Age-Related Cognitive Decline

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Age-Related Cognitive Decline

- Changes in cognitive abilities with age in humans – focus on episodic memory
- Changes in episodic memory in animal models – non-human primates and rodents
- Brain changes that may underlie alterations in cognitive abilities with age
- Future Directions

Question to be Answered:

Are there changes in cognitive ability as individuals get older, in the absence of disease?

OPTIMALLY HEALTHY SUBJECTS VS. AVERAGE SUBJECTS

Memory

- Ability to learn and retain new information over time

- Has been studied for a long time at multiple levels of analysis
  - **humans and non-humans**
  - **individuals and populations**
  - **brain structure and function**
  - **data on potential interventions in humans and animal models**

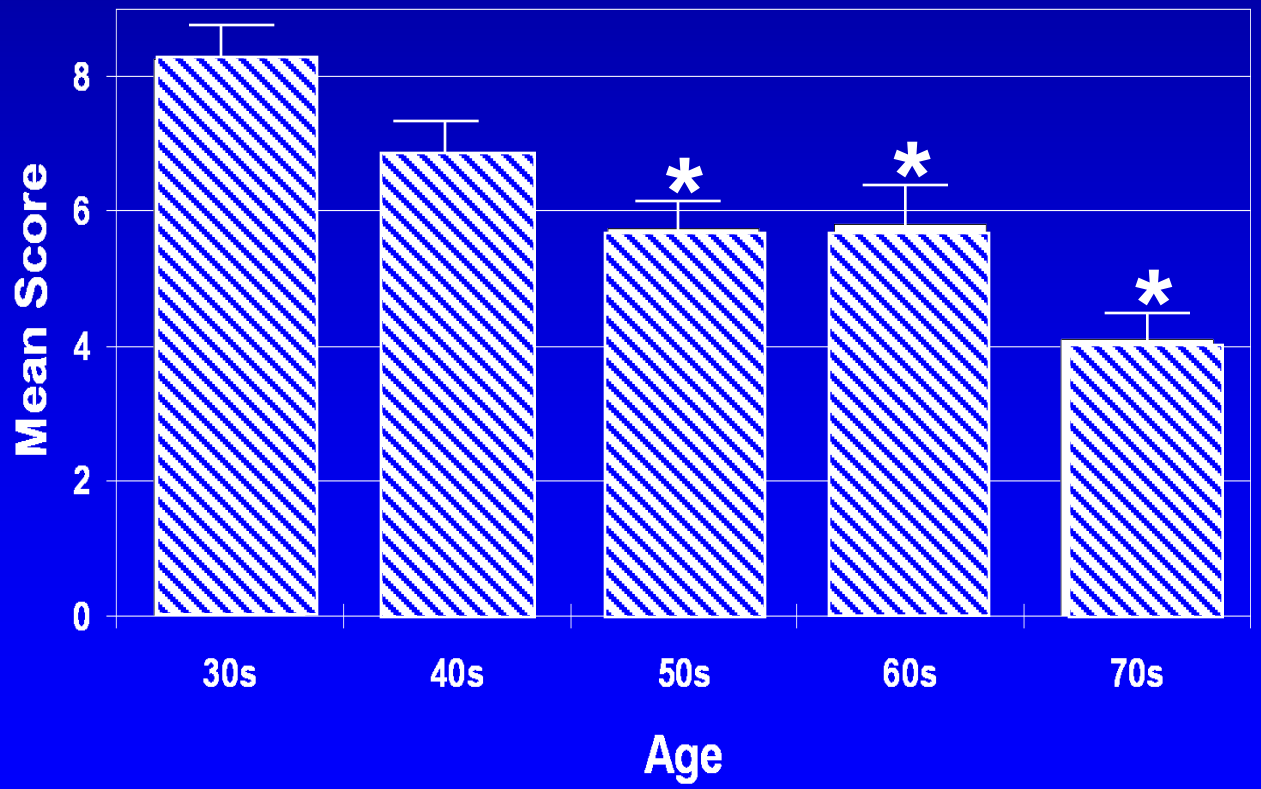
Stories to Learn & Remember

Anna Thompson of South Boston, employed as a scrub woman in an office building, reported at the city hall station that she had been held up the night before on State Street and robbed of fifteen dollars. She had four little children, the rent was due, and they had not eaten for two days. The officers, touched by the woman's story made up a purse for her.

The American Liner New York struck a mine near Liverpool Monday evening. In spite of a blinding snow storm and darkness, the sixty passengers including 18 women were all rescued though the boats were tossed about like corks in the heavy sea. They were brought into port the next day by a British steamer.

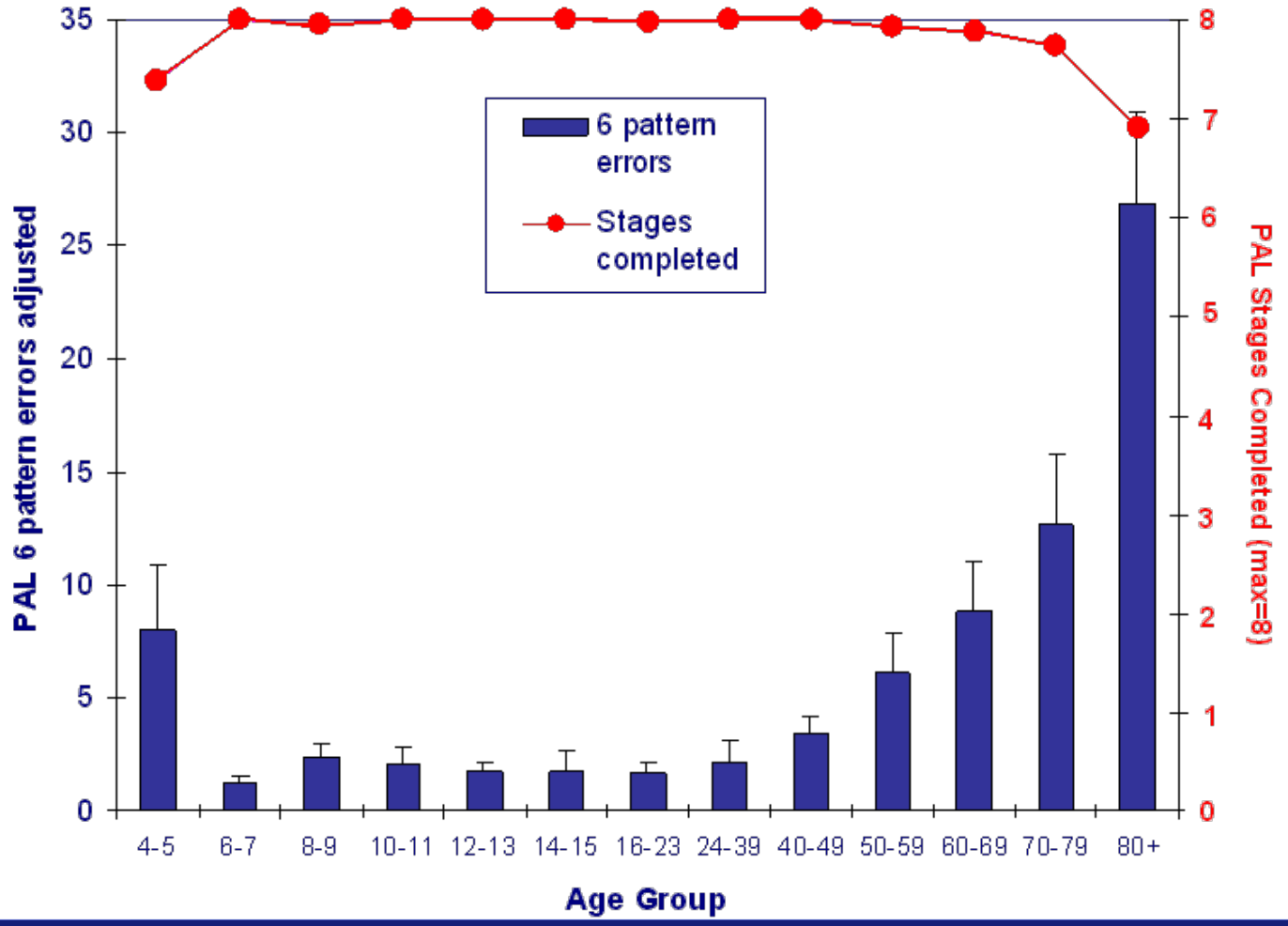
Differences in Delayed Recall with Age

(subjects 30 – 79 years old)

