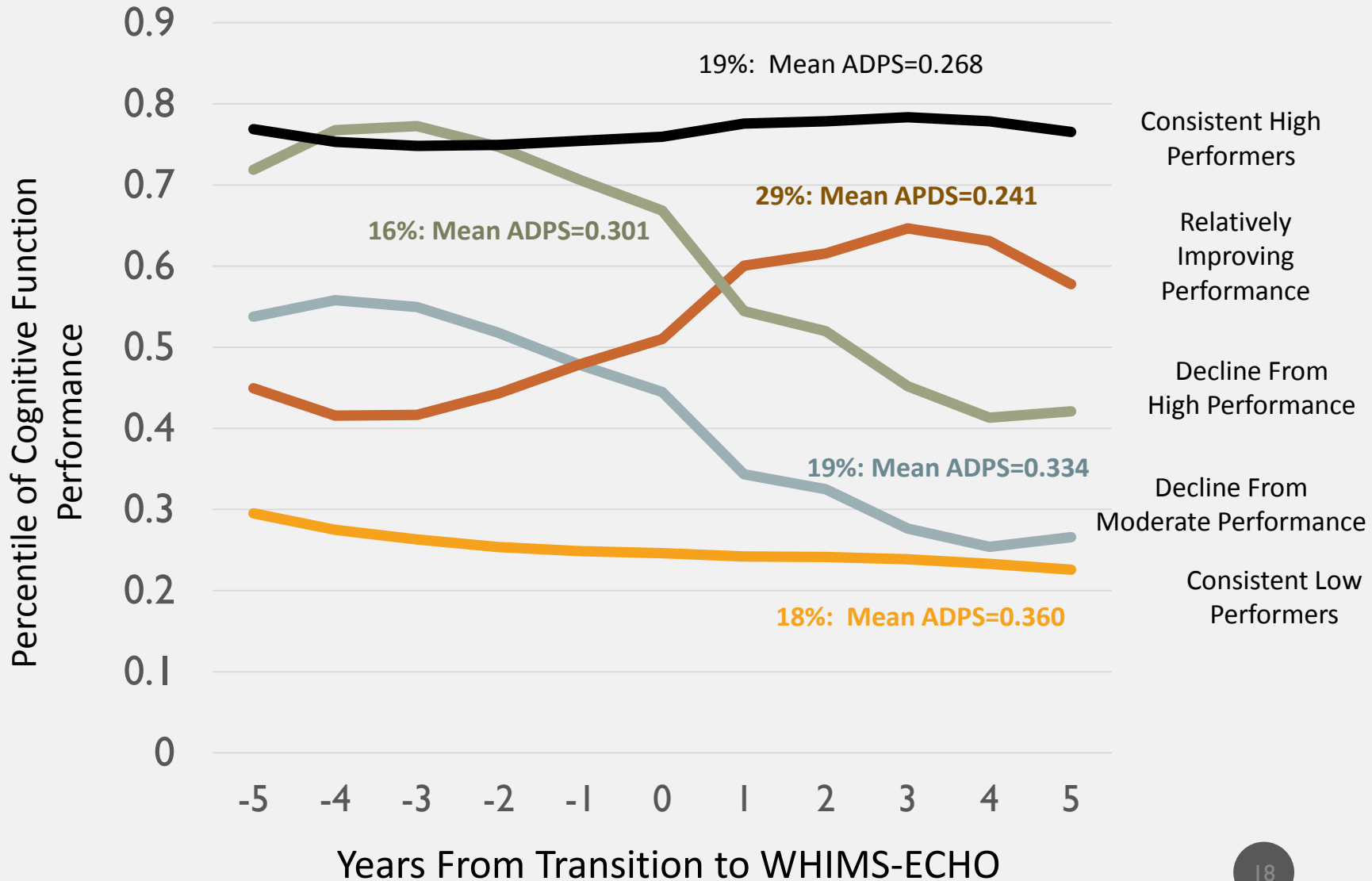
METHODS FOR CLUSTERING TRAJECTORIES

- Sample:
 - ≥ 2 3MSE scores during last 5 years of WHIMS
 - ≥ 2 TICSm scored during the first 5 years of WHIMS-ECHO
- Rank residuals of 3MSE and TICSm scores within each year
 - Adjustment for age, sequence, and race/ethnicity
- PROC TRAJ* to identify 5 major clusters
- PROC GLM to identify relationships with representative risk factors

