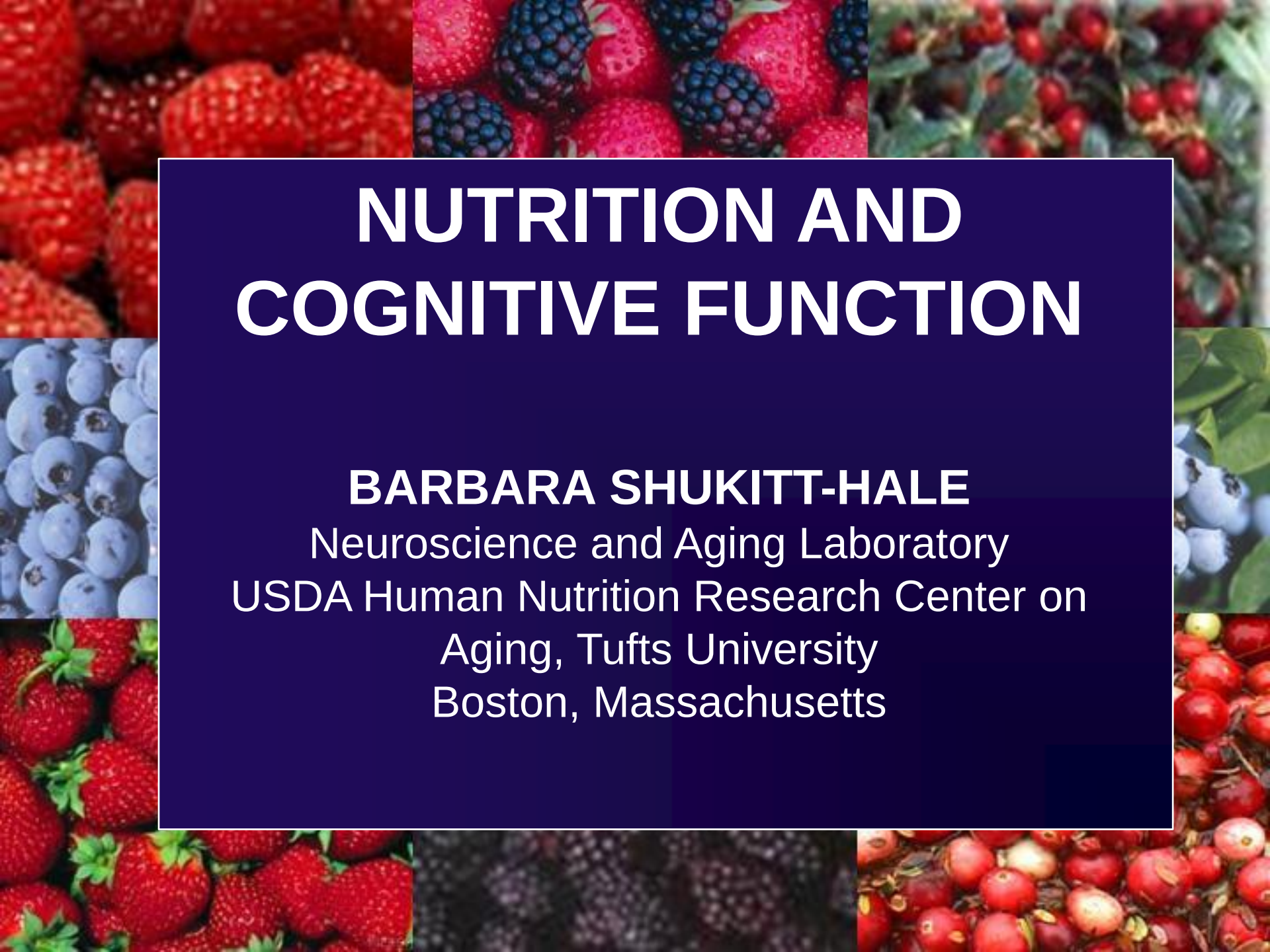


NUTRITION AND COGNITIVE FUNCTION

BARBARA SHUKITT-HALE
Neuroscience and Aging Laboratory
USDA Human Nutrition Research Center on Aging, Tufts University
Boston, Massachusetts

DISCLOSURES

- Employer: USDA, ARS

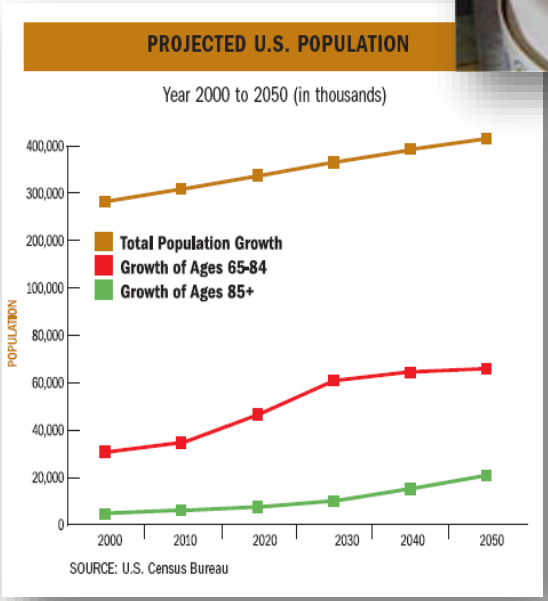
- Research Support: California Strawberry Commission; U.S. Highbush Blueberry Council