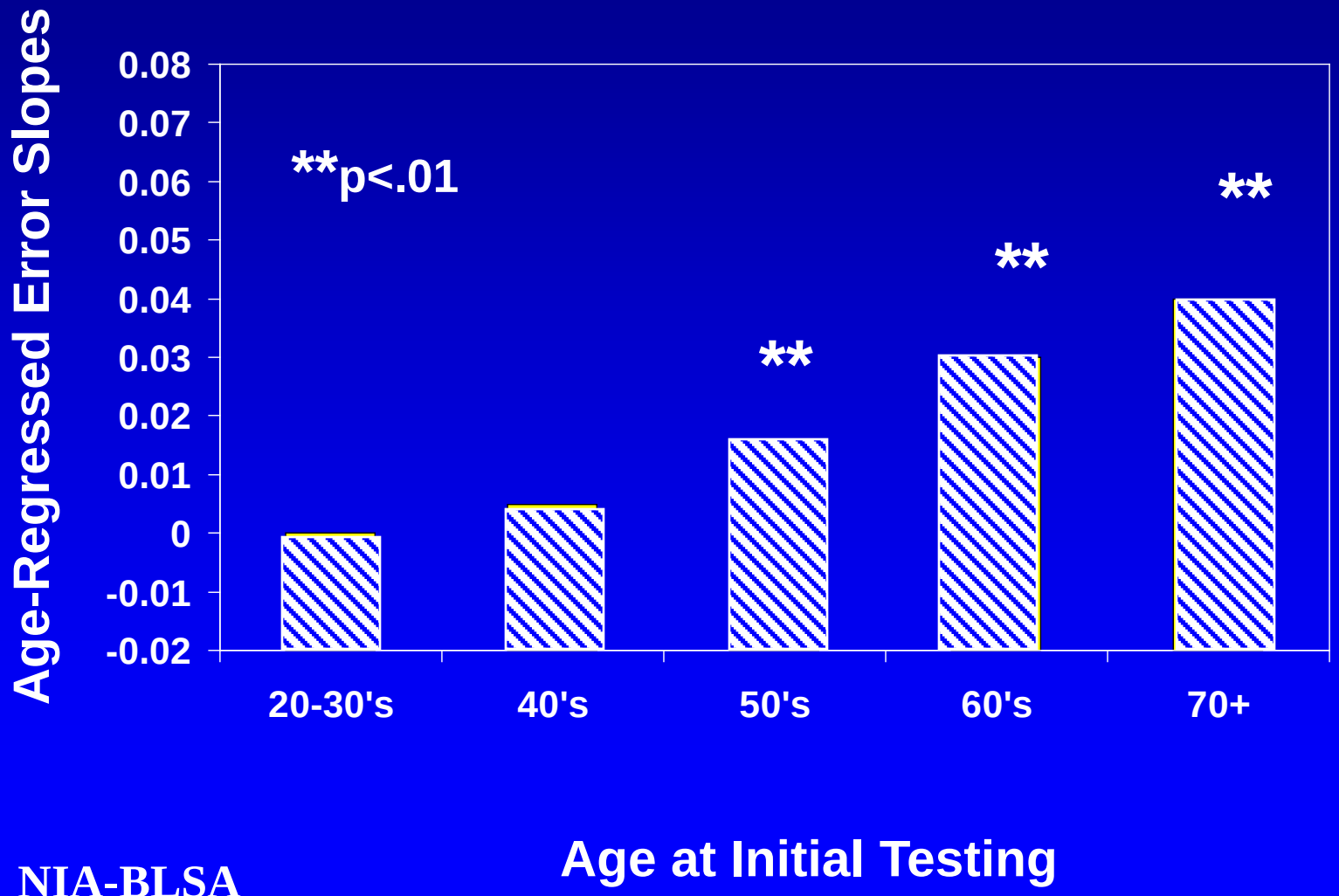


Albert et al, 1987

Paired Associate Learning (errors)– Computerized Task (n=1444)



Rate of Change in Visual Memory with Age



NIA-BLSA

Changes in Memory with Age

- Humans
- Monkeys
- Rodents

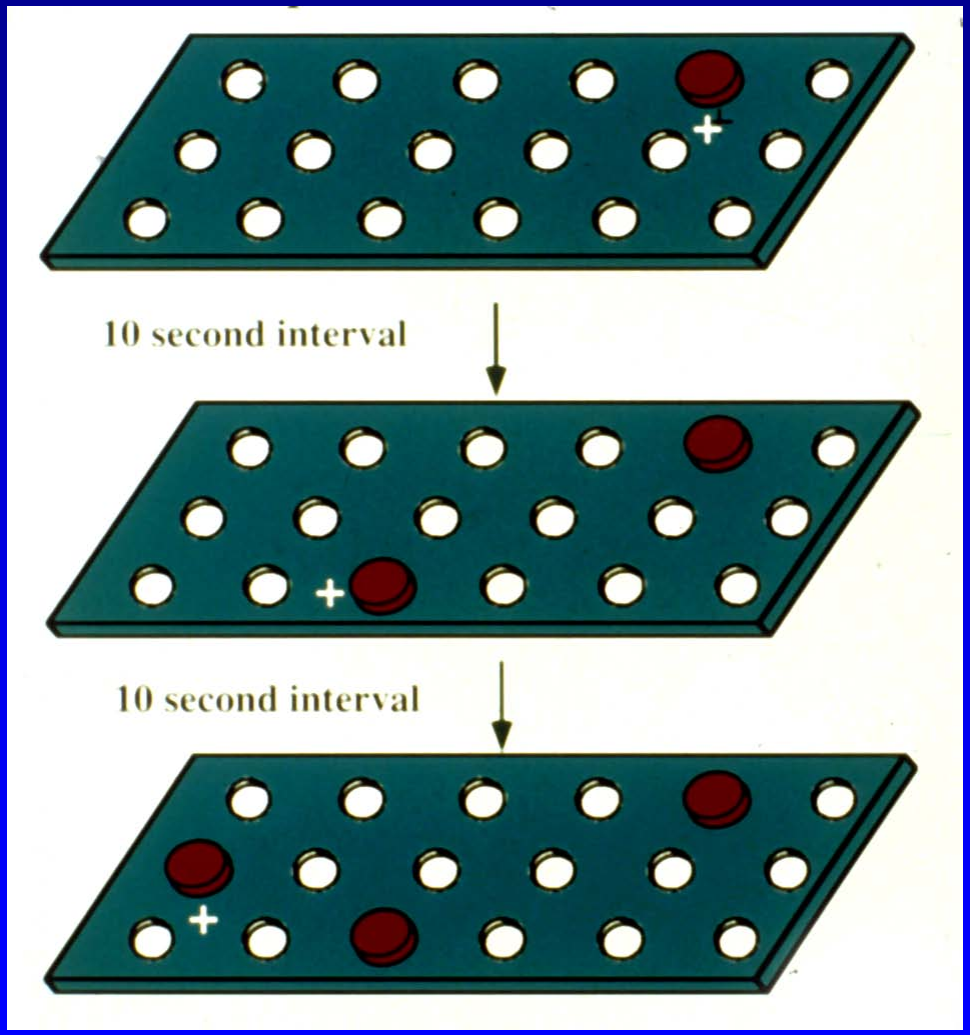
Studies of Optimally Healthy Rhesus Monkeys

