



# Nutritional Management of Cognitive Dysfunction in Geriatric Dogs





# Nutritional Management of Cognitive Dysfunction in Geriatric Dogs



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# Outline

- Background
  - Relevance
  - Define
  - Symptoms & diagnosis
  - Brain aging
- Nutritional management
  - Functional ingredients and their effectiveness
- Final remarks
- Future research
- Take home message





# Aging Dogs



- Improved nutrition and medical care has increased canine longevity
- U.S. canine population
  - 70 million
- More than 45% is older than 6 y of age
  - 15% →  $\geq 11$  years old



# Aging Dogs

- Average life span of a dog
  - 1930's  $\approx$  7 years old
  - 2000's  $\geq$  12 years old
- Longer life spans mean **increased prevalence of age-related medical conditions**
  - Behavioral and cognitive problems





# Dog Years

*Relative Age of Dogs in Human Years*

<i>Pet's age</i>	1	2	3	4	5	6	7	8	9	10	11	12	13
<b>Mature weight</b>													
0-20 lbs	15	23	28	32	36	40	44	48	52	56	60	64	68
21-50 lbs	15	24	29	34	38	42	47	51	56	60	65	69	74
51-90 lbs	14	22	29	34	40	45	50	55	61	66	72	77	82
> 90 lbs	12	20	28	35	42	49	56	64	71	78	86	93	101

**Growth**

*Table Adapted from Purina – The Aging Rate of Dogs*

**Petfood** Industry **Senior**



# Aging Dogs and Humans

- Aged dogs show a parallel with several aspects of human brain aging
  - Progressive decline in both cognitive and behavioral function
  - Neuropathological changes
    - Alzheimer's disease

*Mongillo et al., 2013. Age (Epub ahead of print)*  
*Head E. 2013. Biochem Biophys Acta. (Epub ahead of print)*



# Aging Dogs and Humans

- Dogs
  - Present a sophisticated repertoire of complex behaviors
  - Share same environment
  - Thrive on similar diet as humans

*Osella et al., 2007. Applied Anim. Behav. Sci. 105: 297-310*  
*Axelsson et al., 2013. Nature. 495: 360-364*





**Canine Cognitive Dysfunction Syndrome (CDS) is described as a **progressive neurodegenerative disorder** of senior dogs, characterized by a **gradual decline in cognitive function** (learning, memory, perception and awareness).**





# CDS in Dog's Population

- **Early effects** of CDS can be seen in **7y** old dogs
- CDS was **more pronounced** in dogs **> 9y**
- 75% of owner of dogs **> 7y**
  - Reported 1 or more signs



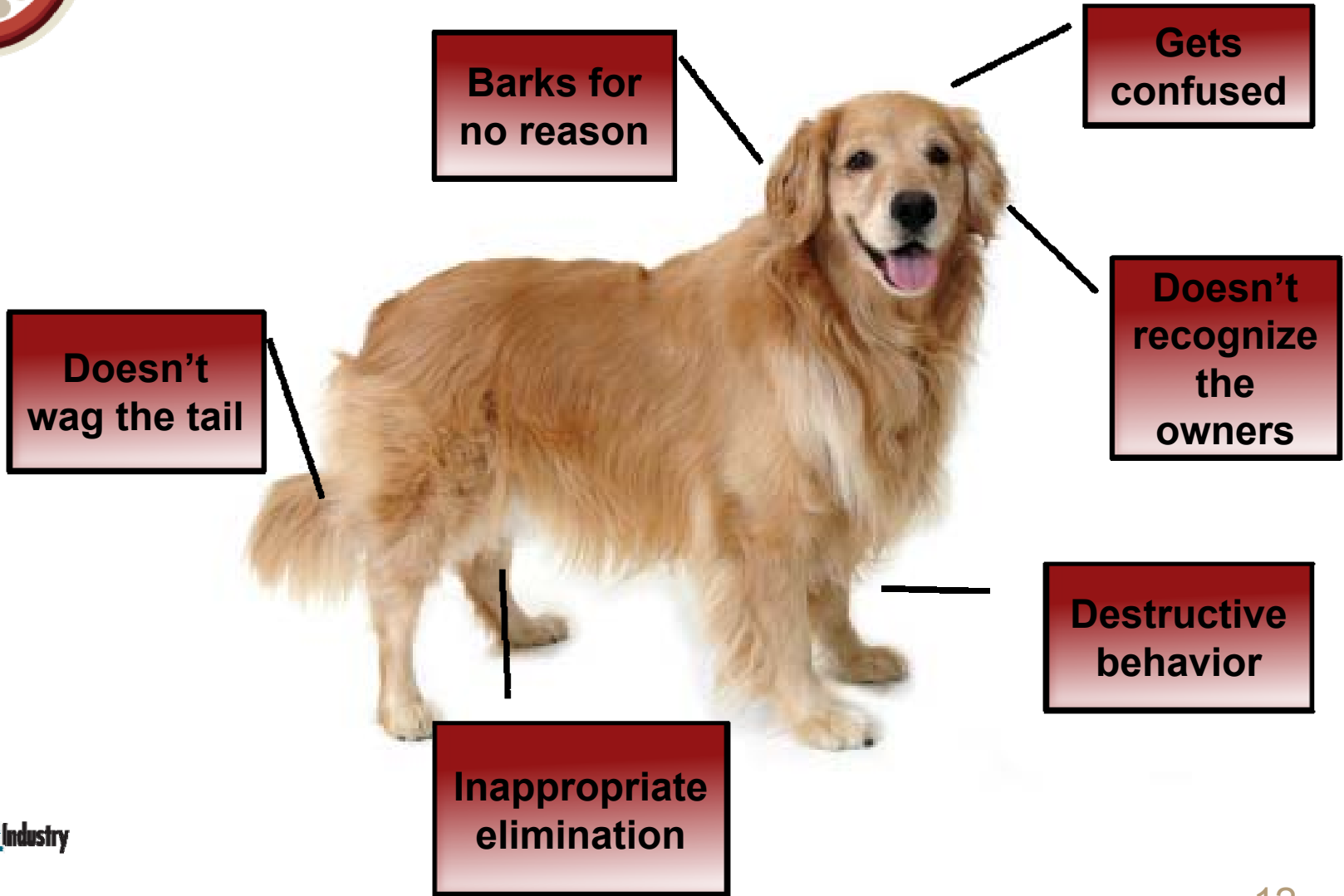


# Symptoms of CDS

- DISHA
  - **D**isorientation
  - Altered **i**nteractions with people/pets
  - **S**leep-wake cycle alterations
  - **H**ouse-soiling
  - Altered **a**ctivity level
- Other symptoms
  - Increased anxiety
  - Altered appetite
  - Decreased responsiveness to stimuli
  - Deficits in learning/memory

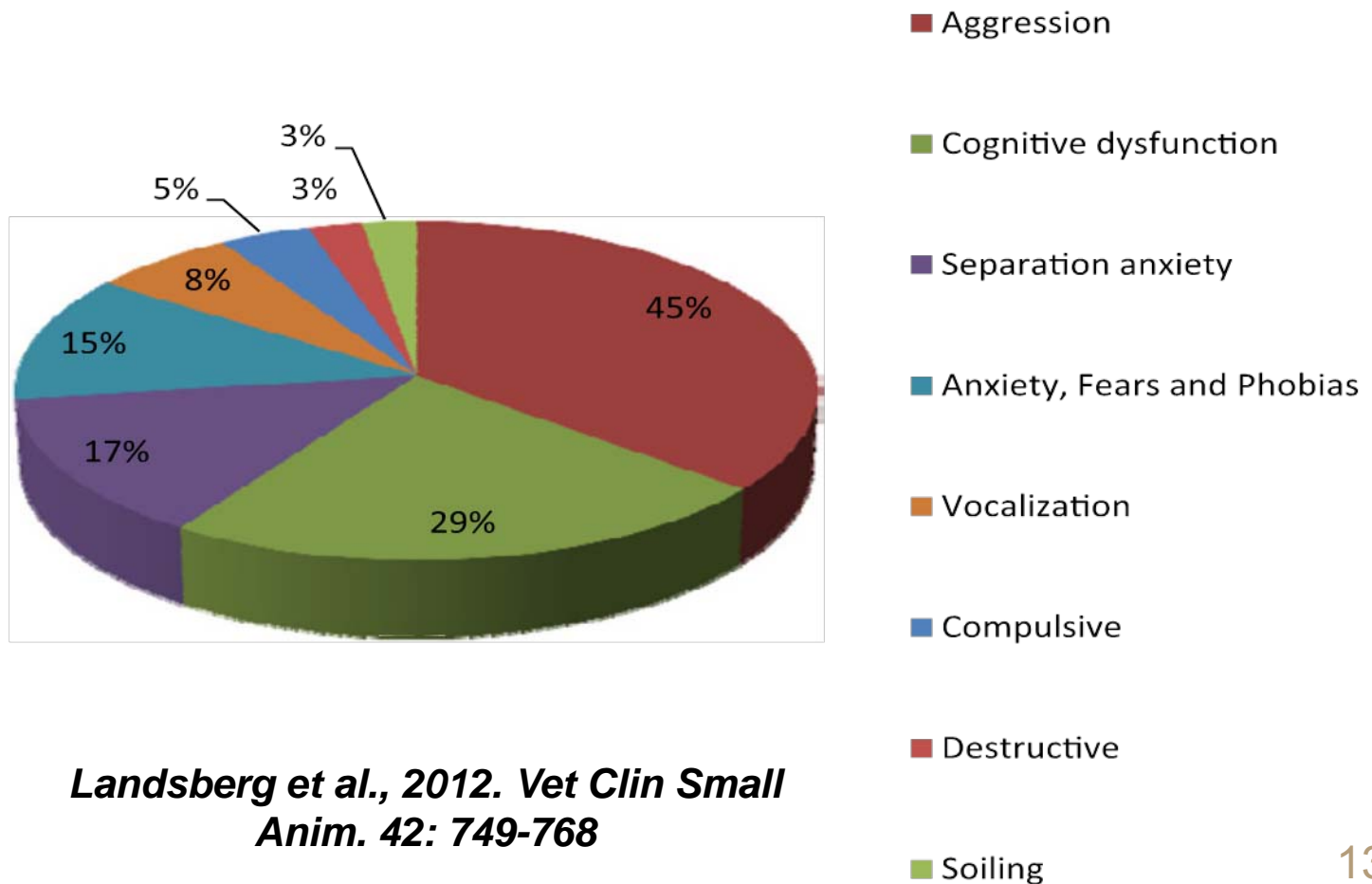


# Symptoms of CDS





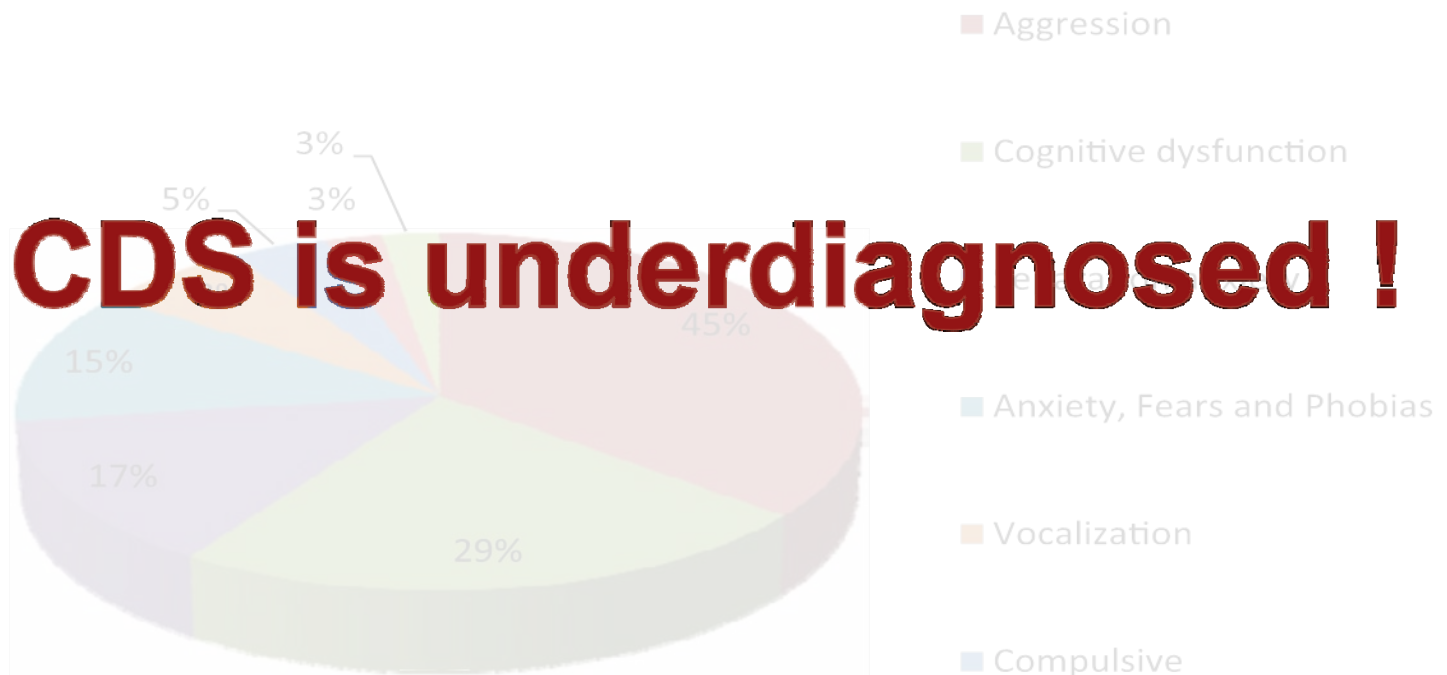
# Prevalence of Owner Reported Signs in Senior Dogs



Landsberg et al., 2012. *Vet Clin Small Anim.* 42: 749-768



# Prevalence of Owner Reported Signs in Senior Dogs





# CDS Diagnosis

- **Owner** observation and reporting still the **main form of detection** of CDS
  - Insensitive to early and subtle changes in learning and memory
  - Subjective: owners are untrained evaluators

*Head and Zicker, 2004. Vet. Clin. Small Anim. 34: 217-228*





# Diagnosis – Vet Clinics

- Identifying the clinical signs
- **Excluding other diseases processes**
  - Behavioral effects of medications
    - Steroids
  - Other medical conditions
    - Pain







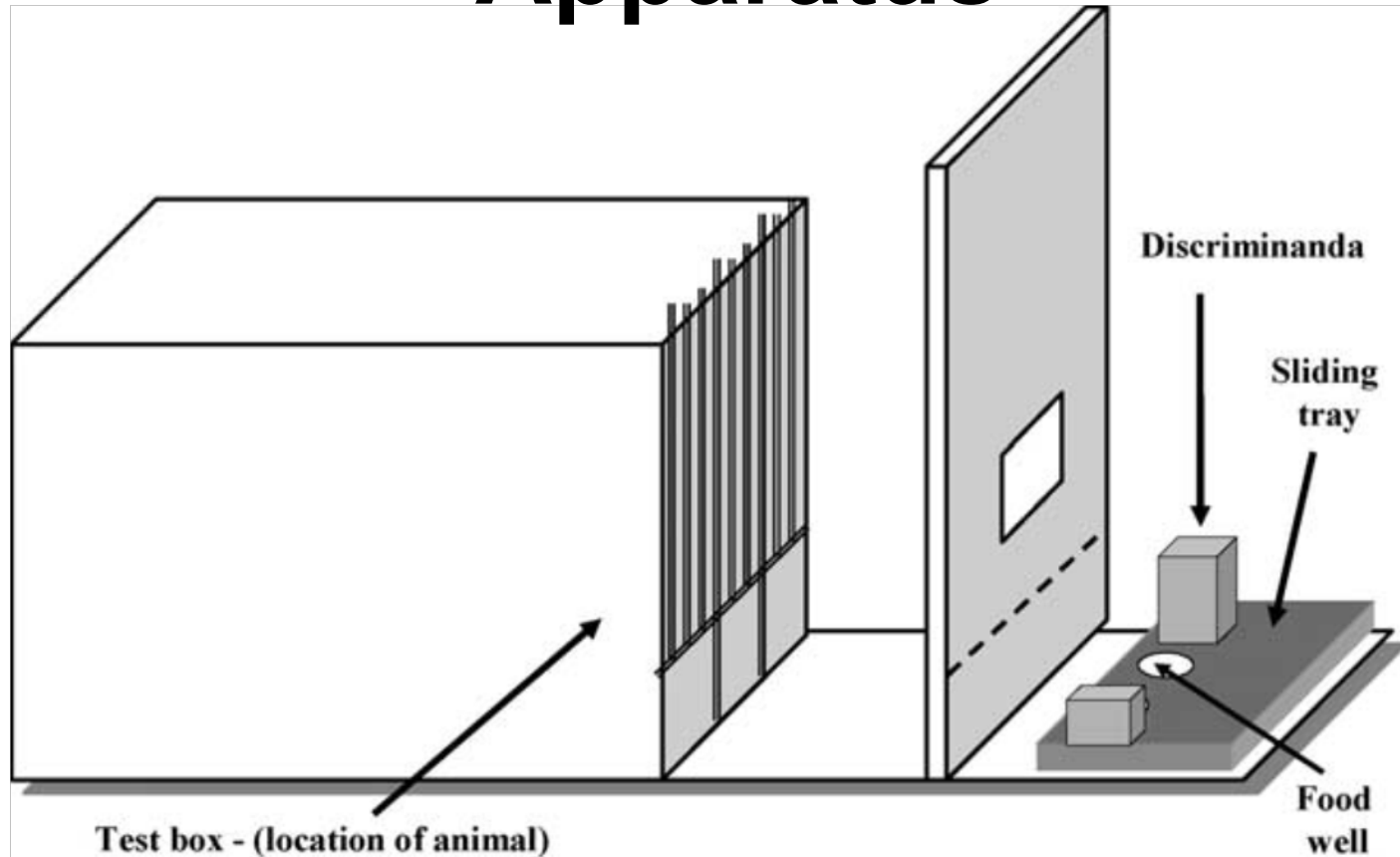
# Diagnosis - Research

- Laboratory **cognitive tasks** are used to verify a decline in performance in older dogs
  - Discrimination learning
  - Reversal learning
  - Landmark discrimination task (LDMT)





