

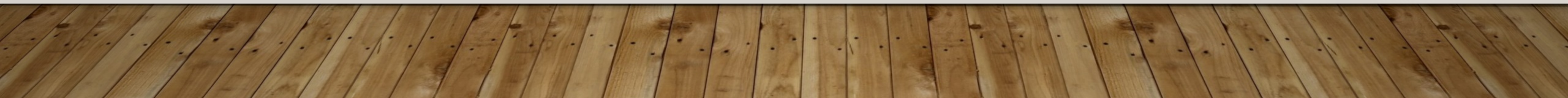
GROWING OLD WITH GRACE

The Science of Canine Cognitive Dysfunction

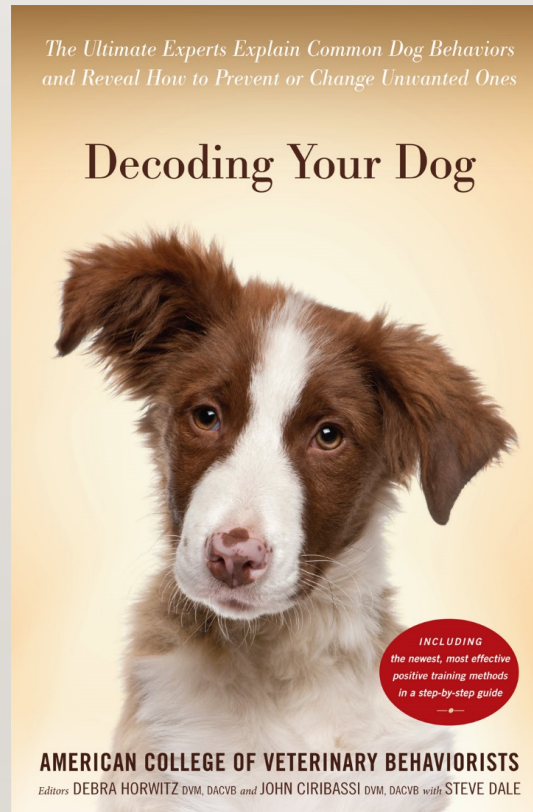
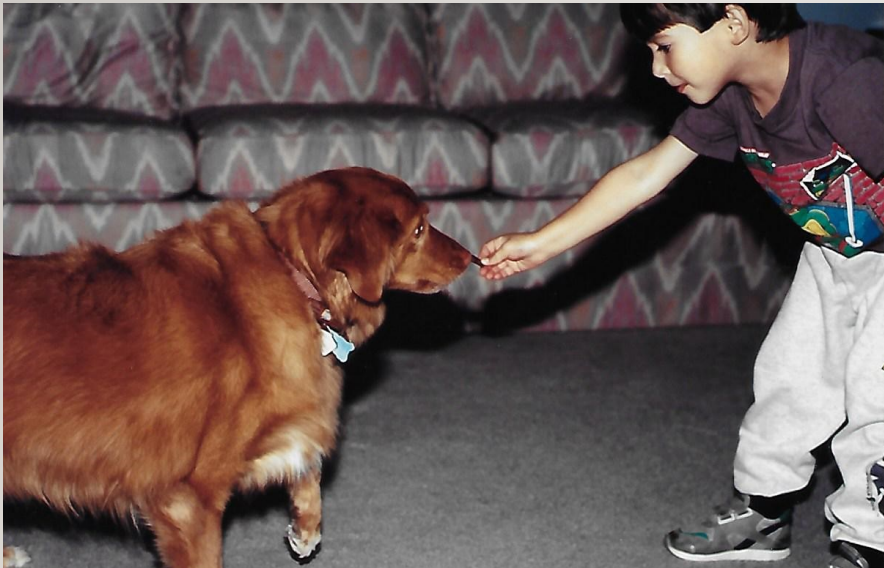
Gary Landsberg, DVM, DACVB, DECAWBM

