Age-Related Molecular Networks Underlying Resilience to AD

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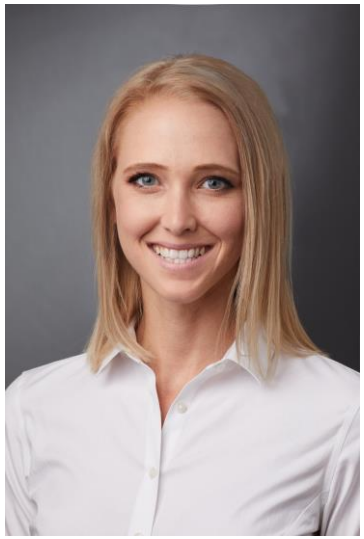
LEADERSHIP TEAM



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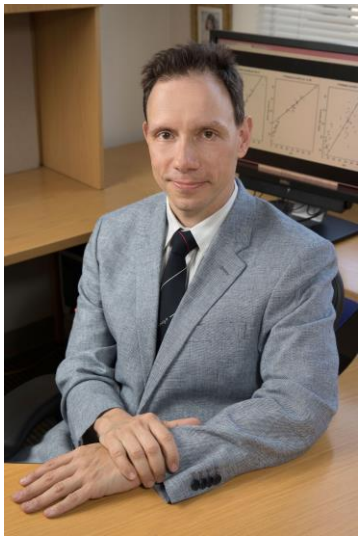
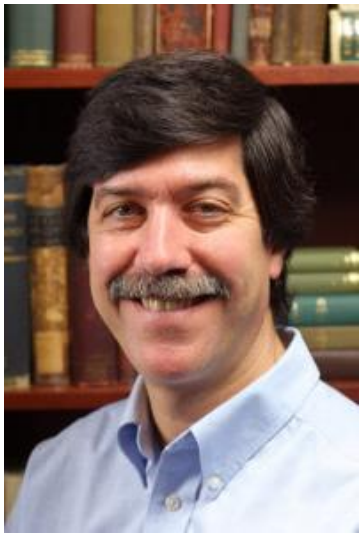




Yale University School of Medicine

RUSH UNIVERSITY

David Geffen School of Medicine

AGE IS THE #1 RISK FACTOR FOR LOAD

Alzheimer’s is a disease, and is not a normal part of the aging process.

Normal Aging vs. **Pathological Aging**

Risk for Alzheimer's disease increases exponentially with age.

After age 65, the risk of doubles every 5 years.

After age 85, the risk reaches nearly one-third.

Age-related biological changes (rather than time itself) likely predisposes to AD pathology.

Shared predisposing factors

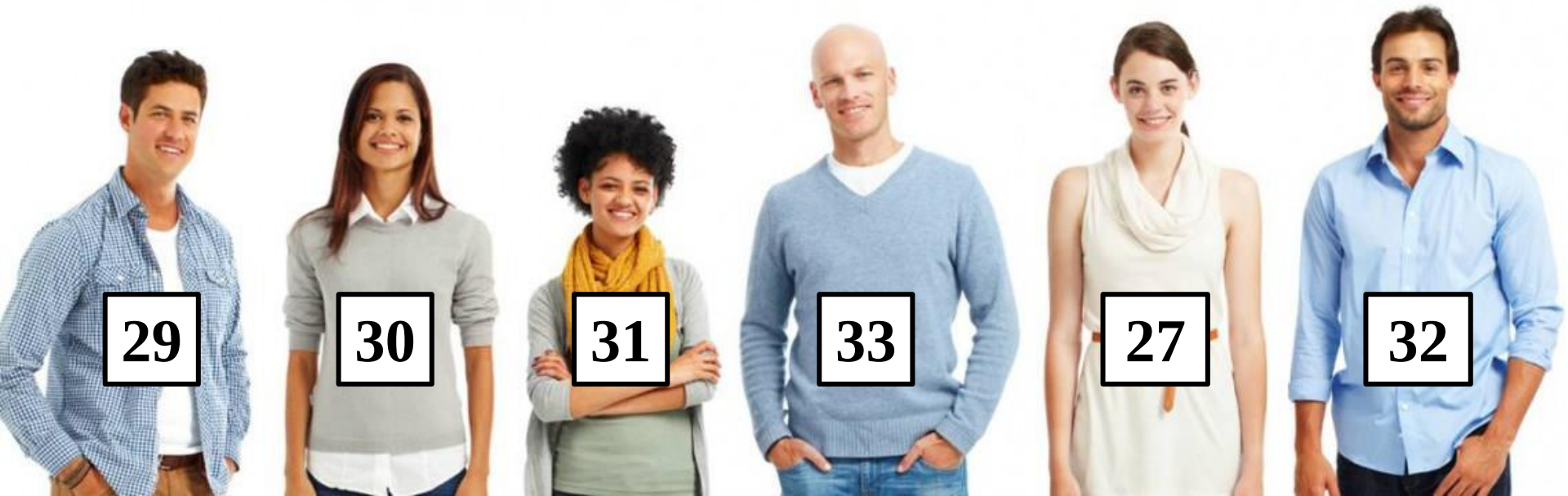
IS SLOWER BIOLOGICAL AGING LINKED TO DECREASED AD RISK?