5 year old Male

25 year old Male

Delayed Recognition Span Test

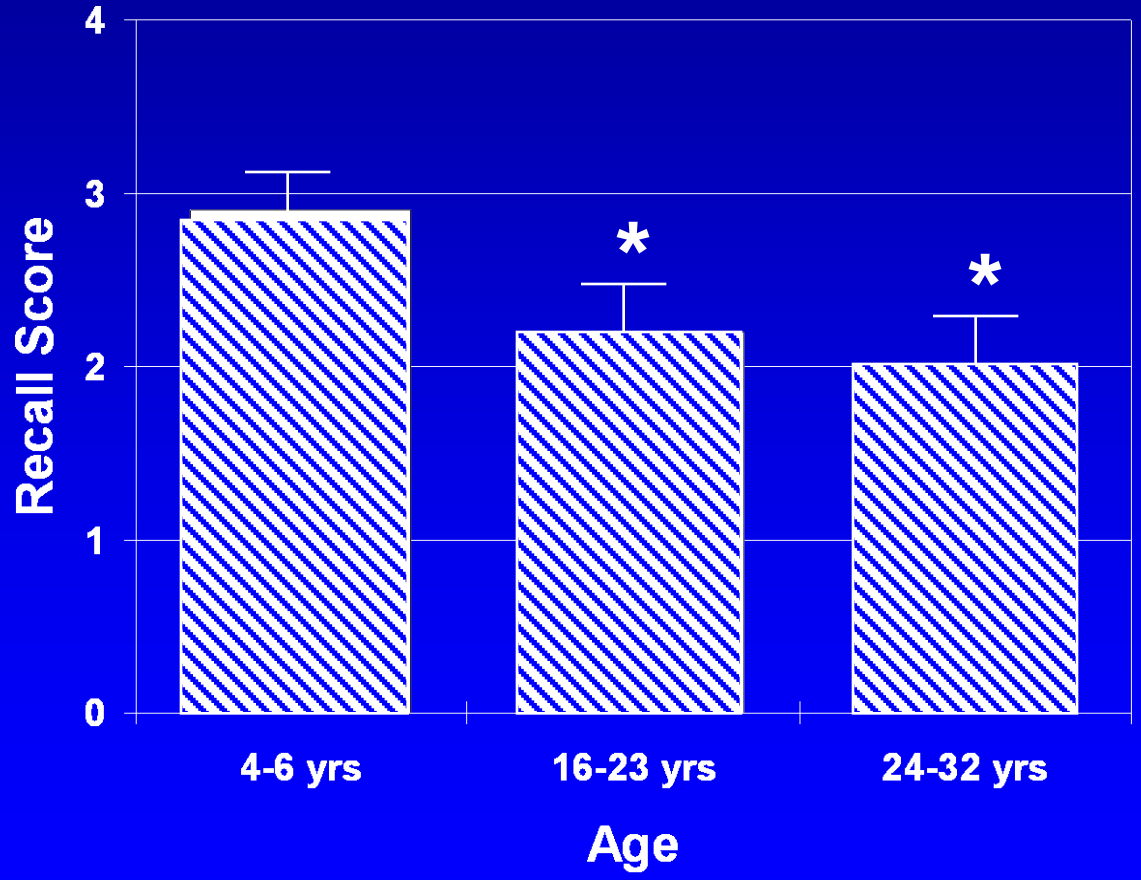
Spatial condition



Courtesy M. Moss

Differences in Delayed Recognition with Age

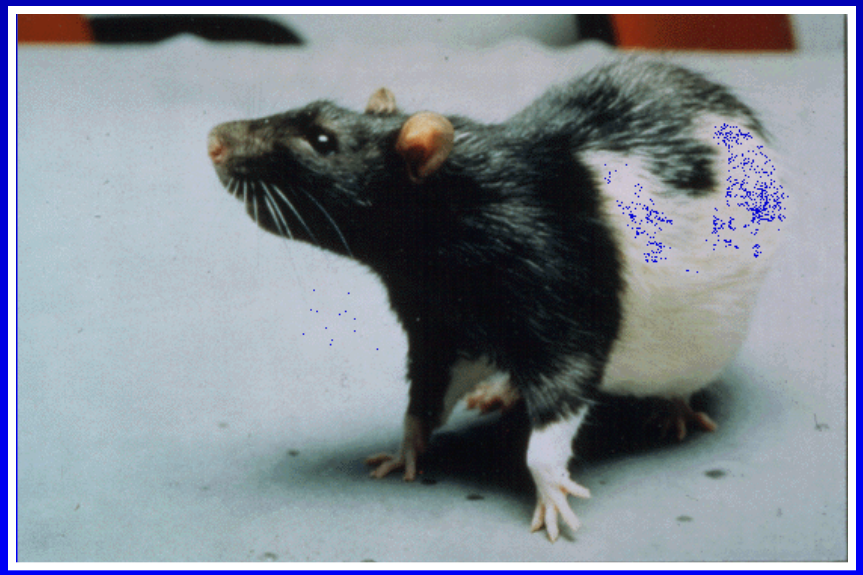
(Monkeys 4 – 32)



Moss et al, 1988

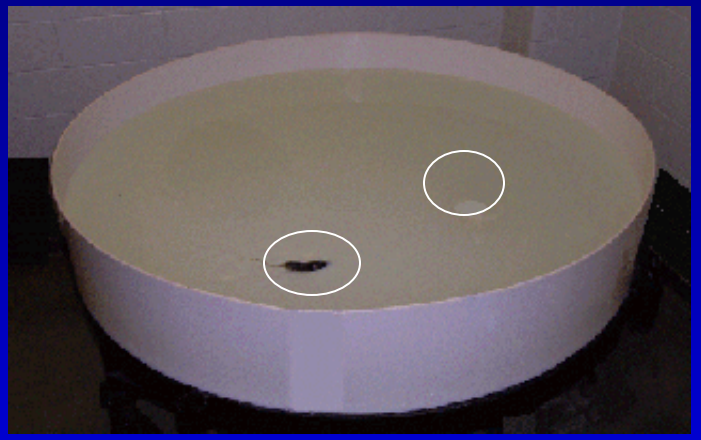
Studies of Optimally Healthy Rodents

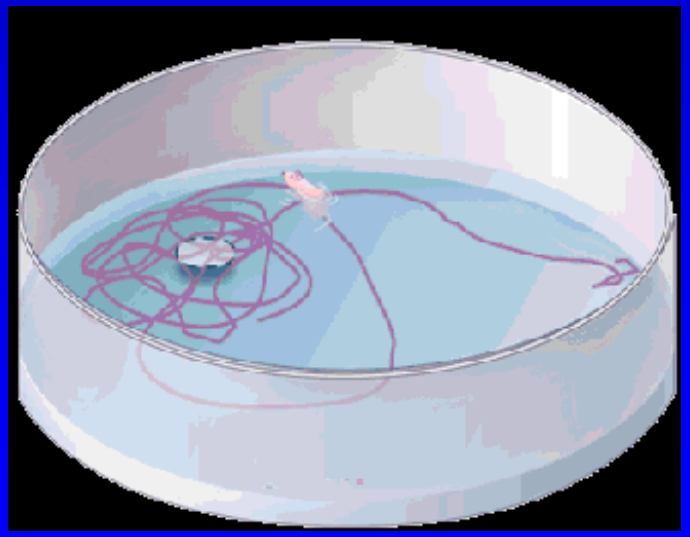
Young Rat



Old Rat

Morris Water Maze

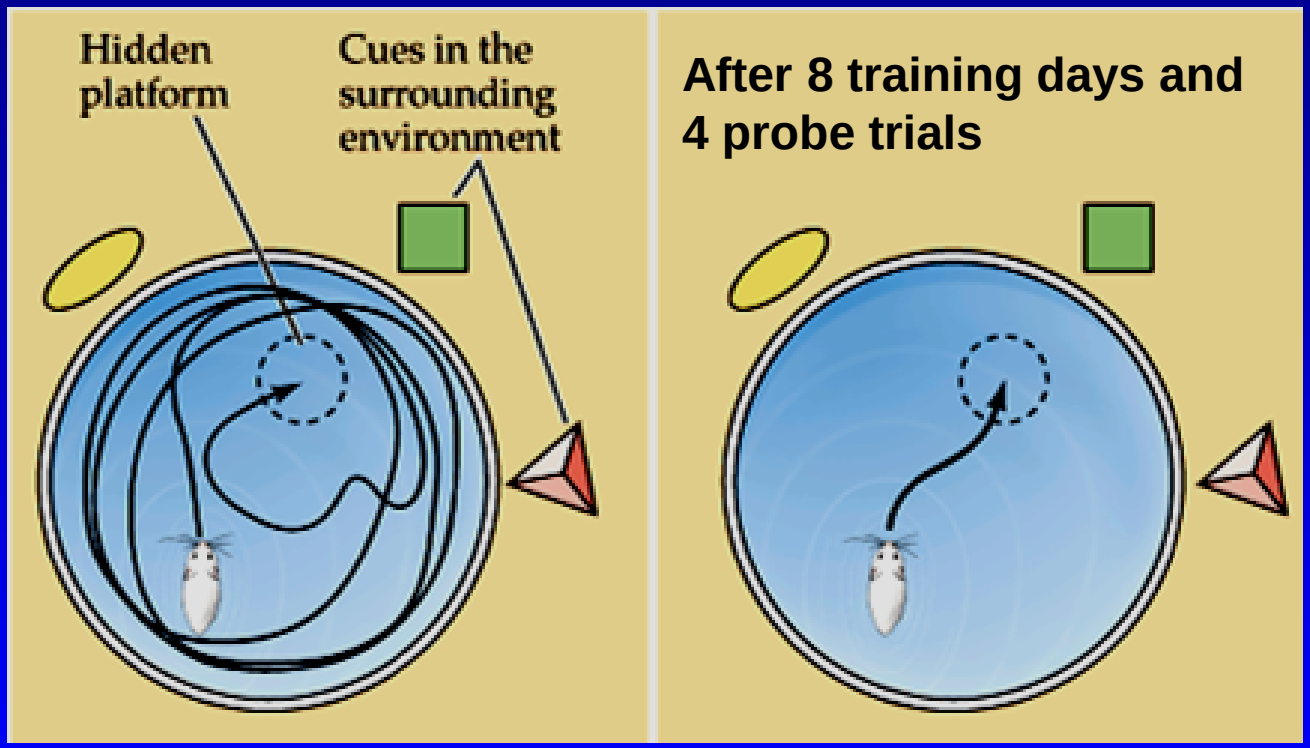




Morris, 1984

Assessment of Memory in Water Maze

8 training days, same platform location (3 trials/day)
1 probe trial every other training day = 4 probe trials