Vice President, Cancog Technologies

Head, Fear Free Research



Grace's Story – Kishkahdina's Amazing Grace



Grace - 12 Years F(s) – NSDTR

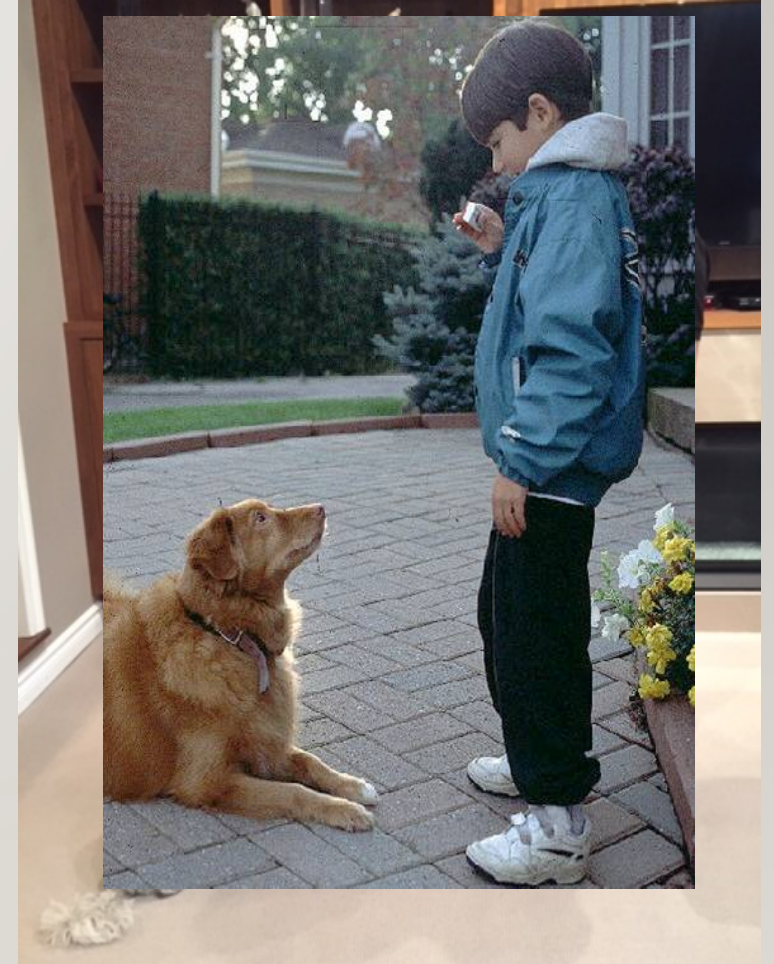
“The Dog Who Wouldn’t Get Up”

- Excessive whining, restless
- Less responsive - “Hears but doesn’t listen”
- Housesoil
- What does your dog want?
- Welfare – Pet / Owner / Bond
- Health - Medical
 - Hearing / visual decline
 - Arthritis / less mobile
 - Low FT4



Grace: 20/12/85 – 24/12/01

- Selegiline 4 y. - b/d™ 4 m.
 - More responsive
 - Normal sleep (13 hr)
 - Whining within limits
- Thyroid – 5+ years
- Meloxicam – 3 yr.
- Theophylline – 1 year
- Obesity – always
- Restore / maintain - Health / welfare / bond

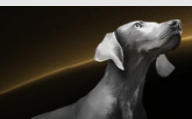


Grace and Jordan – circa 1998
Pepper and Jordan 2018



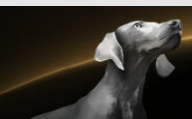
Overview - Cognitive Dysfunction Syndrome (CDS)

- Neurodegenerative disorder of the aging brain similar to Alzheimer's disease characterized by progressive impairment in cognitive function, ability to learn and response to stimuli with altered awareness, social relationships, sleep, and activity
- Normal aging - mild or borderline - may progress to CDS
- Identification based on pet parent observations and reporting
- Diagnosis by exclusion of medical / behavioral causes – may be concurrent
- Treatment to improve signs, manage, slow progression