Demographics & Brain Aging

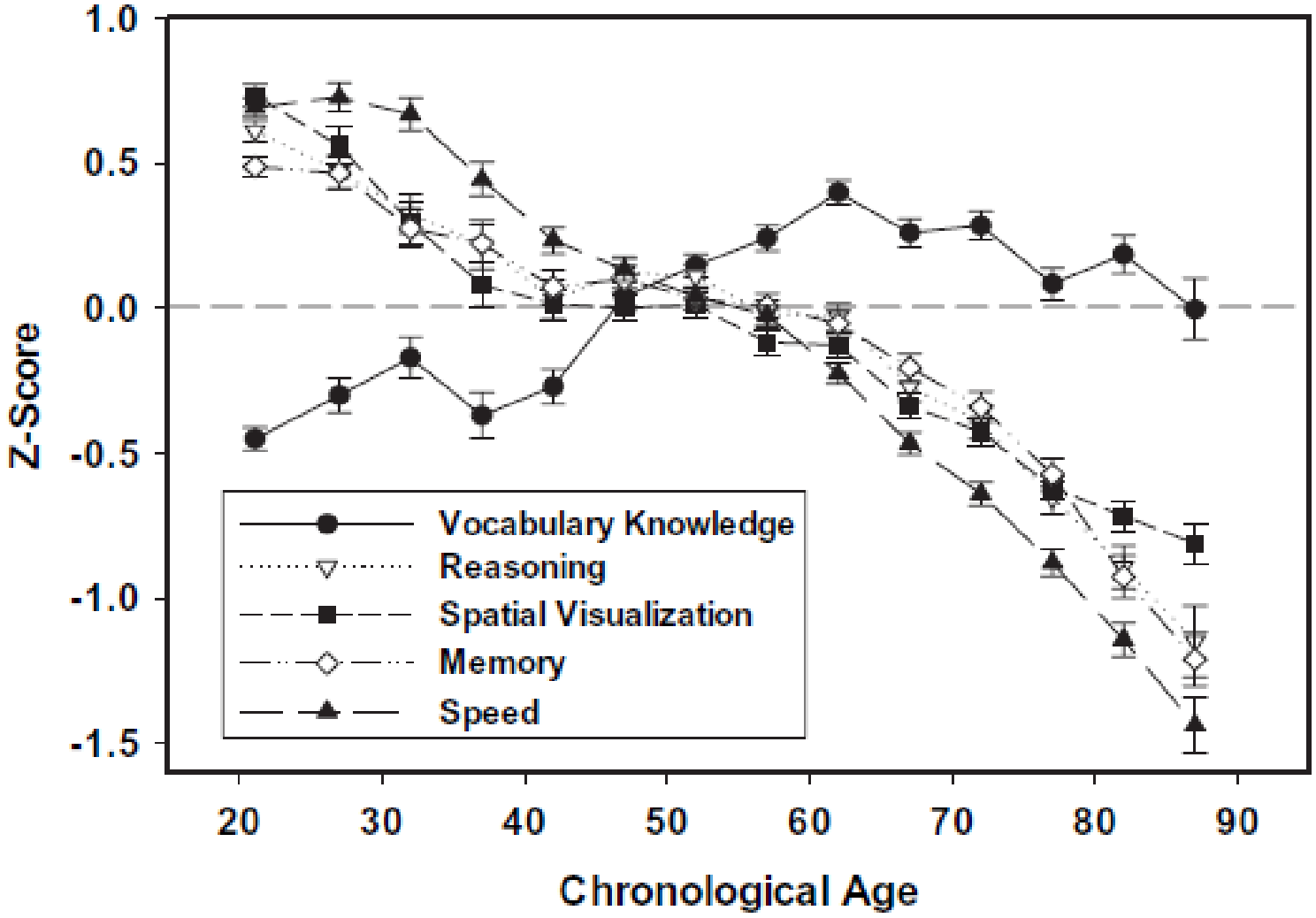
By 2050, 30% of the US population will be over age 65

Many will exhibit impairments in motor and cognitive function.

This will be due to neurodegenerative diseases like AD & PD and normal brain aging.



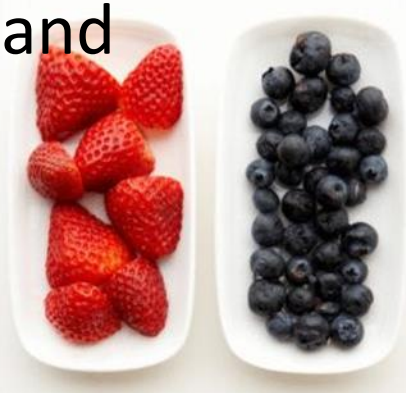
Age-Related Cognitive Decline



Salthouse, *J Internat Neuropsychol Soc.* 2010;16:754-60.

Oxidative Stress and Inflammation in Brain Aging

- At rest the brain utilizes 20% of the body's oxygen.
- Inflammation and oxidative stress biomarkers increase with age; brain sensitivity to these biomarkers increases with age.
- Inflammation, oxidative stress, reduced maintenance functions and genetic changes appear to make the brain more vulnerable to cognitive decline and Alzheimer's disease.

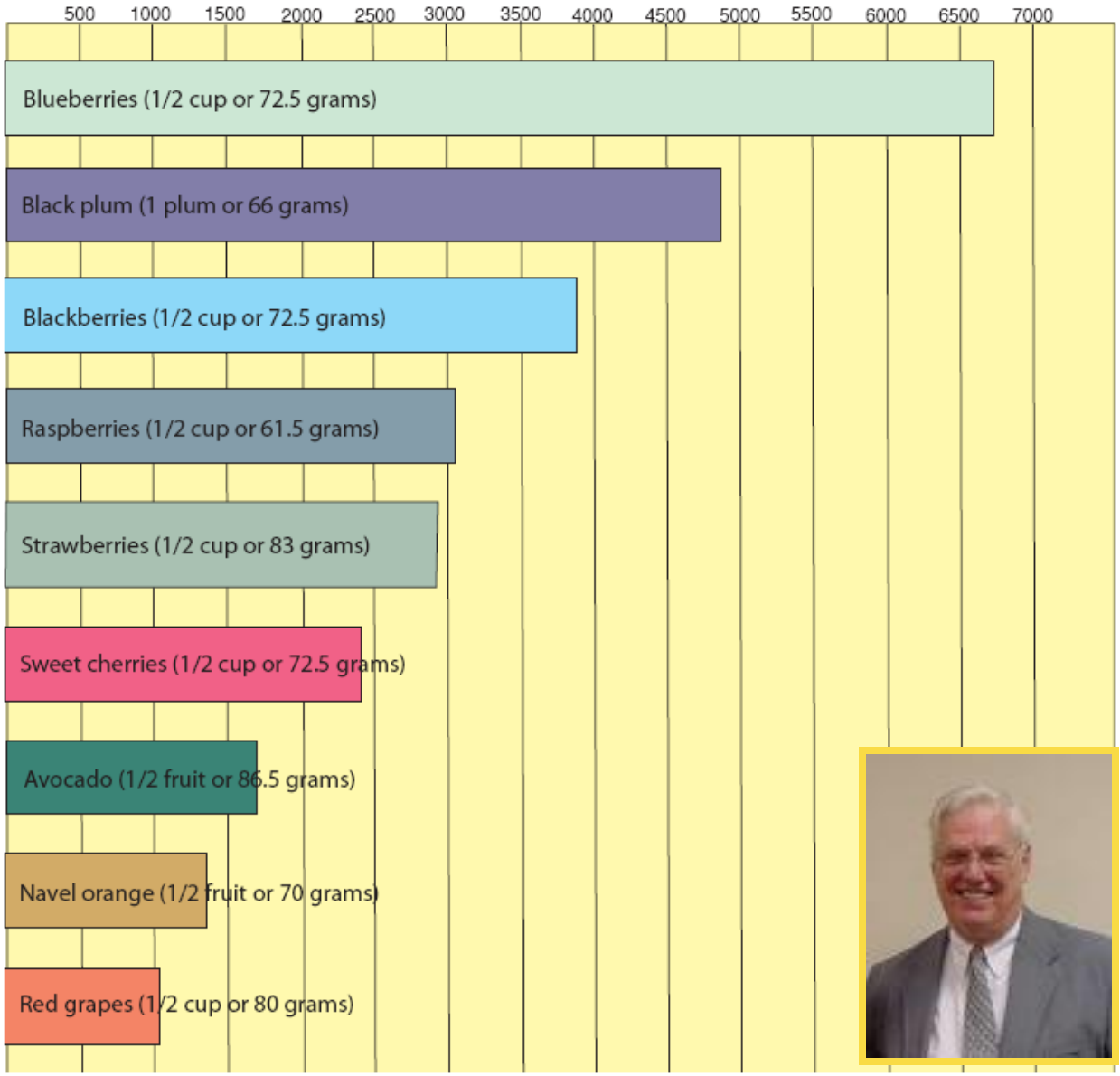


Poulose et al., *J Nutr.* 2014;144: 561S-566S

•We must find strategies to improve behavior, possibly by changing the neuronal environment by altering oxidative stress and inflammatory components.