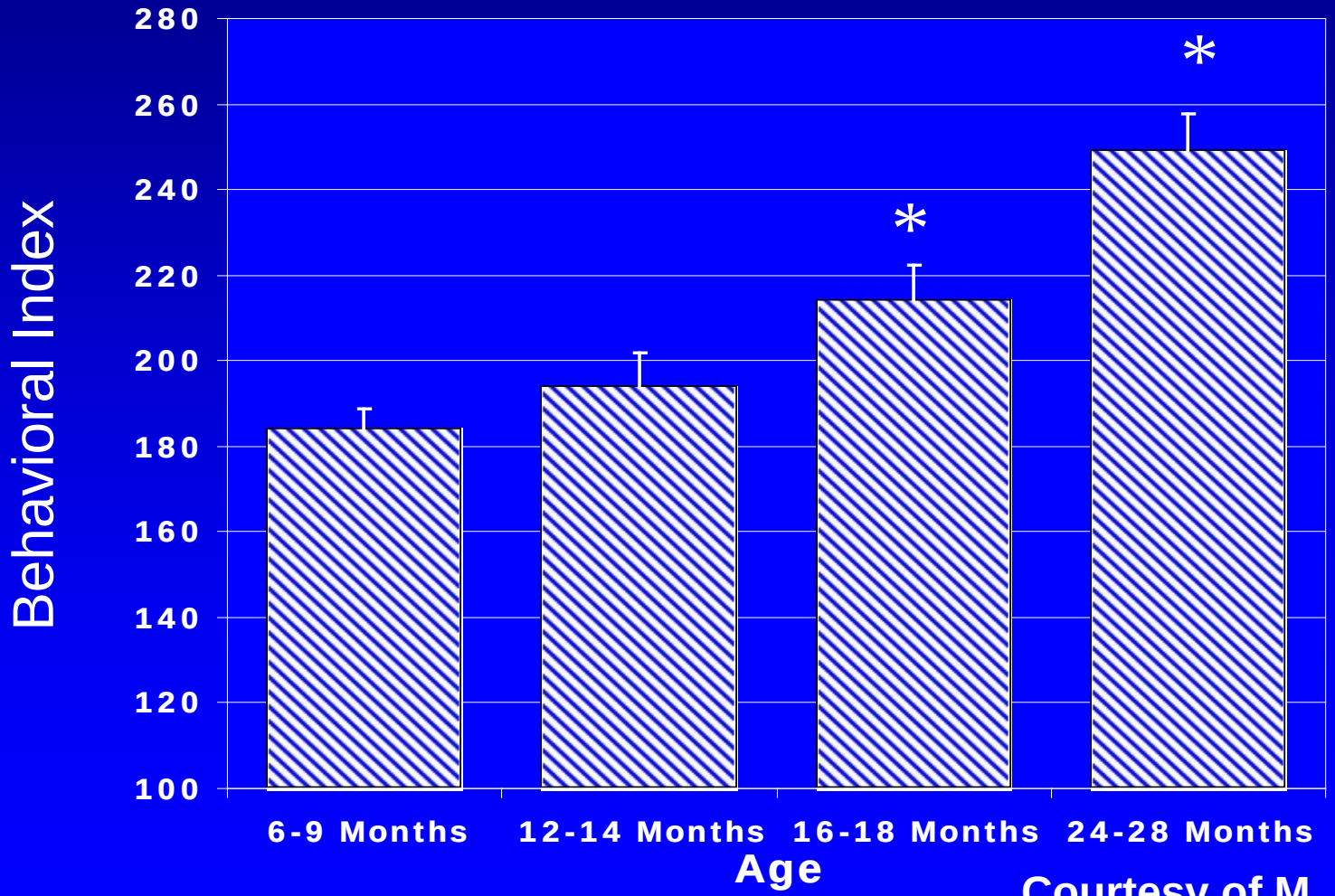
Memory Index = Proximity of Animal to Hidden Platform on Each Probe Trial

Measurement is integrated over 4 probe trials;
Weighting scheme gives credit for early learning;
Automated image tracking permits measurement in x,y coordinates

Gallagher et al., 1993

Differences in Memory Performance on Water Maze With Age

(Rats 6-28 months)