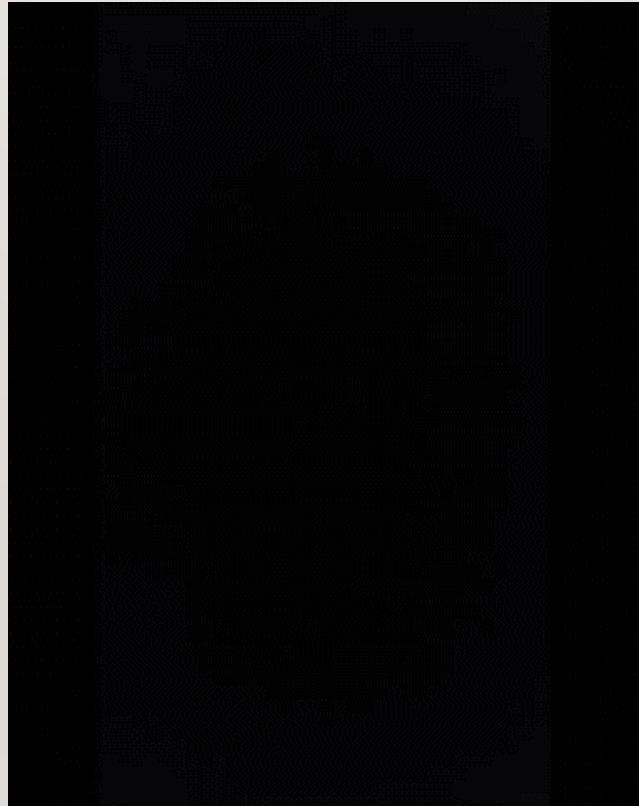
Cognitive Dysfunction Syndrome (CDS) – Clinical Signs

- **D** - Disorientation
- **I** - Social Interactions
- **S** - Sleep / wake
- **H** - Housesoiling - Learning / memory Neilson 2001; Madari 2015
- **A** - Activity – impairment and activity Rosado 2012, Siwak 2001
 - Increased repetitive, locomotor, aimless, humans, toys
- **A** - Anxiety – increase with age / CDS – passive vs. active
 - n=94 > 8 – Anxiety: CDS 46%, borderline 11%, no CDS 4%
 - Fast 2013; O’Brian 2021; Pan 2018; Rème CA 2008; Mongillo 2013



Anxiety

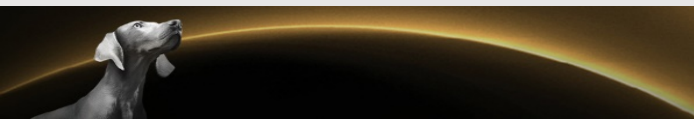
Teagan – 9 Yr F(S) – German Shephard



CDS - Health and Welfare

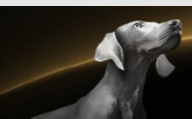
Manteca X, Purina Symposium, ECVIM-CA, 2018

- Impact on Pet
 - Negative impact on behavioral health, well-being
 - Confusion - Interactions – Sleep – HouseSoil – Anxiety - Repetitive
 - Less interest / able to engage in pleasurable activities - social, play, explore
 - Less able to adapt to change / stress
- Impact on pet parent – bond / relationship
 - Pet Anxiety / irritability, soiling, sleep/wake, altered social interactions
 - Welfare / Quality of life – Pet, Parent