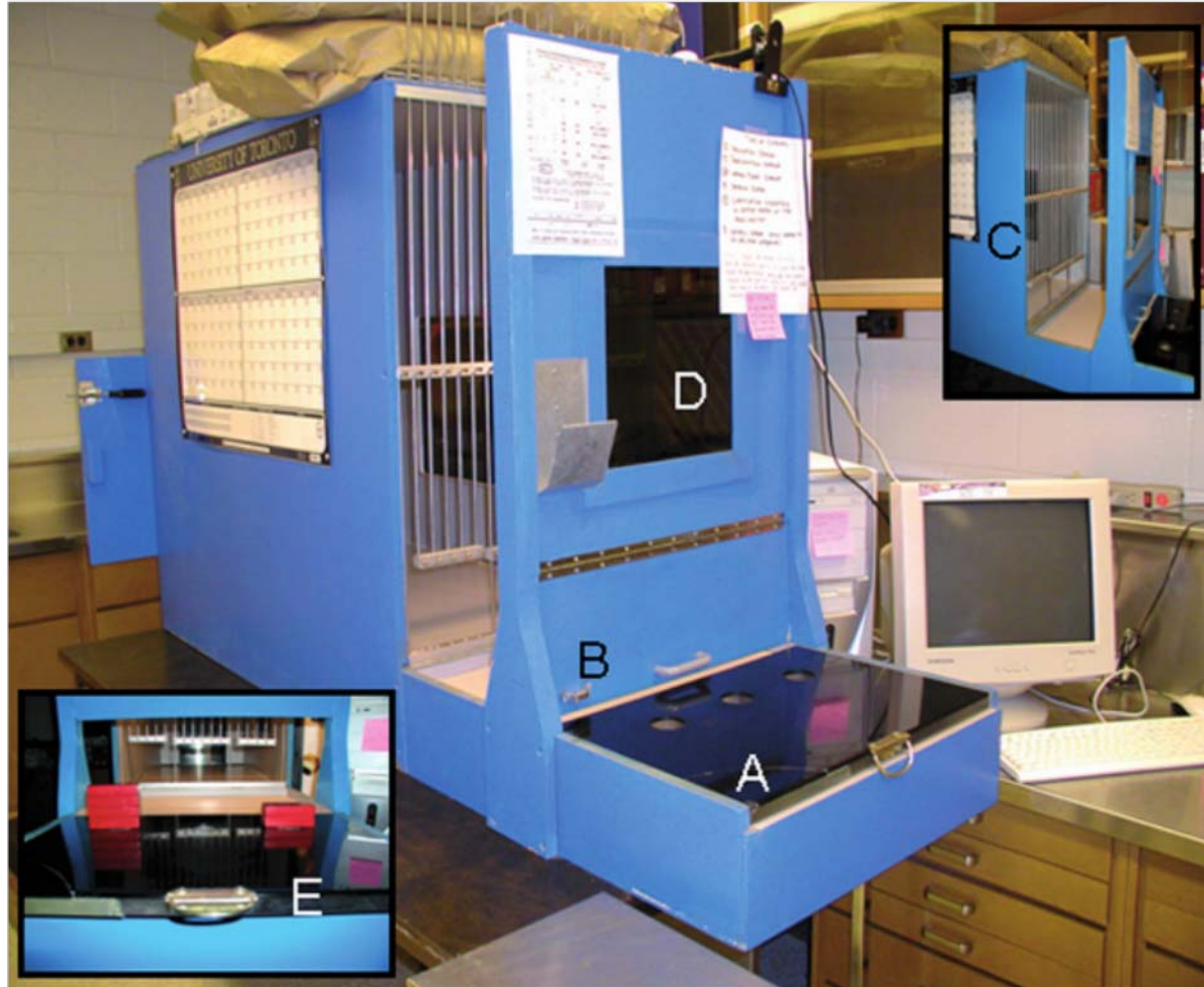
# Toronto General Testing Apparatus



*Milgram et al., 2004. Exp. Gerontol. 39: 753-765*



# Toronto General Testing Apparatus



Petfood Industry

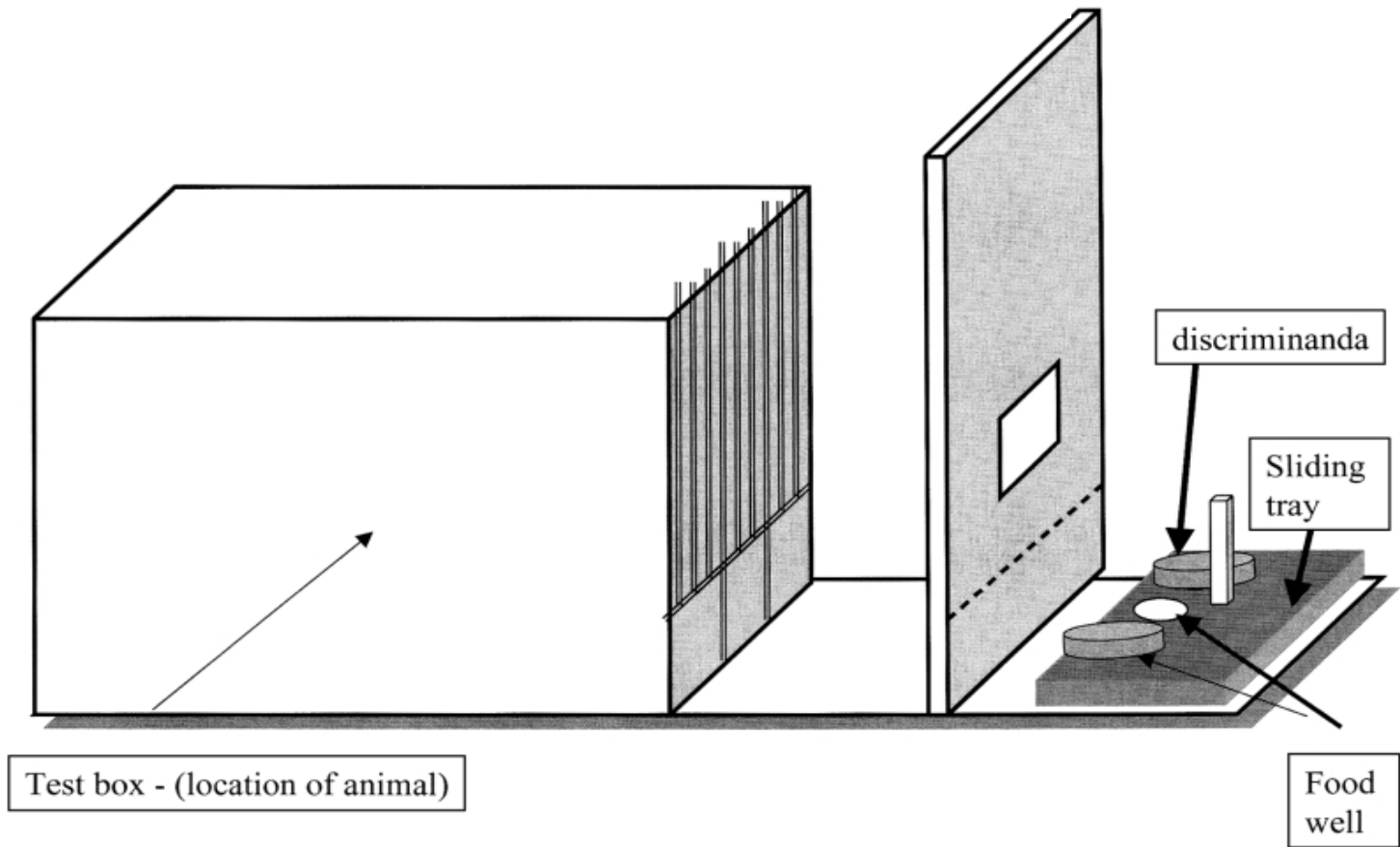
WATT

*Tapp and Tapp, 2009. Non-Primate Models of Normal Brain Aging. 1213-1219*



# Cognitive Testing

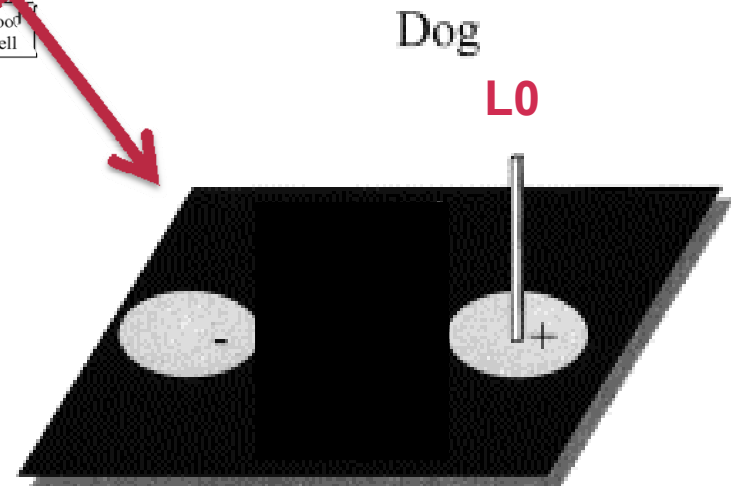
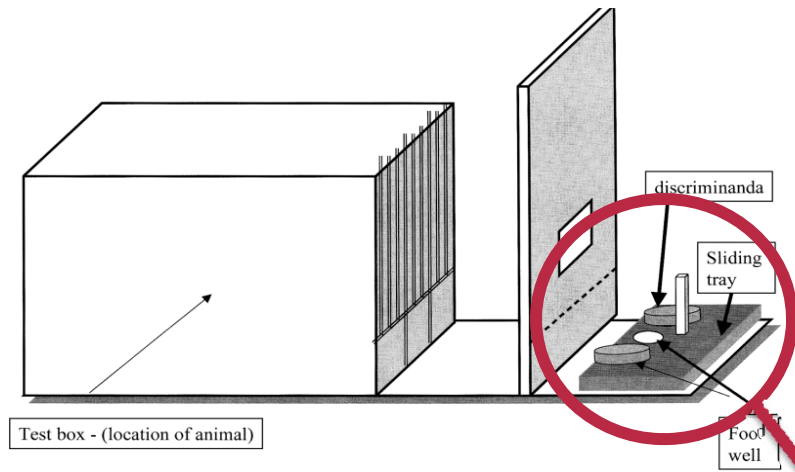
## Landmark Discrimination





# Cognitive Testing

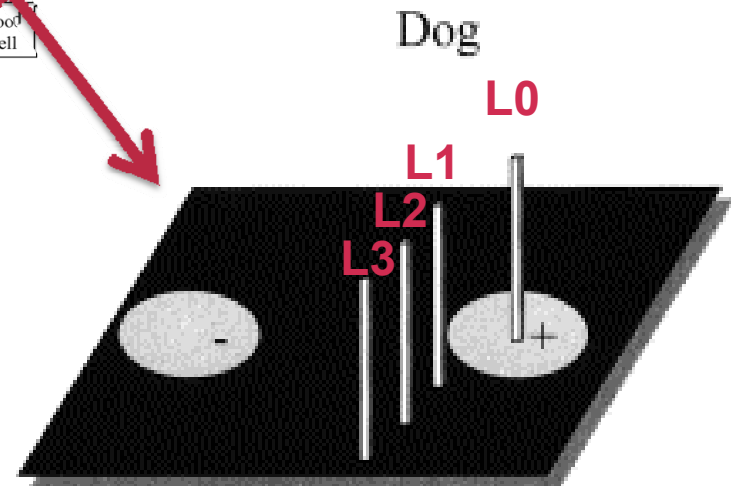
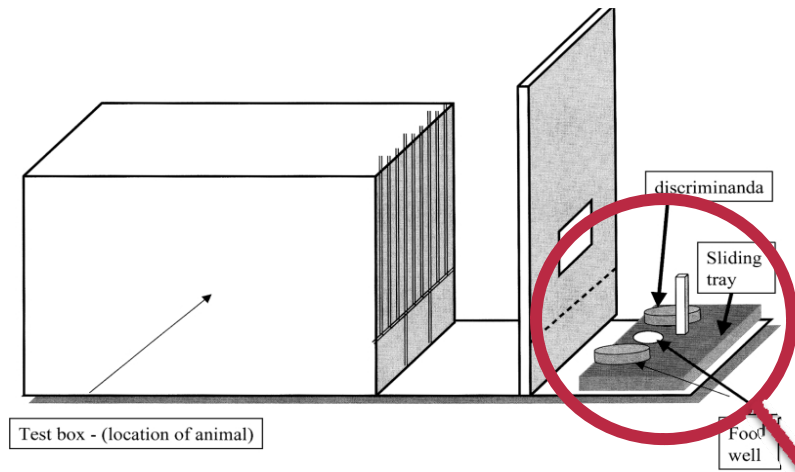
## Landmark Discrimination





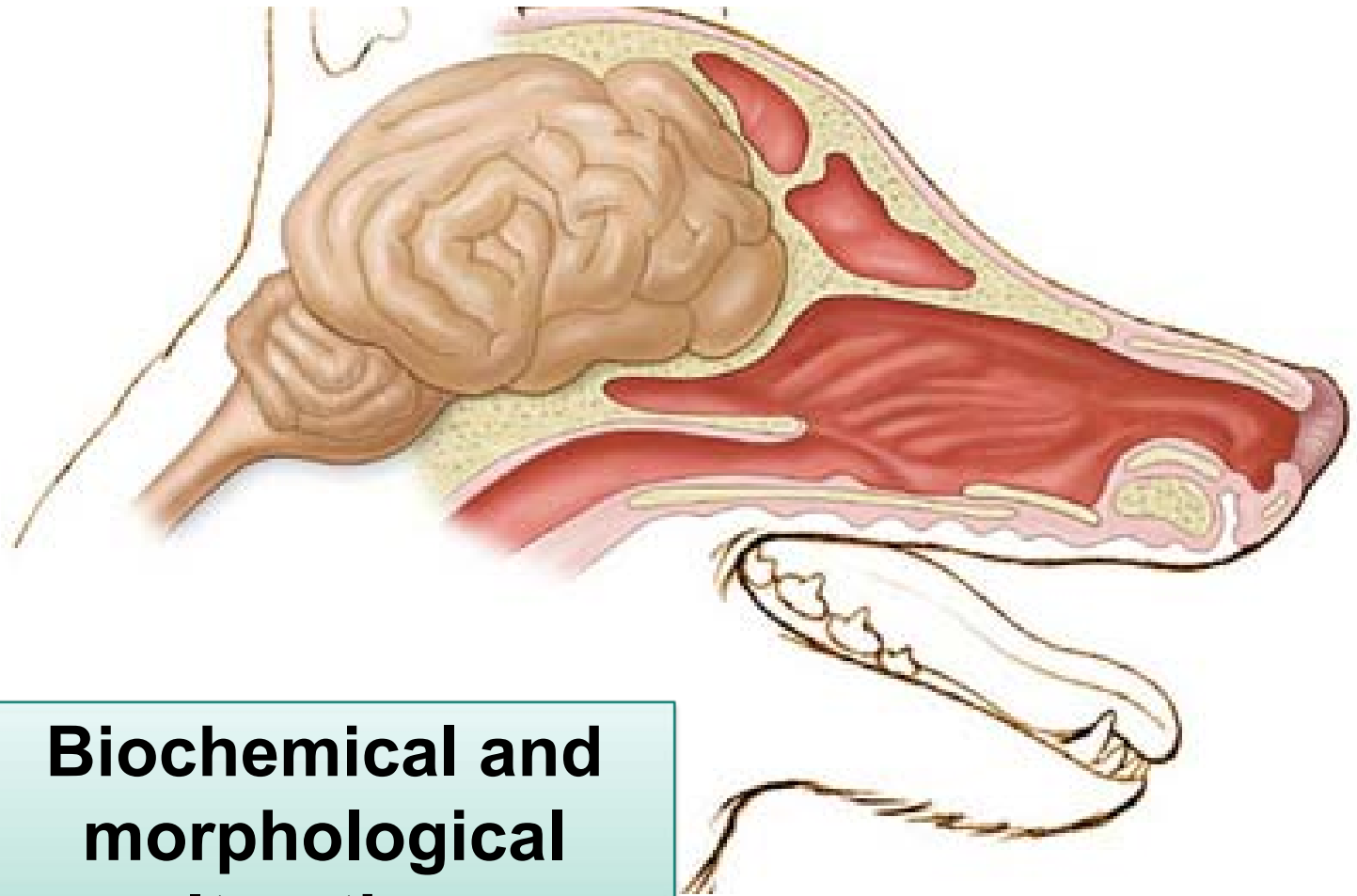
# Cognitive Testing

## Landmark Discrimination





# Brain Aging



**Biochemical and morphological alterations**



# Brain Aging - Biochemical

- Activity of endogenous antioxidants decreases relative to the production free radicals
- Nervous system (NS) is highly susceptible to oxidative stress
  - Iron-lipid rich environment
  - Limited anti-oxidative capacity
  - Highly oxygenated





# Brain Aging - Biochemical

- ↑ Oxidative damage to lipids, proteins, and DNA/ RNA
  - ↑ Malondialdehyde in the canine frontal lobe and serum
  - ↓ Glutamine synthase activity and superoxide dismutase
    - Accumulation of carbonyl groups
  - ↑ Reactive oxygen species (ROS)
    - Damage nervous tissue
    - Impair mitochondrial function

*Head E. 2013. Biochem Biophys Acta. (Epub ahead of print)*



# Brain Aging - Biochemical

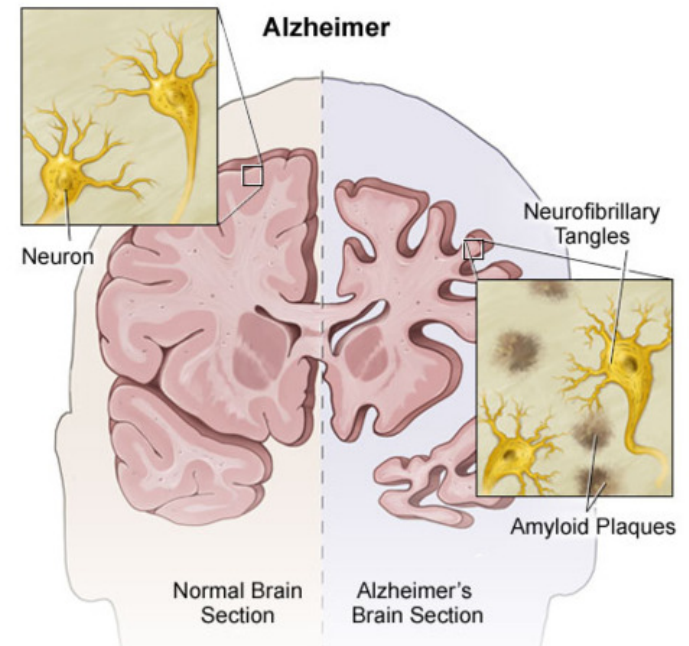
- Increase in monoamine oxidase B (MAOB)
  - An enzyme located in the outer mitochondrial membrane in the CNS
  - ↑ ROS
  - Responsible for the breakdown of neurotransmitter dopamine
    - ↓ in dopamine found to correlate with cognitive and degenerative changes
- Reduction in neurotrophic factors
  - Brain derived neurotrophic factor (BDNF)
  - Nerve growth factor (NGF)