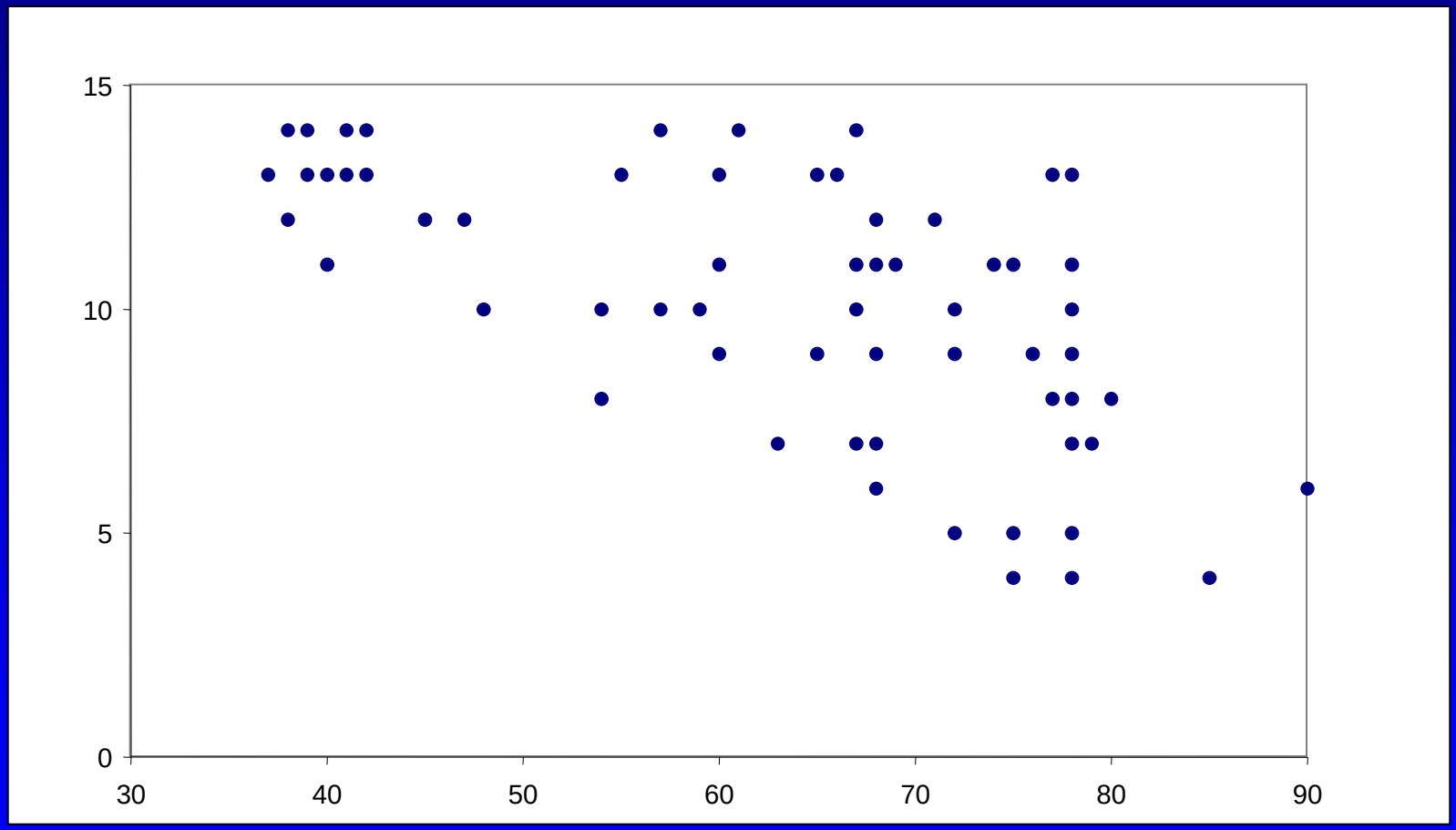


Courtesy of M. Gallagher

Variability in Memory Performance with Age

- Humans
- Non-human primates
- Rodents

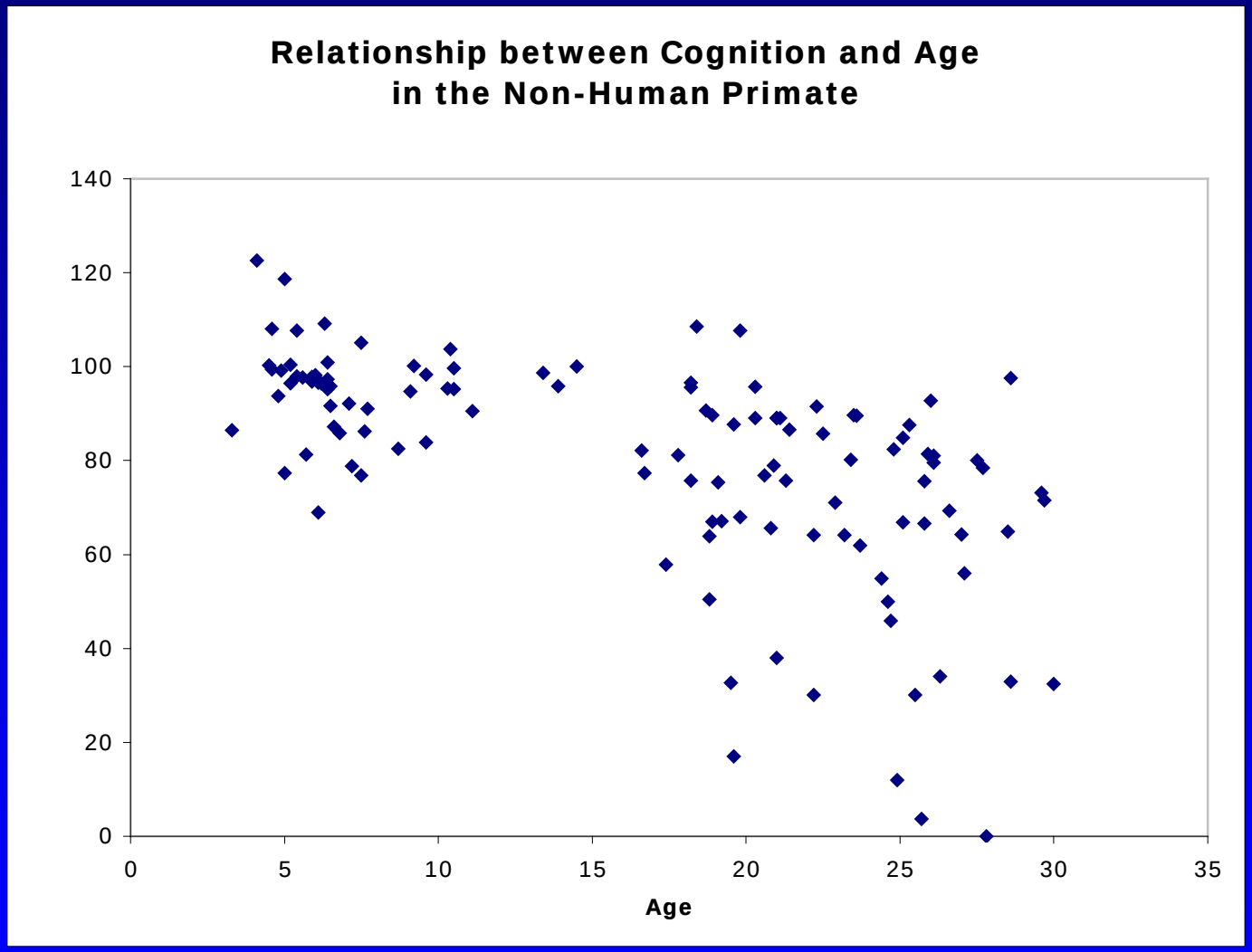
Delayed Recall of Stories



Age

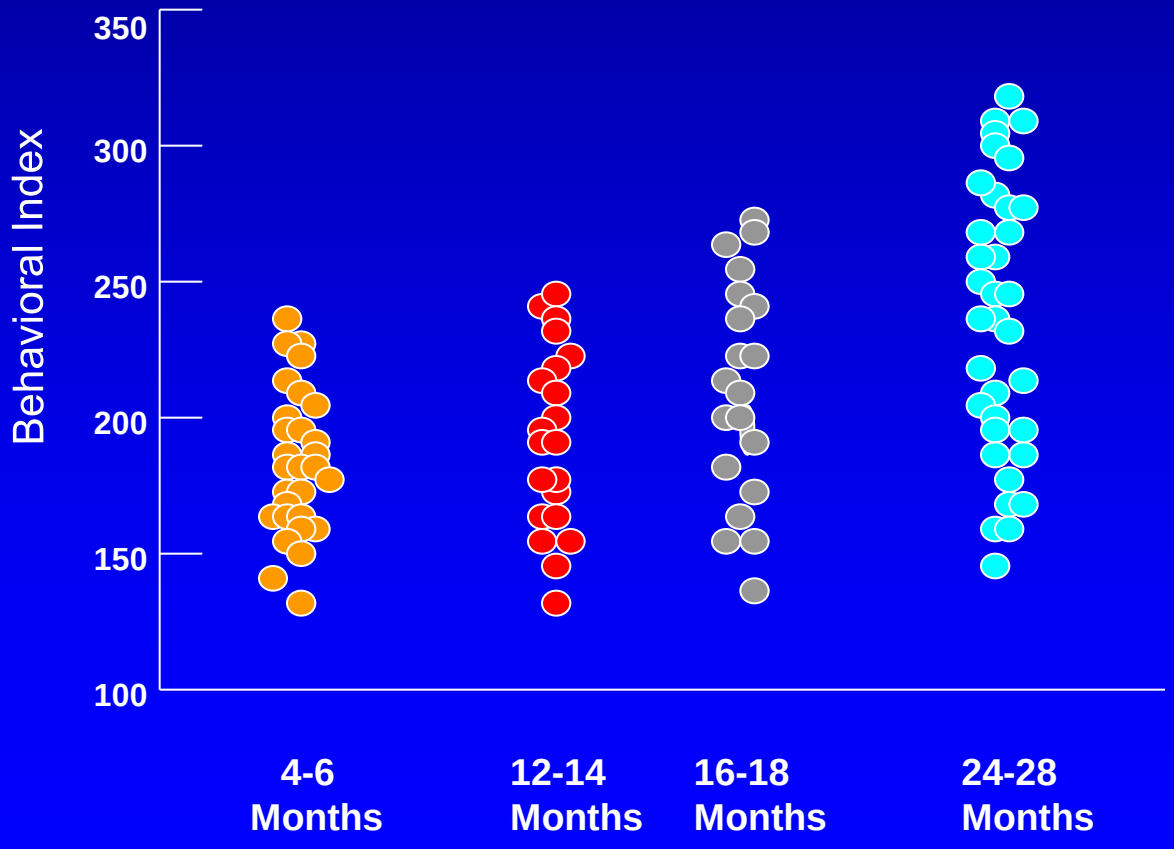
Humans

Recognition Memory Performance

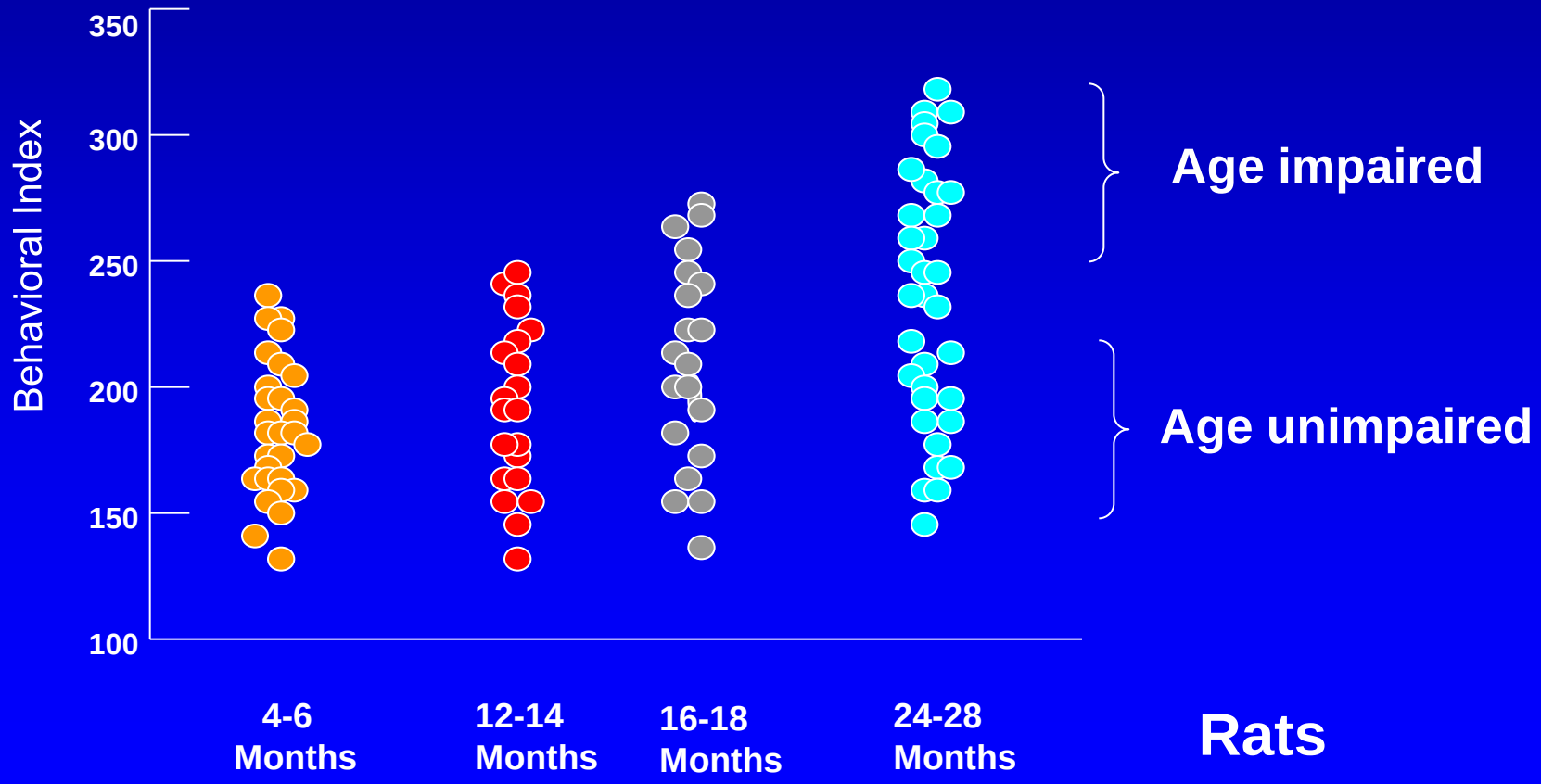


Rhesus Monkeys

Memory Performance in Water Maze



Memory Performance in Water Maze



Neuropsychological Manifestations of Brain Aging

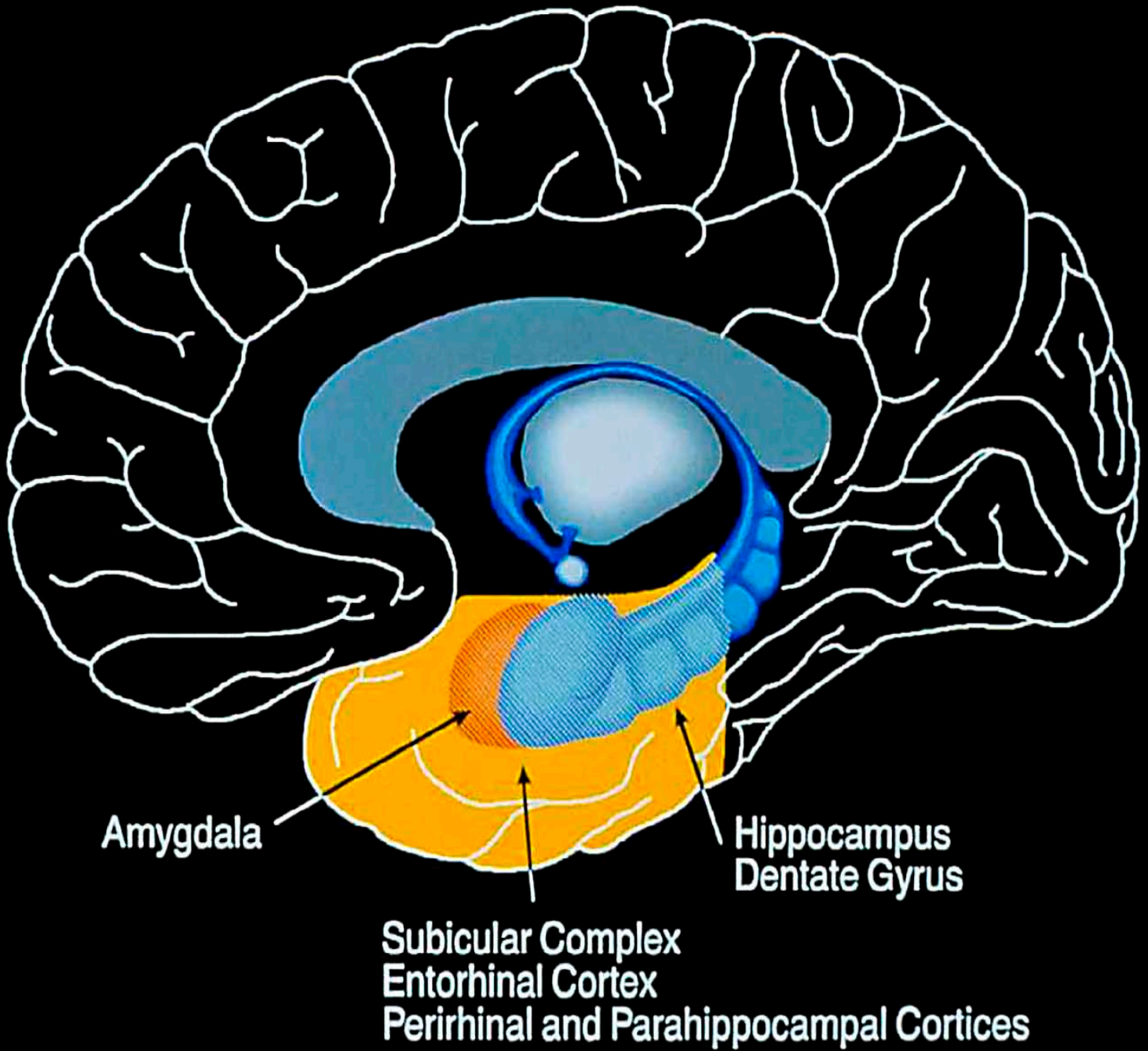
- Cognitive changes with age - declines occur at middle age with respect to memory (declines in other domains occur at varying ages)
- Variability with advancing age in all species studied – some preserve function well
- Mechanisms – why do some decline?

Question to be Answered:

What brain mechanisms underlie alterations in cognitive abilities (memory) with advancing age?