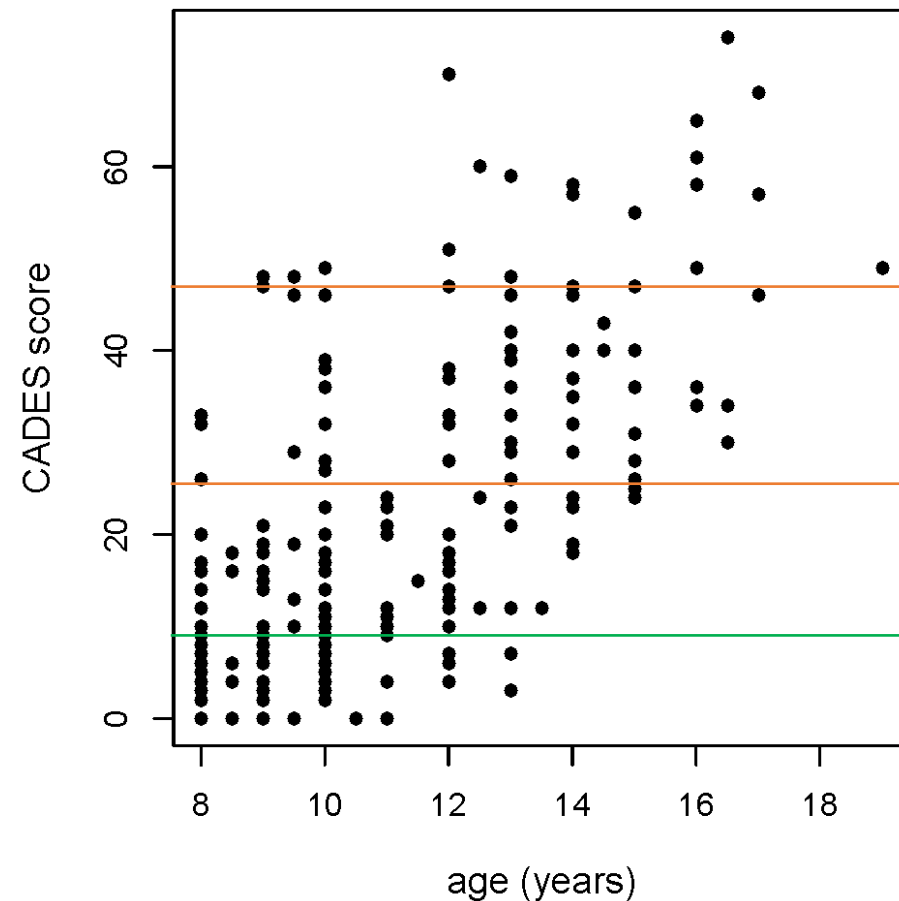
Prevalence Increases with Age

- DISH questionnaire - Retrospective study (180 dogs) (Neilson et al, 2001)
 - 1 or more categories – 11-12 years: 28% - 15-16 years: 68%
 - 2 or more categories 11-12 years: 10% - 15-16 years 36%
- DISH (CADES) questionnaire – Prospective study (300 dogs) (Madari et al, 2015)
 - 8-11 years – 13% <15kg – 16% > 15 kg
 - 11-13 years – 41% <15 kg – 65% > 15 kg
 - > 13 years – 87% <15 kg – 100% > 15 kg
- Canine Cognitive Dysfunction Rating Scale – CCDR - Web (Salvin et al, 2010)
 - 14.2% overall - 10-12 years: 5% - 12-14 years – 23% - > 14: 41%



Risk factors

- Increased prevalence / severity with age
- Sex / neuter status: none
 - M(n) vs. M(n) or F(s) vs. Female (spayed or intact)
- Size / breed: none
 - Small dogs vs. >15 kg (11-13)
- Housing: none
- Diet: 2.8 X ↓ with any therapeutic diet vs. low quality commercial / left overs or scraps



Normal ageing (Score 0–7)

Mild cognitive impairment (8–23)

Moderate impairment (24–44)

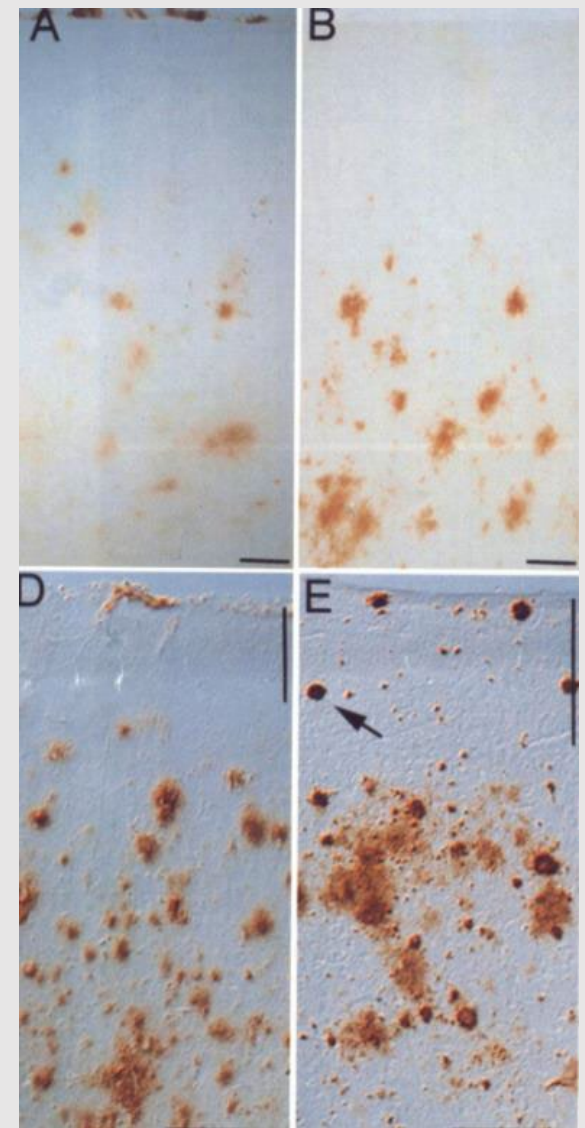
Severe impairment (45–95)



