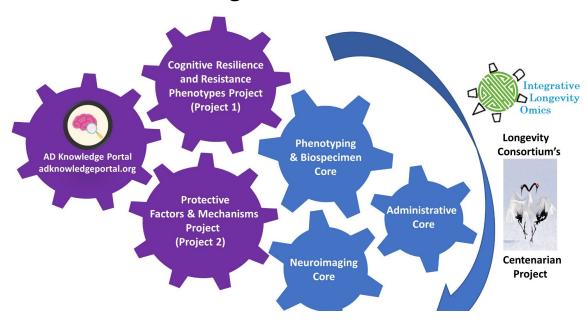
Update on Projects sponsored through the Research Partnership on Cognitive Aging

May 2025



RADCO: <u>Resilience/Resistance to Alzheimer's Disease and Related Disorders in Centenarians and their Offspring Led by Drs. Thomas Perls, Stacy Andersen, Susan Bookheimer</u>

Overall Scientific Objective: To gauge cognitive resilience in this sample, delineate the underlying protective biology and translate that into therapeutic targets.

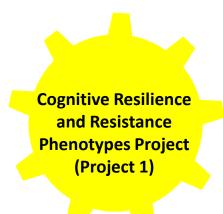


Resilience/Resistance to AD in Centenarians and their Offspring RADCO

- 3 cores and 2 projects
- The 2 centenarian studies refer centenarian cognitive superagers, normal centenarians, offspring and spouses for enrollment into RADCO that provide already generated data and resources from these participants to RADCO.
- RADCO performs longitudinal follow-up of subjects with measures that are uniform with the centenarian studies and in addition generates neuroimaging and neuropathological data that serve the two Projects.

RADCO Enrollment

	Pending	Enrolled	Total
Centenarian Average	34	39	73
Centenarian Superager	2	27	29
Offspring Average	64	92	156
Offspring Superager	65	172	237
Spouse Control	8	9	17
TOTALS	173	339	512









Three different aims or approaches to gauging level of resilience.

Compare Annual Neuropsychological Evaluation Results to:

Aim 1: Neuroimaging (MRI) Results

Including novel blood brain barrier integrity measure. 64 scans to-date, 26 pending

Aim 2: AD Biomarker Levels

Levels to be generated on all participants so far

Aim 3: Neuropathology Results

Alzheimer's pathology and rarer diseases such as Aging-related Tau Astrogliopathy (ARTAG) & Limbic-predominant age-related TDP-43 encephalopathy (LATE-NC), 14 brain donations to date, 86 registered donors so far)

Partnership with Chicago Superager Study for specialized electron microscopy and Von Economo neuron studies

Protective Factors & Mechanisms Project (Project 2)

Three aims:

Aim 1: Discover protective gene variants associated with Cognitive Superaging Analyzing whole exome sequence data and later this year, whole genome sequence data

Aim 2: Discover transcriptomic signatures of resilience ("the Resiliome") from neuropathologically characterized RADCO participant brain tissue samples and iPSC-derived microglia studied in aim 3.

Aim 3: "Resilience in a Dish".

iPSc from Centenarian Cognitive Superagers (n=4) and offspring (n=7), Cognitively Normal Centenarians (n=3) and Offspring N=1), Cognitively Impaired Centenarians (n=4) and Offspring (n=2) are differentiated into microglia. Expression profiles have revealed two genes in particular that appear to be important to preserving normal microglial function versus microglia becoming inflammatory.

Generated Resources

All generated phenotypic and omics data are shared via NIA-sponsored databases.

Biospecimens available upon request from Boston University:

- Serum and plasma aliquots
- RNA
- DNA
- Brain tissue



iPSCs are generated as well as differentiated into specific cell types at the Center for Regenerative Medicine at Boston Medicine Center and are available for sharing.



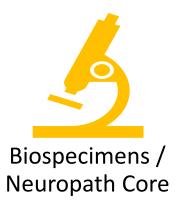
Discovering protective factors to promote healthy aging.

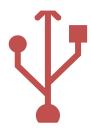
Led by Drs. Emily Rogalski, Changiz Geula, Marsel Mesulam