• Research in our lab and others has shown that the behavioral deficits seen in aging can be retarded or even reversed by the polyphenolics in foods, possibly by increasing antioxidant and/or anti-inflammatory levels.

ORAC Units* (Micromole TE/grams)**



Source: USDA-ARS, Arkansas Children's Research Center, Little Rock, AR, 2004 data.

ORAC: Oxygen Radical Absorbance Capacity

*ORAC units include both fat- and water-soluble values.

**Micromole TE/gram means the number of micromoles of Trolox, a vitamin E equivalent, per 1 gram weight of fresh fruit.

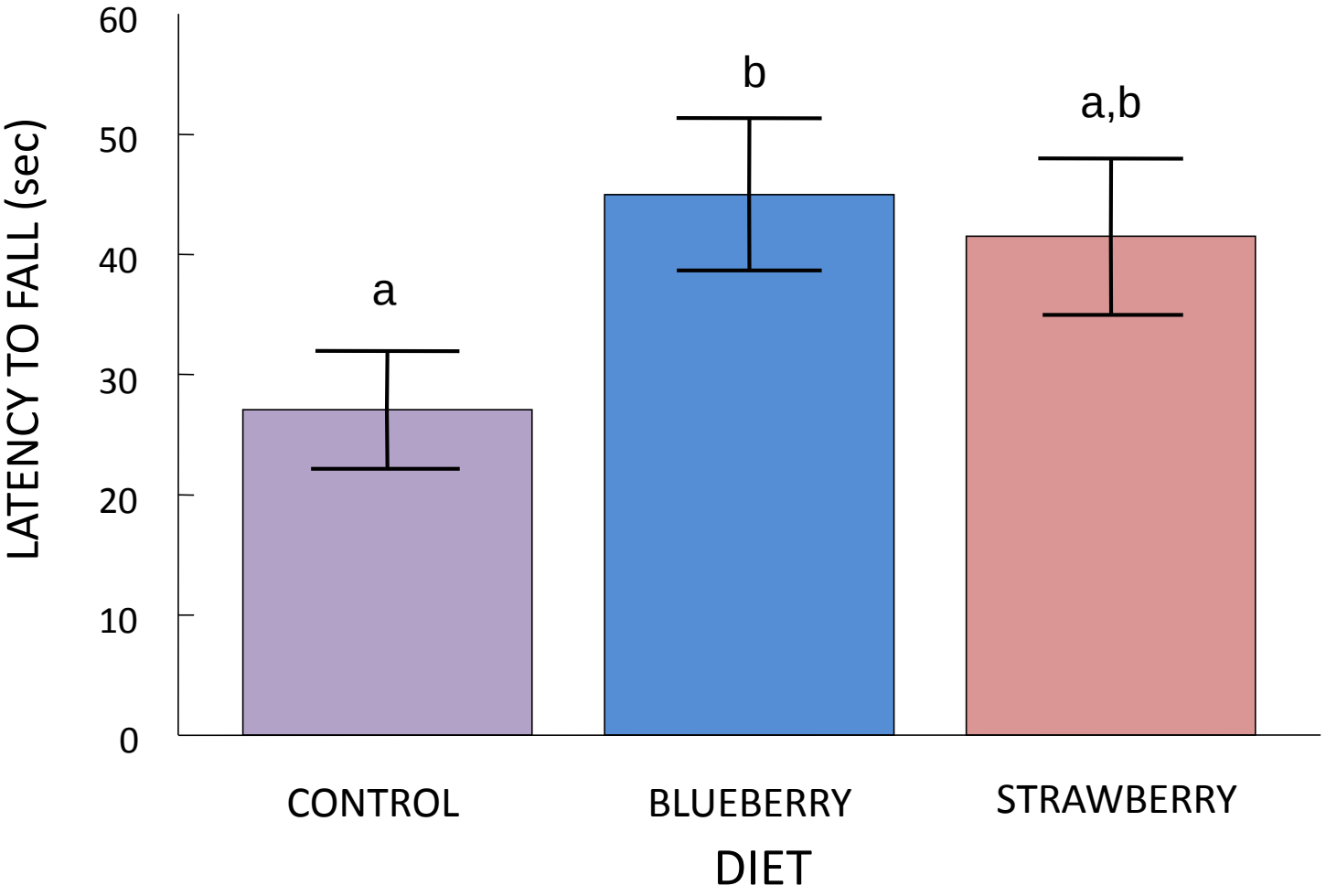
BEHAVIORAL STUDIES IN RODENT MODELS OF AGING

Procedures

- In all of our supplementation studies in aging, the rats were 19 months of age and supplemented for 8 weeks, typically at 2% of the diet.
- In the original study, an AIN 93 diet was used, and in all others an NIH-31 diet was used.
- In the purple grape juice and plum juice studies the animals drank the juice. For all others, the fruit, vegetable, or nut extract was added into the diet.