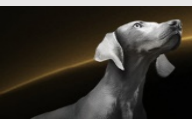
Brain Aging and CDS

Analogous to early Alzheimer's disease

1. Cognitive decline – behavioral signs - DISHAA
2. Social relationships
3. Measurable deficits in learning, memory
4. Parallels in age-associated brain pathology
 - Structural and functional changes
 - ↓ frontal/temporal lobe volume, ventricles enlarge
 - Neuronal loss – decline in neuronal function
 - Diffuse beta-amyloid (A β) plaques
 - Intraneuronal hyperphosphorylated tau
 - Vascular damage / compromise
 - Oxidative stress and mitochondrial dysfunction
 - Neuroinflammation (non-resolving)
 - Altered cholinergic neurotransmitter systems
 - Impaired glucose metabolism



A. 13 yr. Beagle; B. 90 yr female
D. 12 yr. Beagle dementia
E. 86 yr. male AD - senile plaque

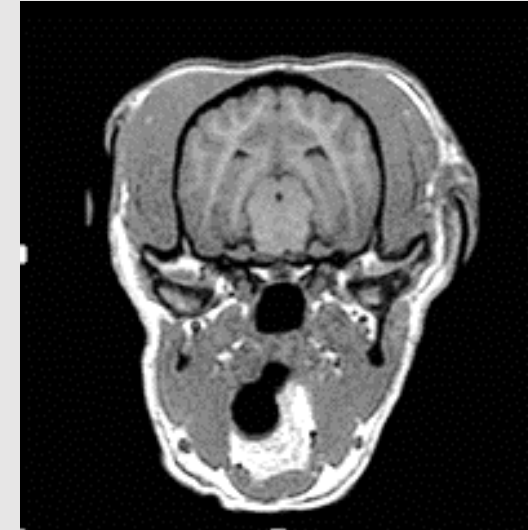
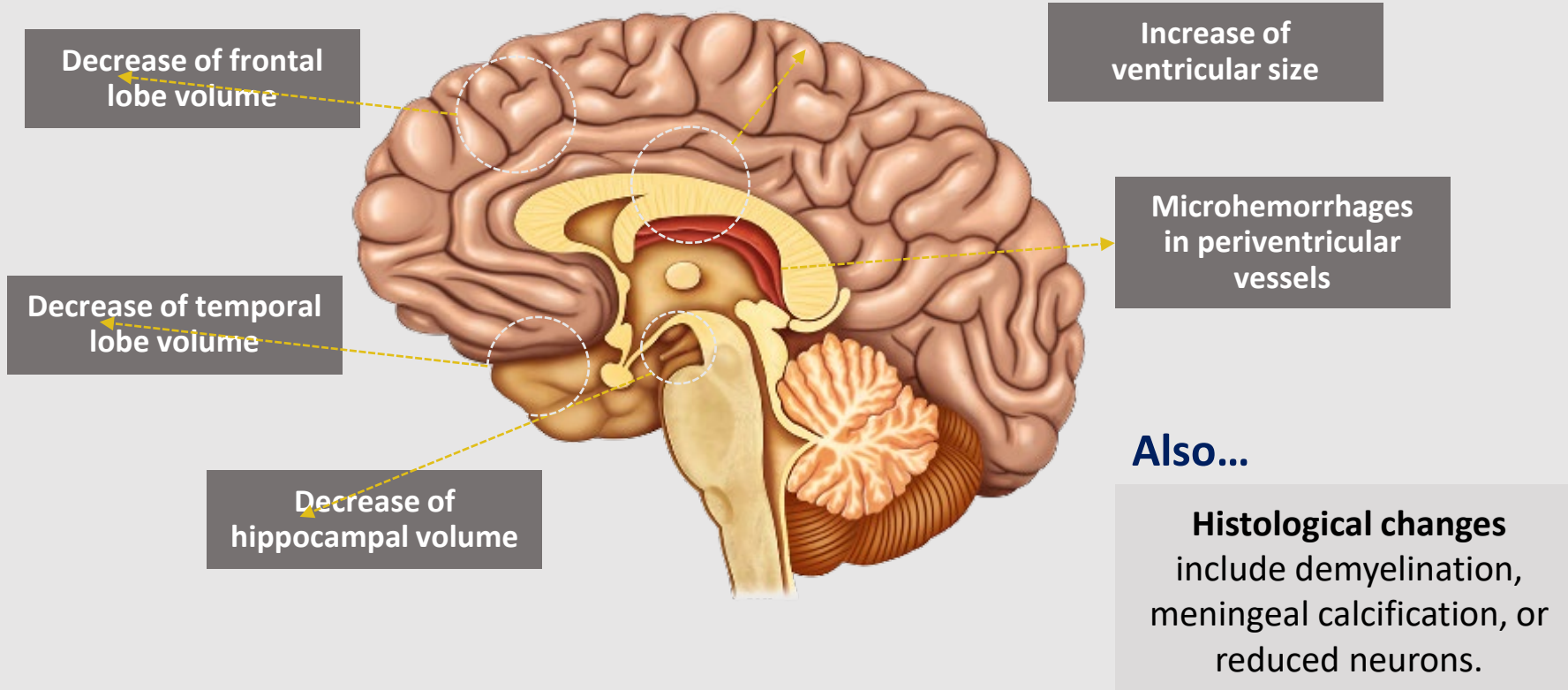


