The myth of cognitive decline
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Individual change varies
Individual change varies
Cognitive aging trajectories

![Graph showing cognitive aging trajectories over age.](Image)
Take home points

• Decline in cognition with age and brain is not inevitable; there is considerable variability in how much and how fast

• Age-related declines in cognition and brain structure and function are the result of pathological processes

• The better we understand these processes, the better equipped we are to do something about it
Vision

• Annual wellness visits will include cognitive test results, structural and molecular neuroimaging, proteomics, vascular and other risks, health-related behaviors, and genomic profile.

• This information will identify risks for current and future problems with brain structure or function and lead to targeted, patient-specific interventions.
UCSF cohort

- Over 850 functionally intact, community dwelling older subjects
- 365 active in longitudinal studies
- Comprehensive evaluations:
  - Cognitive, neurologic and functional assessment
  - DNA
  - Banked serum, plasma, whole blood, lymphocytes
  - MRI: structural, DTI, resting state, ASL
  - PET scans
  - CSF
Genetics

Health and Exposures

Lifestyle

Cerebrovascular risk factors

Oxidative stress

Inflammation

Proteins

Cortical grey matter

White matter

Hippocampal volume

APOE

Klotho

Dopamine receptors

Serotonin receptors

Processing Speed

Executive, language, & spatial skills

Episodic Memory
Klotho: aging regulator and cognitive enhancer

- **KLOTHO (KL)**
  - Transmembrane protein; hormone
  - Circulates throughout body, brain
  - AMPA and NMDA receptors; insulin response

- **KLOTHO (KL): F352V and C370S (“KL-VS”)**
  - 20-25% heterozygosity
  - 1.6x increase in protein levels
  - Longevity; protection against age-related disease
  - Cognitive enhancement in aging humans
Variation in Longevity Gene \textit{KLOTHO} is Associated with Greater Cognition and Cortical Volumes in Aging

Jennifer Yokoyama and Dena Dubal
Protective KL-VS genotype

- Carrying 1 copy of KL-VS is associated with better executive function in two healthy aging cohorts.
- This occurs independent of age.
Protective KL-VS genotype

- Greater volume in a relevant brain region

- Carrying 1 copy of KL-VS is associated with greater volume in right DLPFC in two healthy aging cohorts

- This occurs independent of age
# Neurodegenerative diseases

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<th>Protein</th>
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<td>Tau</td>
<td>Behavioral variant FTD</td>
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<td>Progressive aphasia (non-fluent)</td>
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<td>Progressive supranuclear palsy</td>
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<td>Progressive aphasia (semantic)</td>
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<td>ALS (Lou Gehrig’s disease)</td>
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Cog normal: low amyloid

Cog normal: intermediate amyloid

Cog normal: high amyloid

Alzheimer’s disease
Implications

• Some of the cognitive changes that we associate with aging could very well reflect underlying, accumulation of abnormally folded proteins
Cerebrovascular disease
### Predicting executive functioning: Insulin resistance

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Frazier et al., 2015
Predicting executive functioning: Triglycerides

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Parthasarathy, 2015
The neuroinflammation story

- Inflammation is a normal response to injury
- Peripheral injury rapidly leads to an inflammatory response in the brain
- This inflammatory response is adaptive as long as the inflammation subsides
Aging and Immunosenescence

Degradation of immune system with advancing aging

Increased susceptibility to disease and infection

Up-regulation of inflammatory responses

Result: Low-grade, chronic systemic pro-inflammatory state.
Inflammation and white matter

• Looked at CRP, TNF-α, and IL-6

• Detectable levels of inflammatory markers were related to lower white matter integrity

• This relationship is more pronounced with age
What can super-agers teach us?

- We can reliably measure declines in processing speed over 2-3 years.
- Studying the extremes of this variability can offer valuable clues about mechanisms.

![Graph showing response latency and processing speed over time for different age groups.](image)
Results

- No groups differences were found in BMI, cholesterol, or APOE genotype.
Cardiorespiratory fitness

We can estimate cardiorespiratory fitness using measures of physical activity, BMI, and heart rate.
Better white matter integrity

![Bar chart showing fractional anisotropy with categories superagers, average agers, and sub-agers. The chart indicates a higher fractional anisotropy for superagers compared to average and sub-agers.](chart.png)
Lower inflammation
Summary

• Aging significantly impacts brain structure & function, but these changes are neither universal nor inevitable.

• Multiple factors influence how the brain changes with age, some of which are under our control, and some may be modifiable in the future.

• A better understand of these factors can lead to more successful cognitive aging.