Potential Explanations for Declines in Cognitive Abilities with Age

- Loss of nerve cells diffusely throughout the brain
- Loss of nerve cells in highly selective regions in the brain
- Changes in physiological mechanisms that modulate brain function


Amygdala
Hippocampus
Dentate Gyrus
Subicular Complex
Entorhinal Cortex
Perirhinal and Parahippocampal Cortices

Neuronal Loss with Age

Human, Monkey and Rat Studies

Hippocampal Complex

- CA1
- CA2 - 3
- Dentate (granule cells)
- Entorhinal Cortex

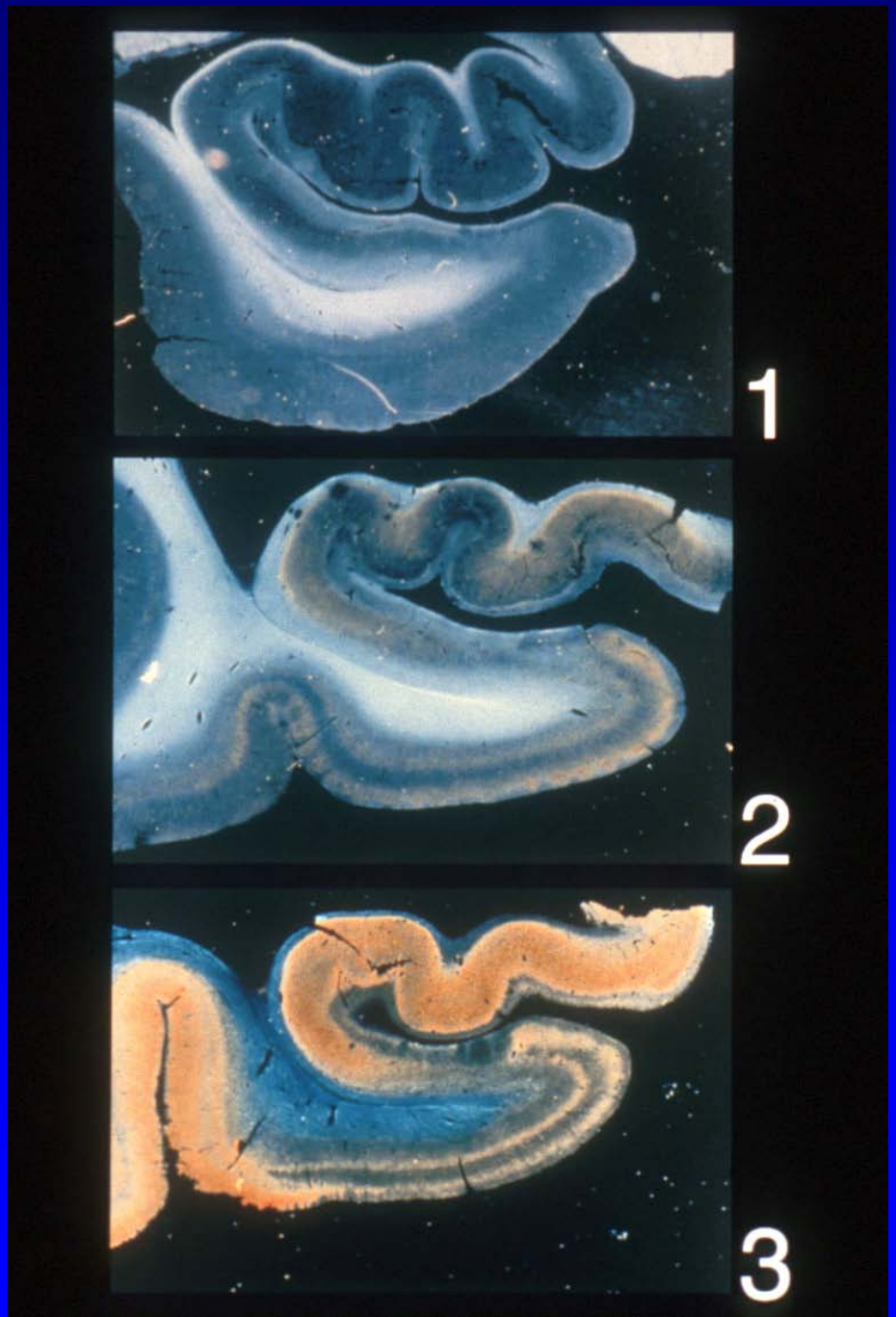
} 0 - 5 %

- CA4
- Subiculum

} 35 %

Gomez-Isla et al., 1996
West et al, 1993
Peters et al., 1996
Merrill et al., 2000
Rapp & Gallagher, 1996

Unbiased Stereology



Normal

MCI

AD

Alterations in Gray Matter with Age

- **Minimal loss of neurons in cortex**
  - **striate cortex**
  - **motor cortex**
  - **frontal cortex**
- **Alterations in dendrites in layer 1 of cortex**
- **Minimal accumulation of lipofuscin in cortex**