Effects of age on the brain

Aging produces structural and functional changes in the brain which can be associated with cognitive dysfunction.^{1,2}

1. Vite, C.H., Head, E. (2014). Aging in the canine and feline brain. *Vet Clin N Am Small Anim Pract* 2014

2. Tapp, P.D. *et al.* (2004). Frontal lobe volume, function, and beta-amyloid pathology in a canine model of aging. *J Neurosci* 2004.



Normal Brain



Dementia



Risk factors

Beta-amyloid pathology

Tau pathology

Genetic factors

Impaired glucose metabolism

Oxidative stress

Inflammation damage

Hypoperfusion

DHA deficiency

Low B6, B12 and folate

High homocysteine

Hypertension

Mitochondrial dysfunction

Ischemia / microinfarcts

Coronary heart disease

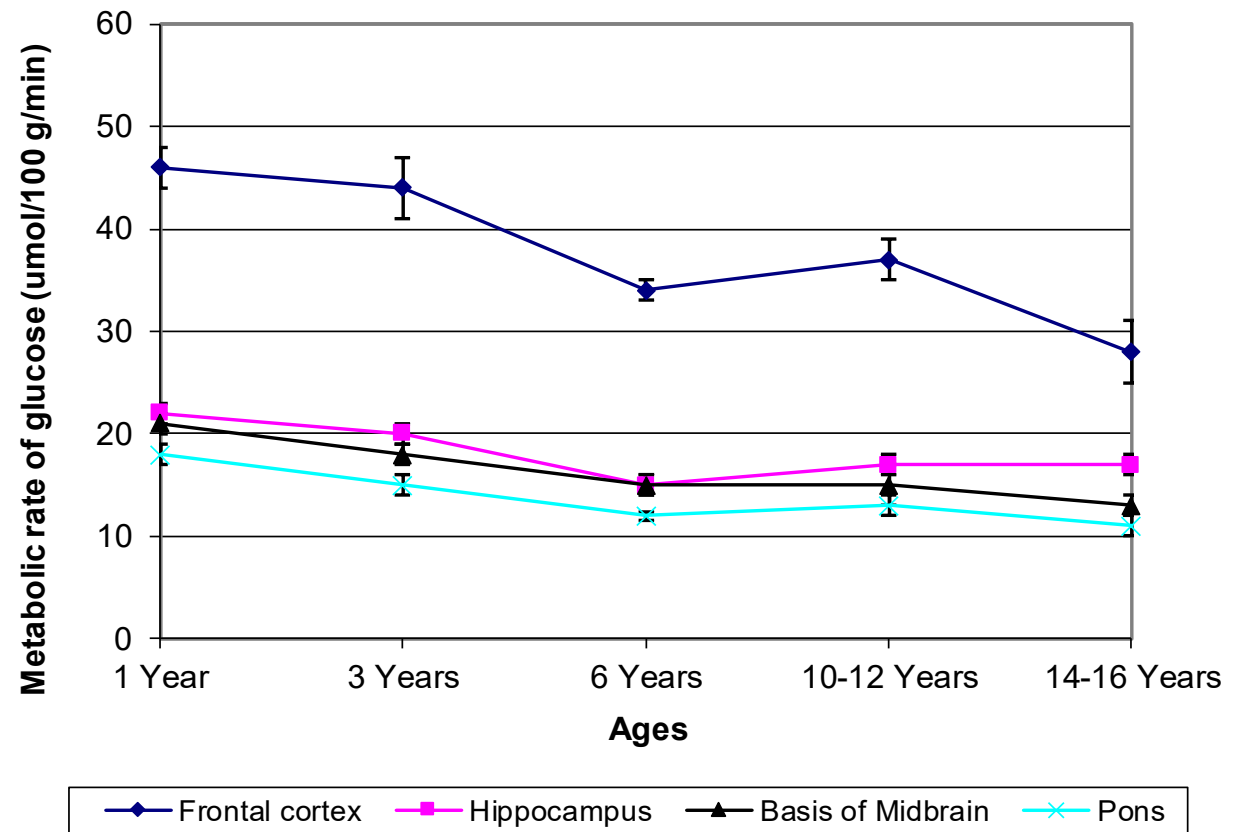
Brain injuries (concussion)