The rotarod evaluates balance and coordination

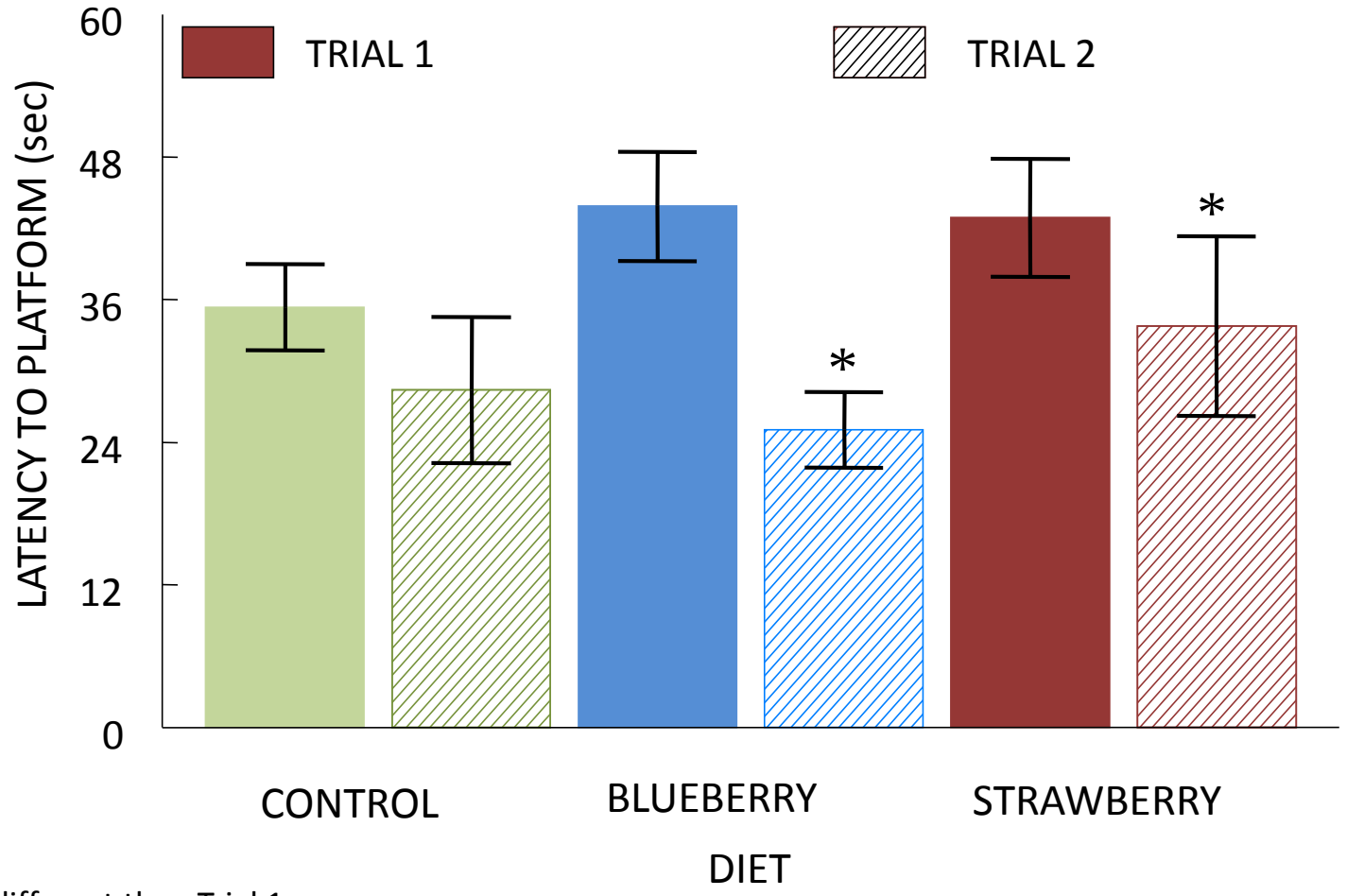
Rotarod



Shukitt-Hale, et al., *Brit. J. Nutr.* 2015;114:1542-1549

MORRIS WATER MAZE

TRIAL 1 vs TRIAL 2, DAYS 3-4



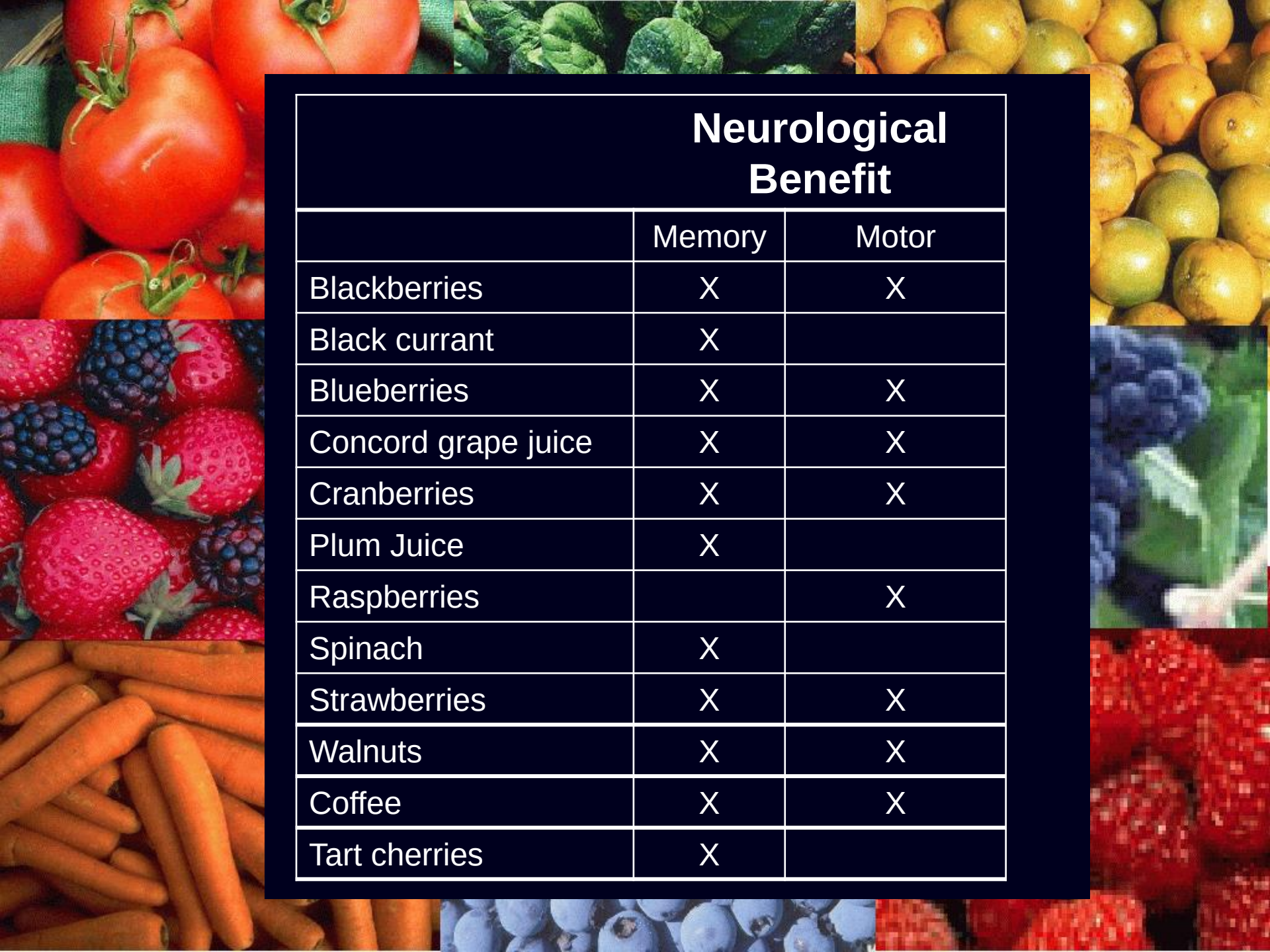
*=different than Trial 1

Shukitt-Hale, et al., *Brit. J. Nutr.* 2015;114:1542-1549

Summary Of Findings

- Nutritional interventions can reverse deficits in learning and memory and declines in motor behavioral performance.

- The beneficial effects of berries on behavioral performance were seen even when superimposed on an already well-fortified, healthy diet.



	Neurological Benefit	
	Memory	Motor
Blackberries	X	X
Black currant	X	
Blueberries	X	X
Concord grape juice	X	X
Cranberries	X	X
Plum Juice	X	
Raspberries		X
Spinach	X	
Strawberries	X	X
Walnuts	X	X
Coffee	X	X
Tart cherries	X	

Do the results seen in animal studies translate to humans?

Summary of Human Pilot Study

- Cognition and mobility decline with age. Our results replicated previous findings.
- Our methods were sufficient to detect age-related declines.
- Age-related declines were measurable younger than expected.
- These tests parallel the changes we see in rodent studies, where interventions with dietary supplements improve motor function and cognition.