*Jones BL, Nagin D, Roeder K. A SAS procedure based on mixture models for estimating developmental trajectories. *Sociological Meth Res* 2001;29:374-393.

*Jones BL, Nagin DS. Advances in group-based trajectory modeling and a SAS procedure for estimating them. *Sociological Meth Res* 2007;35:542-574.

TRAJECTORIES OF RELATIVE COGNITIVE FUNCTION

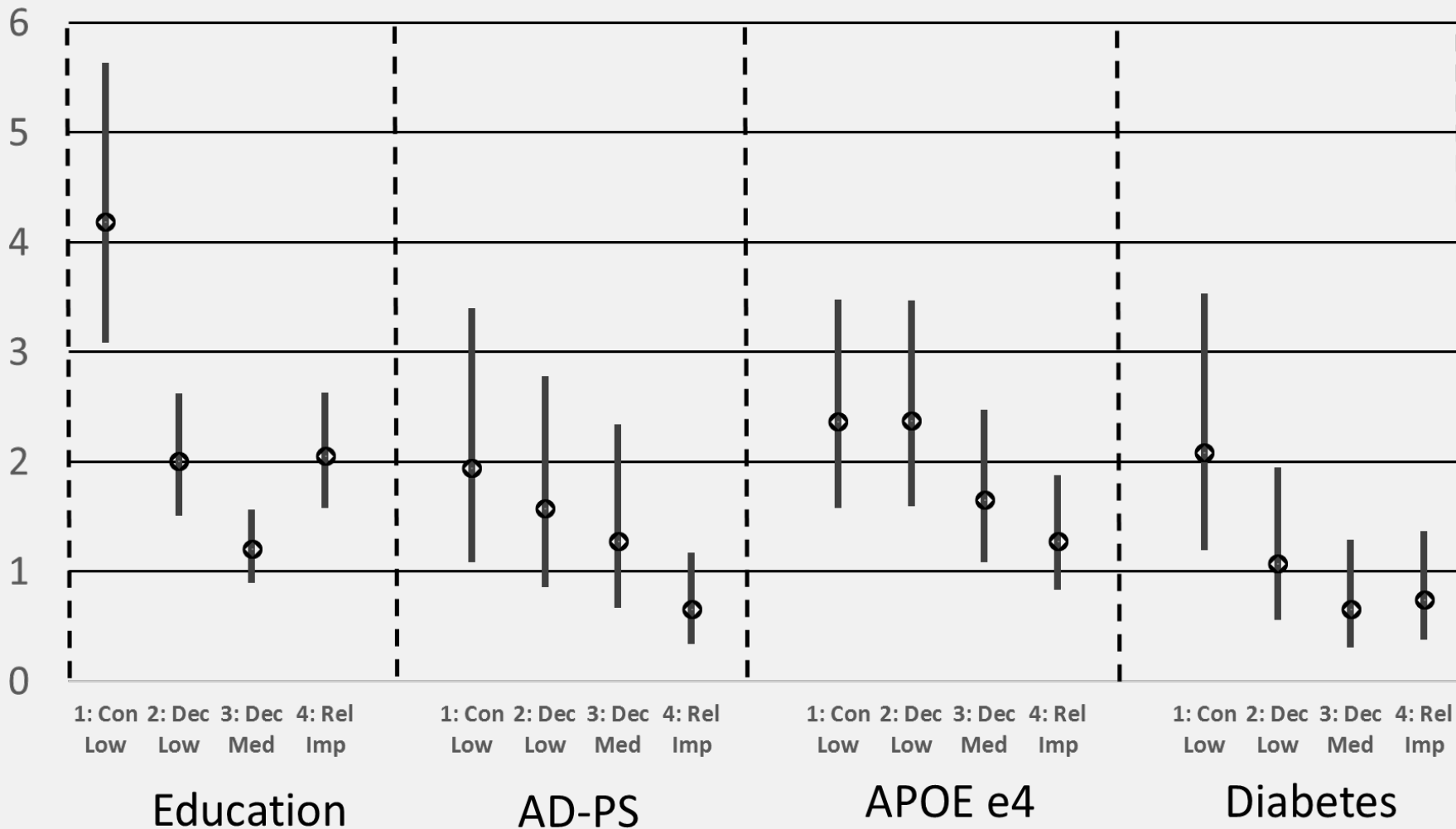


RISK FACTOR RELATIONSHIPS

Risk Factor	Cognitive Trajectory Group					p-value
	1. Consistently Low	2. Decline to Low	3. Decline to Median	4. Relative Improvement	5. Consistently High	
Education						
< High school	12.2%	4.1%	1.2%	4.2%	1.0%	<0.001
High school graduate	34.5%	22.0%	17.0%	23.3%	13.8%	
Some post-HS education	34.5%	41.4%	37.2%	40.5%	36.2%	
College graduate	18.7%	32.5%	44.6%	32.0%	49.0%	
ADPS Score						
Initial MRI (N=817)	0.35 (0.02)	0.33 (0.02)	0.30 (0.02)	0.23 (0.01)	0.28 (0.02)	<0.001
Follow-up MRI (N=567)	0.52 (0.03)	0.50 (0.03)	0.42 (0.03)	0.36 (0.02)	0.41 (0.02)	<0.001
Apo-E Alleles (1 or 2) (N=1800)	29.2%	30.1%	22.8%	18.7%	15.1%	<0.001
Diabetes						
At WHI enrollment	9.1%	4.9%	3.1%	3.5%	4.6%	<0.001
Prior to midpoint	11.9%	6.8%	8.0%	9.0%	6.0%	0.03