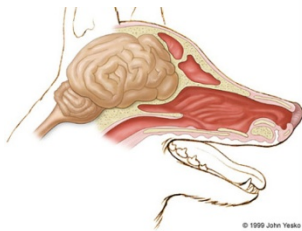
© 1999 John Yesko



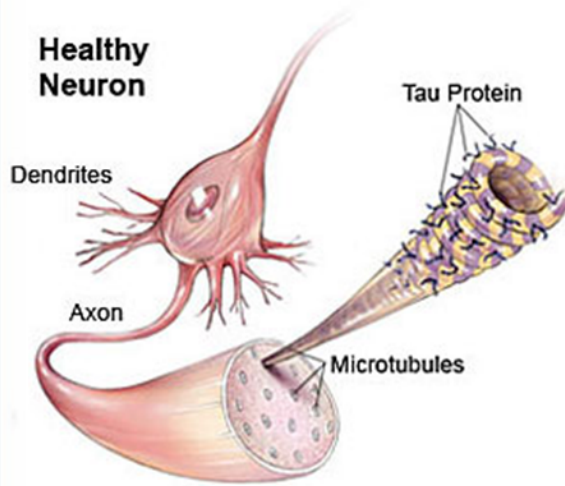
# Brain Aging - Morphology

- Similar to humans
  - Beta-amyloid plaque deposition
  - Hyperphosphorylated tau protein
    - Pre-tangle pathology
- Neurodegeneration
  - Neuron loss
  - Cortical atrophy

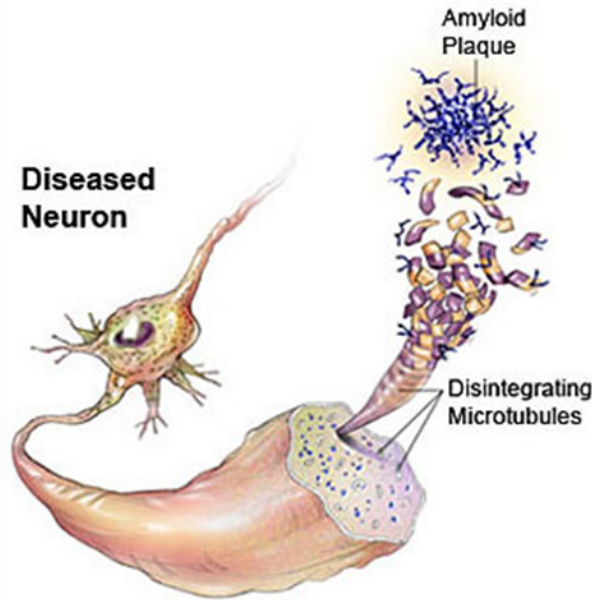




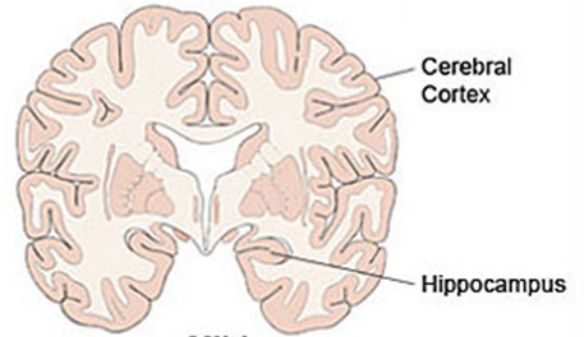
### Healthy Neuron



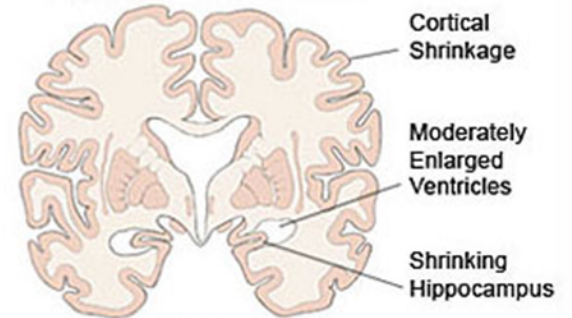
### Diseased Neuron



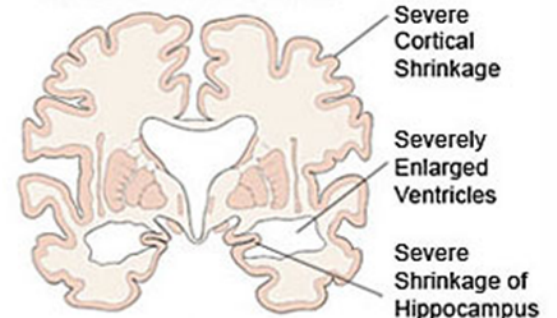
### Healthy Brain



### Mild Alzheimer's Disease



### Severe Alzheimer's Disease





# Nutritional Management of CDS

- Objectives:
  - Prevent the progression or the onset of CDS
  - Ameliorate clinical signs
  - Improve quality of life





# Nutritional Management of CDS

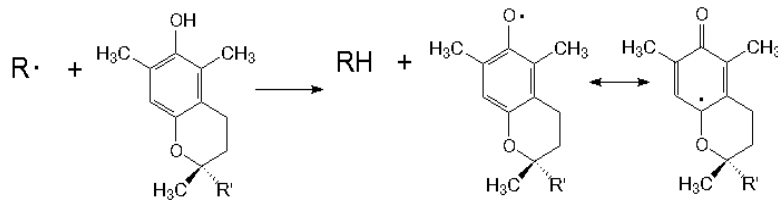
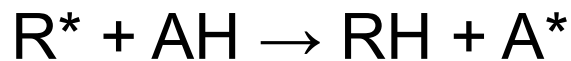
- Antioxidants
- Mitochondrial co-factors
- Branched chain amino acids (BCAA)
- Medium-chain triglycerides (MCT)
- Additional nutraceutical supplements
  - Ginko biloba
  - Phosphatidylserine
  - Pyridoxine (vitamin B6)



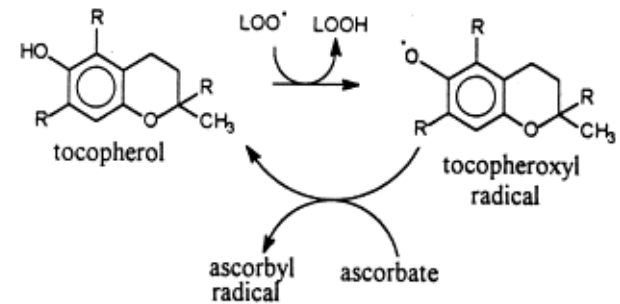
# Nutrition and CDS

- **Antioxidants**

- Control oxidative damage in cells
  - Antioxidants: vitamin E and C



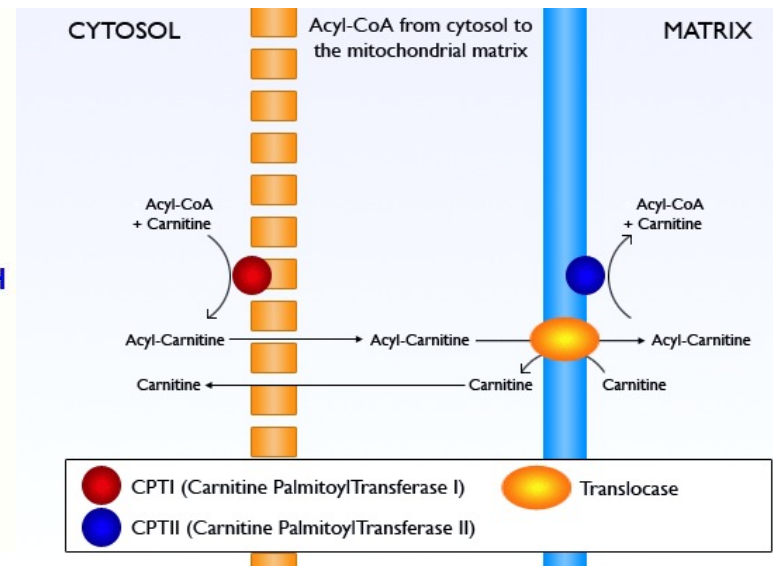
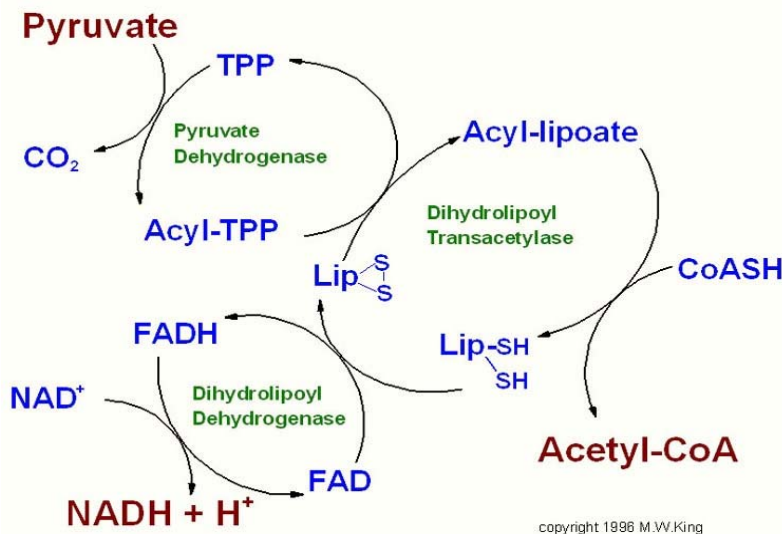
Resonance-stabilized radical





# Nutrition and CDS

- **Mitochondrial co-factors**
  - Antioxidant and mitochondrial function enhancer
    - L-carnitine and lipoic acid







# Flavonoids & Carotenoids

- Substances that come from fruits & vegetables and have **antioxidant properties**
- Sources
  - Spinach flakes
  - Tomato pomace
  - Grape pomace
  - Carrots granules
  - Citrus pulp





# Effect of Diet and Age

- Dogs
  - Older dogs (8-12y; n=24)
  - Young dogs (2-4.5y; n=17)
- 4 progressive degrees of complexity of LMDT
  - L0 = landmark was on the top of coaster
  - L1, L4, L10 = landmark was 1, 4 and 10 cm away from reward object



# Antioxidant Supplementation

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## Antioxidant Enriched Diet

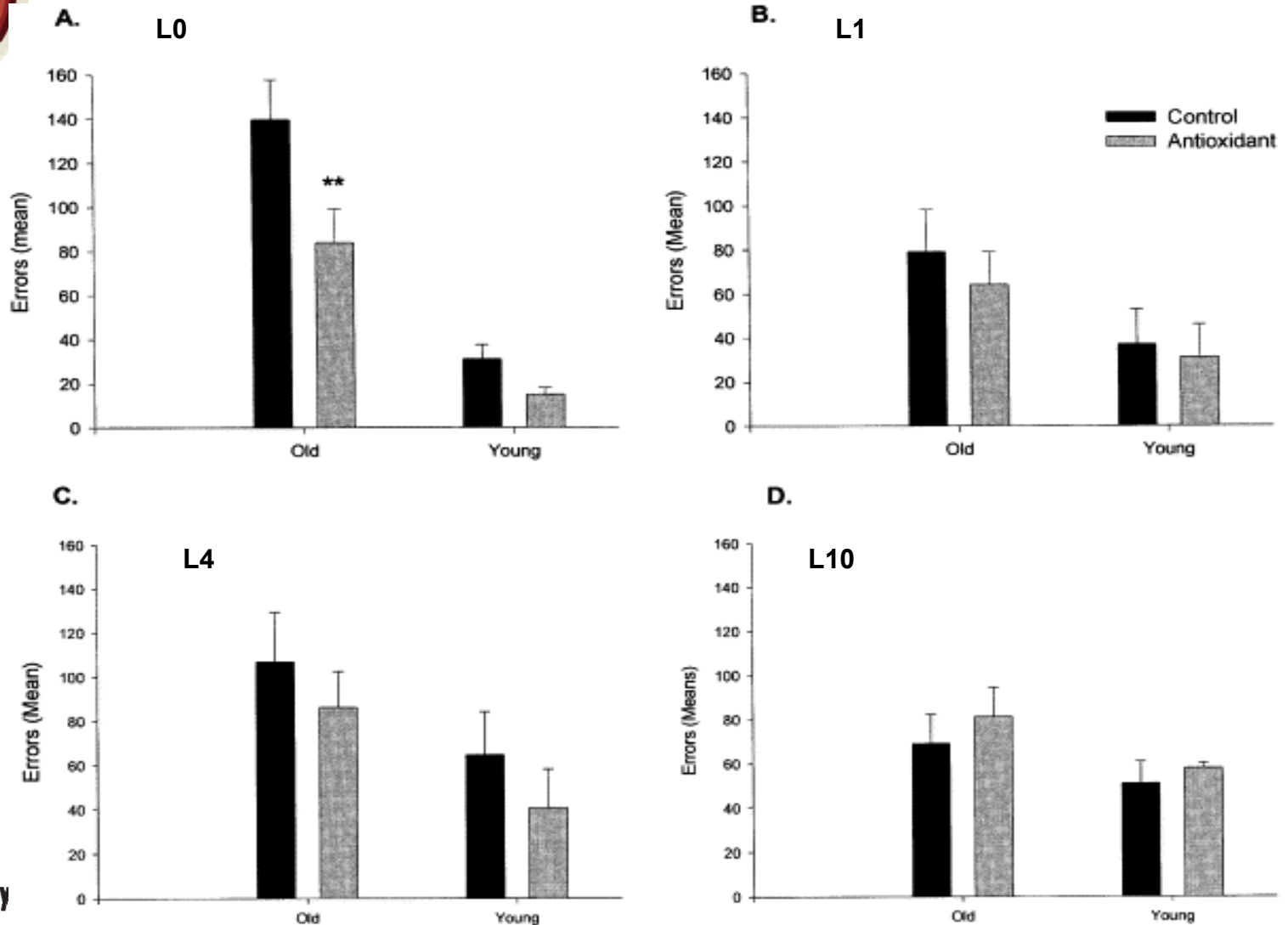
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<i>Components (DM basis)</i>	<i>Amounts</i>
L-carnitine	300 ppm
DL- $\alpha$ -lipoic acid	150 ppm
DL- $\alpha$ -tocopherol acetate	1550 ppm
Vitamin C	100 ppm
<i>Inclusion at expense of corn (1:1)</i>	
Spinach Flakes	1%
Tomato pomace	1%
Grape pomace	1%
Carrot granules	1%
Citrus pulp	1%

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# Effect of Diet Within Age Group





# Effect of Gradient Levels of Antioxidants in Cognitive Function

Constituent	Low-Antioxidant	Moderate-Antioxidant	High-Antioxidant
Moisture (%)	9.5	8.0	8.0
Protein (%)	22.4	19.0	19.1
Fat (%)	10.4	13.9	14.2
Fiber (%)	3.6	2.8	3.0
Ash (%)	7.3	4.0	4.1
Calcium (%)	1.6	0.6	0.6
Phosphorus (%)	1.2	0.6	0.6
Vitamin E (ppm)	83	173	799
Vitamin C (ppm)	<32	<32	114
L-carnitine (ppm)	13	42	294
Lipoic acid (ppm)	<20	<20	135

*Ikeda- Douglas et al., 2004. Veterinary Therapeutics. 5: 5-16*



# Antioxidant Supplementation Increased Serum Vitamin E Concentration

Variable	Days after Food Change	Serum Vitamin E Concentration ( $\mu\text{g/ml}$ )		
		Low Antioxidant	Moderate Antioxidant	High- Complex Antioxidant
Before vitamin E supplement	0	18.2	18.3	16.5
After vitamin E supplement	90	17.9 <sup>a</sup>	23.8 <sup>b</sup>	37.0 <sup>c</sup>
Change*		-0.3 <sup>a</sup>	5.5 <sup>b</sup>	20.5 <sup>c</sup>

a, b, c Values within a row having different superscripts are significantly different (  $P < .05$  )

\*Change = Value after vitamin E – Value before vitamin E



# Antioxidant Supplementation Improved Cognitive Function

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Landmark Study	Low-Antioxidant Food	Moderate-Antioxidant Food	High – Complex Antioxidant Food
0	28.9	49.2	59.5
1	93.8 <sup>a</sup>	50.9 <sup>b</sup>	30.2 <sup>b</sup>
2	75.7 <sup>a</sup>	49.1 <sup>b</sup>	34.9 <sup>b</sup>
1 + 2	169.5 <sup>a</sup>	100.0 <sup>b</sup>	65.1 <sup>c</sup>

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<sup>a, b, c</sup> Group means within a landmark task (row) having different superscripts are significantly different using serum vitamin E as a covariate (P < .05)

*Ikeda- Douglas et al., 2004. Veterinary Therapeutics. 5: 5-16*

# Effect of Diet and Environment



- Dogs
  - Older dogs (10 y; n=23)
- Antioxidant supplementation and environmental enrichment
  - Improve cognitive function
- Brain derived neurotrophic factor mRNA expression
- Cognitive task performance
  - Delayed non-matching to position