We don’t all age in the same way or at the same rate.

Can heterogeneity in aging account for differences in AD risk?

Quantifying “biological aging”

Measure numerous age-related molecular changes to predict a person’s biological age.



QUANTIFYING "BIOLOGICAL AGING"

Carlos López-Otín et al. The Hallmarks of Aging.
Cell 2013 153, 1194-1217DOI: (10.1016/j.cell.2013.05.039)

DNA Methylation & Age

Chronological age has been shown correspond with distinct changes in DNA methylation (DNAm) at specific CpG sites.

"EPIGENETIC AGE"

Horvath: Weighted average of 353 CpGs.
Horvath (2013) Genome Biology

Hannum: Weighted average of 71 CpGs.
Hannum et al. (2013) Molecular Cell

Levine: Weighted average of 513 CpGs.
Levine et al (2018). Aging.

EPIGENETIC CLOCKS

Horvath, Hannum, & Levine

	Levine DNAm Age	Horvath DNAm Age	Hannum DNAm Age
Levine DNAm Age	1	0.460	0.482
Horvath DNAm Age	0.460	1	0.511
Hannum DNAM Age	0.482	0.511	1

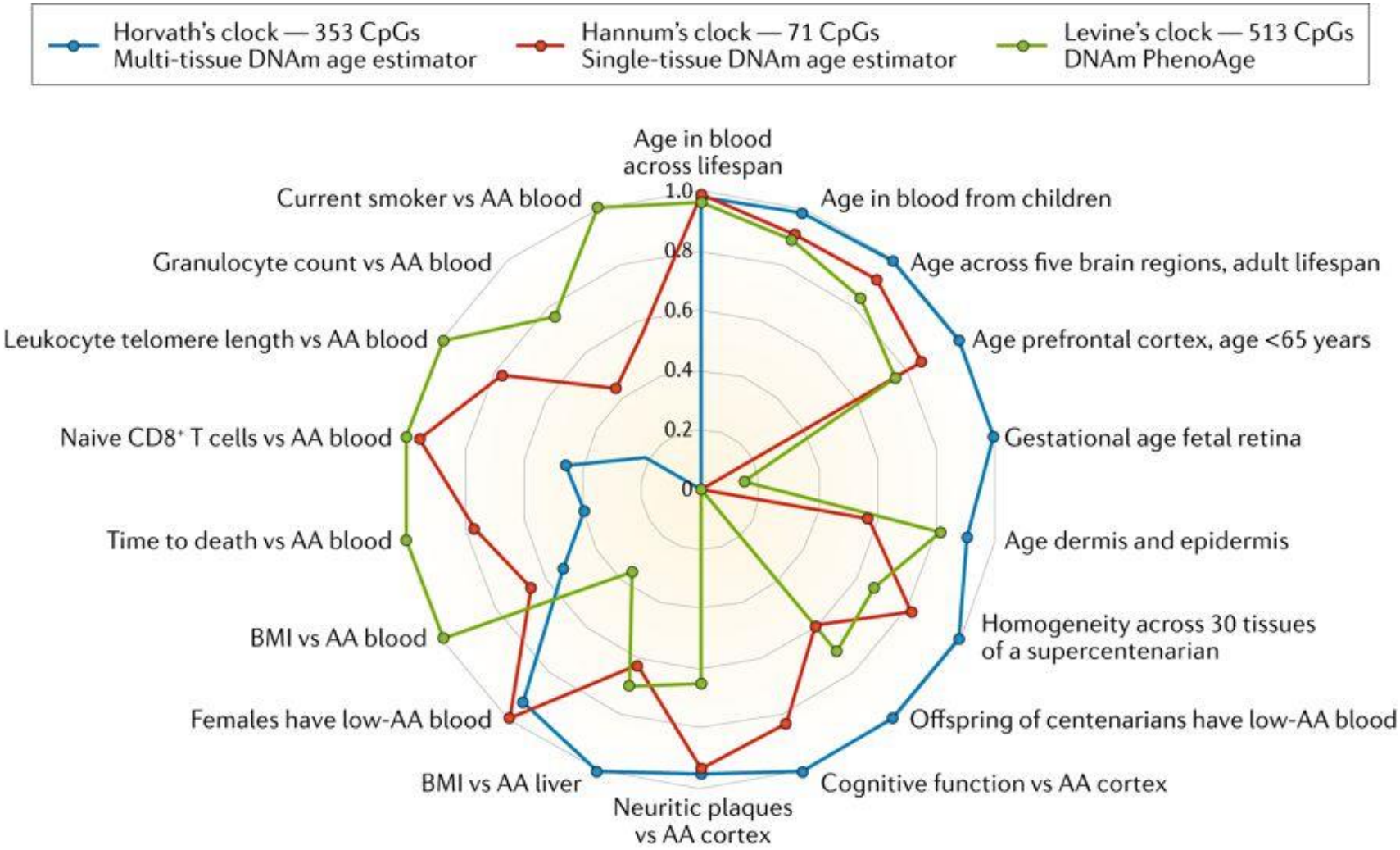
Only moderate correlations between the three clocks after adjusting for chronological age.

The clocks are not using the same CpGs.

They appear to be capture different phenomena.