RISK FACTOR RELATIONSHIPS

Odds Ratio Relative to Cluster 5: Consistently High



SUMMARY

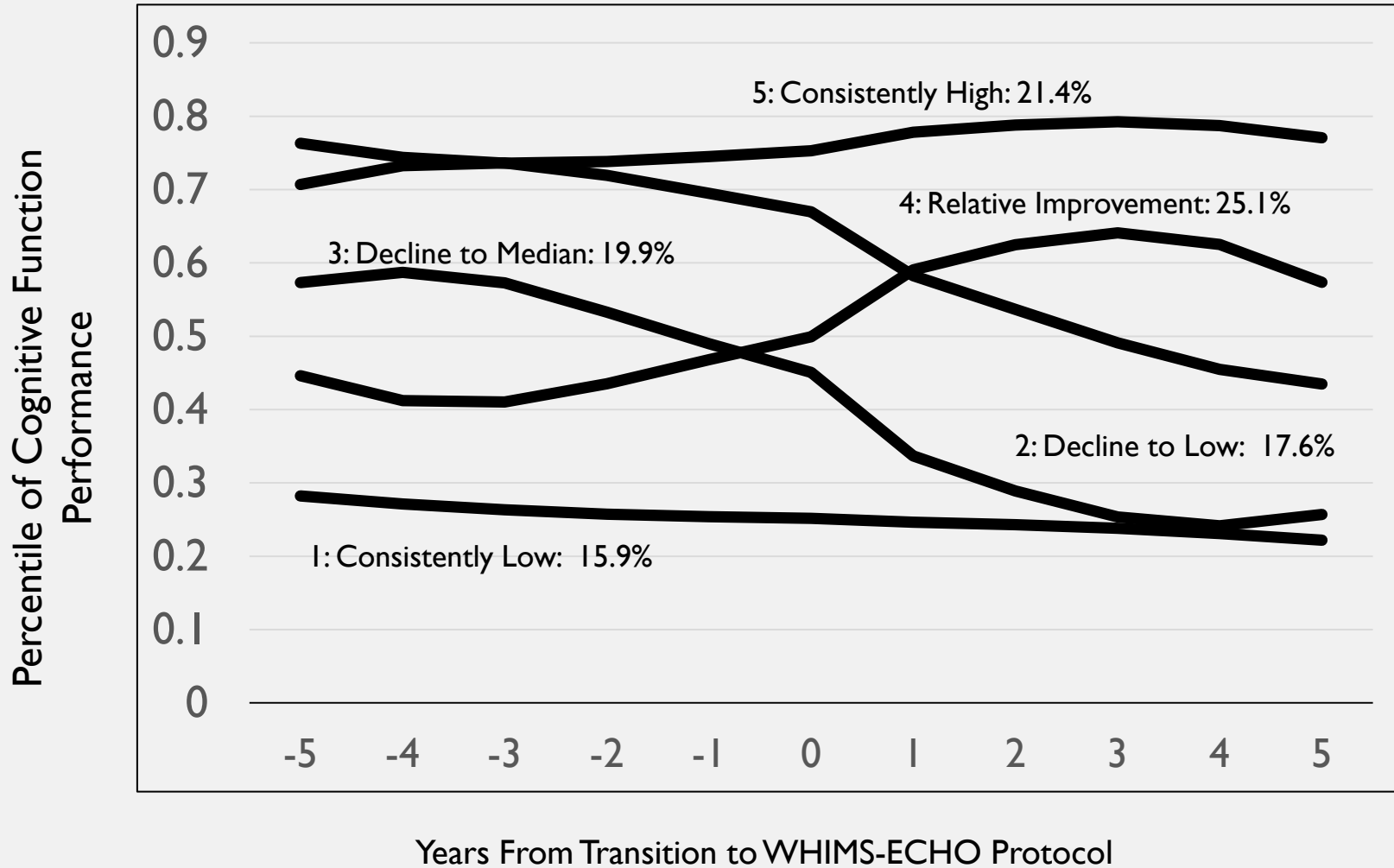
- Relative performance in global cognitive function can be bridged across WHIMS and WHIMS-ECHO
- Reasonable clusters of trajectories can be identified
- Risk factor relationships with trajectories exist

QUESTIONS ?