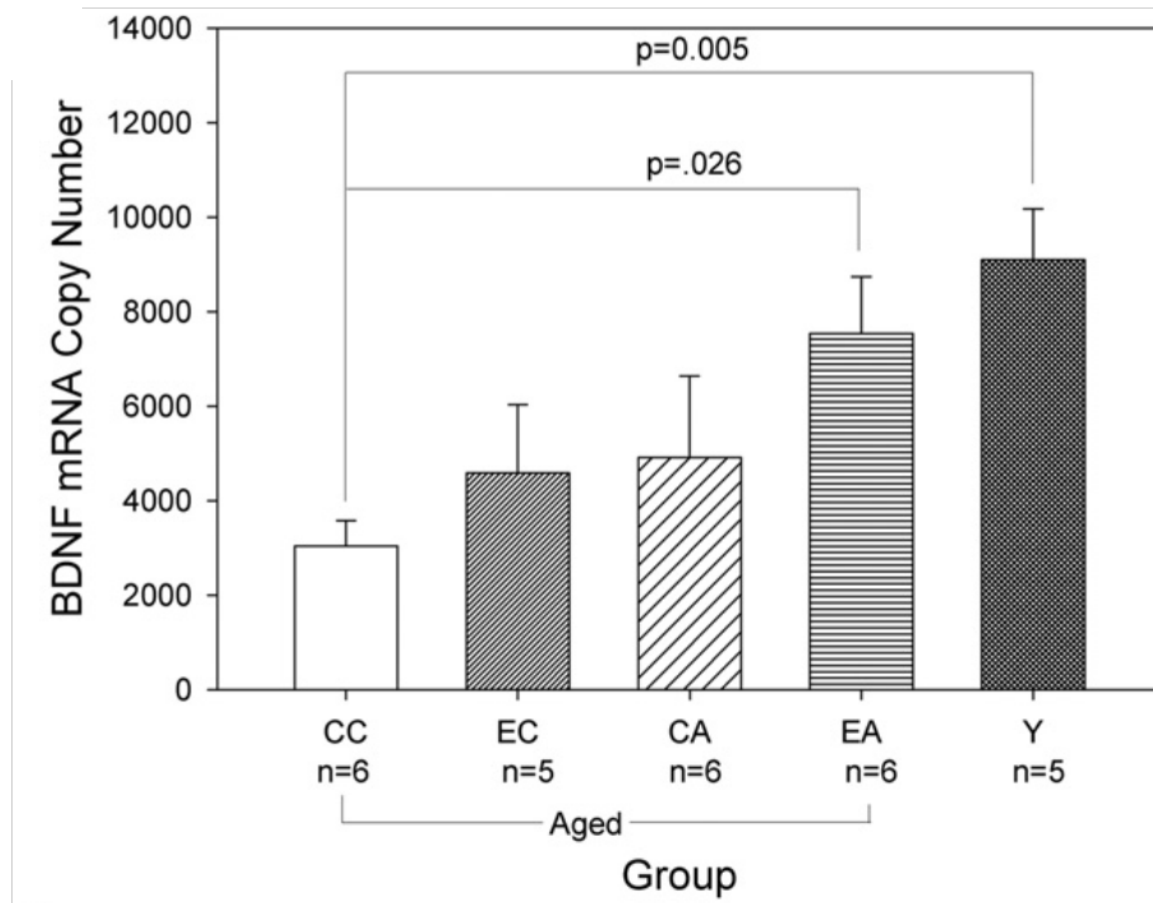
# Antioxidant Supplementation

<b>Dietary Treatments</b>		
	<b>Control</b>	<b>Enriched</b>
<i>Components (as is basis)</i>		
L-carnitine	20	260 ppm
DL- $\alpha$ -lipoic acid	20	128 ppm
DL- $\alpha$ -tocopherol acetate	120	1050 ppm
Vitamin C	30	80 ppm
<i>Inclusion at expense of corn (1:1)</i>		
Spinach Flakes	-	1%
Tomato pomace	-	1%
Grape pomace	-	1%
Carrot granules	-	1%
Citrus pulp	-	1%

*Fahnestock et al., 2012. Neurobiol. Aging. 33: 546-554*

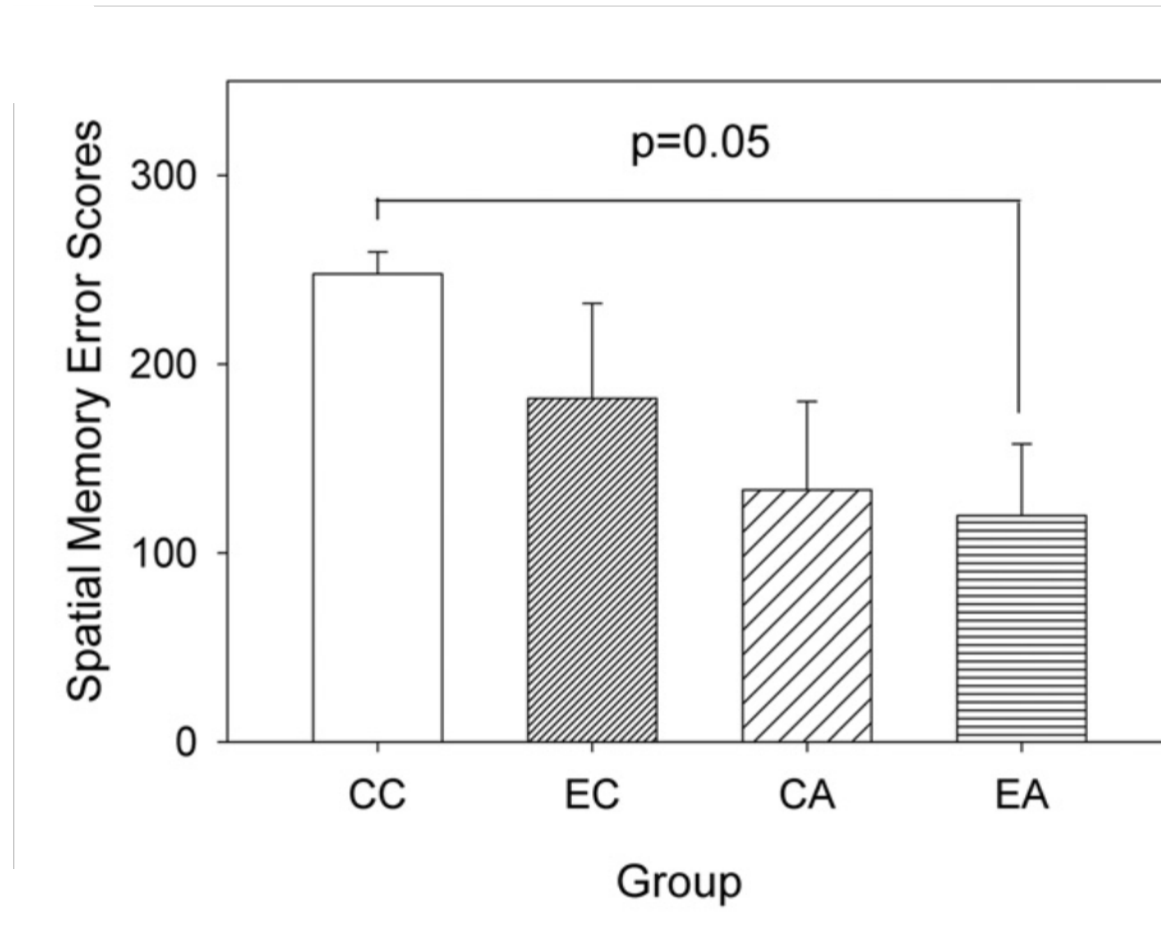


# Antioxidant Diet and Enriched Environment Increased BDNF mRNA





# Antioxidant Diet and Enriched Environment Improved Spatial Memory



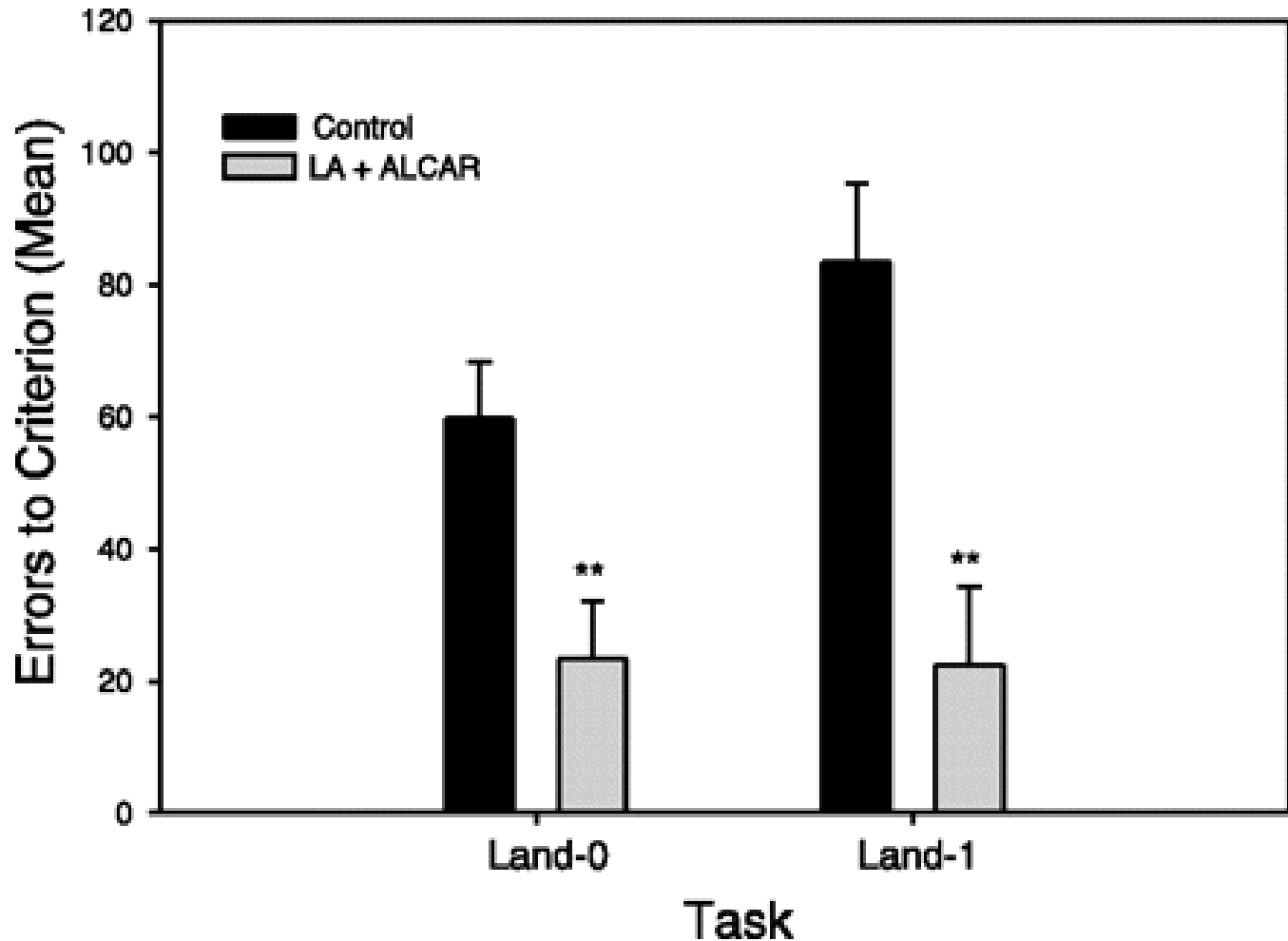


# Lipoic Acid and L-Carnitine

- 12 senior beagles (ave. 8y)
- 2 treatment groups
  - Control
  - Lipoic acid (110 ppm) + L-carnitine (275 ppm)
    - 2 mo period
- Landmark discrimination task
  - L-0
  - L-1 (visual cue was placed 1 cm away from the object)



# Improvement in Cognition



Milgram et al., 2007. *FASEB J.* 21: 3756-3762

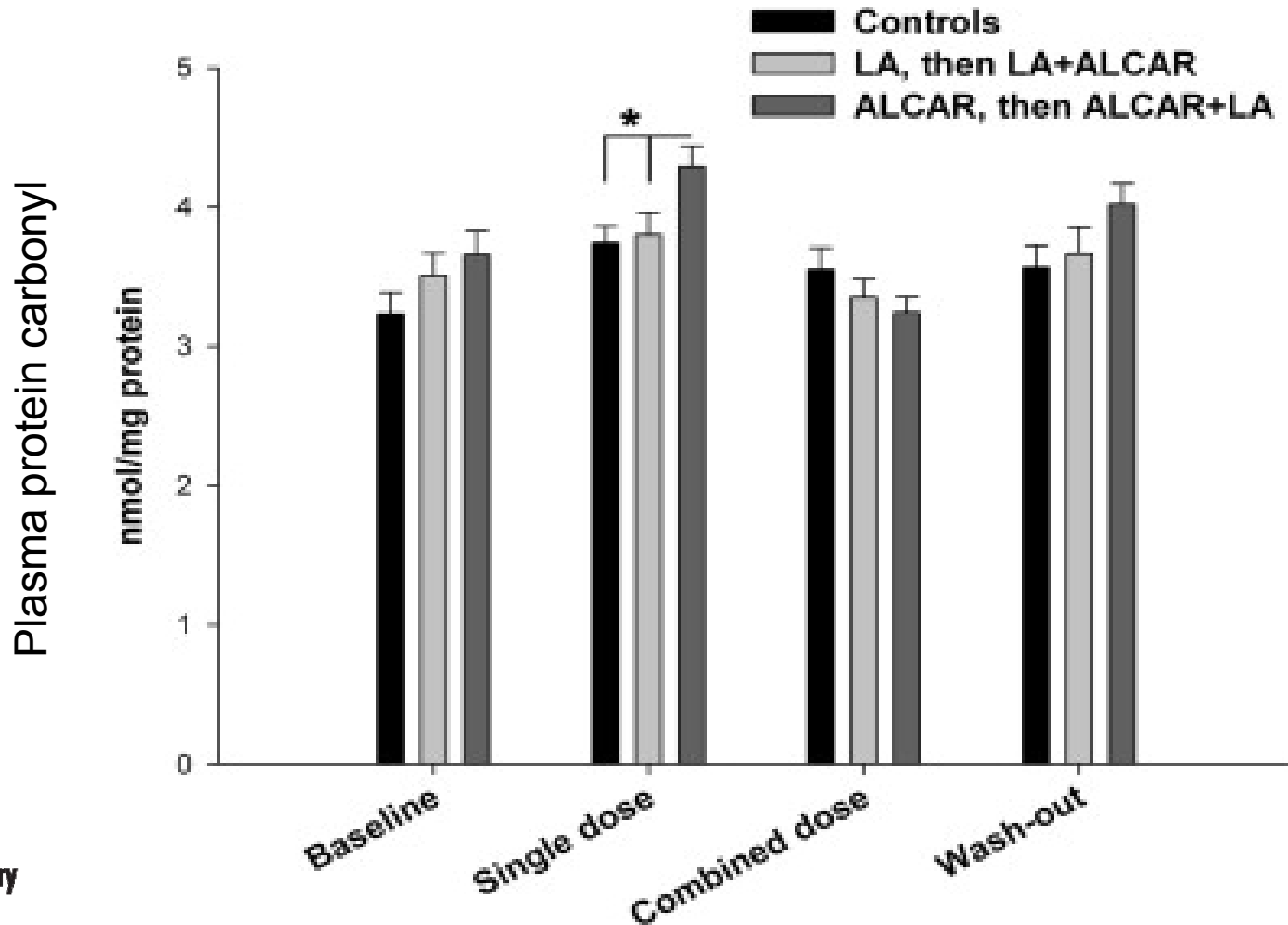


# Individual and Synergistic Effect of Lipoic Acid and L-Carnitine Supplementation

- 30 senior beagles (ave. 9y)
- 3 treatment groups
  - First phase (129 d)
    - Control
    - Lipoic acid (11mg/kg)
    - Carnitine (27.5mg/kg)
  - Second phase (79 d)
    - Control
    - Lipoic acid (11mg/kg) + Carnitine (27.5mg/kg)
    - Carnitine (27.5mg/kg) + Lipoic acid (11mg/kg)
- Landmark discrimination task

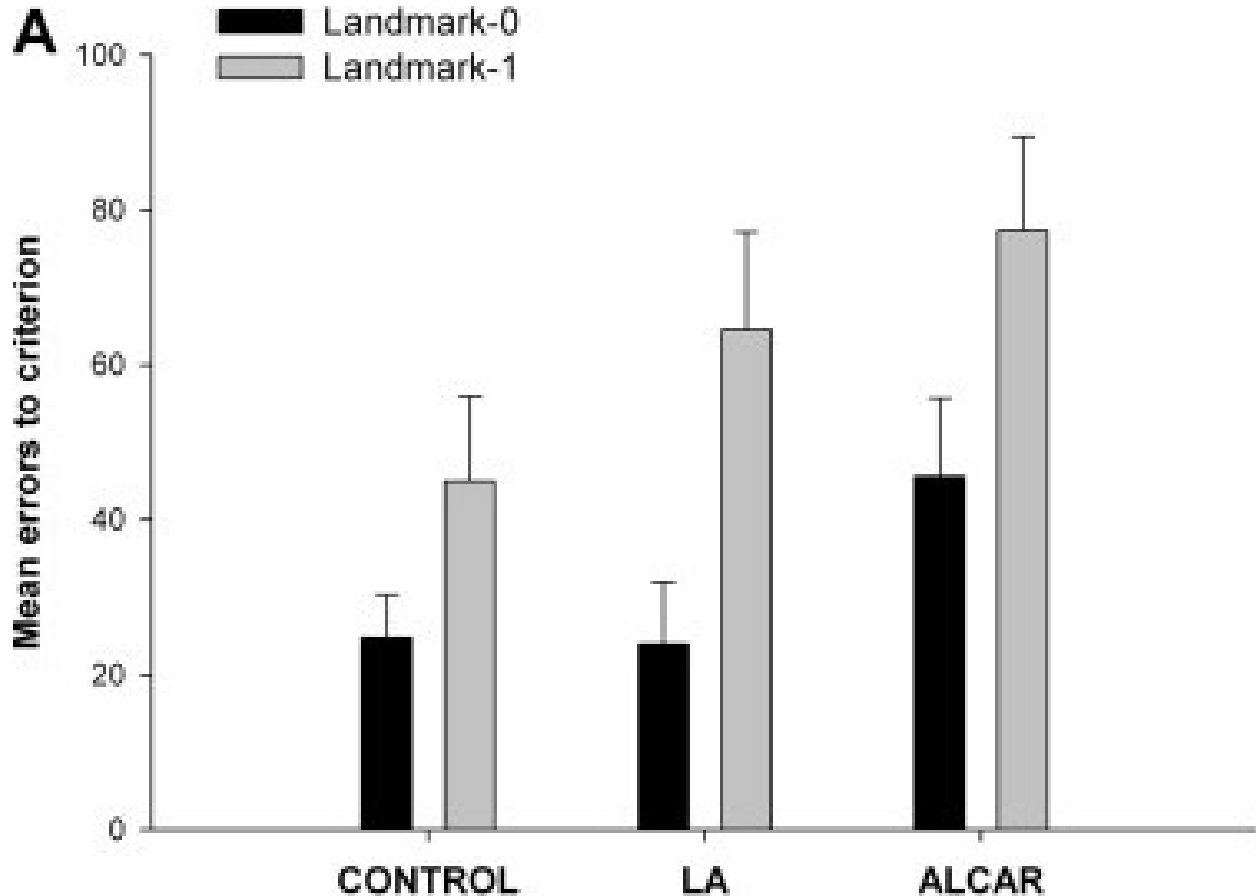


# L-Carnitine Supplementation Increased Marker of Oxidative Stress





# Effect of Individual Supplementation of Mitochondrial Co-Factors on Cognition

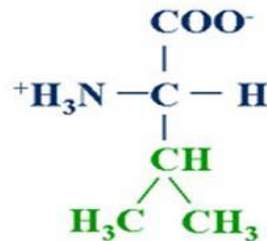




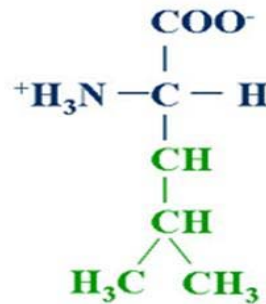


# Nutrition and CDS

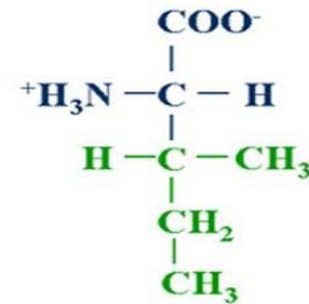
- **Branched-chain amino acid (BCAA)**
  - Valine, leucine, isoleucine
  - Compete with tryptophan (Trp) for entry into the brain