EPIGENETIC CLOCKS

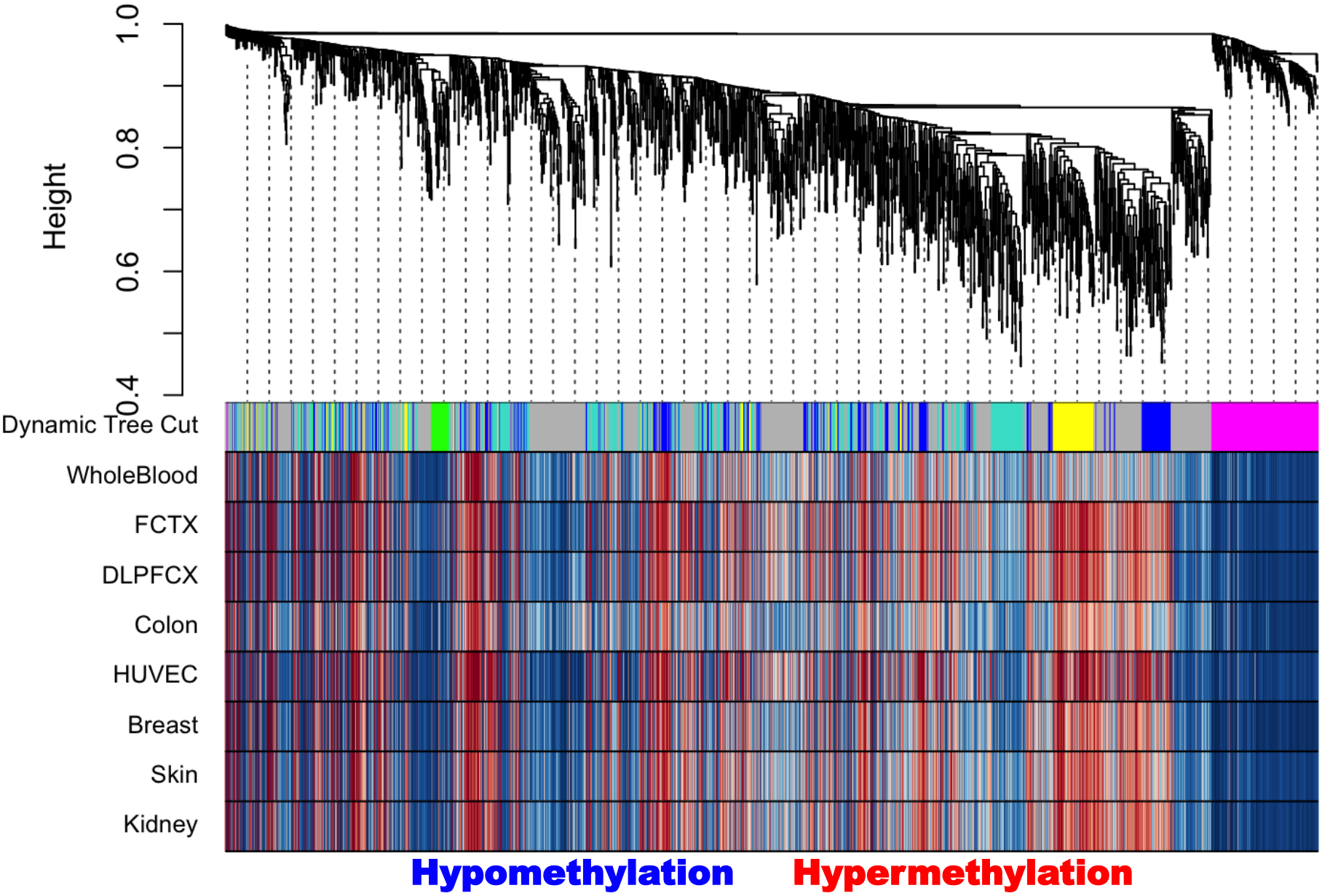
Horvath, Hannum, & Levine



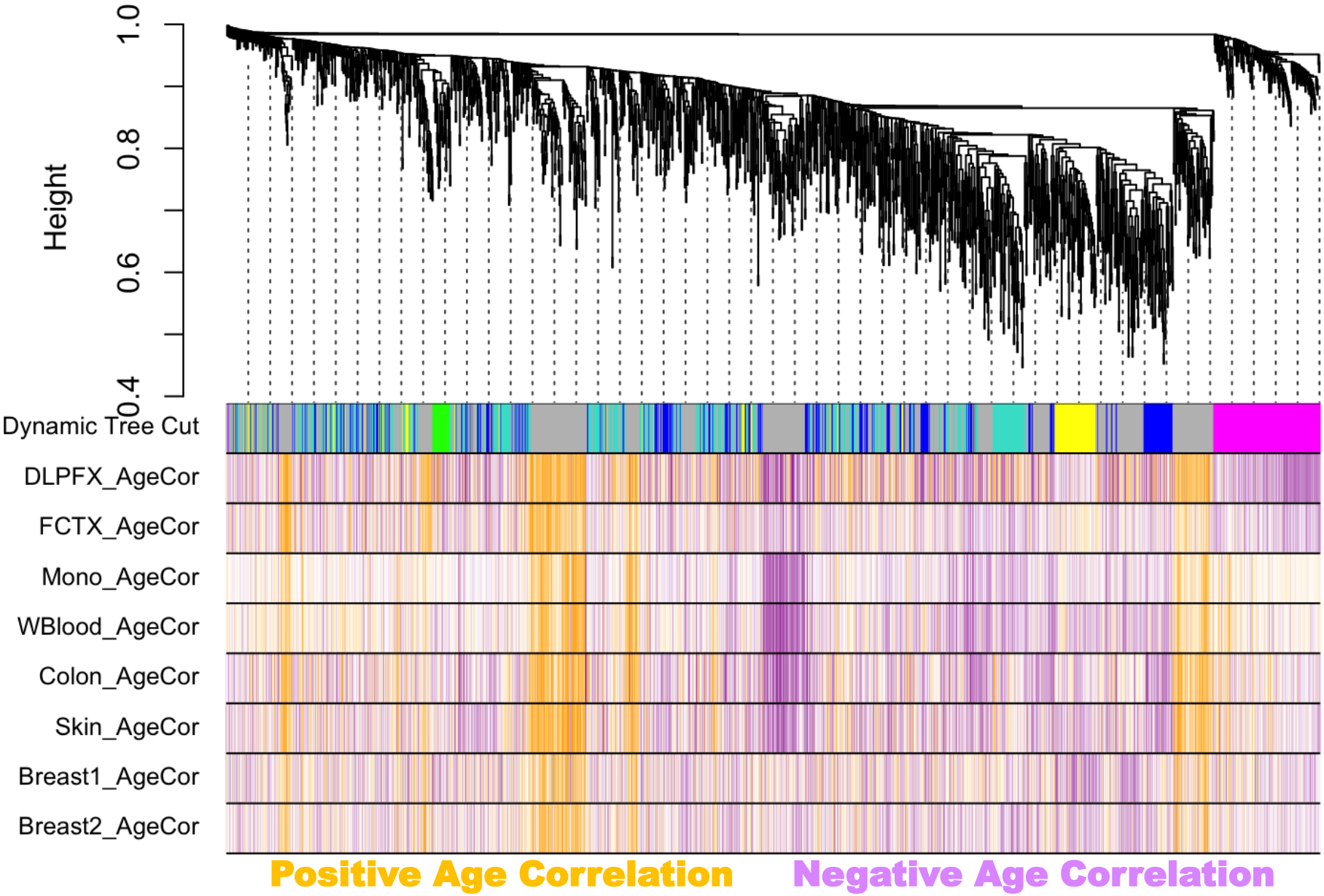
Horvath et al. DNA methylation-based biomarkers and the epigenetic clock theory of ageing. *Nature Reviews Genetics* (2018)