Project components: 3 Cores, 2 Projects, 5 Sites





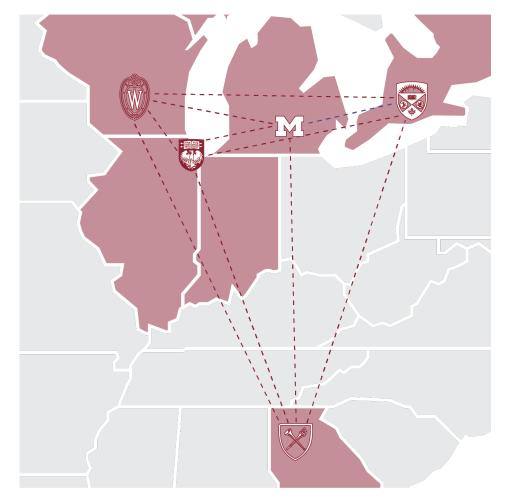






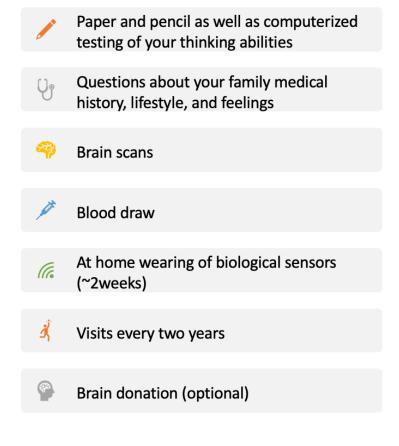
Project 1: Wearable Sensors

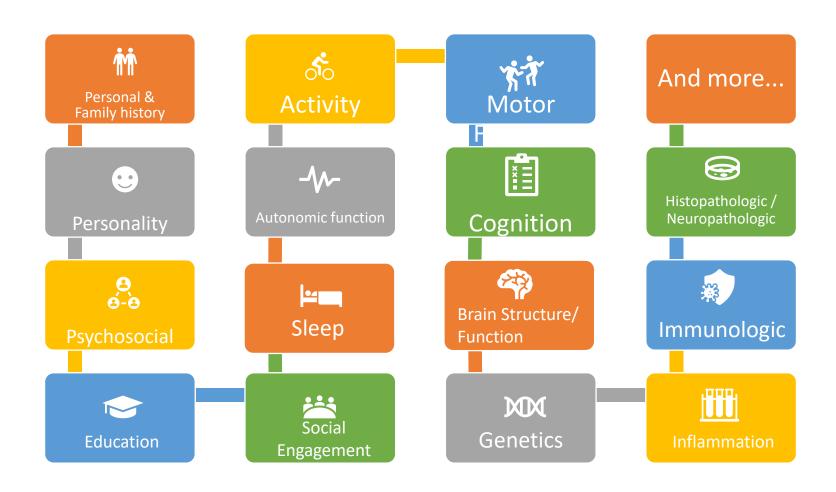
Project 2: Immune/ Inflammation





Deep phenotyping across disciplines

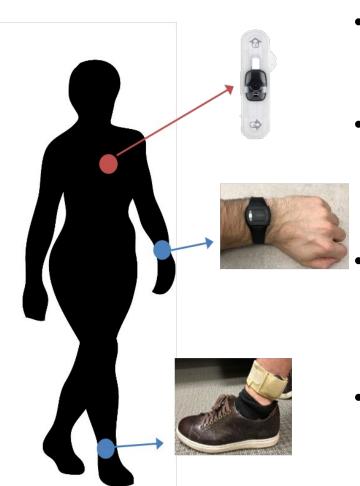






Project 1: Use wearable technology to obtain real-time measurements of sleep, physical activity, autonomic responsivity, and social engagement

Lead: Dr. Angela Roberts, Western University

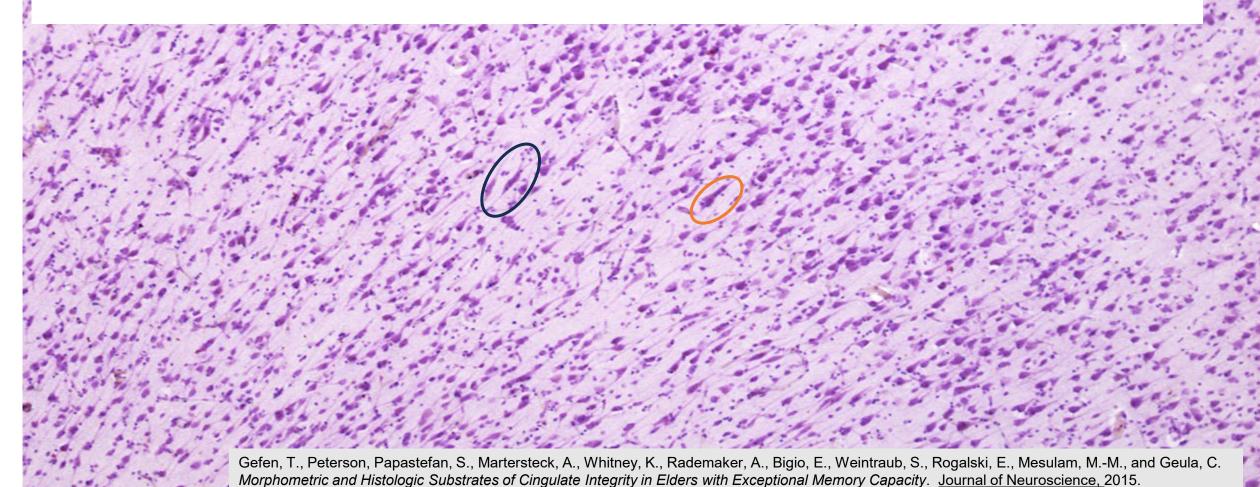


- ECG sensor + IMU data generates similar quality data to a sleep lab. Accurate measures of sleep quality, efficiency, duration, and stages.
- 'True' ECG leads minimize challenges with some systems that may generate less accurate data on dark skin tones due to increased absorption of green light.
- Measuring arm, leg, and trunk movement generates more accurate activity level data in older adults. Capture broader range of activity signatures.
- Coupling of physiological systems (cardiac dynamics and activity levels or sleep stages) and at differing timescales.