Miller, et al., *Nutrition and Aging*. 2014; 2:213-222

Cognition

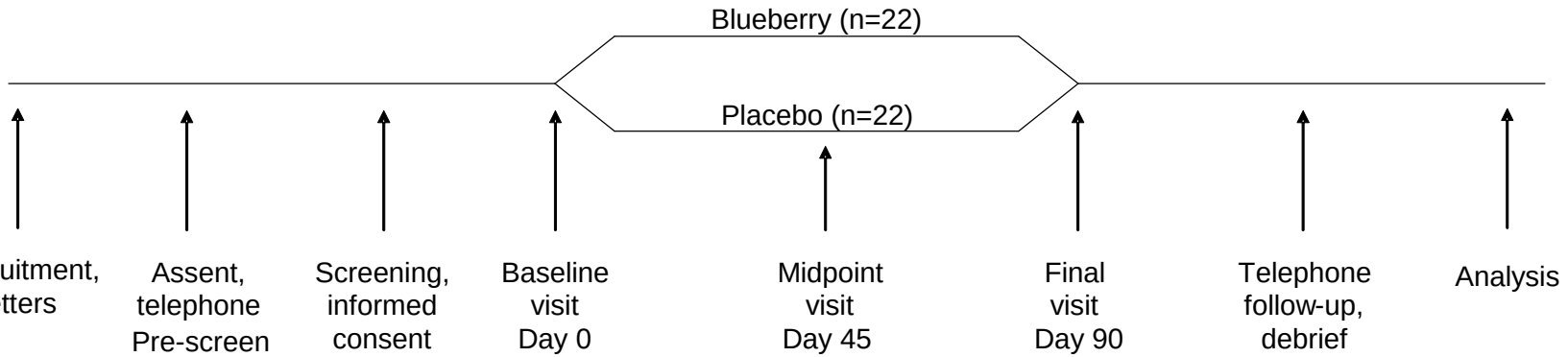
Will dietary blueberry improve mobility and cognition among older adults?

Balance

Gait

Blueberry Intervention Study

- Design: Double-blind, placebo-controlled trial
- Population: Healthy older adults, age 60-75 years
- Intervention: freeze dried Tifblue blueberry or placebo, powder ≈1c/day fresh blueberries, 3 mo, abstinence from berry fruit consumption



Outcome Measures

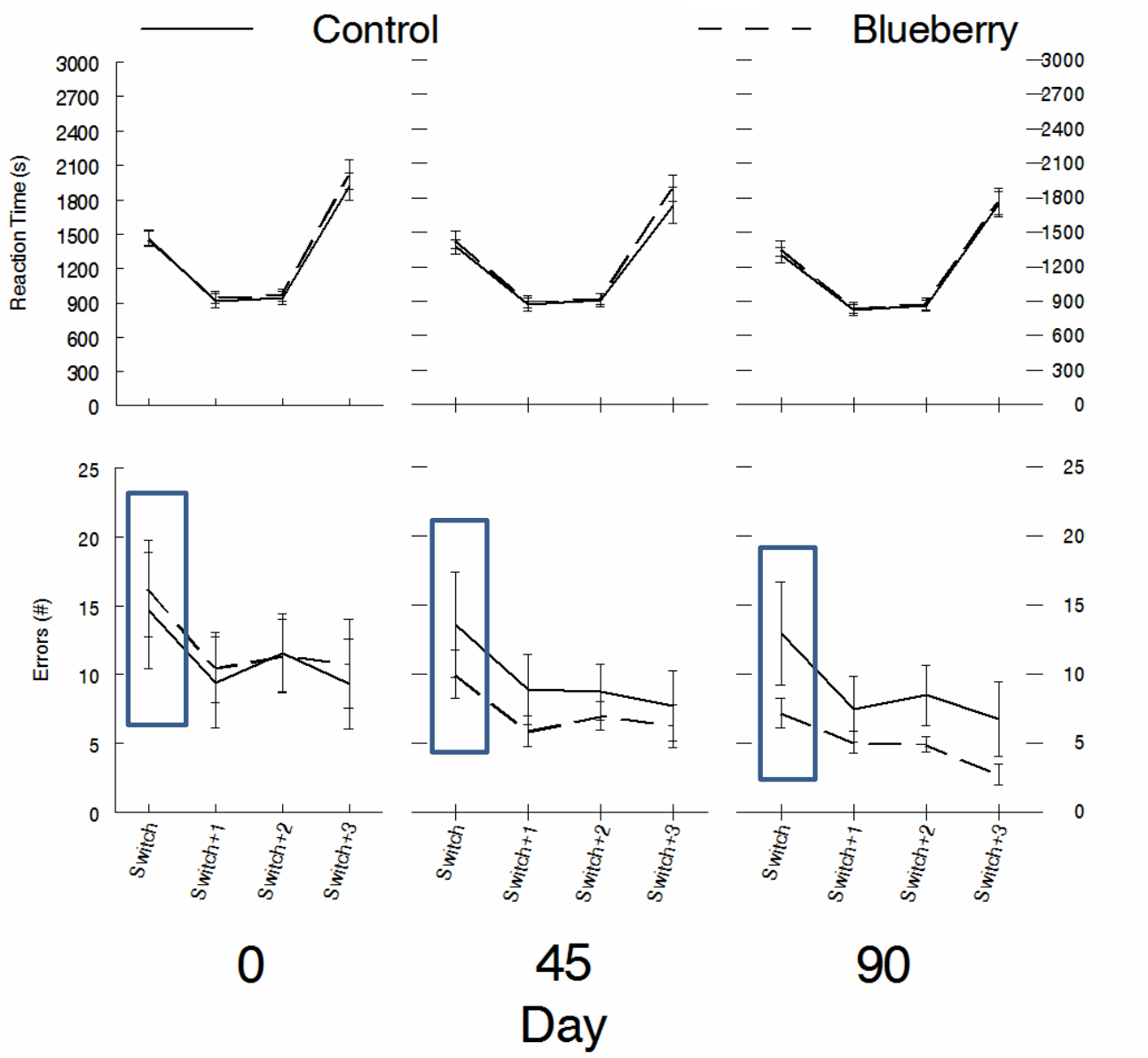
Mobility

- Balance
  - Postural Sway
  - Falls Efficacy Scale
- Gait
  - Gait Speed
  - Gait Variability

Cognition

- Executive Function
  - Attention Network Test
  - Trail-Making Test
  - Task-Switching Test
- Learning & Memory
  - Digit Span
  - Virtual Morris Water Maze
  - California Verbal Learning Test