What are the different phenomena being captured?

METHYLATION MODULES



METHYLATION MODULES



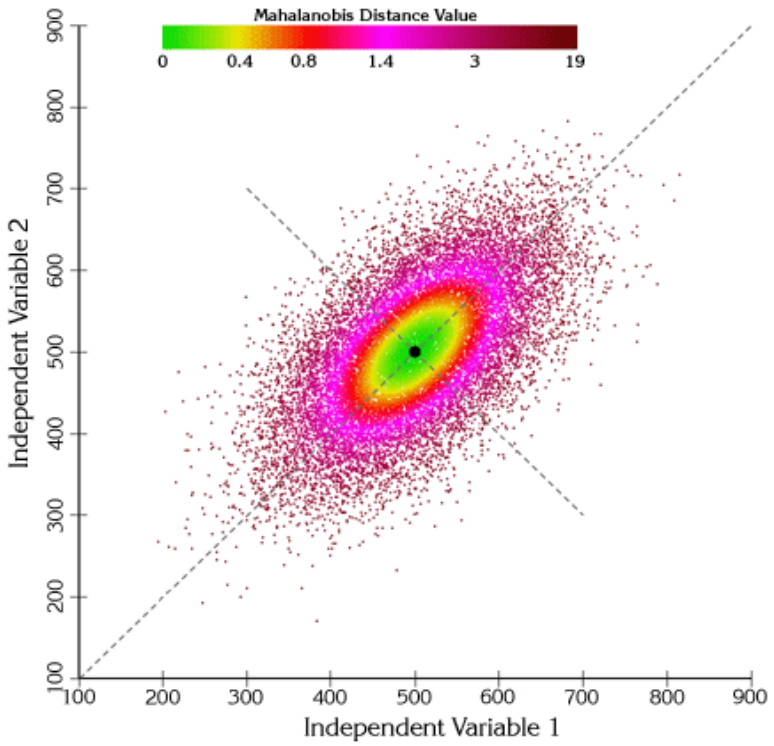
EPIGENETIC DRIFT (ENTROPY)

Divergence of the epigenome as a function of age due to stochastic changes. With increased entropy, methylation state becomes less predictable across the population of cells, (tends towards 50%).

