

Aging Brains, Stress and Alzheimer's Disease

Kellie L. K. Tamashiro, Ph.D.

Department of Psychiatry & Behavioral Sciences



JOHNS HOPKINS
M E D I C I N E

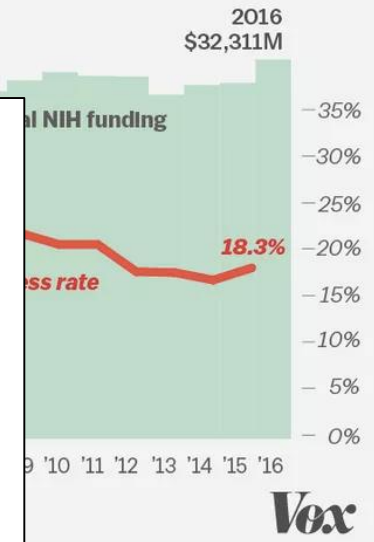
Overview

- **What is Stress?**
 - Normal stress response
 - Negative consequences of “toxic” stress
- Aging brain, stress, and cognitive deficit
- Challenge: Find Interventions

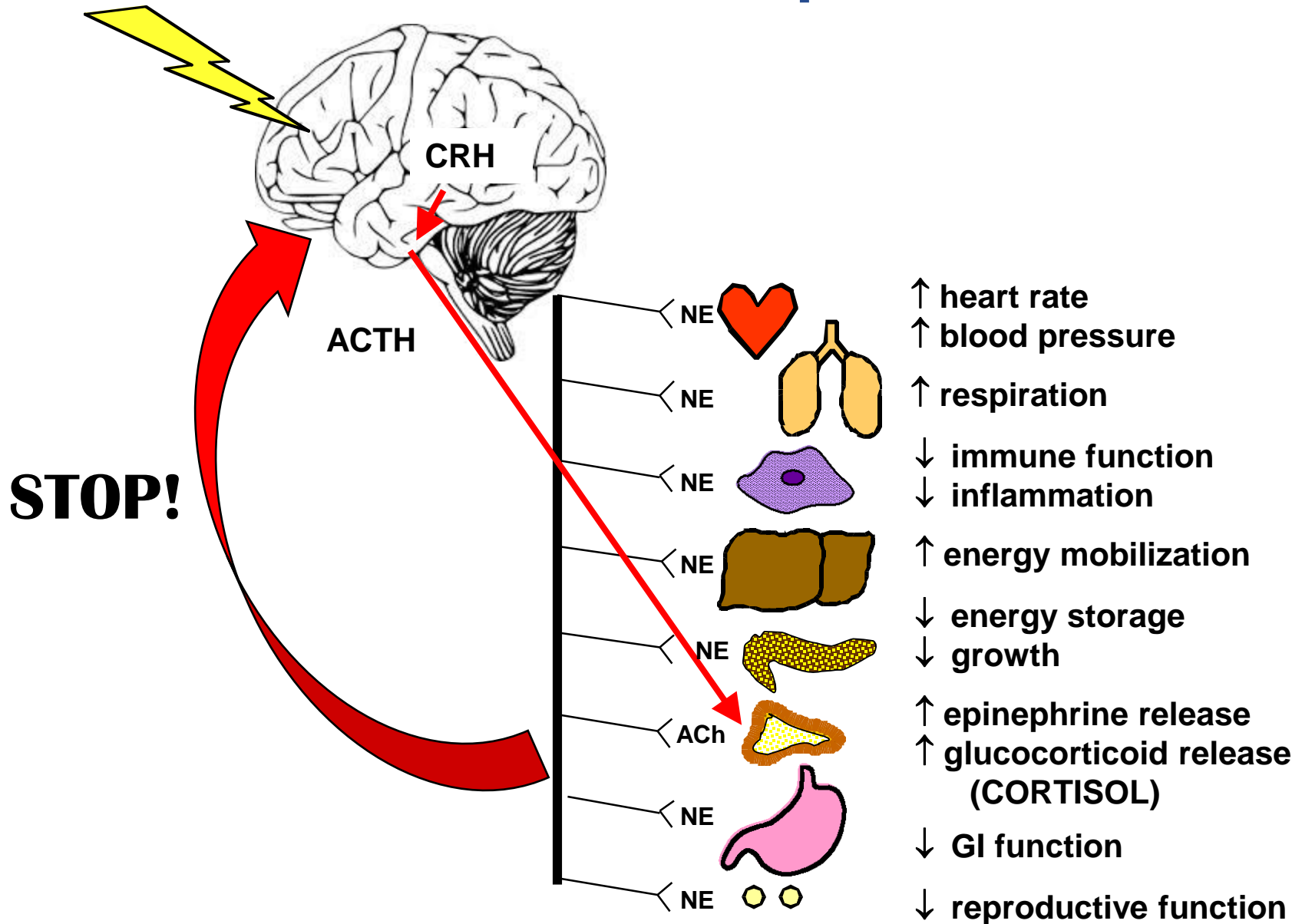
What is "Stress"?