Tigges et al., 1992
Peters et al., 1994
Peters et al., 2001

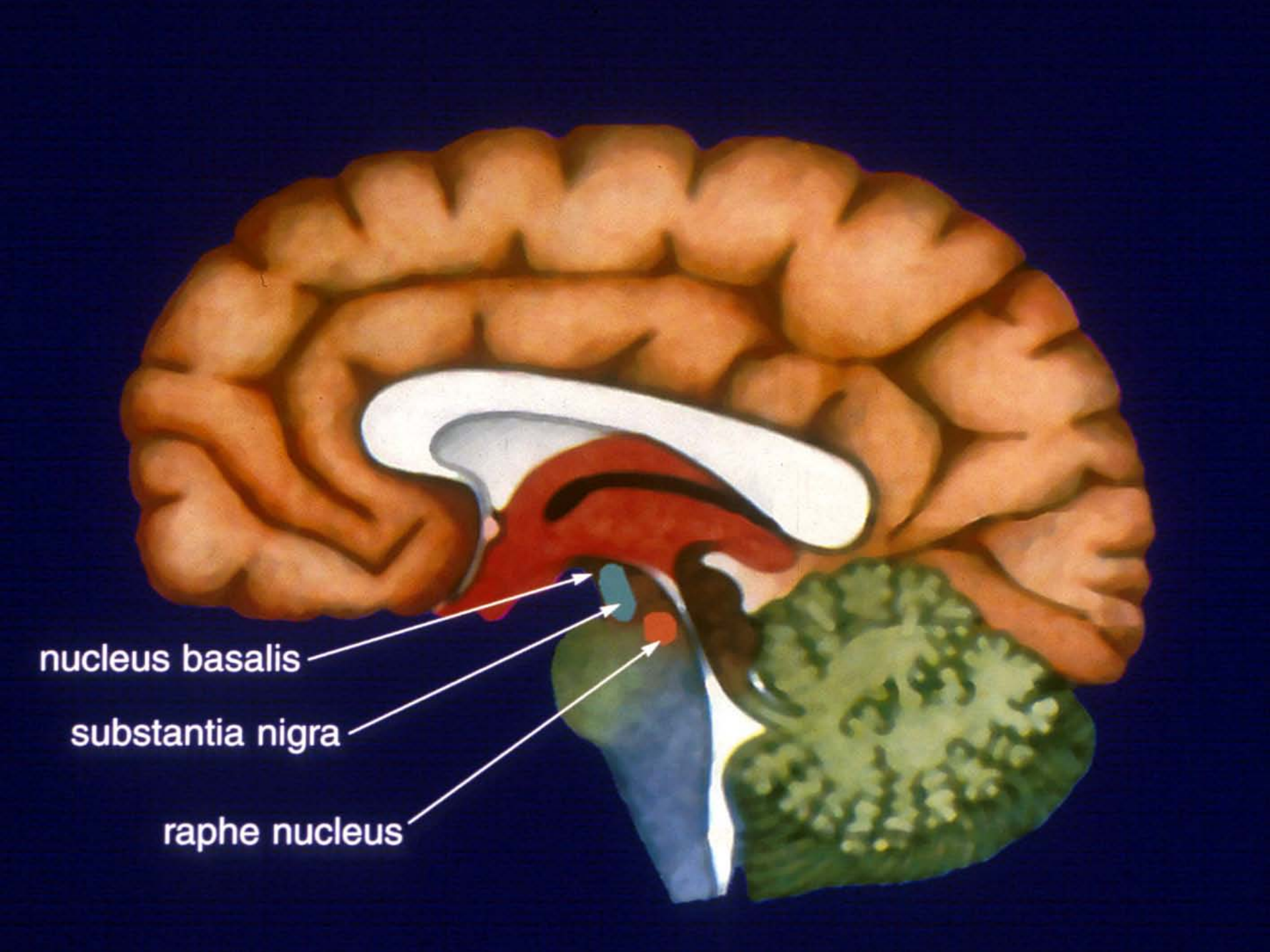
Neuronal Loss with Age
Human and Monkey Studies

Subcortical Nuclei

- **Nucleus Basalis - 50%**
- **Substantia Nigra - 35 - 40 %**
- **Raphe Nucleus - 35 - 40 %**

neurotransmitters that influence plasticity and learning in adult brain

Rosene 1993
Arnsten et al., 1995
Kemper, et al, 1997


nucleus basalis
substantia nigra
raphe nucleus

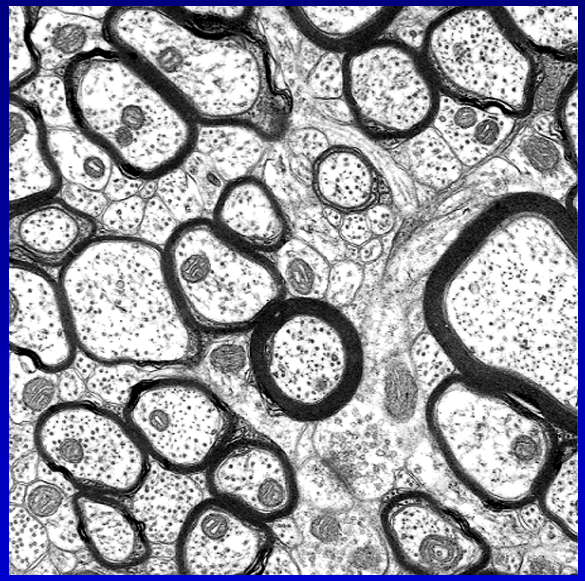
Alterations in White Matter with Age

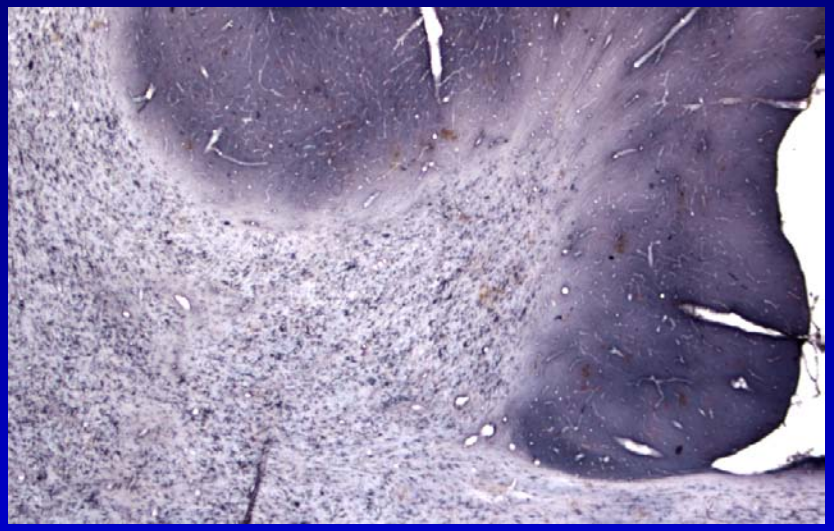
- Degeneration of myelin (e.g., split sheaths, debris within sheath)
- Membranous inclusions
- Substantial accumulation of lipofuscin in neuroglia

Peters et al., 1994
Peters et al., 1996
Nielson & Peters, 2000

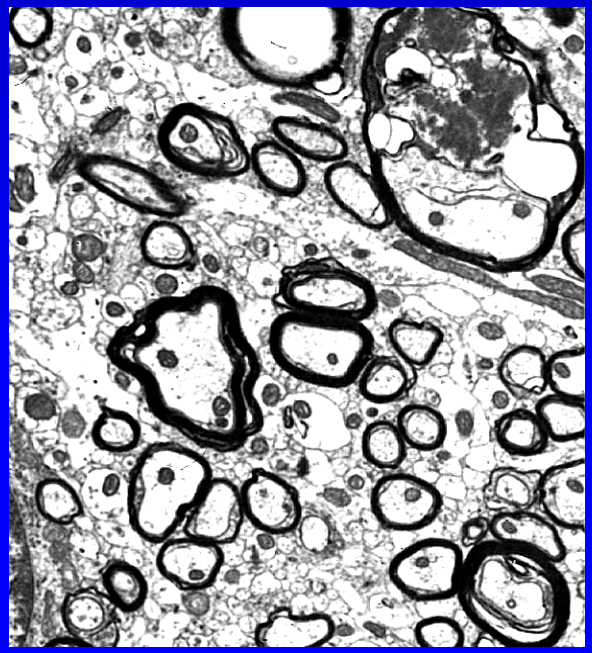
Alterations in Myelinated Fibers of White Matter

Young
5 Yrs





Old
25 Yrs

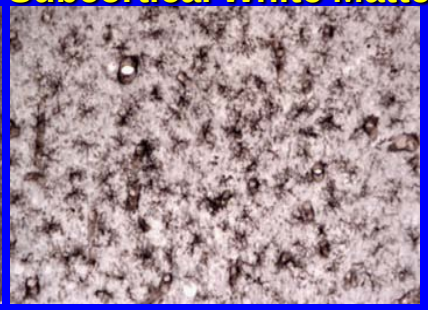


Young
8 Yrs

Cortical Gray Matter

Subcortical White Matter

Old
25 Yrs



Functional Changes with Age

Hippocampal Complex

Synaptic number

- Synaptic number altered in some regions (e.g., dentate gyrus)