Diabetes

Obesity

Reduced neurogenesis

Heavy metal toxicity (Pb, Hg, Al)



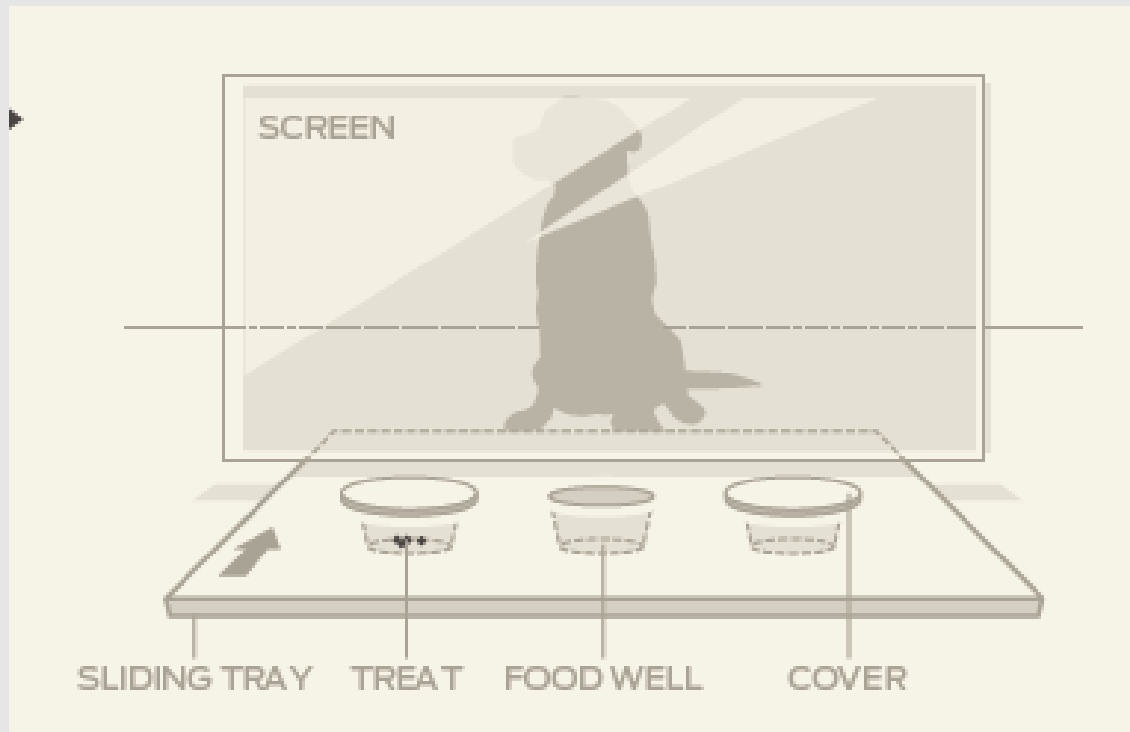
Decline in brain metabolic rate for glucose with age