As NIH funding plateaued, grant applications grew much more competitive

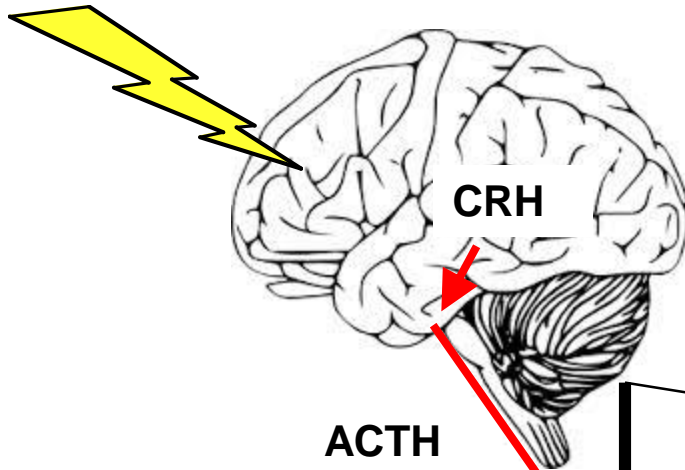
Millions
\$35,000 -
\$30,000 -



The Stress Response

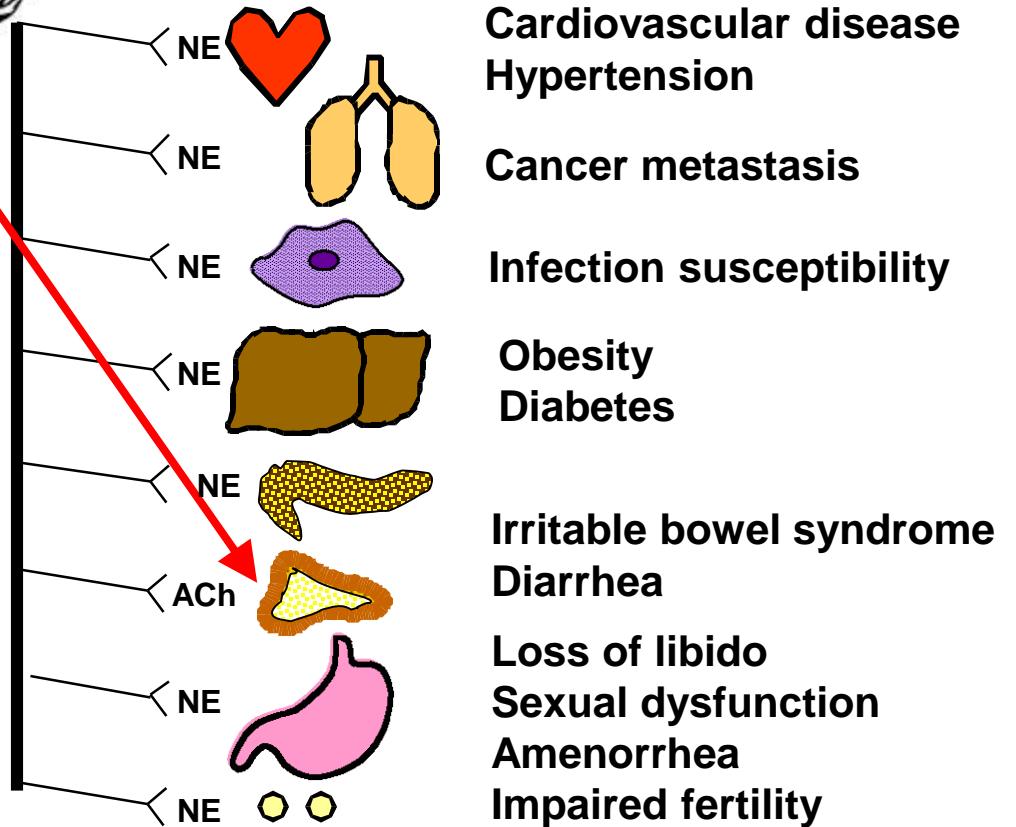


Stress and Disease



Depression
Anxiety disorders
Cognitive deficits