Plasticity

- LTP, LTD, NMDA receptor function altered

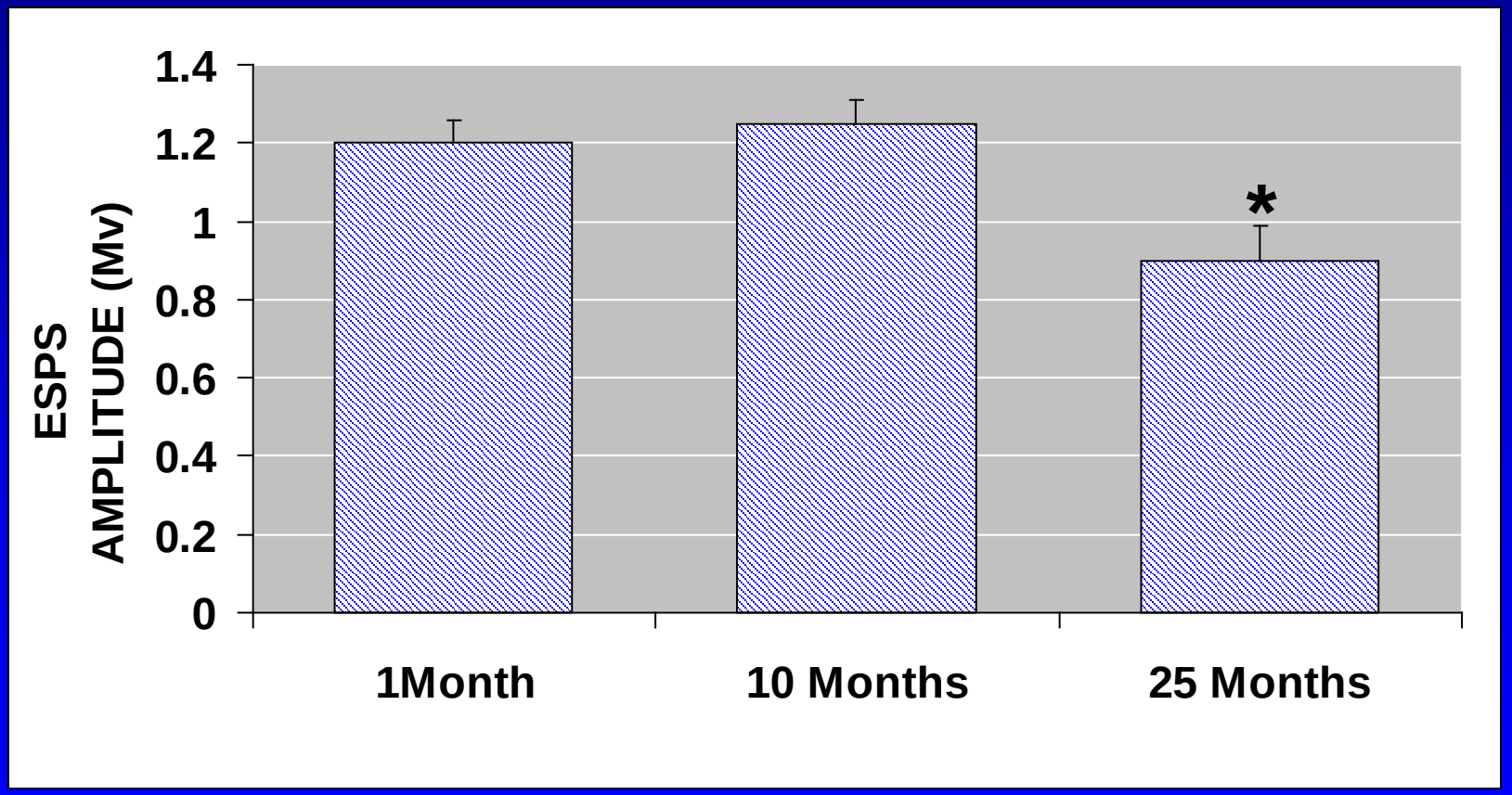
Connectional integrity

- Layer II entorhinal neurons altered

Rosensweig & Barnes, 2003
Gallagher et al., 2003

LTP Differences with Age

Water Maze Performance



Correlation with performance

Barnes et al., 2000
Barnes et al., 1992

Current Explanations for Decline in Cognitive Abilities with Age

- Loss of nerve cells diffusely throughout the brain does NOT occur
- Loss of nerve cells in highly selective regions in the brain
- Changes in physiological mechanisms that modulate brain function

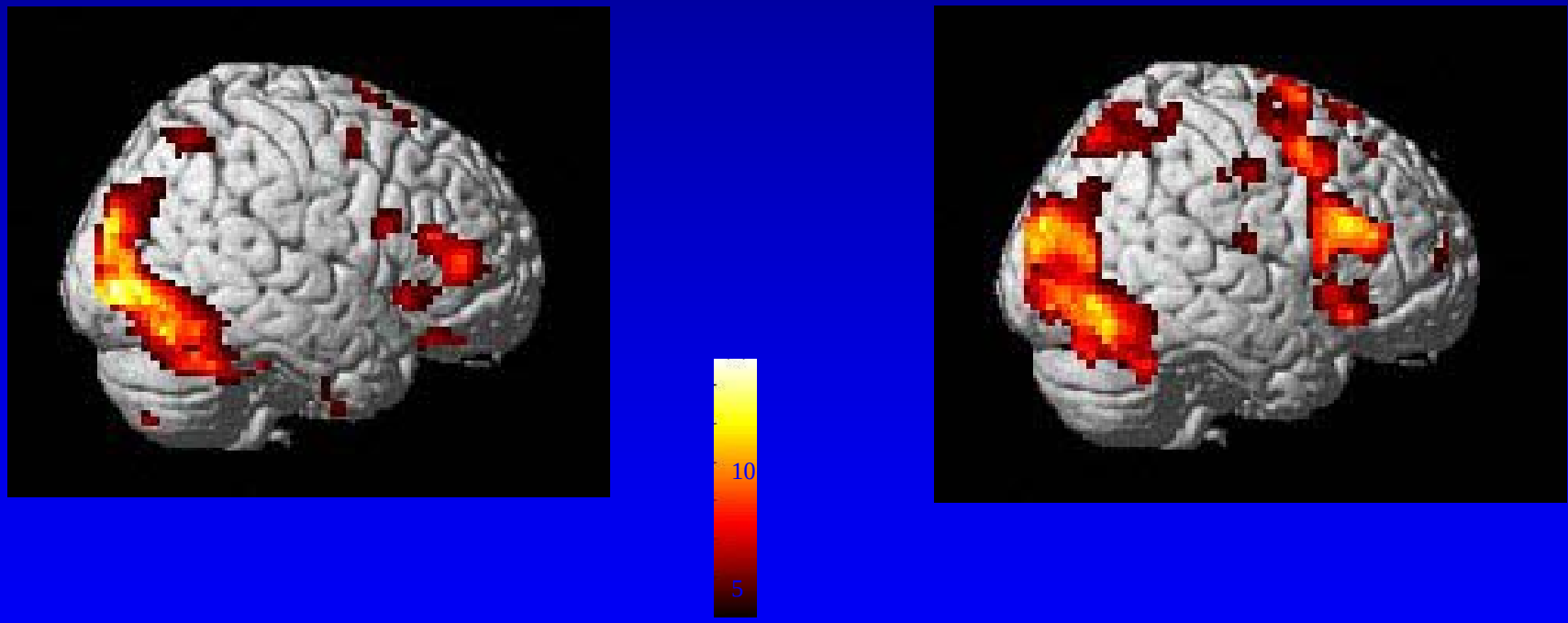
Neurobiology of Preservation of Cognitive Function

- Likely explanations for variability in performance among healthy individuals
  - Some do NOT demonstrate age-related declines in structure and function
  - Some may activate adaptive mechanisms

Increased fMRI Activation Successful Memory Task Performance

Young

Older



correct high confidence successful responses > fixation

Sperling et al., 2005
Cabeza et al., 2004

Neurobiological Manifestations of Brain Aging

- Preservation of cognitive ability with age likely results from both:
  - Absence of age-related declines in function
  - Activation of adaptive mechanisms
- Neuronal loss limited: If neuronal loss is limited in the normal aging brain, then therapies (i.e., behavioral or drug therapies) might be targeted at promoting cell health and function, rather than at recreating cells in appropriate regions
- Genetic factors: Is optimal function related entirely to genetic factors?

Genetic Influences on Learning

Studies of Identical Twins Reared Together & Apart

- Swedish Adoption Twin Study of Aging
  - **Heritability: 32%-44% (mean age 66)**
- Minnesota Twin Study
  - **Heritability: 50%-60% (mean age 67)**
- Octo Twin Study
  - **Heritability: 37%-49% (mean age 83)**

Pedersen et al., 1992
Finkel & McGee, 1993
Johnsson et al., 1999

Neurobiological Manifestations of Brain Aging

- Genetic factors can explain part, but not all, of the variance
- Appropriate to examine life-style factors that may modify age-related cognitive decline

Future Directions

- Examination of Adaptive Mechanisms – neurobiological underpinnings and possibility of promoting adaptation

- Age-related change vs. disease related change - change within normal limits vs. change that is harbinger of progression to impairment

Future Directions

- Role of Early Experience – do cohort differences in nutrition, infections, etc influence cognitive decline in later life

- Potential for Modification – life style factors that may be modified (intensity of intervention, timing of intervention, multiplicity of interventions)