Valine



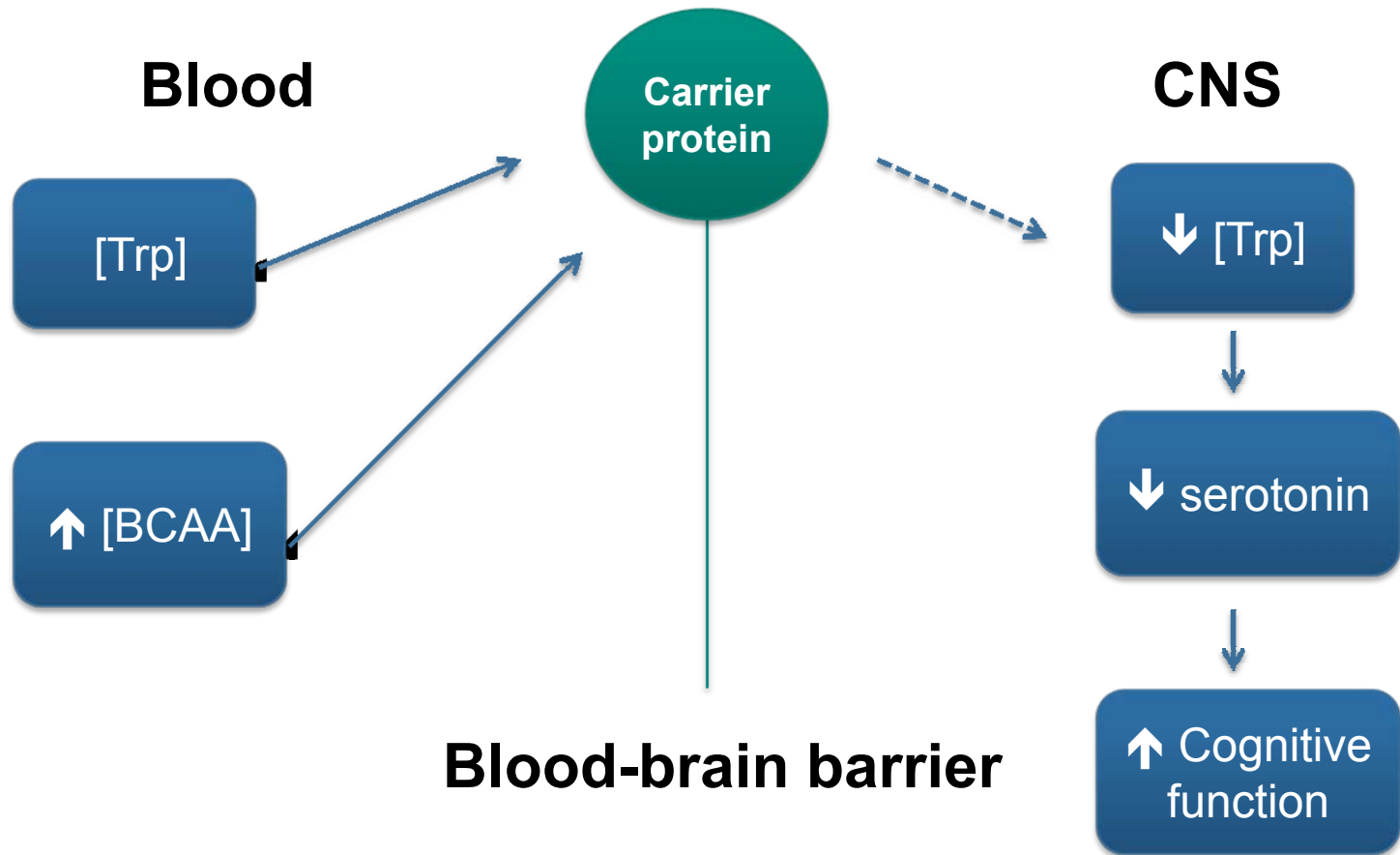
Leucine



Isoleucine



# Nutrition and CDS



*Adapted from Grimmett and Silience, 2005*

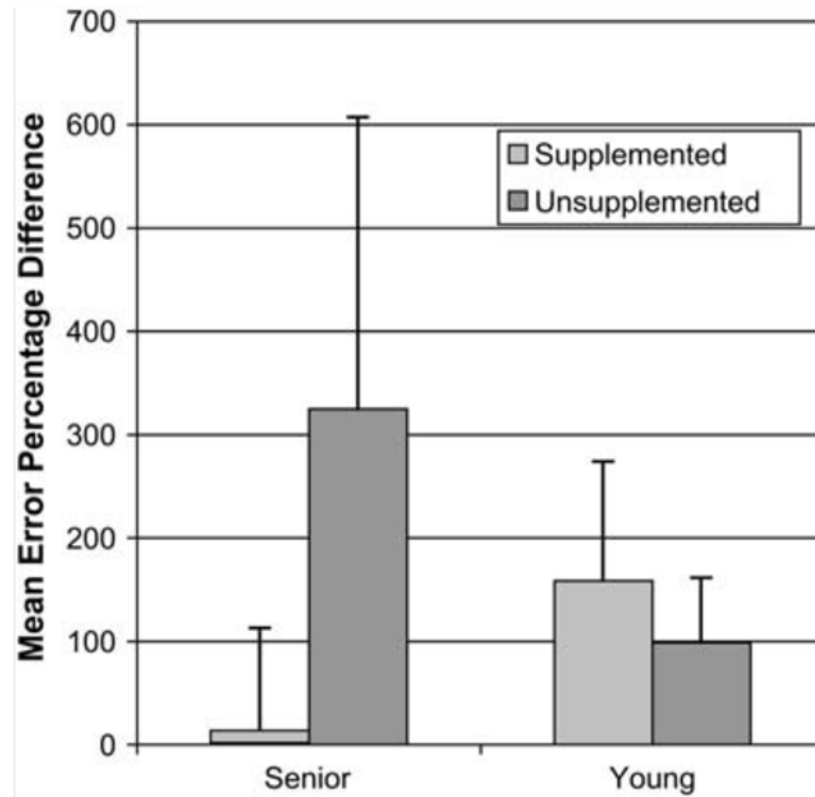


# BCAA and Cognition

- 24 dogs
  - Young: 1.5-3.5 y
  - Senior: 11.1-13.1 y
- 2 dietary treatments
  - Control
  - Enriched
    - 40% valine
    - 35% leucine
    - 35% isoleucine
    - 7% CH<sub>2</sub>O solution
- Training: 7-obstacle agility course



# BCAA Improved Cognition in Senior Dogs



**FIGURE 3** Supplementation provides a greater benefit to senior dogs ( $n = 12$ ) than to young dogs ( $n = 12$ ). MANOVA,  $P < 0.02$ ; error bars represent SD.



# Medium-chain Triglycerides and CDS

- Decline of cerebral glucose metabolism
- MCT alternative source of energy
  - Ketones
    - $\beta$ -hydroxybutyrate

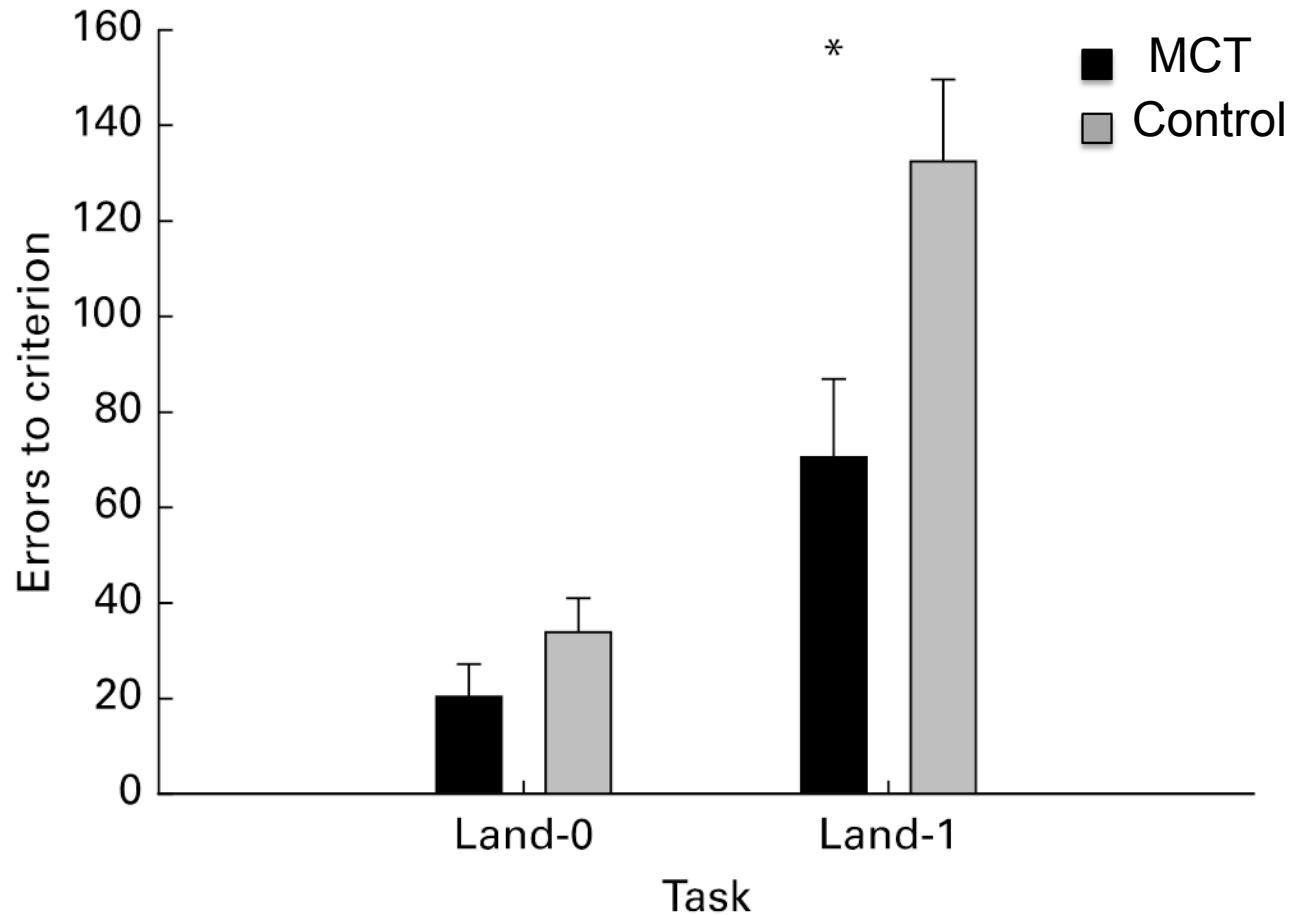


# MCT and Cognition

- 24 dogs
  - Senior: 7.5-11.6 y
- 2 dietary treatments
  - Control
  - Enriched
    - 5.5% MCT
      - 97% caprylic acid (C8)
      - 3% capric acid (C10)
      - » 100d period
- Discrimination, reversal and landmark tests

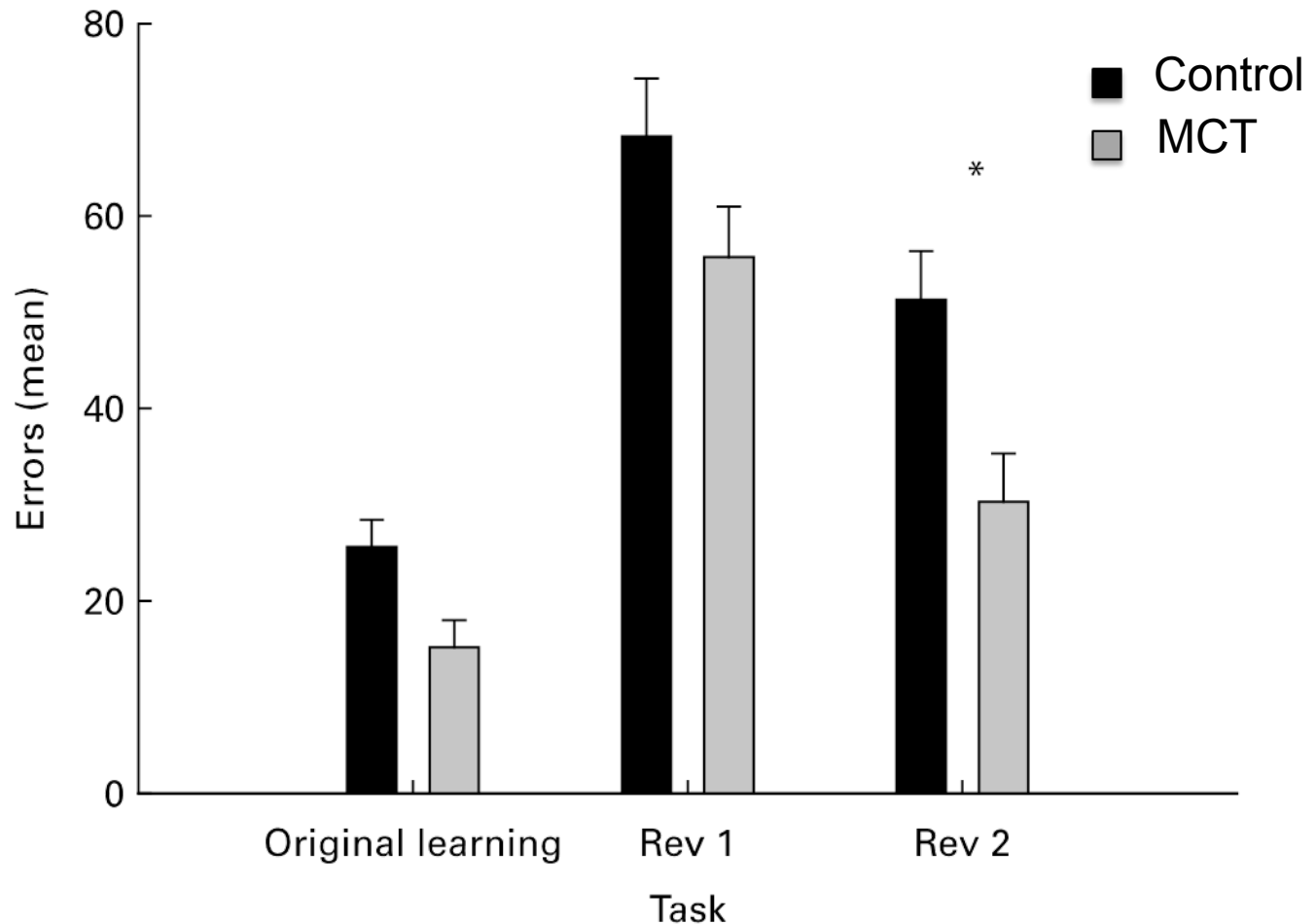


# MCT Improved Cognition in Senior Dogs





# MCT Improved Cognition in Senior Dogs







# Nutraceutical Supplementation

- **Phosphatidylserine (PS)**
  - Natural phospholipid of cell membranes
  - Facilitate membrane-dependent neuronal processes
    - Signal transduction
    - Release of secretory vesicles



# Nutraceutical Supplementation

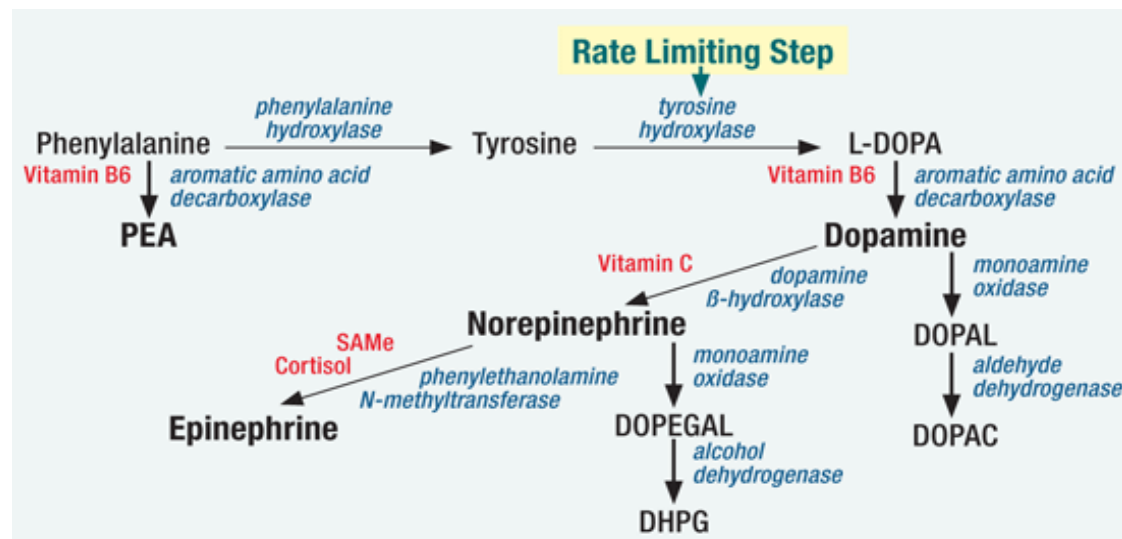
- **Gingko Biloba Extract (GBE)**
  - Inhibits monoamine oxidase B activity, thereby  $\uparrow$  dopamine levels
  - May protect against neuronal apoptosis induced by beta-amyloid
    - Due to antioxidant properties of GBE





# Nutraceutical Supplementation

- **Pyridoxine (B6)**
  - Co-factor in synthesis of dopamine
    - Act synergistically with PS & GBE to ↑ dopamine





# Neuroprotective Nutraceutical

## Senilife®

- Phosphatidylserine (25 mg)
- Ginkgo Biloba Extract (50 mg)
- Vitamin B<sub>6</sub> (20.5 mg)
- Vitamin E (33.5 mg)





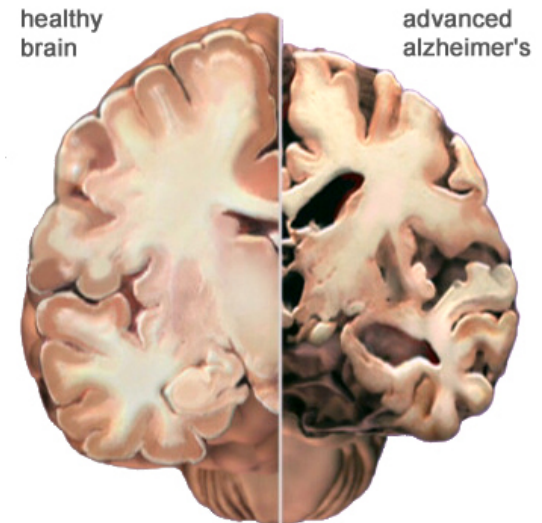
# Neuroprotective Nutraceutical

- Senilife<sup>®</sup>
  - Pilot study
    - Positive effects on behavioral status
    - 3 mo supplementation
      - Non-controlled, open-label (n=8)
  - Cross-over study
    - Supplementation increased performance compared to baseline (n=5)
      - 2 mo supplementation



# Final Remarks

- Nutritional management of CDS
  - Ameliorate clinical signs
  - Postpone onset of this condition
  - Model for human brain aging
    - Alzheimer's disease





# Final Remarks

- Diets enriched with antioxidants and mitochondrial cofactors
  - Improve cognitive performance in senior dogs
  - Little information on potential benefits of supplementation of individual components
    - Effectiveness?
    - Ideal dose?