Post-traumatic stress disorder

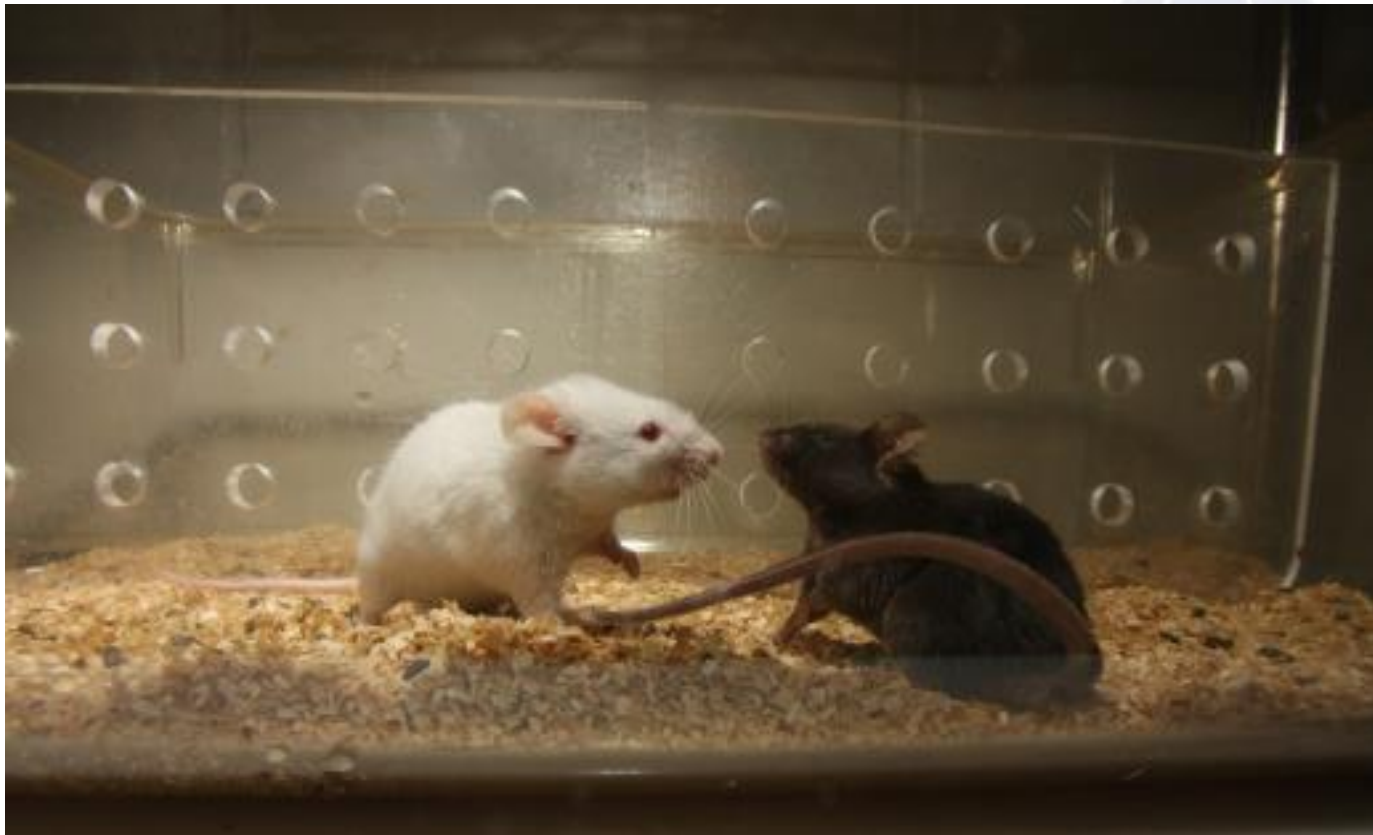
ACTH



Overview

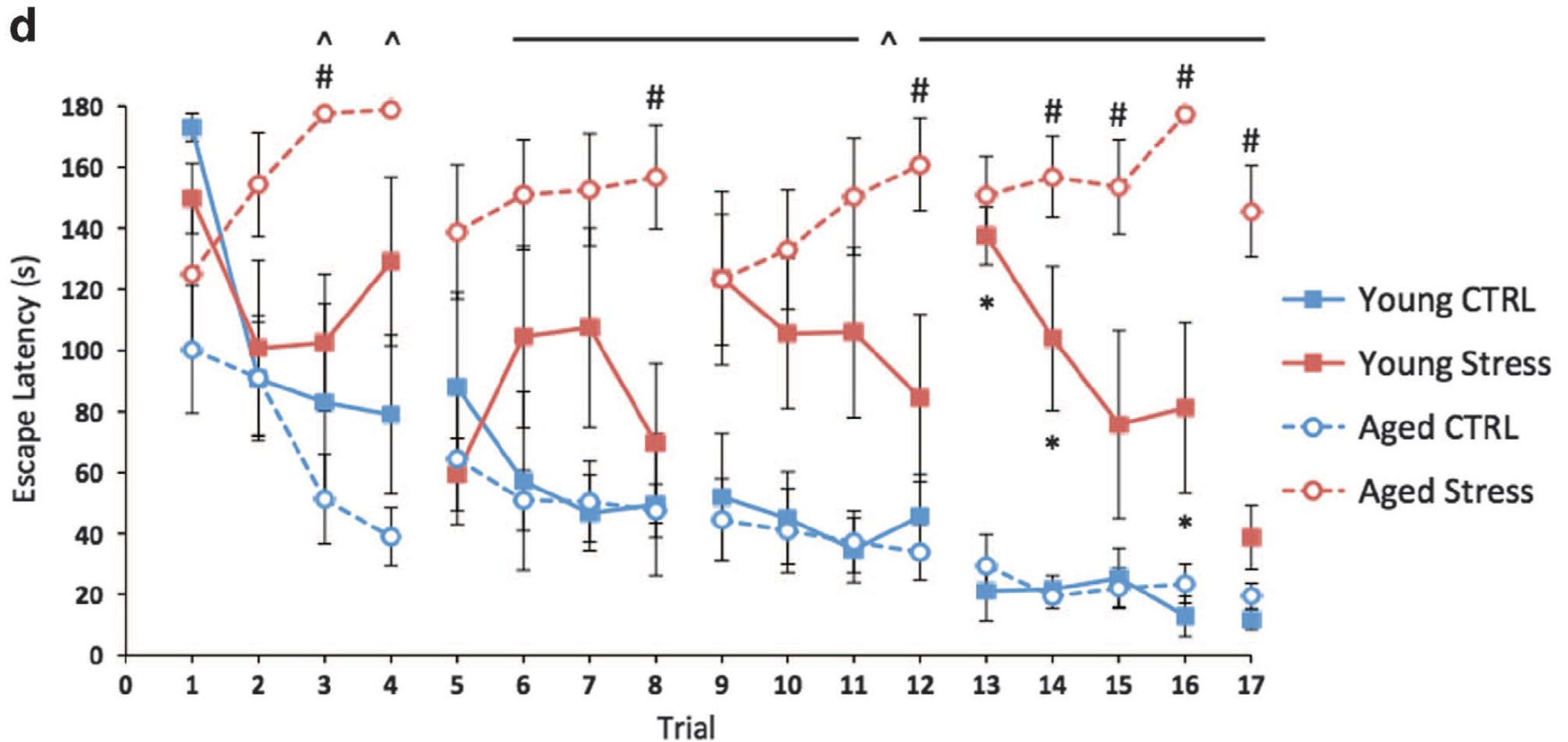
- What is Stress?
 - Normal stress response
 - Negative consequences of “toxic” stress
- **Aging brain, stress, and cognitive deficit**
- Challenge: Find Interventions