1. Repeat Consensus WGCNA for HUVEC, fetal DLPFC , and age correlations.

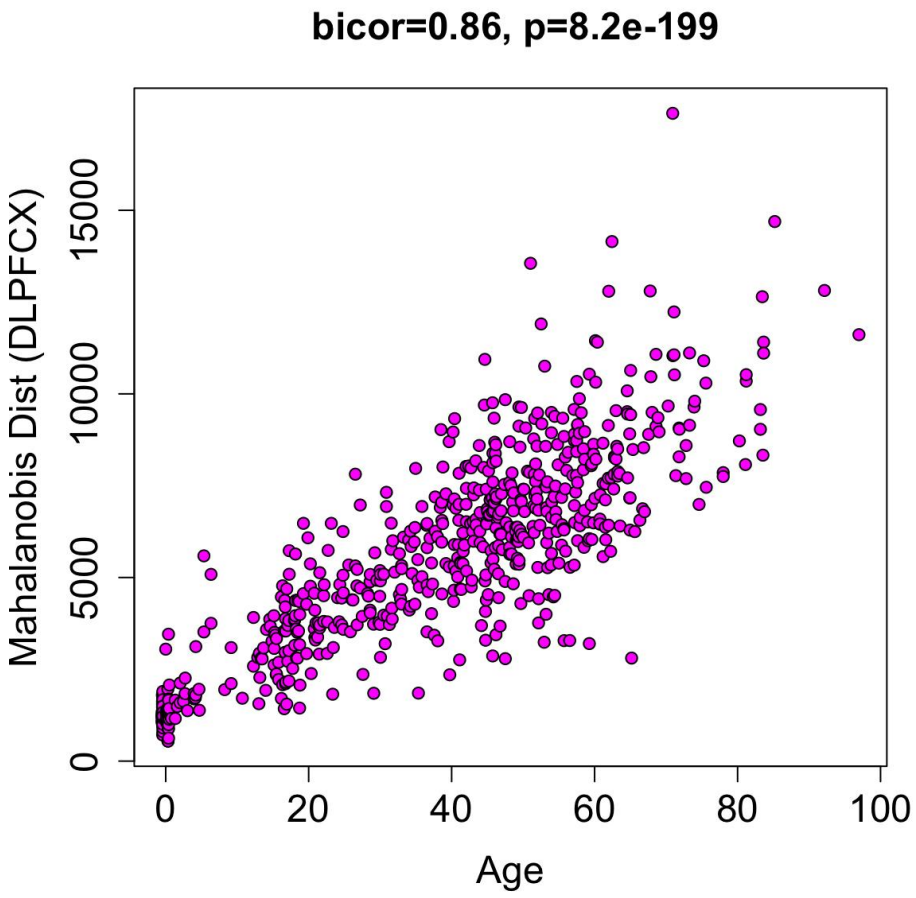
2. Calculate Mahalanobis Distance (MD) for each module, using HUVEC as the reference. Represents dysregulation/entropy.