# Final Remarks

- BCAA and MCT supplementation
  - Improve ability of senior dogs to sustain cognitive performance
- Phosphatidylserine, ginkgo biloba and vitamins B<sub>6</sub> and E
  - Potential in ameliorating CDS





# Additional Considerations

- Environmental enrichment and stimulation
  - Synergistic effect with nutrition therapy
  - Positive effect on CDS management





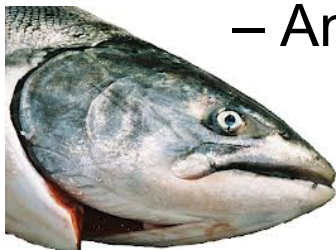
# Future Research

- Limited information on nutritional management
  - Minerals (e.g. Fe, Cu, Se)
    - Pro- or antioxidant function
  - Polyphenols (e.g. curcuminoids)
    - Antioxidant
    - Anti-inflammatory
    - Anti-amyloid activity
    - Turmeric – considered “generally recognized as safe” (GRAS)



# Future Research

- Limited information on nutritional management
  - $\omega$ 3 PUFAs
    - Brain tissue cell membranes rich in PUFAs such as DHA
    - $\uparrow$  age,  $\uparrow$  ROS, and  $\downarrow$  [PUFA]
    - Promote cell membrane fluidity and health
    - Anti-inflammatory



*Araujo et al., 2005. Age. 27: 27-37*

- Long-life study, protective effect?



# Future Research

- Better characterize longitudinal neuropathologic, metabolic, and behavioral changes
  - Metabolites, genomic, imaging, etc.
- Current technology support the study of CDS **without the need of invasive techniques**
- **Identification of pre-clinical biomarker**
  - Early intervention





# Future Research

- Potential interactions of CDS
  - Obesity
    - Pro-inflammatory
    - Increase oxidative stress
  - Spay/ neuter
    - Removal of reproductive hormones have been related to decline in cognition
    - Protective effect of testosterone in dogs



*Hart B. 2001. JAVMA 219: 51-55*



# Take Home Message



- CDS - no cure
- **Nutritional management** appears to **improve cognitive function** and hallmarks of **neurodegeneration** in senior dogs
  - Current literature still controversial
- Technology is available to better understand CDS
- Improving the quality of life and well being of pets and their owners



# Thank you!

*“Because humans created dogs through domestication, the canine mind reflects back to us how we see ourselves through the eyes, ears, and nose of other species”.*

*Berns et al., 2012*





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# Neuroprotective Nutraceutical

## Novifit®

- S-adenosylmethionine (SAME) tosylate supplement for senior dogs and cats
- SAME is a methyl donor
  - Involved in transmethylation of nucleic acid, proteins, phospholipids, and neurotransmitters
- Stimulates brain glutathione
  - Antioxidant activity