Mouse models of stress



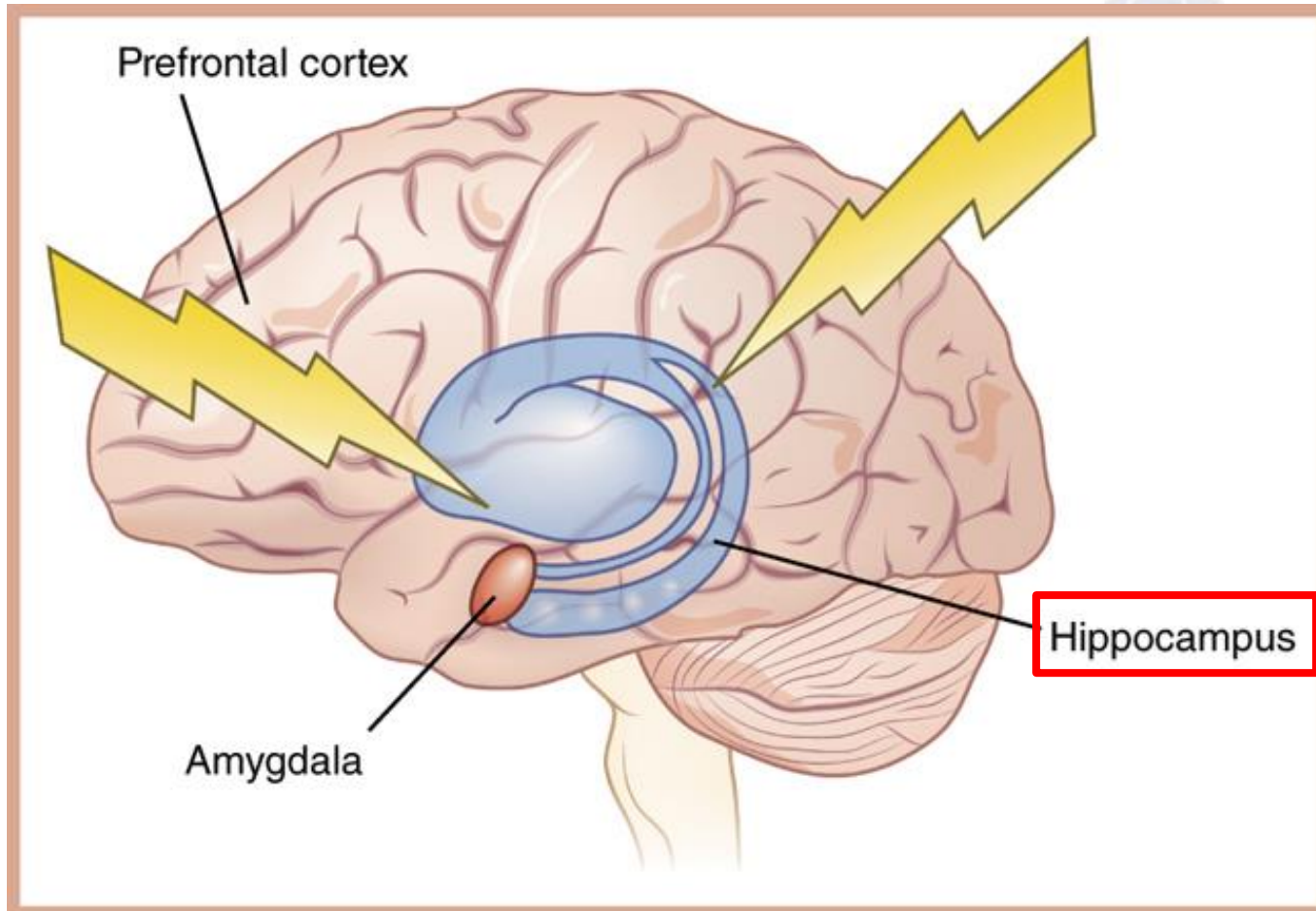
Mouse Maze Learning and Memory

Aged mice have severe cognitive deficit after stress



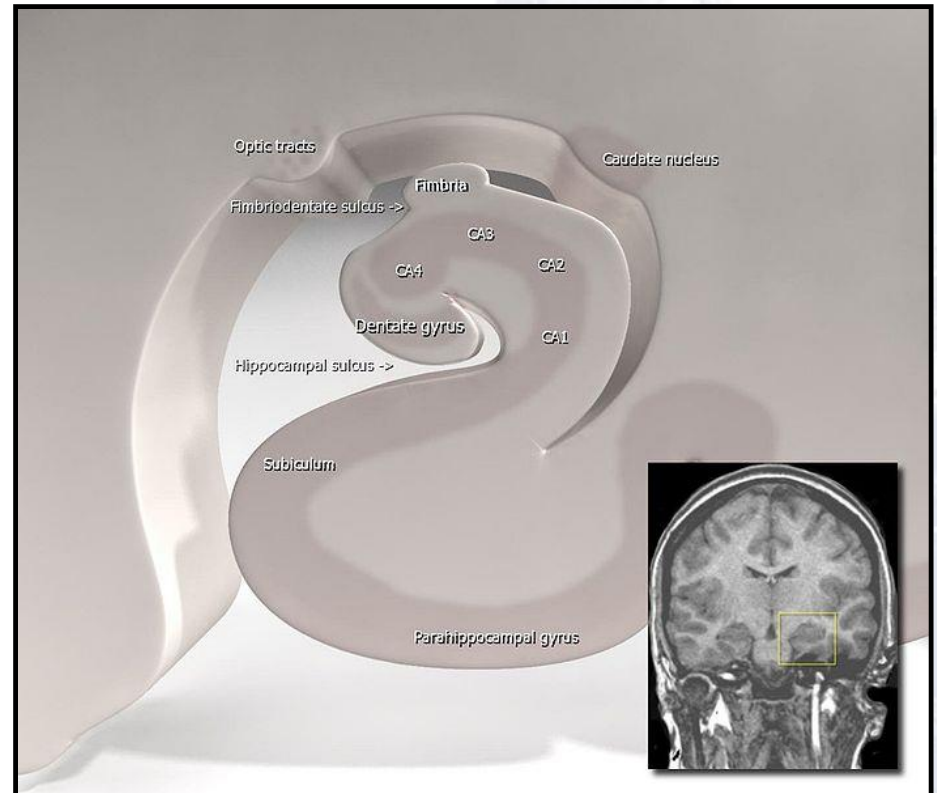
Cordner and Tamashiro, *Transl Psych* (2016)

Stress Effects on the Brain



Hippocampus

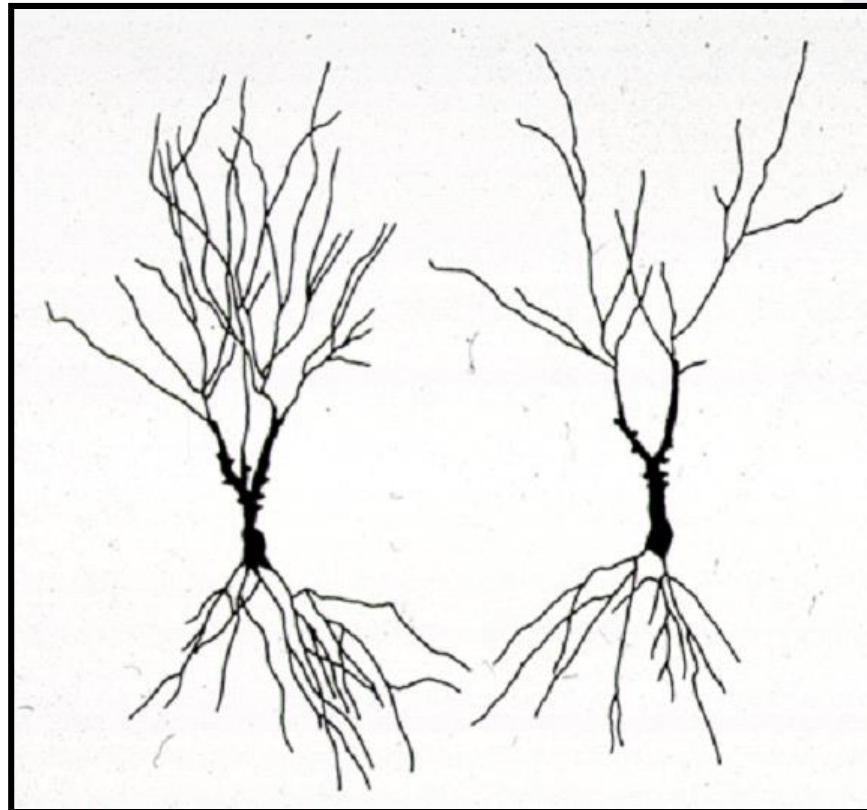
Greek for 'seahorse'