Mental Flexibility



CA Verbal Learning Test

- Acquisition
- Distractor
- Recall
- Cued Recall

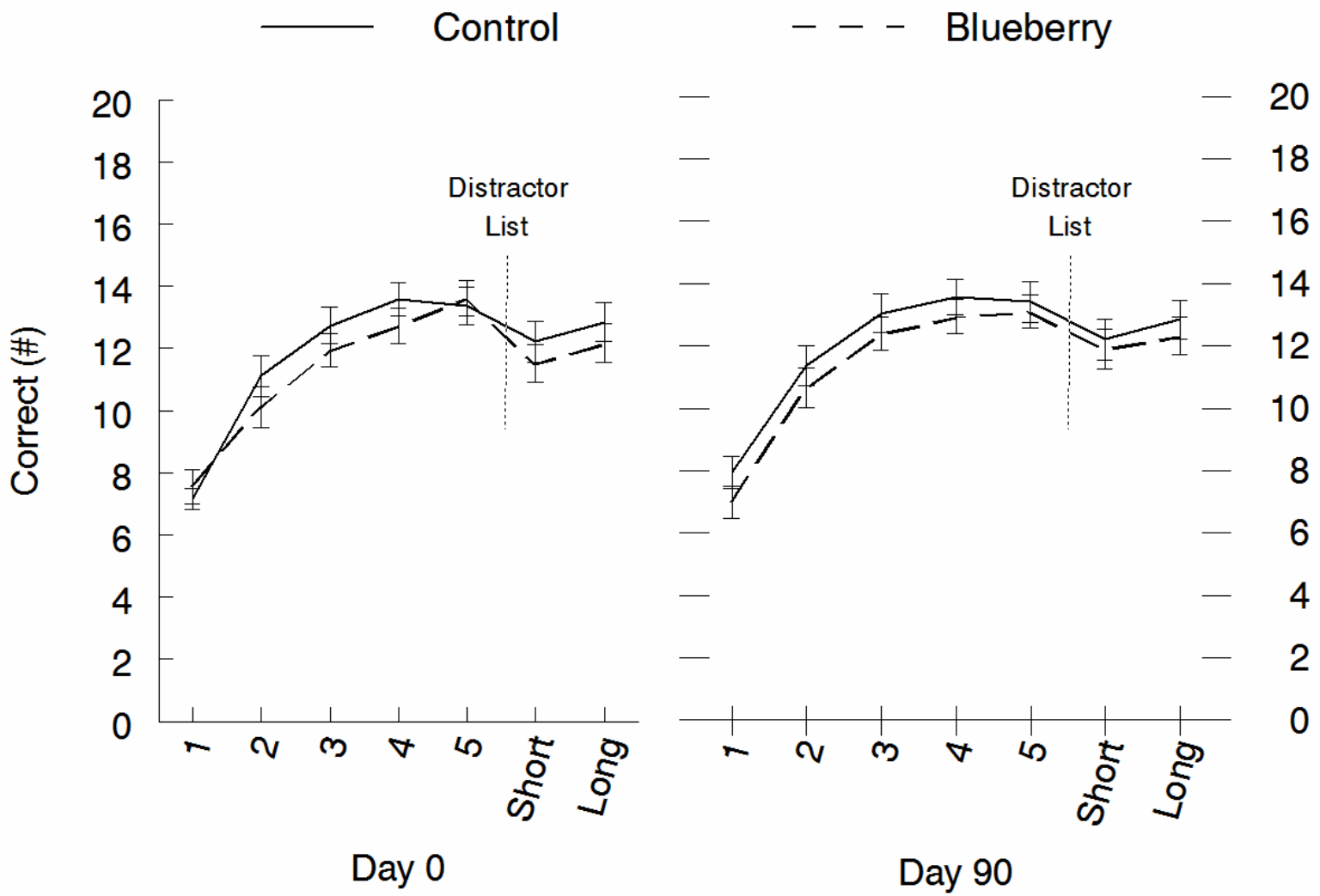
} Short Delay

- 20 min delay
- Recall
- Cued Recall

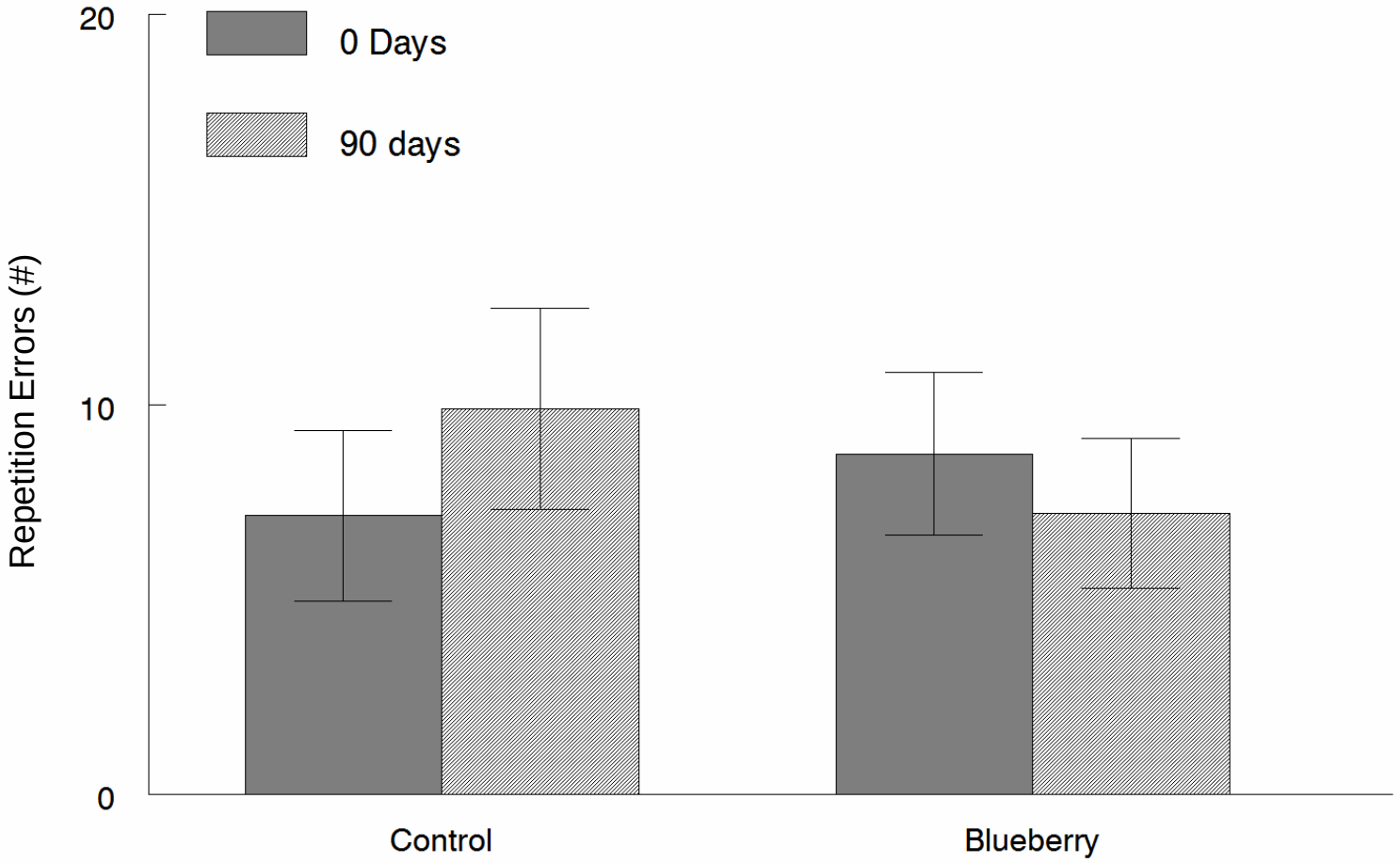
} Long Delay

- Recognition
- 10 min delay
- Forced-Choice Recognition

CVLT: Free Recall



Response Monitoring/Inhibition



Interaction: $p = 0.032$

Blueberry Study Conclusions

- Blueberry improved measures of executive function.
- Both measures have been associated with prefrontal cortex function.
- Prefrontal cortex particularly vulnerable to age-related degeneration.