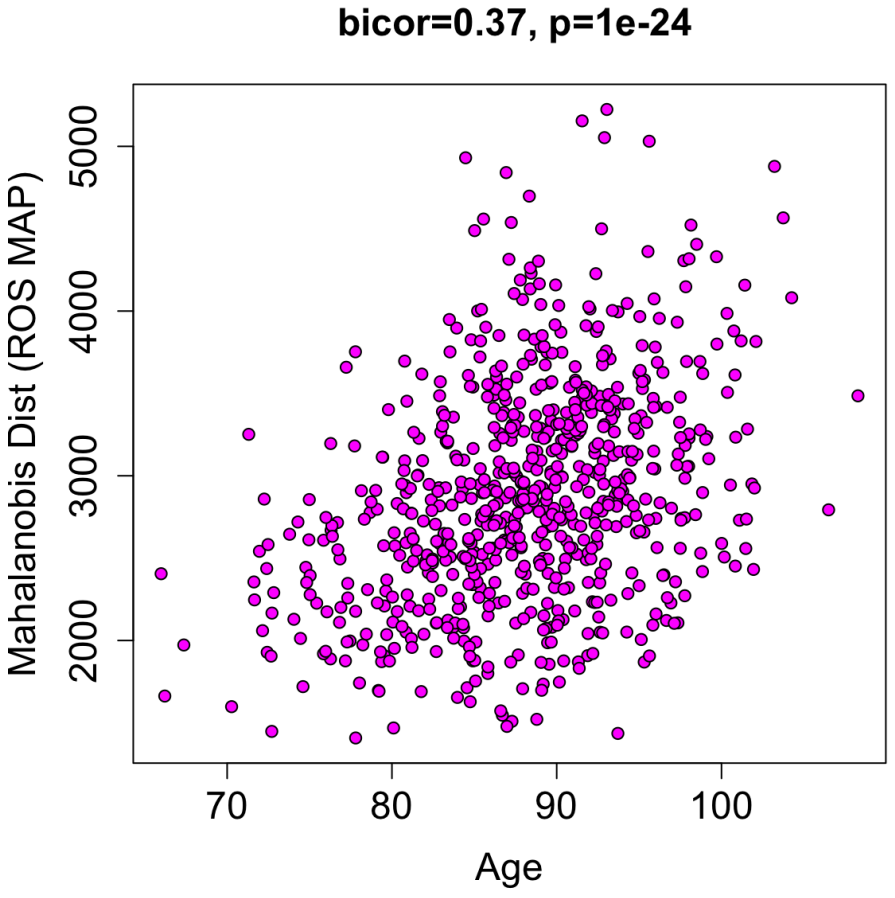
3. Test whether MD is associated with aging and AD neuropathology.