Stress-Induced “Remodeling” of Neurons

Control

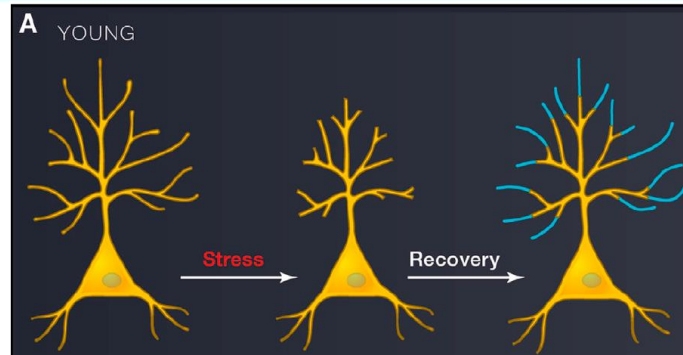
Stress



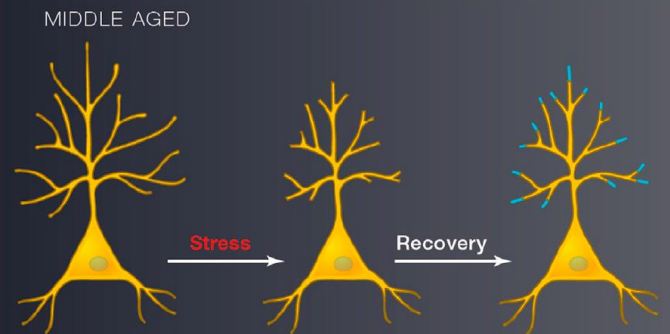
Neuron Structure

Aged brain is less able to recover from stress

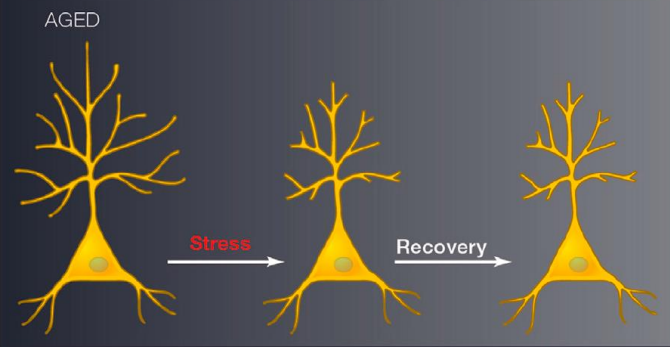
Young



Middle-age



Aged

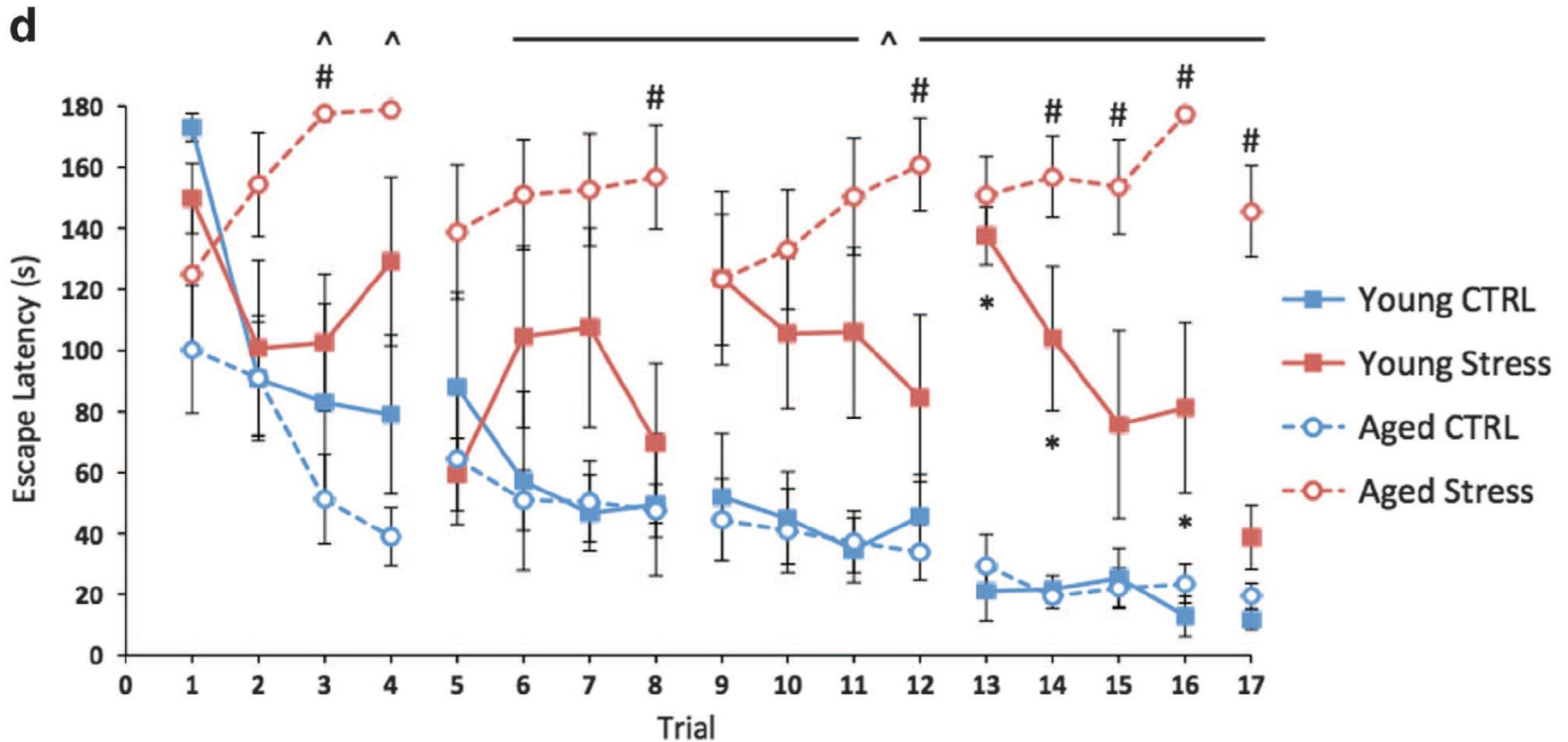


Overview

- What is Stress?
 - Normal stress response
 - Negative consequences of “toxic” stress