Miller, et al. *Euro. J. Nutr*. 2018; 57: 1169-1180

Cognition

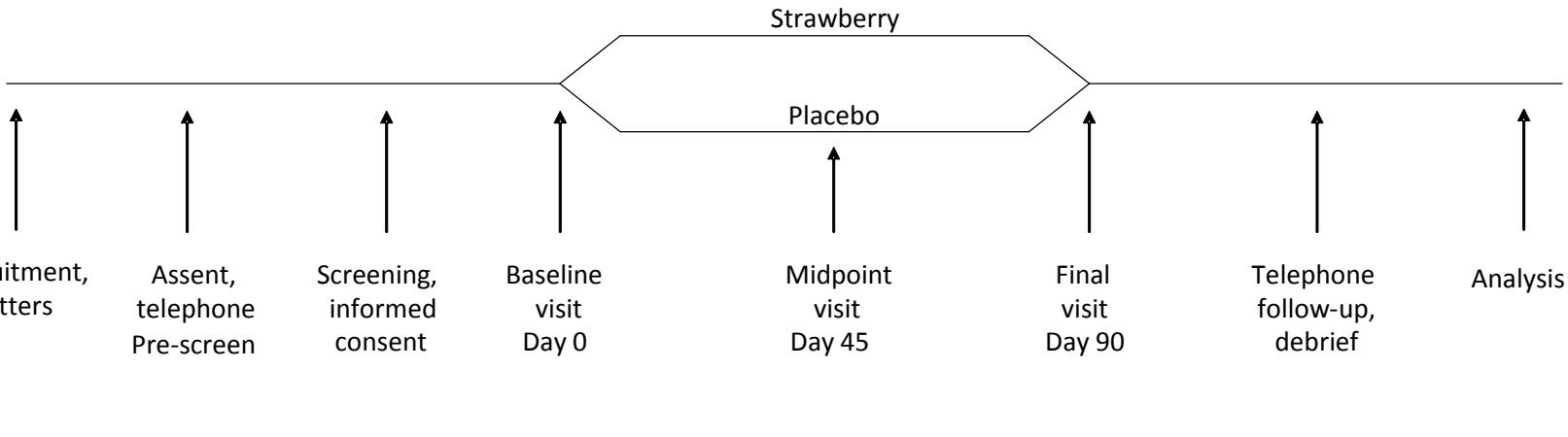
Will dietary strawberry improve mobility and cognition among older adults?

Balance

Gait

Strawberry Intervention Study

- Population: Healthy older adults, age 60-75 years
- Intervention: freeze dried strawberry or placebo, powder ≈2c/day fresh strawberries, 3 mo, abstinence from berry fruit consumption



Outcome Measures

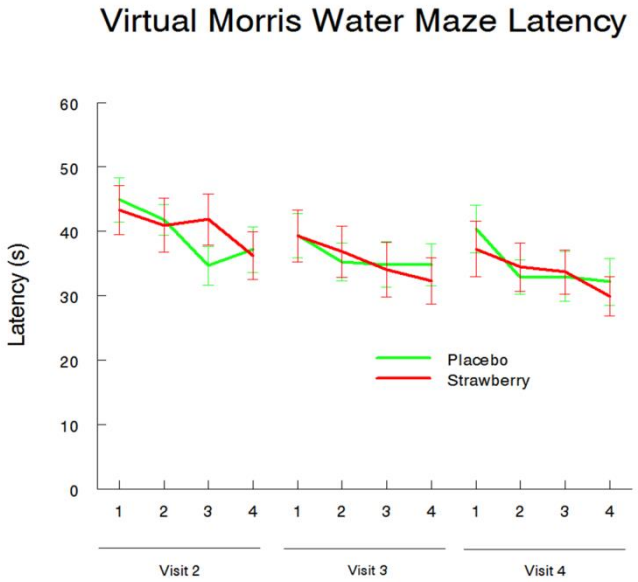
Mobility

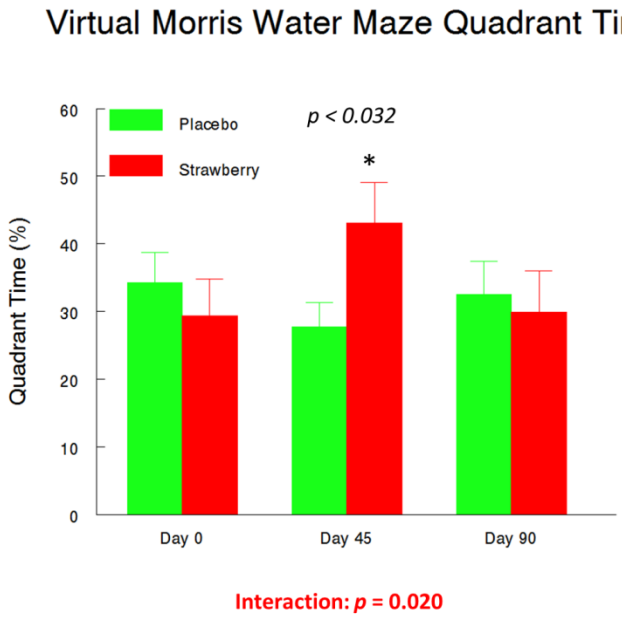
- Balance
  - Postural Sway
  - Falls Efficacy Scale
- Gait
  - Gait Speed
  - Gait Variability

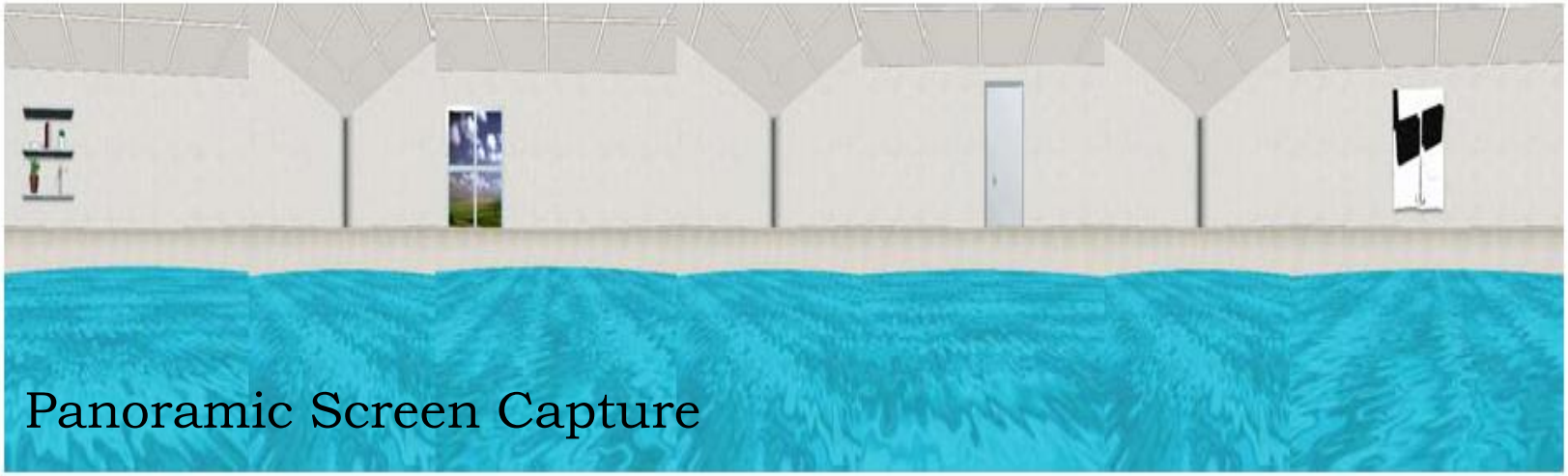
Cognition

- Executive Function
  - Attention Network Test
  - Trail-Making Test
  - Task-Switching Test
- Learning & Memory
  - Digit Span
  - Virtual Morris Water Maze
  - California Verbal Learning Test