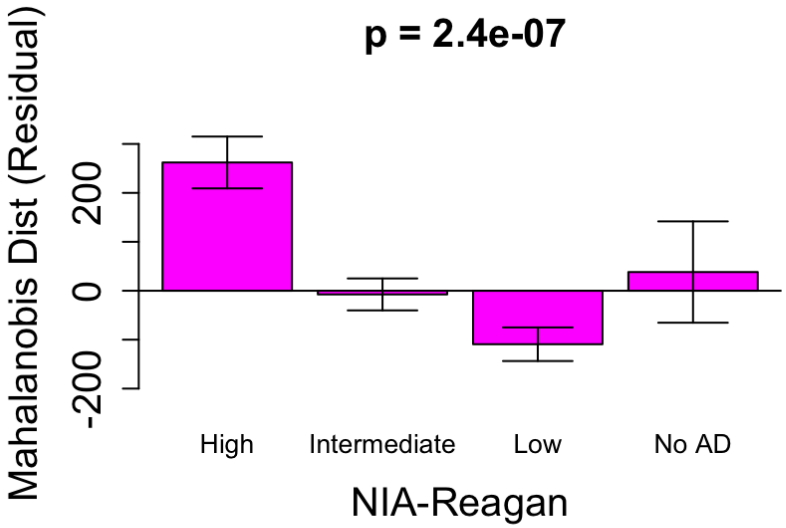
PRELIMINARY RESULTS USING ROS-MAP DATA

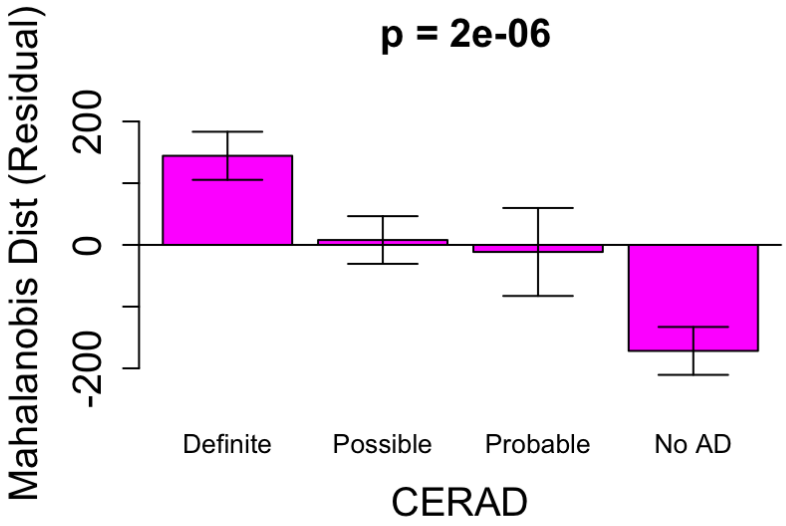
Nine Modules Identified

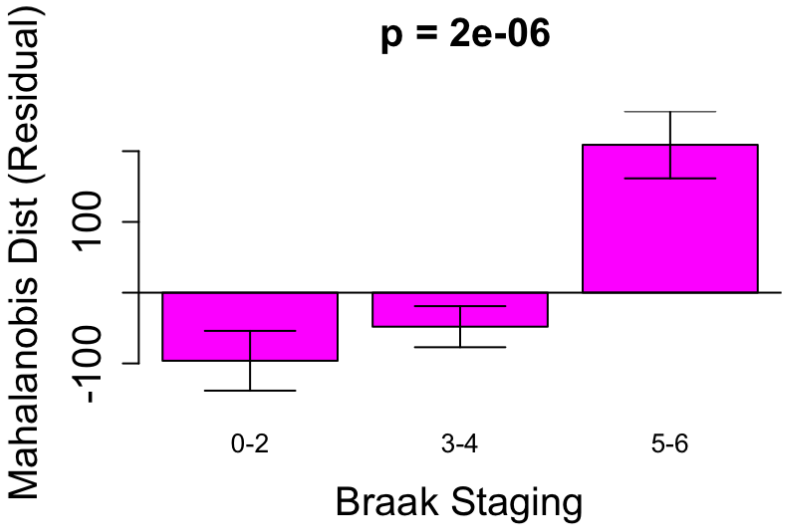


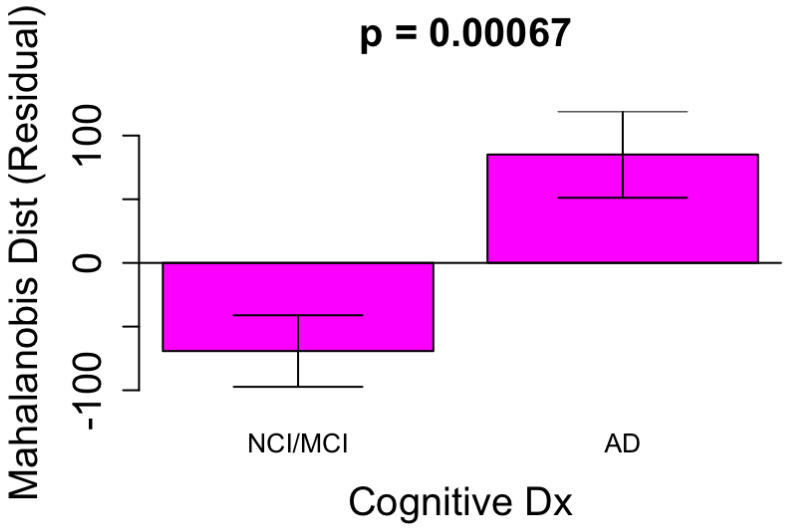


AMP-AD Knowledge Portal









PRELIMINARY RESULTS USING ROS-MAP DATA

	Standardized Beta Coefficient	P-value
NFT	0.20	8.0E-7
Tangle Density	0.19	4.8E-6
Neuritic Plaques	0.18	2.0E-5
Diffuse Plaques	0.11	1.0E-2
Amyloid Load	0.14	6.6E-4

MOVING FORWARD

Generating New Data from ROS-MAP Samples

Oversampling of *APOE* e4+:

- 232 heterozygous (68% AD),
- 18 homozygous (89% AD)
- 100 e4- (55% AD)

Multiple Brain Regions

- Compare samples from three regions
  - Superior temporal cortex (BA22)
  - Prefrontal cortex (BA10)
  - Cerebellum

Integromics Networks

- Identify hubs, pathways, and potential drug targets
- Explore relationship between changes at epigenomic, transcriptomic, proteomic, and phenotypic levels.