- Aging brain, stress, and cognitive deficit
- **Challenge: Find Interventions**

Mouse Maze Learning and Memory

Aged mice have severe cognitive deficit after stress



Cordner and Tamashiro, *Transl Psych* (2016)

Behavioral Intervention

Environmental Enrichment (“EE”)



Standard cage

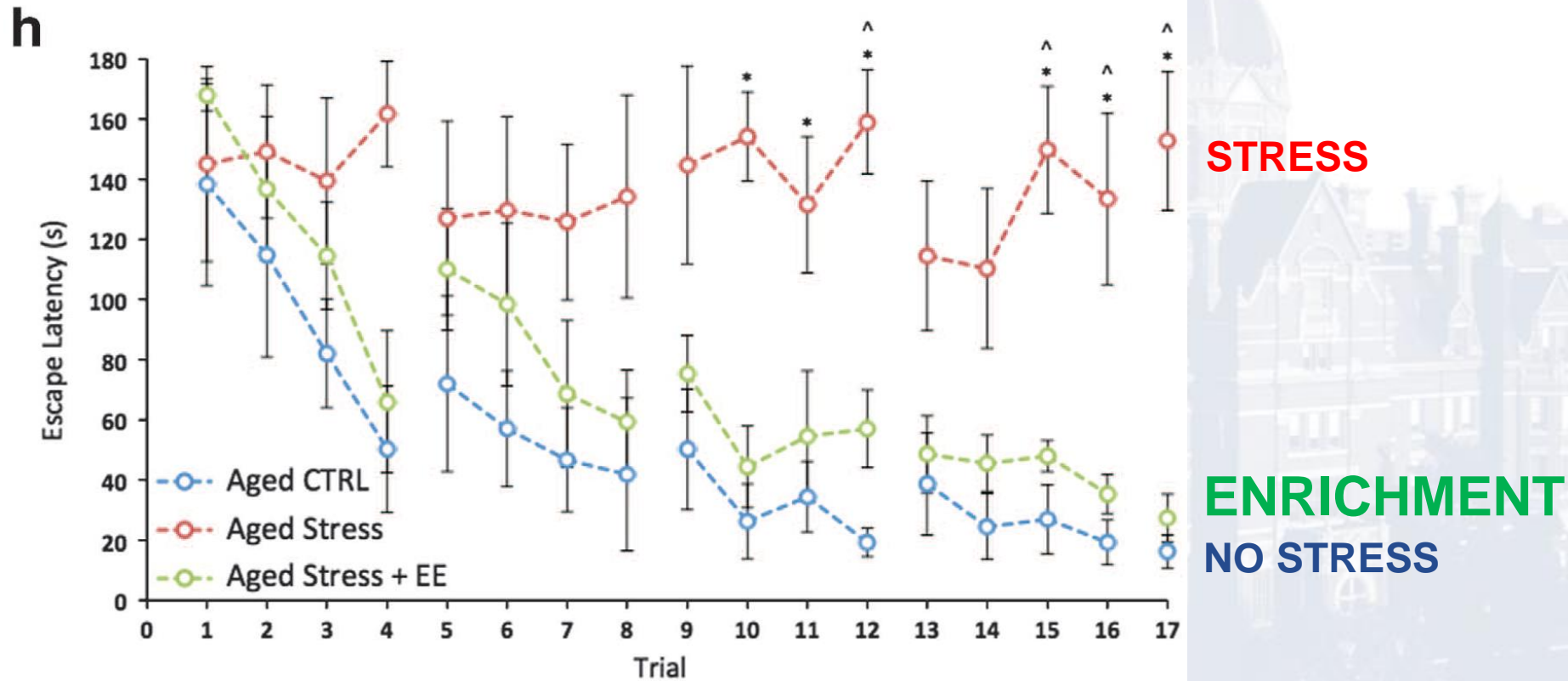


Enrichment cage

- Larger cage area
- Toys to interact with and hide in
- Additional bedding material