Spatial Memory

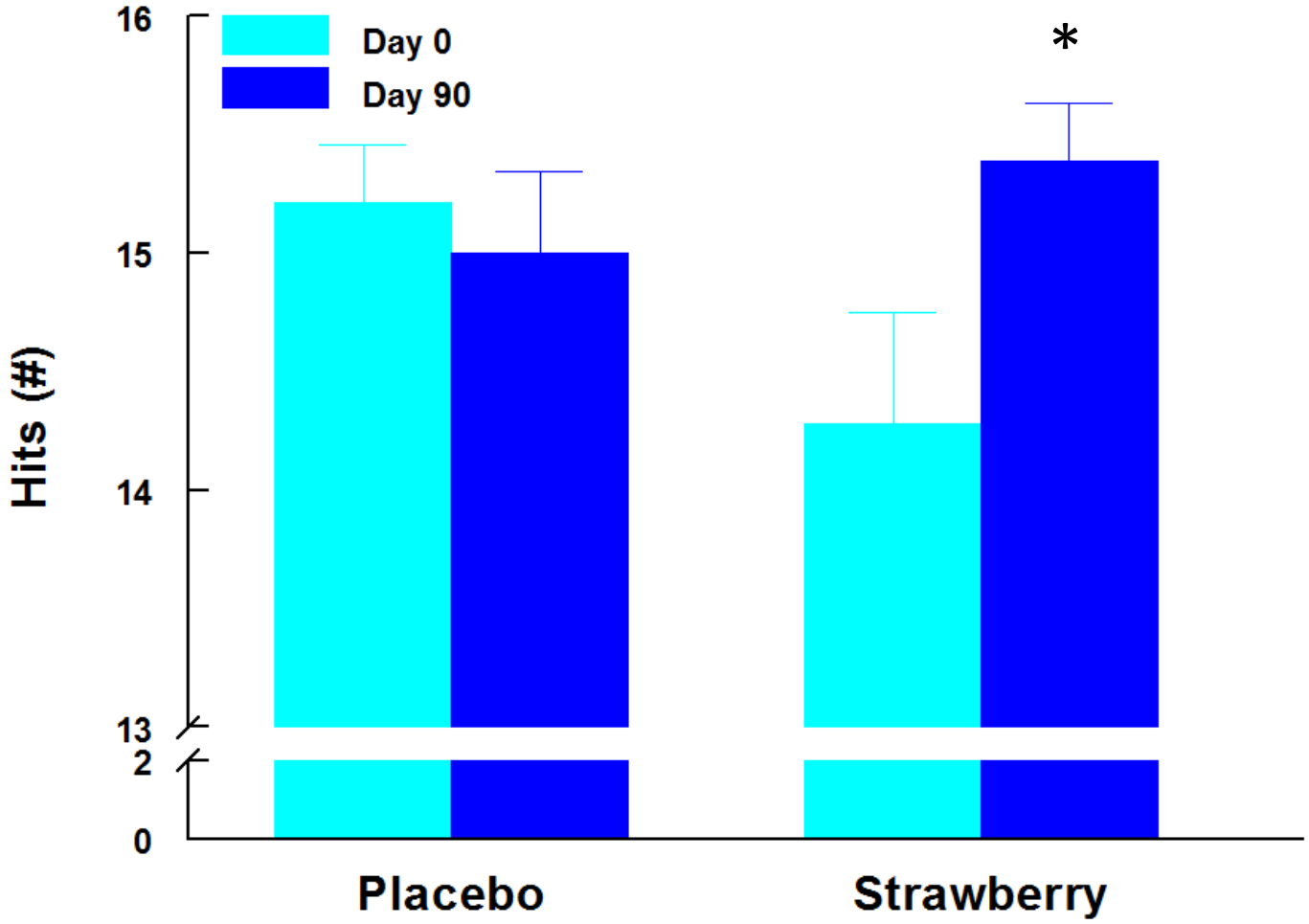






** Denotes p < 0.05, error bars denote SEM.*

WORD RECOGNITION
California Verbal Learning Test Hits



Interaction: p = 0.014

Strawberry Study Conclusions

- Strawberry improved measures of spatial and recognition memory.
- Both measures have been associated with the function of the hippocampal and adjacent brain regions.
- The hippocampus is also particularly vulnerable to age-related degeneration.

Miller, et al. *Brit. J. Nutr*. 2020; under review.

Conclusions

- Functional declines in mobility and cognition are key features of aging in humans and rodents.
- Easily achievable quantities of berry fruit can improve some aspects of cognition in healthy older adults.
- Effects on some measures of mobility and cognition may not have been detected due to the healthiness of the sample.
- Different berry fruit can improve different aspects of cognition.

  Shukitt-Hale, et al., *Neurobiol Aging*. 2007;28:1187-94
- Dietary blueberry did not alter levels of circulating inflammatory biomarkers. However, serum from older adults that consumed blueberry reduced LPS-induced inflammatory-stress-mediated signals in stressed HAPI microglia *in vitro*.

  Rutledge, et al. *Food Funct.* 2019; 10: 7707-7713

What Cognitive Domains are Improved?

Cognitive demand seems critical!

- Executive Function/Attention
  - Response inhibition
  - Response interference
- Learning and Memory
  - Word recall
  - Recognition memory
  - Spatial working memory
- Processing Speed
  - Reaction time

Possible Mechanisms in the Beneficial Effects of the Polyphenolics

- Functional antioxidant/anti-inflammatory effects
  - •Decreased sensitivity to oxidative stress
  - •Decreased sensitivity to neurotoxins and inflammatory agents
- Direct effects on the brain
  - •Increased calcium clearance
  - •Membrane effects
  - •Alterations in signaling
    - Decreased oxidative stress/inflammatory signaling
    - Increased protective signaling
    - Signaling in learning and memory
  - •Increased neurogenesis
  - •Increased arborization
  - •Increased autophagy (natural house-keeping)

Conclusions

- Eating foods, such as berries, may help prevent or reverse age related declines in cognition and brain functioning.
- This may be due to the activity of polyphenols and other components.
- These components may act to inhibit or reduce inflammation and oxidative stress and/or enhance protective mechanisms.
- Whole foods may be more effective in combating oxidative stress and inflammation.

THEREFORE, IN ORDER TO CHOOSE WHAT FOOD YOU SHOULD EAT FOR THOUGHT, YOU SHOULD GIVE SOME THOUGHT TO FOOD.

Neuroscience Lab

B. Shukitt-Hale, Ph.D.

D. Bielinski, Ph.D

D. Fisher, D. Cahoon

G. Rutledge, Ph.D.

Tammy Scott, Ph.D.

Tong Zheng, Ph.D.

Neuroscience Lab (past)

J.A. Joseph, Ph.D.

A.N. Carey, Ph.D., M.G. Miller,

N Thangthaeng, Ph.D.

S.M Poulose, Ph.D., F. Lau, Ph.D.

K. Youdim, Ph.D., G. Casadesus, Ph.D.

L. Willis, Ph.D., A. Martin, MD, Ph.D.

C. Andres-Lacueva, Ph.D.

I. Cantuti-Castelvetri, Ph.D.

R. Galli Ph.D., M. Kelly,

A. Neuman, K. Luskin

A. Szprengiel, H. Stellwagen

L. Simon, V. Cheng,

S. Gomes, F. Ramirez