From the Anterior Cingulate Cortex of a 93 year-old SuperAger

Nerve cells are triangular (orange oval). A very special type of nerve cell known as the von Economo neuron is spindle shaped (black oval). These neurons are said to be related to social skills. They are more frequent in Cognitive SuperAgers than in similarly aged older adults with average cognition. This finding was published 10 years ago and launched our current plans to identify the unique proteins in these cells with transcriptomics. The hope is to find molecular correlates of the Cognitive SuperAging brain.



STARRS - Successful Trajectories of Aging: Reserve and Resilience in Rats

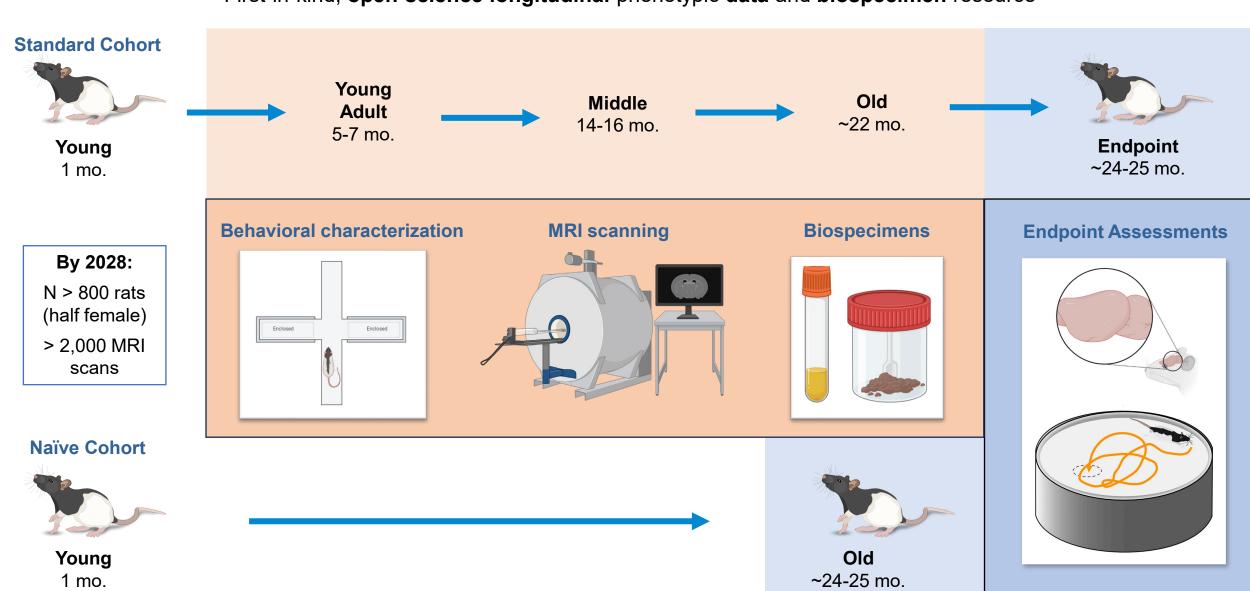
Led by Dr. Peter Rapp, NIA Intramural Research Program

Multiple Pathways to Successful Neurocognitive Aging:

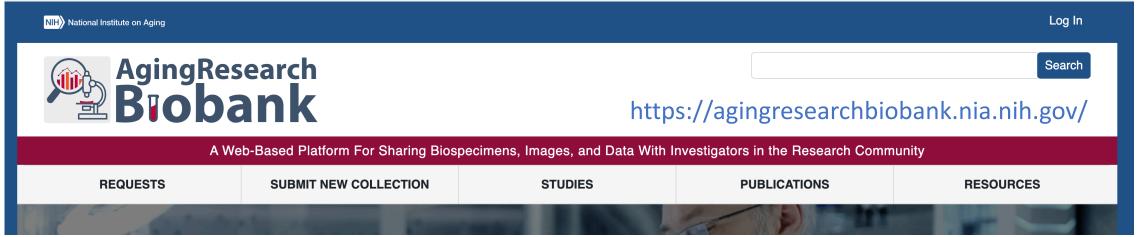
- Preservation of youthful structure and function
 - Brain maintenance, resistance
- Buffer the negative consequence of aging
 - Reserve, compensation, resilience
- Late life brain plasticity
 - Life course development, neuroadaptive aging

STARRS - Successful Trajectories of Aging: Reserve and Resilience in Rats

First-in-kind, open-science longitudinal phenotypic data and biospecimen resource



STARRS Data Management and Sharing



Key STARRRS DMS Requirements

- Robust data linkage & coordination
- Flexible search capability
- Support for neuroimaging data management & sharing
- Active user support & coordination
- Resource advocacy & advertising