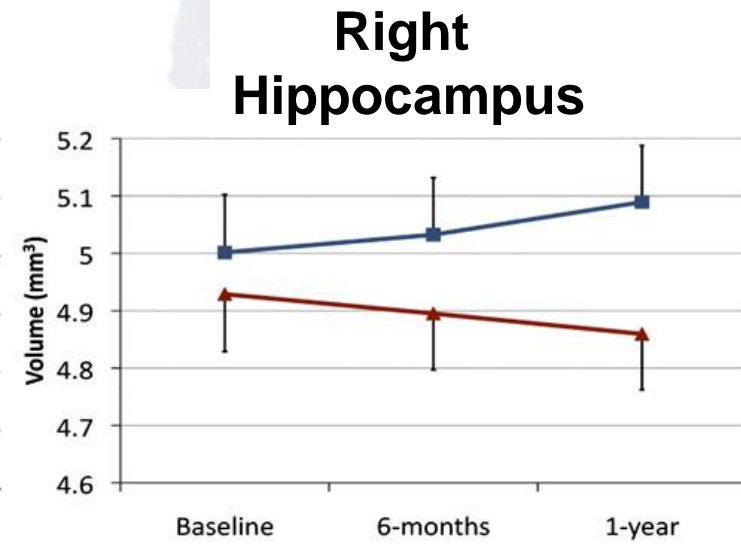
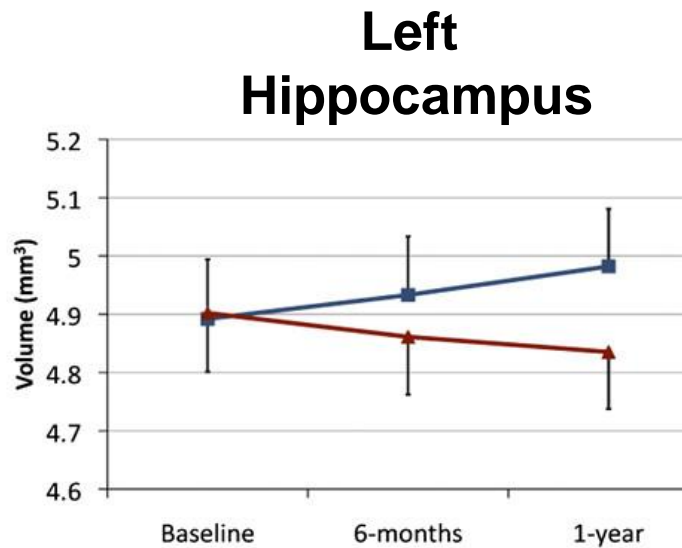
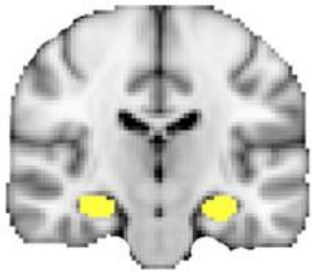
Mouse Maze Learning and Memory

Performance is preserved with EE intervention



Exercise increases size of hippocampus and improves memory in aged adults (65-67 y/o)

A Hippocampus



■ Exercise
▲ Stretching

Erickson KI et al. PNAS (2011)

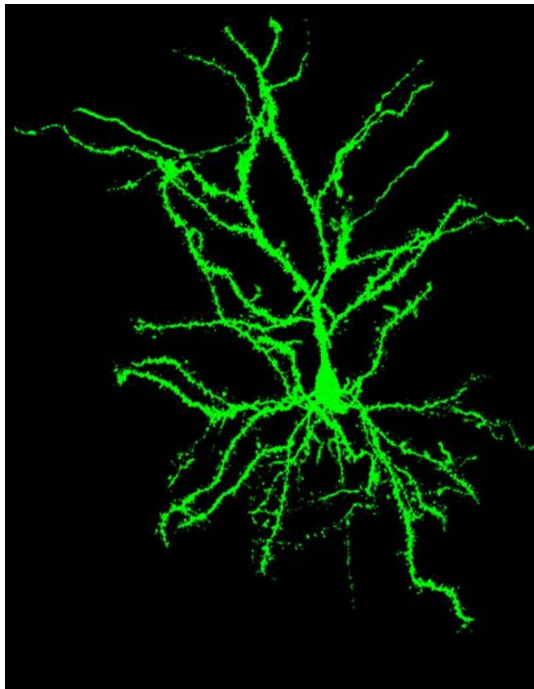
Looking to the Future

Brain Plasticity



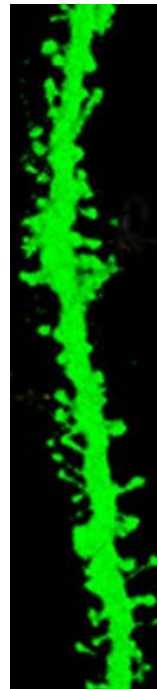
Neurons

Shrink and expand



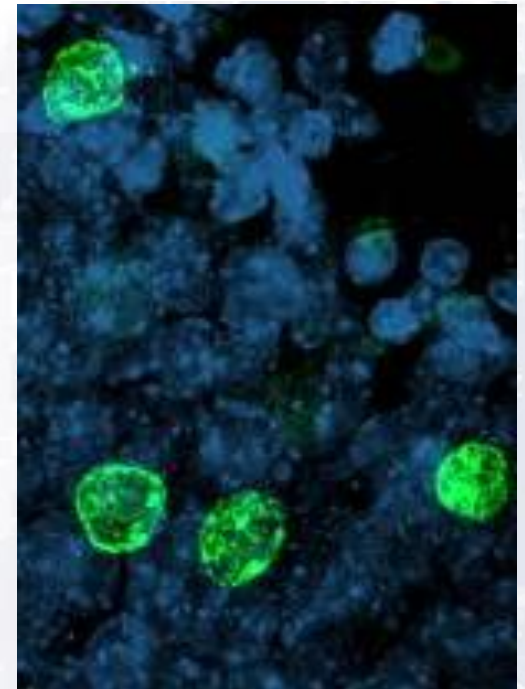
Connections

*Disappear and
are replaced*



New Neurons

*Continue to grow in
some brain areas*



Take Home Messages

- Stress is an inevitable part of life.
- The response to stress is a normal and necessary physiological process.
- Chronic stress has deleterious consequences on the brain and cognitive function.
- The aged brain is more susceptible to chronic stress and less able to adapt.