Photo Courtesy Visit Winston-Salem

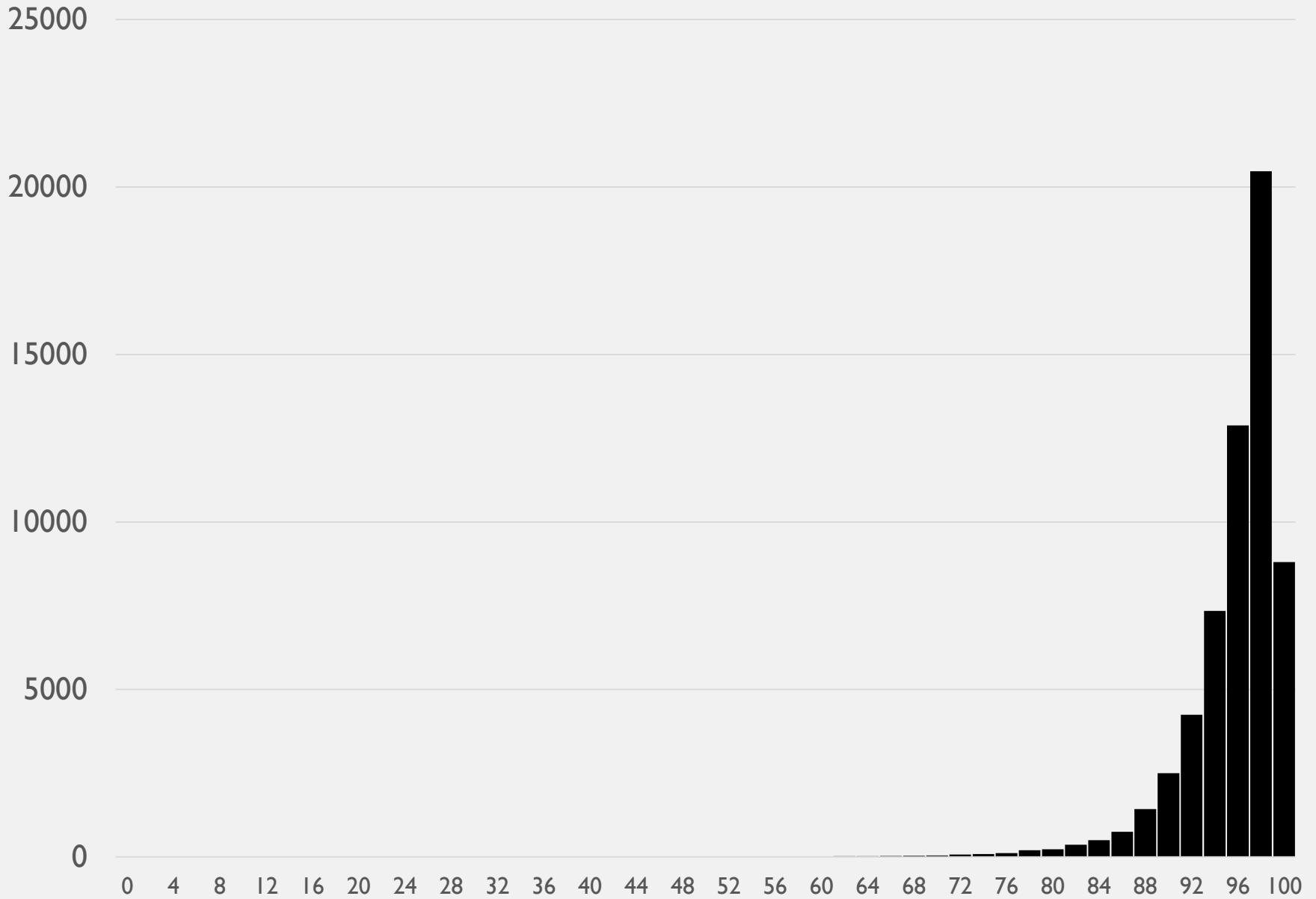
Sensitivity analysis – 3 observations in each mode minimum



Risk Factor for Cognitive Impairment	Mean (standard deviation) or N (Percent) N=2,561
Age at WHIMS-ECHO start	80.8 (3.5)
Age at MRI	
MRI1 (N=1365)	78.5 (3.7)
MRI2 (N=682)	82.8 (3.5)
Timing of MRI relative to WHIME-ECHO	
MRI1	-2.6 (0.3)
MRI2	2.1 (0.4)
Race/Ethnicity, N (%)	
American Indian	5 (0.2%)
Asian	10 (1.9%)
African-American	161 (6.3%)
Hispanic/Latina	37 (1.4%)
White	2289 (89.4%)
Other/Multiple	34 (1.3%)

Risk Factor for Cognitive Impairment	Mean (standard deviation) or N (Percent) N=2,561
Education < High school High school graduate Some post-HS education College graduate	112 (4.4%) 561 (21.9%) 976 (38.1%) 912 (35.6%)
ADPS Score MRI-1 (N=1365) MRI-2 (N=682)	0.33 (0.23) 0.44 (0.26)
ApoE-4, (N=1800) None 1 allele 2 alleles	1390 (77.2%) 384 (21.3%) 26 (1.4%)
Diabetes At WHI enrollment Prior to WHIMS-ECHO	125 (4.9%) 205 (8.0%)

DISTRIBUTION OF 3MS SCORES



DISTRIBUTION OF TICS_m SCORES