# Neuroprotective Nutraceutical

Novifit®

- Potential positive effects in improving cognition in senior cats



# Symptoms of CDS



Gets  
confused



# Symptoms of CDS

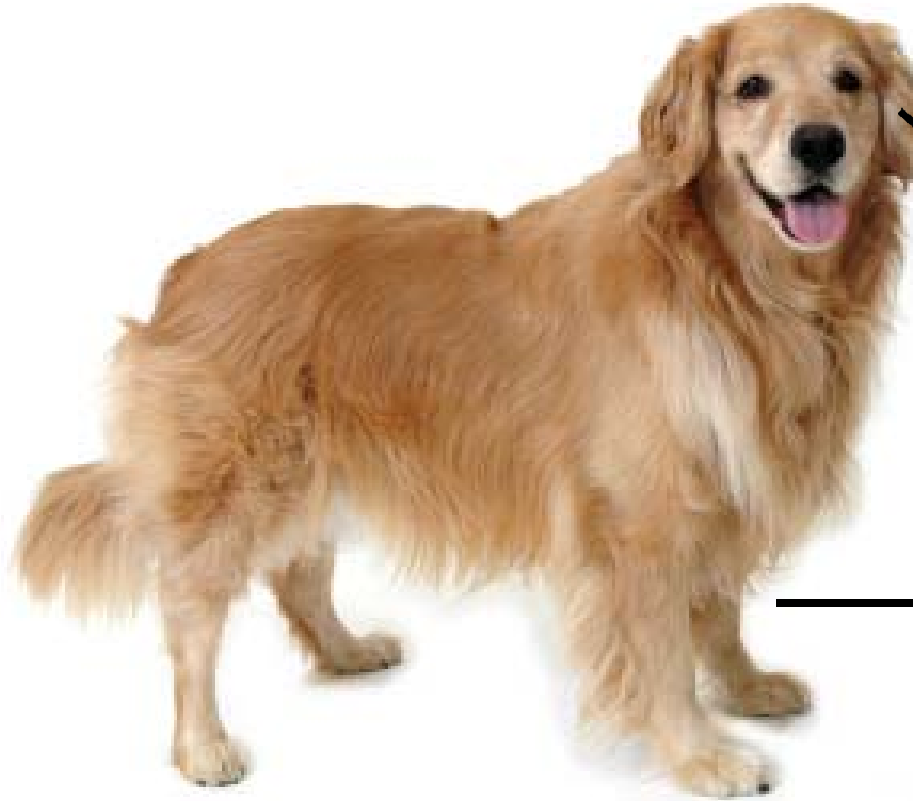


**Gets  
confused**

**Doesn't  
recognize  
the owner**



# Symptoms of CDS



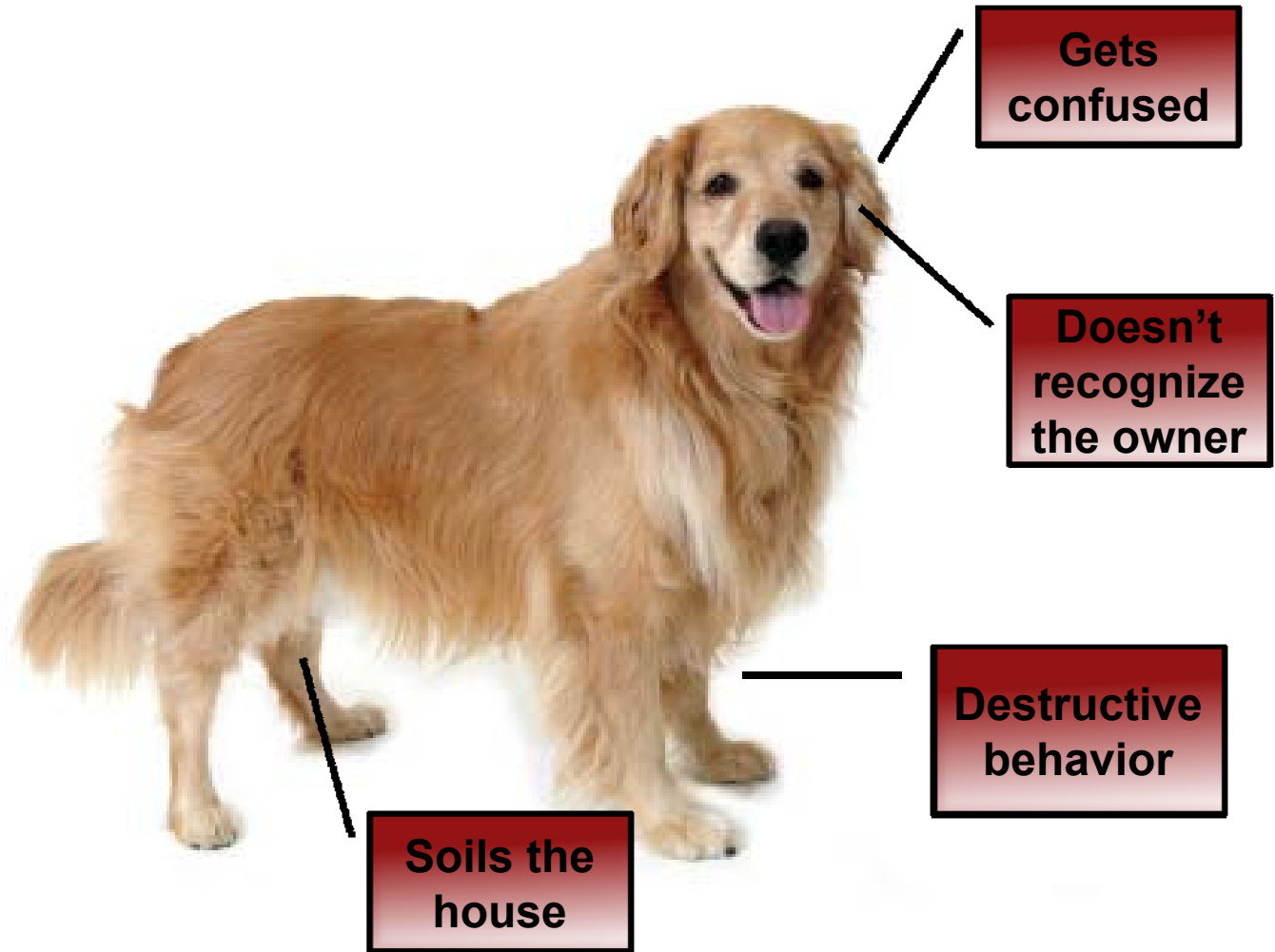
**Gets  
confused**

**Doesn't  
recognize  
the owner**

**Destructive  
behavior**



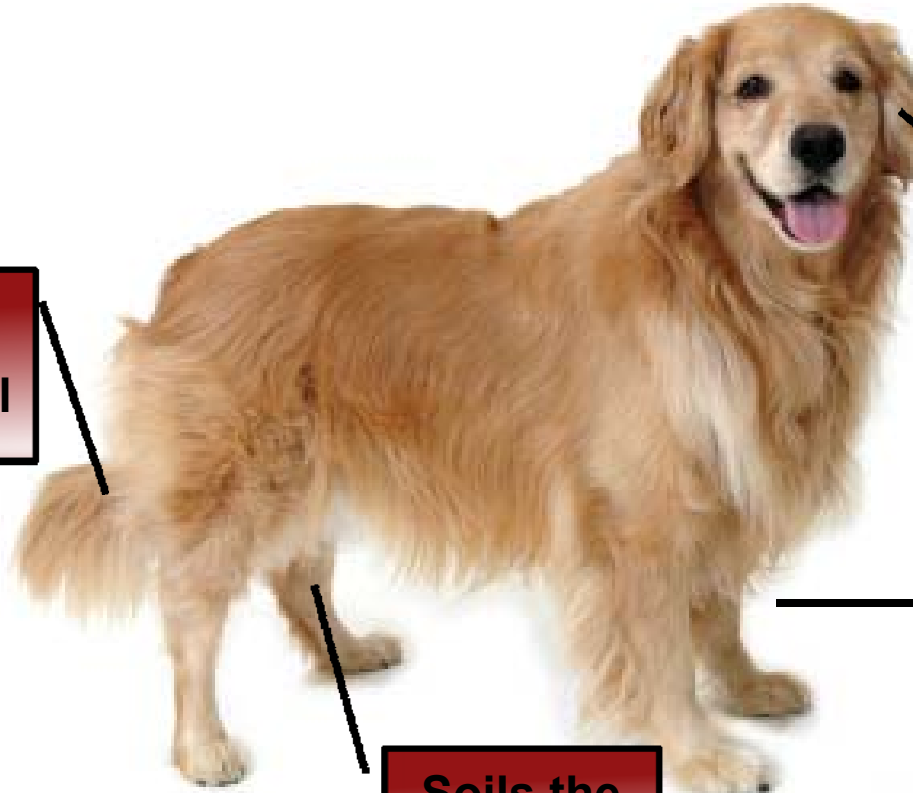
# Symptoms of CDS





# Symptoms of CDS

Doesn't wag the tail



Gets confused

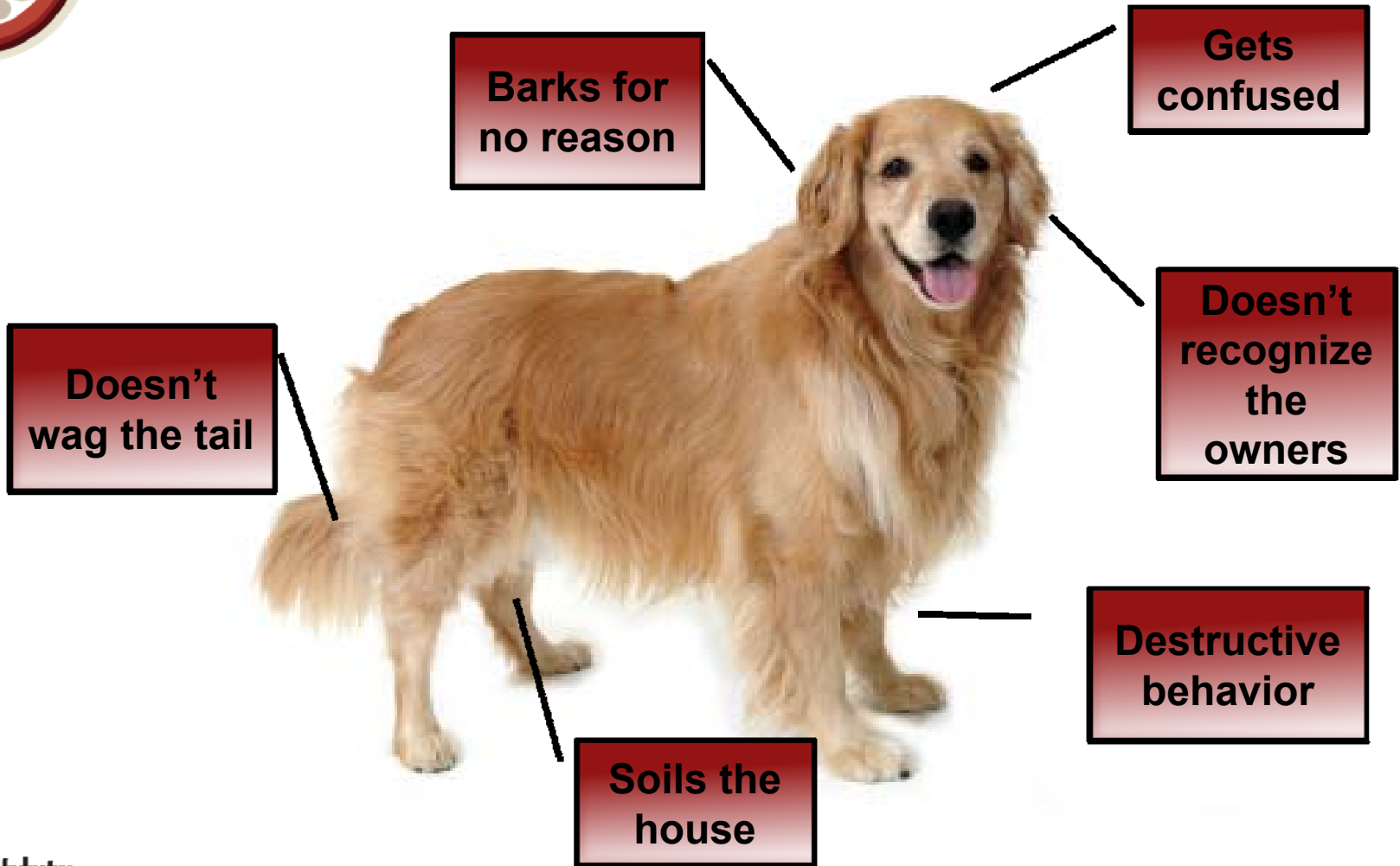
Doesn't recognize the owner

Destructive behavior

Soils the house



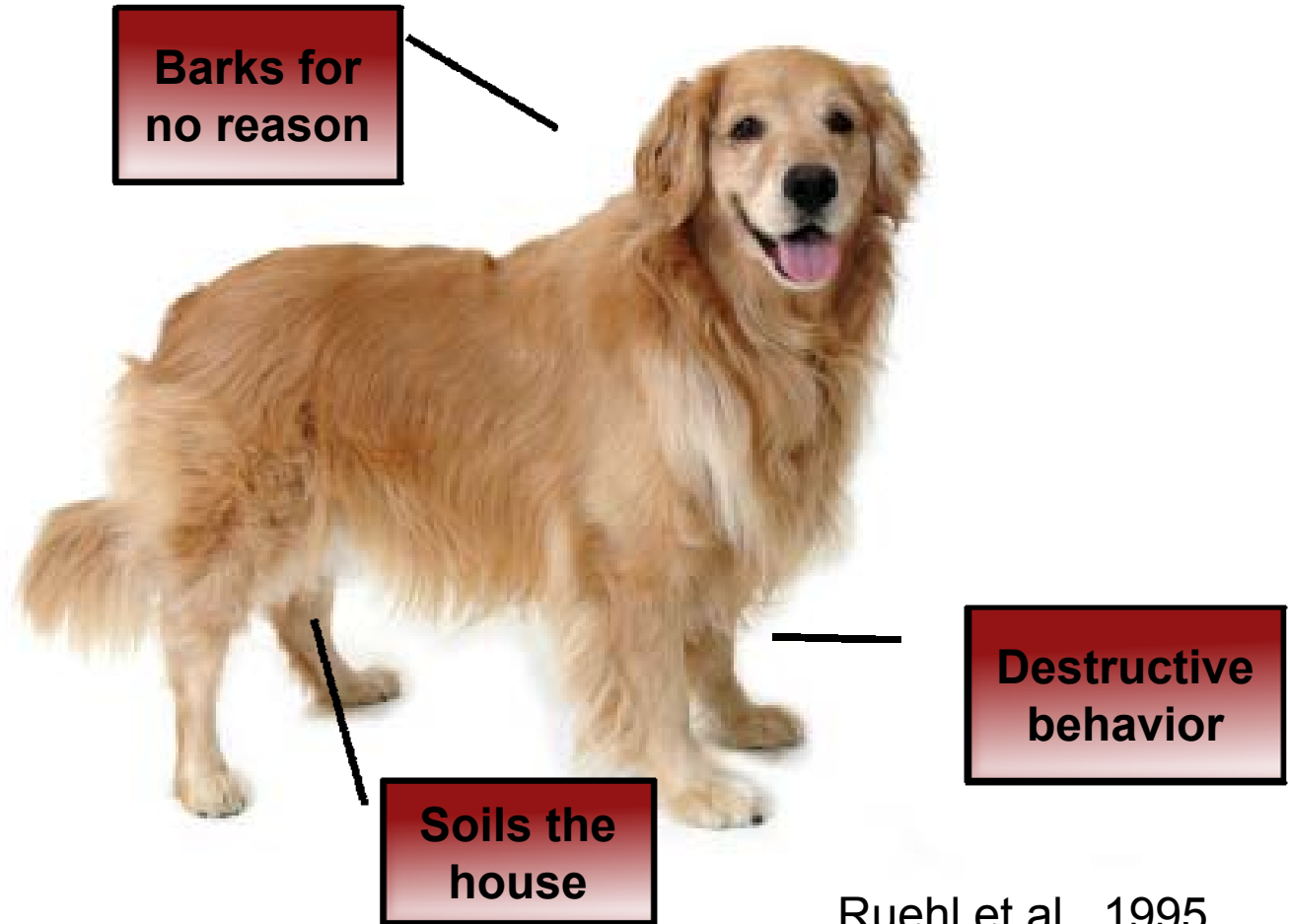
# Symptoms of CDS







# Most Common Symptoms of CDS



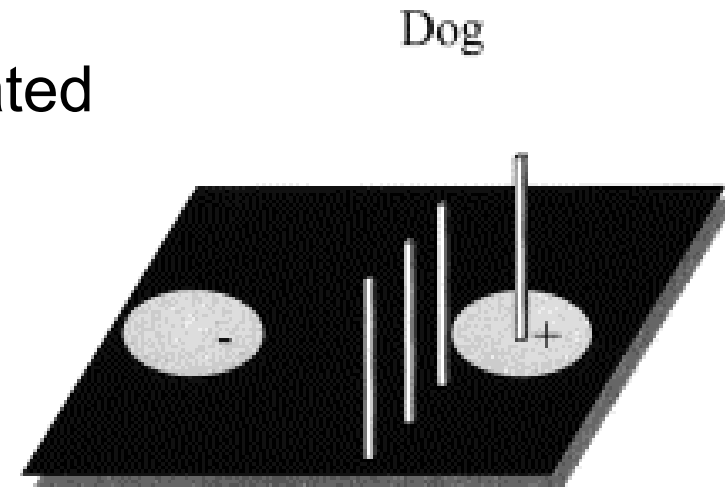
Ruehl et al., 1995



# Cognitive Testing

## Landmark Discrimination

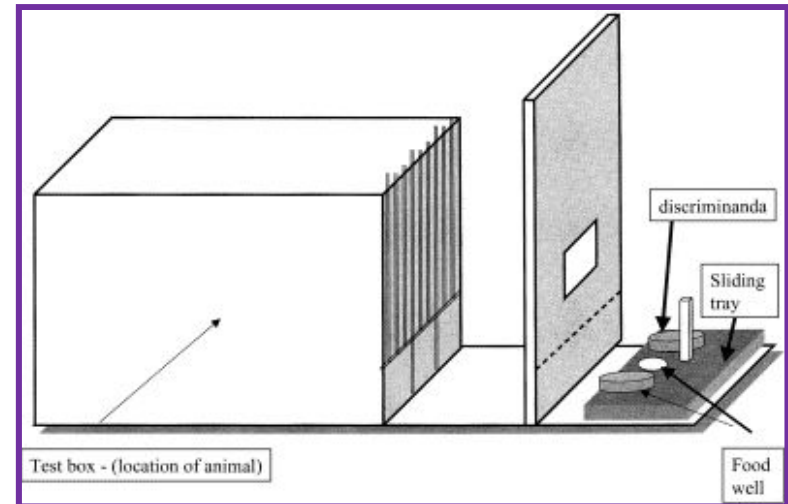
- Tests allocentric knowledge
  - Observer uses external landmarks to locate objects as opposed to body position as reference
- Neurologic damage is associated with allocentric dysfunction
- Landmark moved to different positions
  - L0 : on top of coaster (easiest)
  - L1: removed from coaster
  - L2: further removed from coaster





# Toronto General Testing Apparatus

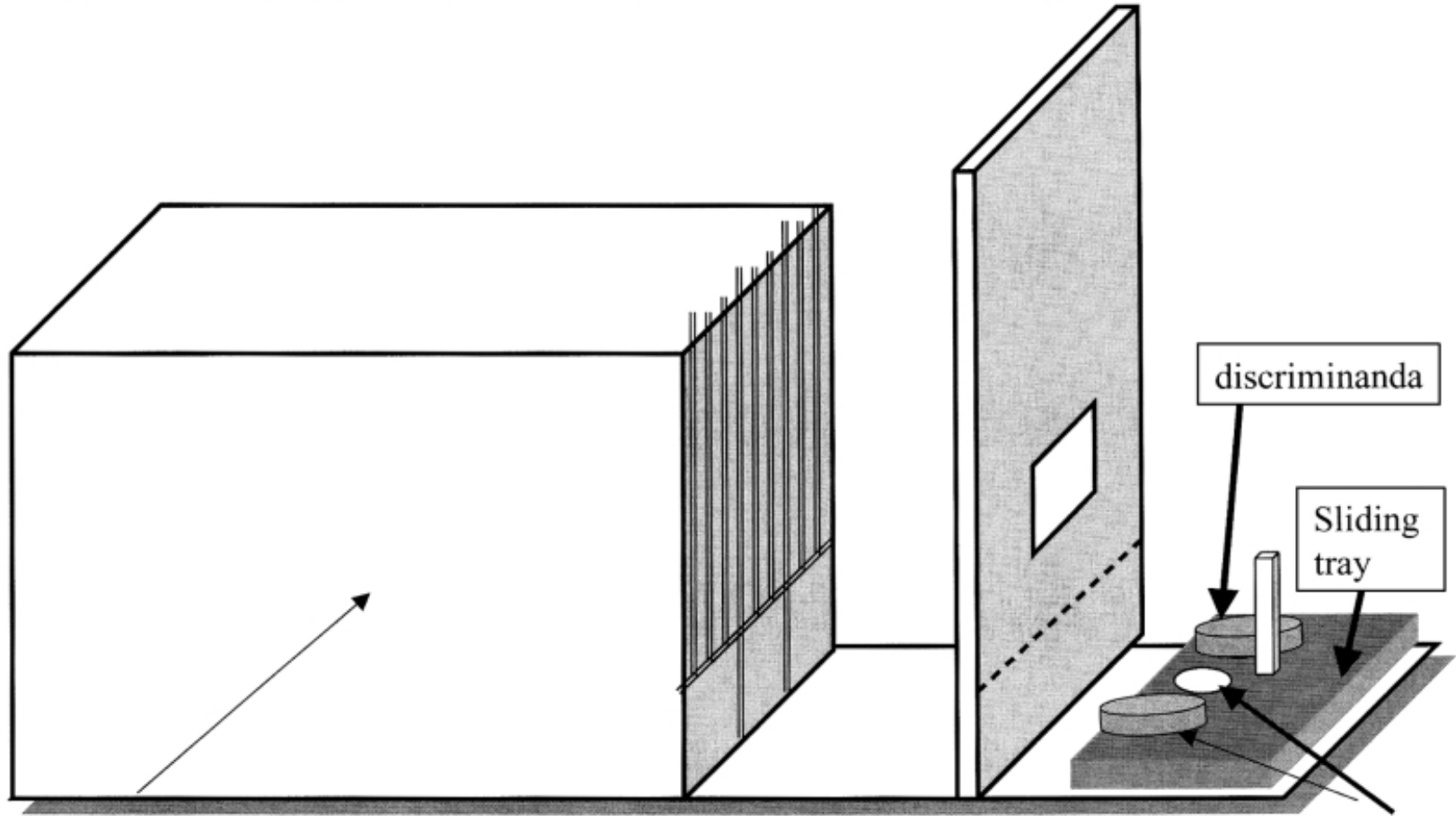
- Dogs are offered a variety of objects (2-3 at a time)
- Object location computer randomized
- Food rewards located under “correct” object
- Dogs “pass” when achieve set criterion
  - 1) Score of 90% OR scores of 80% over 2 days
  - 2) Then 70% over next 3 days





# Cognitive Dysfunction Testing

## COGNITIVE TEST APPARATUS



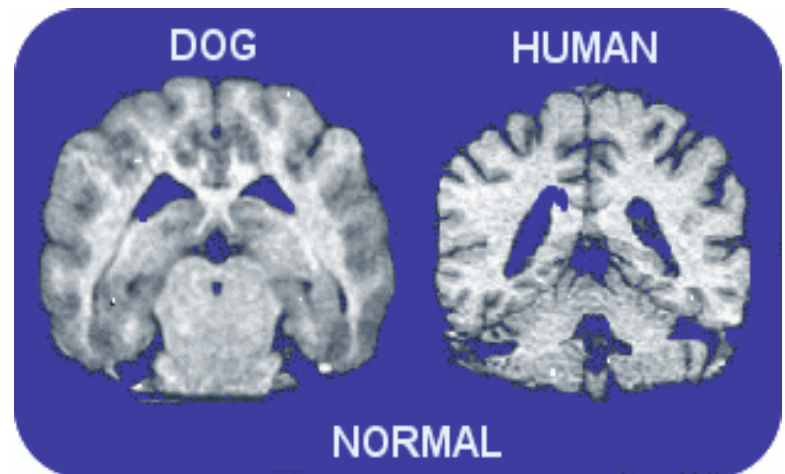
Test box - (location of animal)

Food well



# Dogs as Human Models

- Dogs and humans present similar morphological features in brain aging
  - Cortical atrophy (frontal lobes and hippocampus)
  - Ventricular widening
  - Demyelination
  - Reduced neurons
  - Increased apoptotic bodies





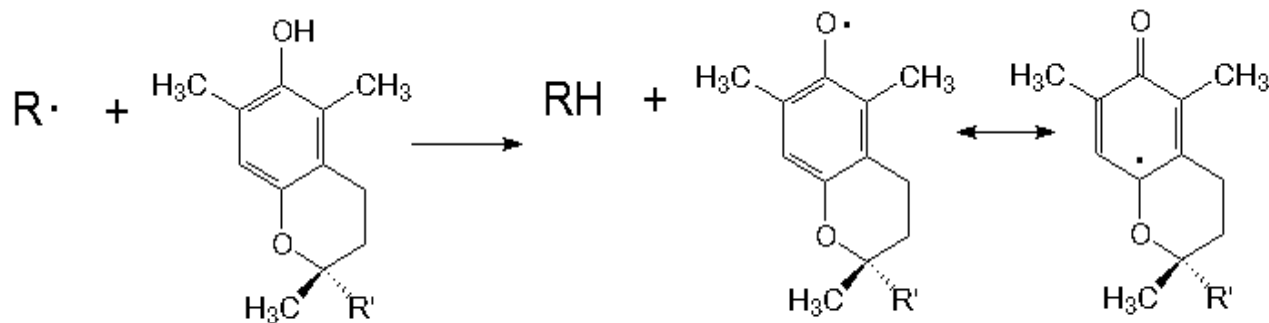
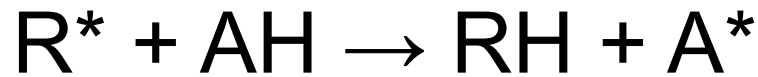
# Nutrition - Aging Dogs

- Traditional
  - Focused on growth and adult maintenance
- Recently
  - Movement towards specialized diets that meet nutritional needs of specific events
  - One example: aging and cognitive health



# Vitamin E

- A lipid soluble antioxidant
  - Can neutralize free radicals & prevent damage to cell membranes

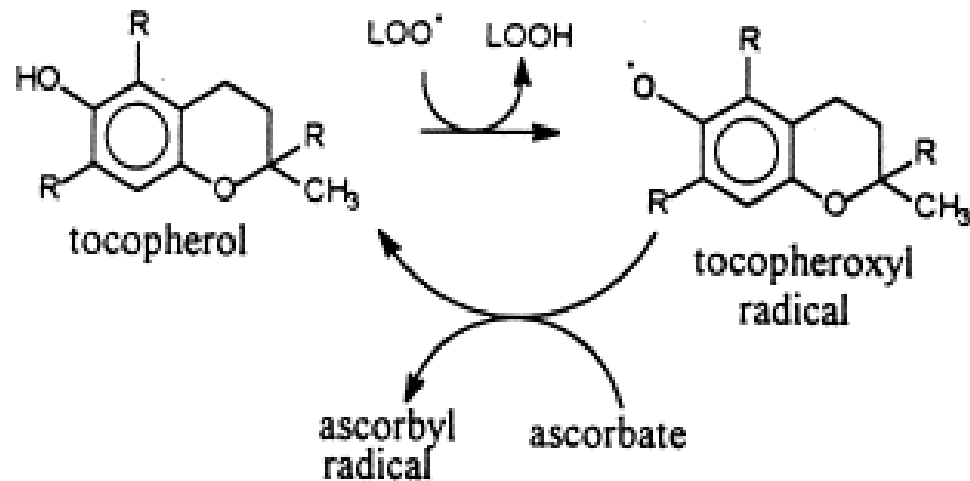


Resonance-stabilized radical



# Vitamin C (Ascorbic Acid)

- May work to restore antioxidant properties of Vitamin E



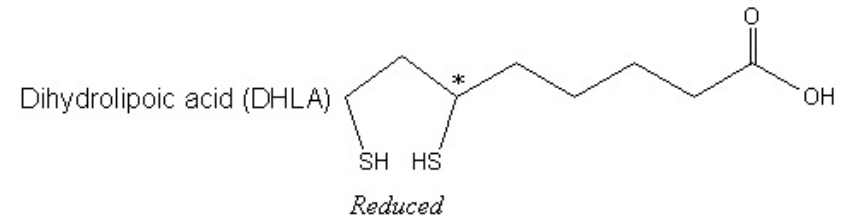
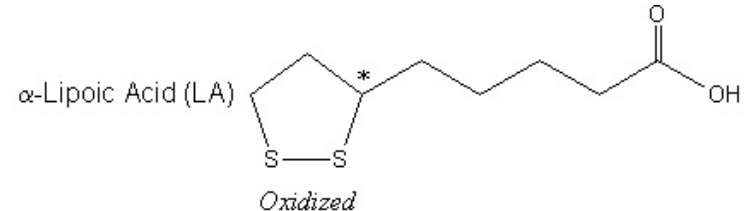
Rock et. al, 1996 "Update on the biological characteristics of the antioxidant micronutrients: Vitamin C, vitamin E, and the carotenoids"





# $\alpha$ – Lipoic Acid

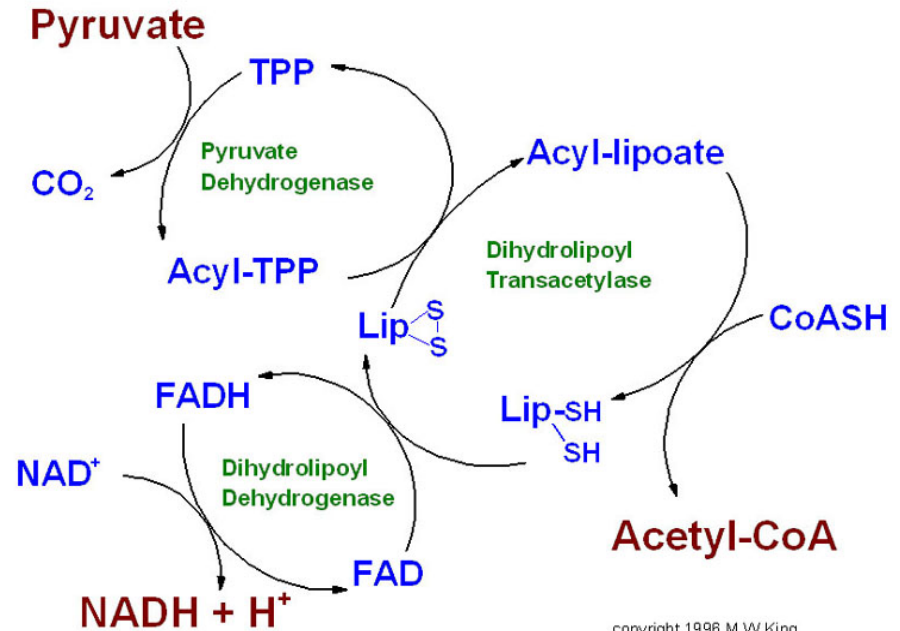
- Organosulfur compound
- Synthesized in the liver
  - L-cysteine
  - Octanoic acid
- Lipophilic property + COOH group
- Small amounts present in the body





# $\alpha$ – Lipoic Acid

- Co- factor
  - pyruvate dehydrogenase complex
  - $\alpha$ -ketoglutarate dehydrogenase complex
  - the branched chain  $\alpha$  -keto-acid dehydrogenase complex