Take Home Messages

- Basic research has an important role in studying stress.
 - Study consequences on brain function
 - Identify markers of brain health and function
 - Find interventions against stress and disease

Acknowledgements

Behavioral Neuroscience

- Tim Moran
- Ellen Ladenheim
- Sheng Bi

Lab members

- Miranda Johnson
- Seva Khambadkone
- Ethan Goodman

Former lab members

- Gretha Boersma
- Zachary Cordner
- Erin Ewald
- Ryan Purcell
- Lin Song
- Bo Sun

Johns Hopkins

- Richard Lee
- Sarven Sabunciyar
- Ryan Riddle

University of Southern California

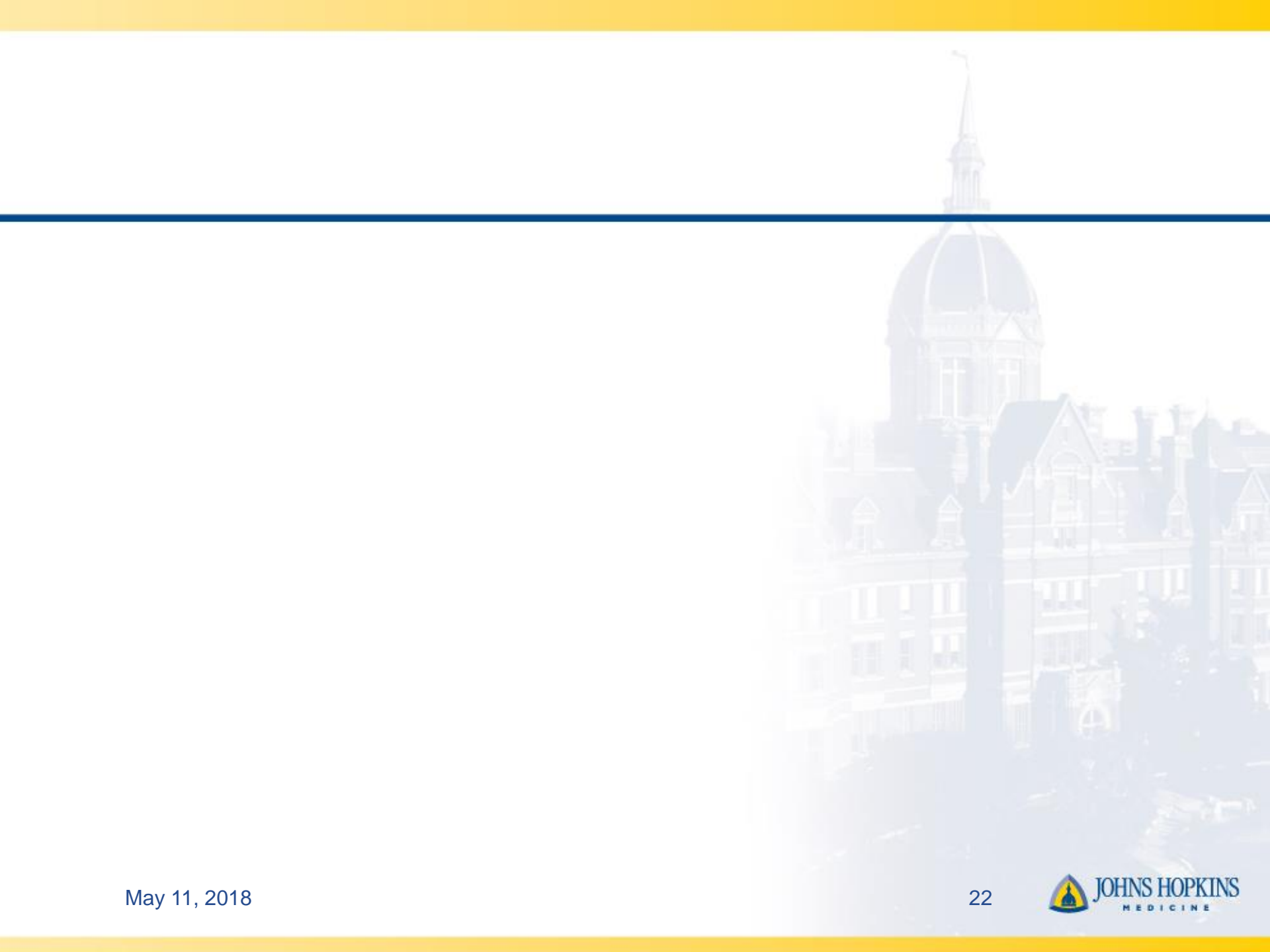
- Sebastien Bouret

University of South Carolina

- Larry Reagan

Support

- NIH NICHD
- NIH NIDDK
- NIH NIMH



May 11, 2018

Animal Models of Stress

Depression and Anxiety

Human

- Weight loss
- Lack of self-care
- Lack of energy
- Anxiety

- Depression (behavioral despair)
- Anhedonia

- Cognitive decline

Rodent

- ✓ Weight loss
- ✓ Decreased coat quality
- ✓ Decreased activity level
- ✓ Elevated Plus Maze closed arm time/entries
- ✓ Forced Swim Test immobility
- ✓ Decreased sucrose preference
- ✓ Barnes Maze performance

Whitehall II Study

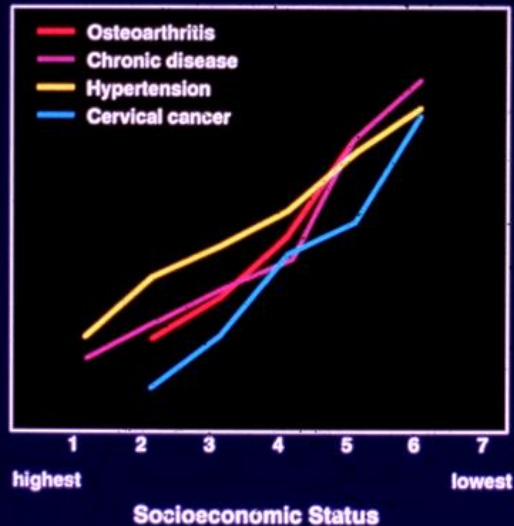
- Population: British civil servants (~10,500 men and women)
- Varying social status (professional, clerical, manual labor)
- Longitudinal follow-up over 20+ years
- Inverse relationship between socioeconomic status and disease morbidity and mortality

EJ Brunner et al. Diabetologia 1997
EJ Brunner Am J Epidemiol 2007
NG Abraham et al., Ann N Y Acad Sci, 2007

Psychosocial Factors and Disease

Linear gradient across socioeconomic status

Morbidity Rate by Socioeconomic Status Level



Standardized Mortality Ratio, by Occupational Status



Courtesy of Bruce McEwen