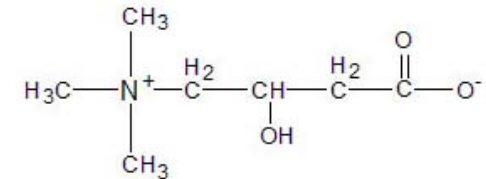
copyright 1996 M.W.King



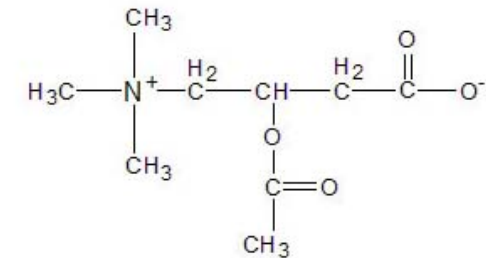
# L-carnitine

- Quaternary ammonium compound
- Synthesized from lysine and methionine in the liver and kidneys
  - Co-factors:  $\text{Fe}^{2+}$  and Vit. C
- 95% is stored in the skeletal muscle

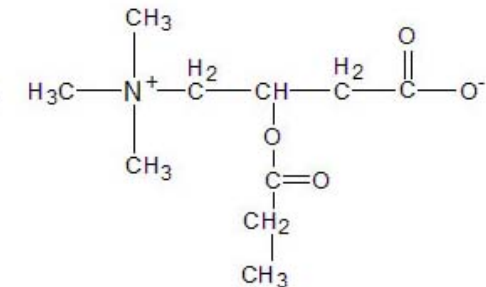
L-Carnitine



Acetyl-L-Carnitine

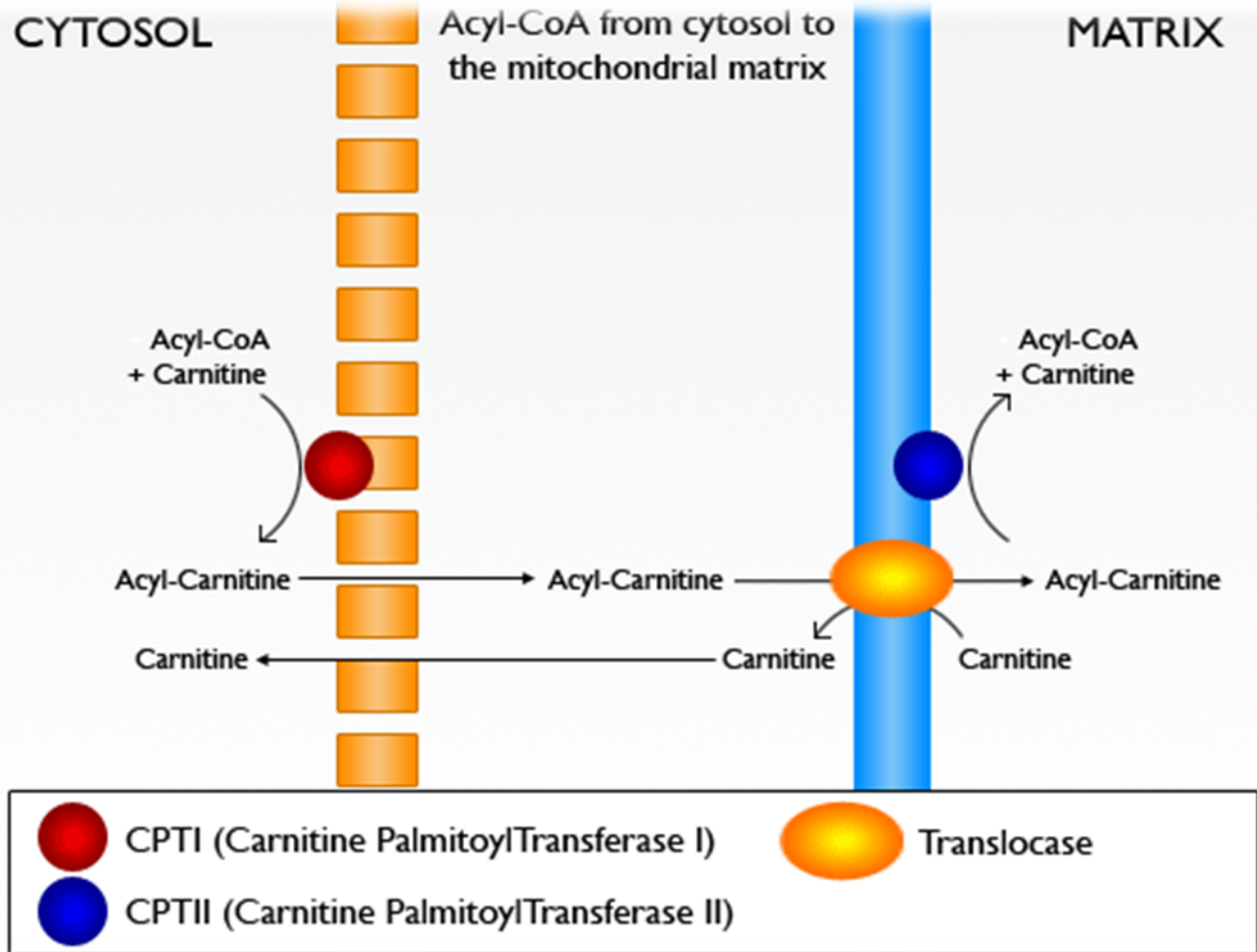


Propionyl-L-Carnitine





# L-carnitine





# Ikeda – Douglas et. al, 2004

- 30 beagles
  - Old dogs (9-13y)
  - 18 beagles experienced (pre-trained)
  - 12 beagles naive
  - 28 completed the study
- 3 progressive degrees of complexity of LMDT
  - L0 = landmark was on the top of coaster
  - L1, L4= landmark was 1, 4 cm away from reward object
- Dogs advanced for next level when succeed in the previous one



# Nippak et. al, 2007

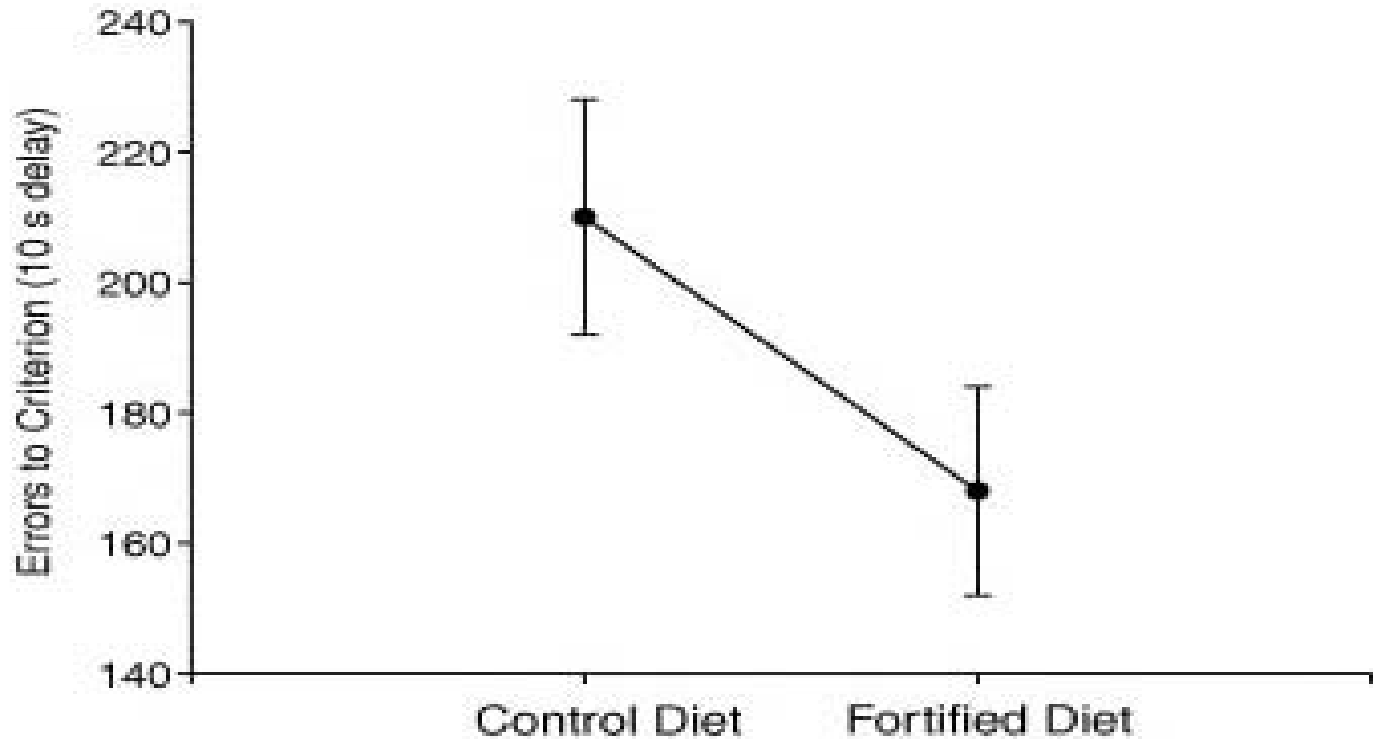
## Diets

Components	Control	Enriched
D, L- $\alpha$ -tocopherol acetate	120 ppm	1000 ppm
L-carnitine	< 20 ppm	275 ppm
D, L- $\alpha$ -lipoic acid	< 20 ppm	125 ppm
Ascorbic acid as Stay - C	< 30 ppm	80 ppm
Inclusion 1:1 exchange for corn		
Spinach flakes	-	1%
Tomato pomace	-	1%
Grape pomace	-	1%
Carrot granules	-	1%
Citrus pulp	-	1%



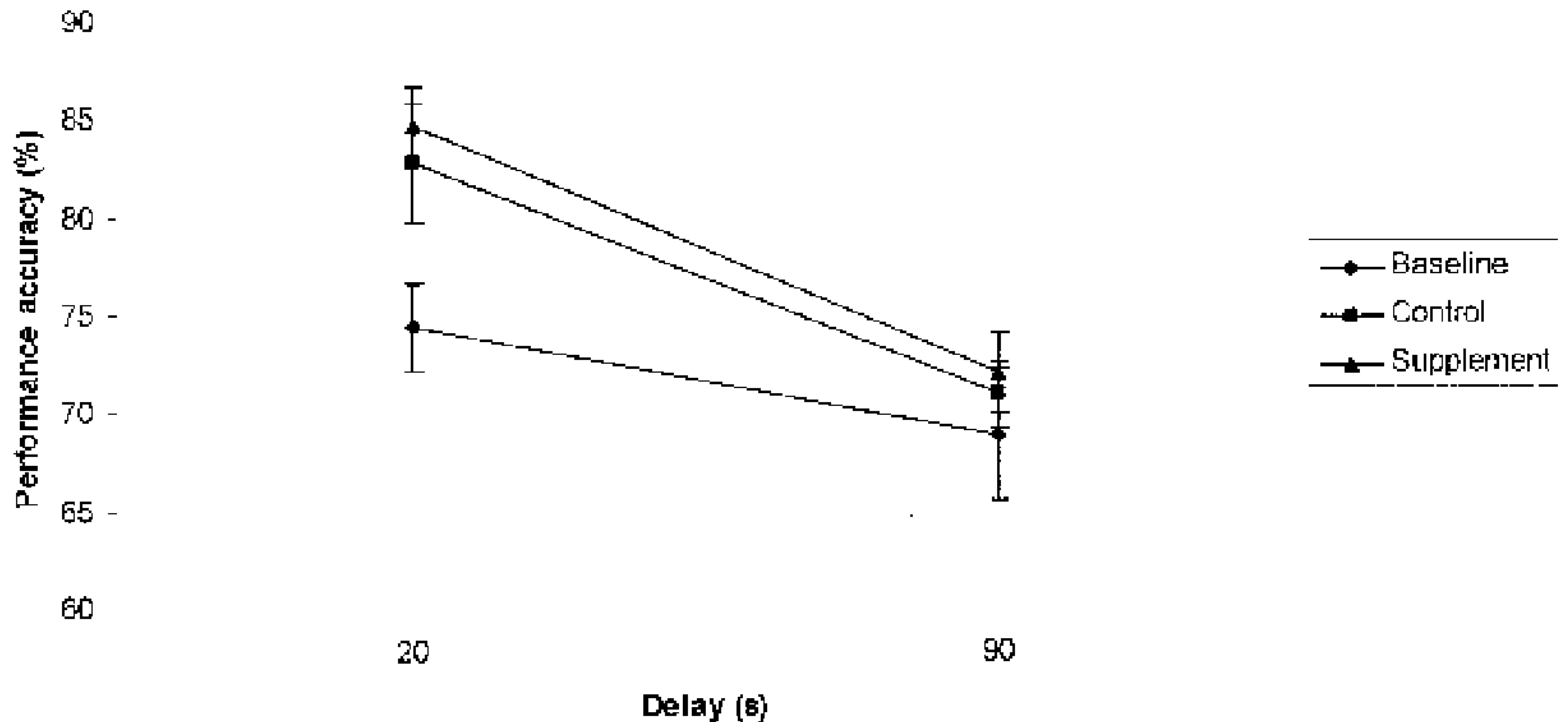
# Nippak et. al, 2007

Fortified Diet Effect in Year 3





# Improvement of Short-Term Memory



*Araujo et al., 2008. Can. Vet. J. 49: 379-385*





# Open-Label Clinical Pilot Trial

- 124 dog were screened for cognitive function
  - 22 exclude due to other medical problems
  - Remaining 102 dogs
    - 75 signs of CDS
    - 18 diagnosed for CDS
- 8 dogs diagnosed with CDS enrolled in the trial
  - Senilife<sup>®</sup> administered at 1 capsule per 5 kg body weight per day for 3 months



Rated behaviors as never, rarely, often, always  
(ranked 0-3 in analysis)

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**Criteria for evaluation of cognitive status in dogs**

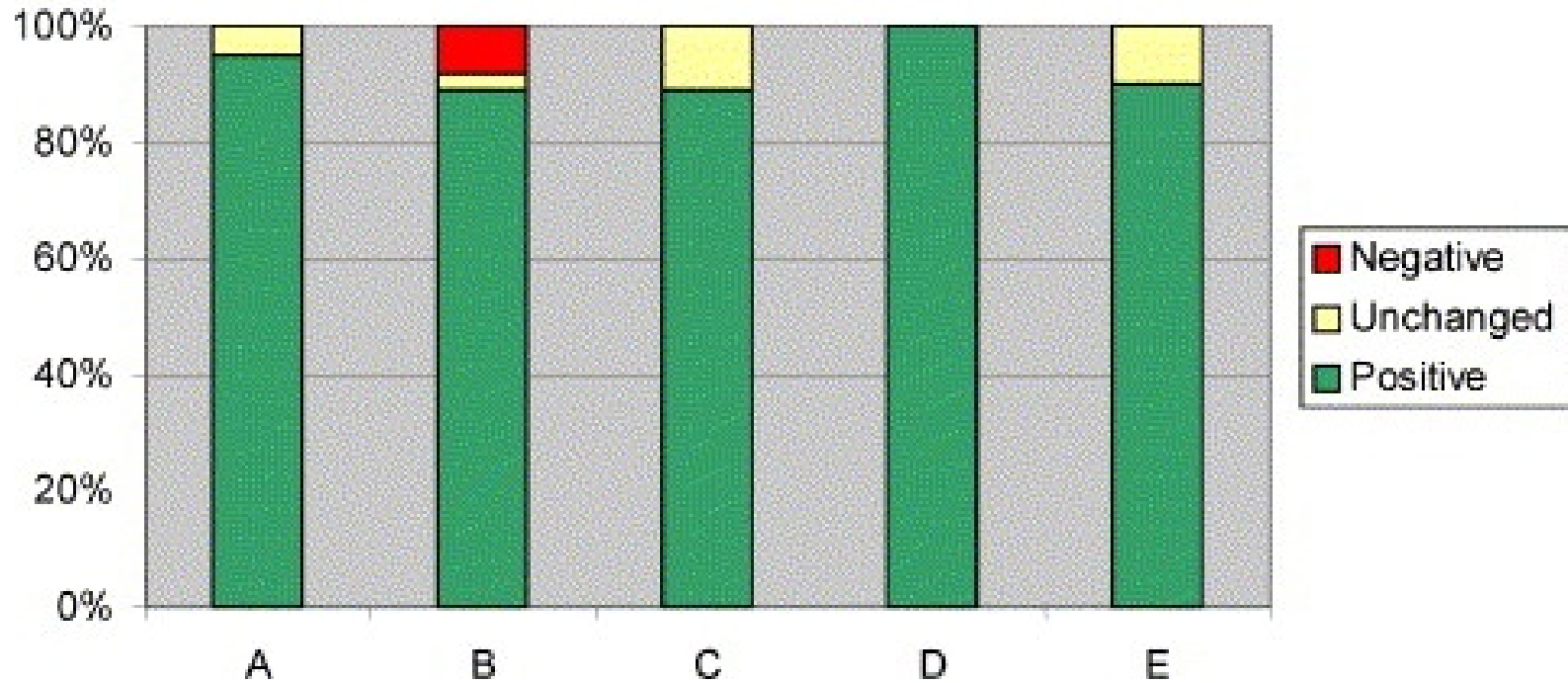
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<b>Category</b>	<b>Description of category</b>
<b>Disorientation (D)</b>	<b>Confusion, altered spatial orientation, failure in recognizing familiar people, surroundings, and routines</b>
<b>Socio-environmental interaction (I)</b>	<b>Altered interaction with people or other dogs, late or no answer to learnt commands</b>
<b>Sleep-wake cycles (S)</b>	<b>Increased daytime sleep, decreased and altered sleep at night</b>
<b>House soiling (H)</b>	<b>Accidents indoors, loss of urination and/or defecation control with or without incontinence</b>
<b>Activity (A)</b>	<b>Decreased purpose activities and increased repetitive aimless activities</b>



# Improvement of Cognitive Status

Distribution of score variations for question subsets



**A:** socio-environmental interaction, **B:** disorientation, **C:** sleep-wake cycles, **D:** house soiling, and **E:** general activity



# Nutrition and CDS

- **Omega-3 long-chain polyunsaturated fatty acids (DHA and EPA)**
  - Brain tissue cell membranes rich in PUFAs such as DHA
    - $\uparrow$  age,  $\uparrow$  ROS, and  $\downarrow$  [PUFA]
  - Promote cell membrane fluidity and health
  - Anti-inflammatory