London et al, Neurobiology of Aging, 4:121-126, 1983

Onset and Presentation of Signs



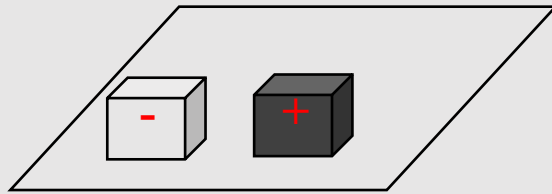
- Clinical signs – soiling, training, sleep – onset 8-11+ years
- Neuropsychological tasks (TGTA) - Ability to learn complex tasks declines by 6



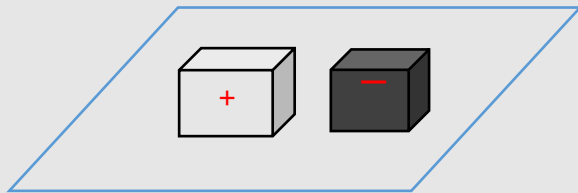
	Task
Procedural learning	Reward approach
Complex learning	Complex discrimination DNMP acquisition
Executive function	Reversal learning, oddity
Working memory	DNMP
Selective attention	Variable object discrimination
Visuospatial function	Landmark, egocentric



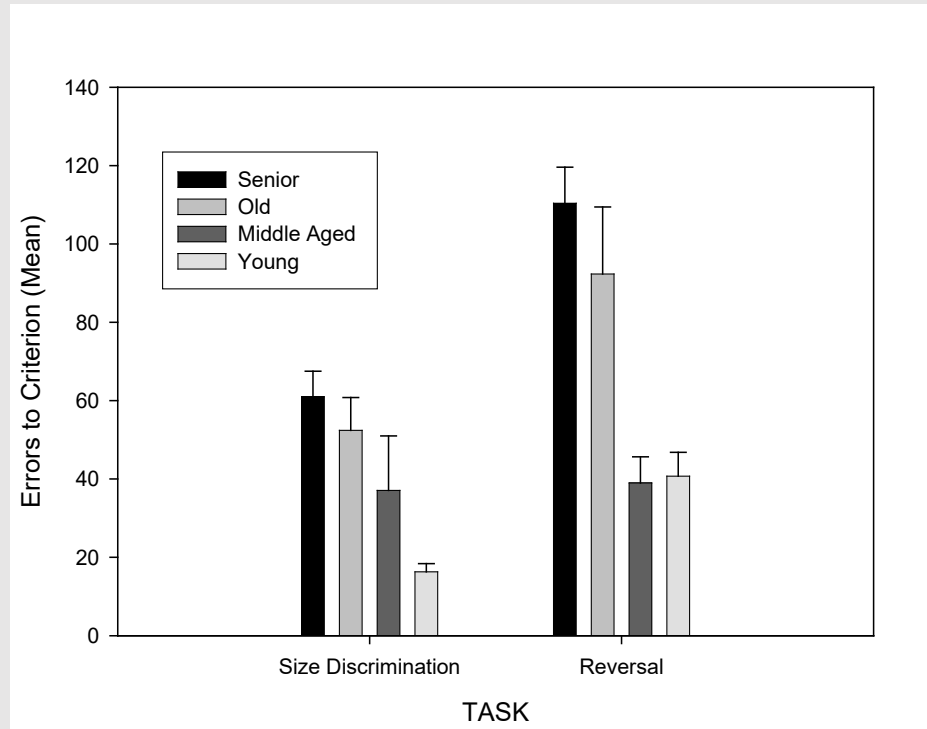
Discrimination and Reversal Learning



**Black White Object
Discrimination**



Reversal

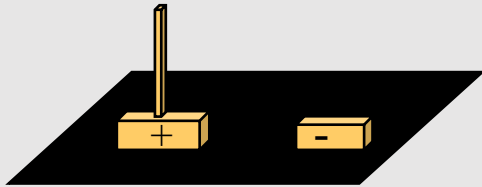


- Simple discrimination learning shows little change with age
- Performance deteriorates when objects similar or more complex
- Significant age differences in errors to criterion with reversal learning

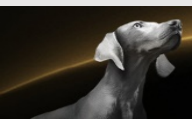
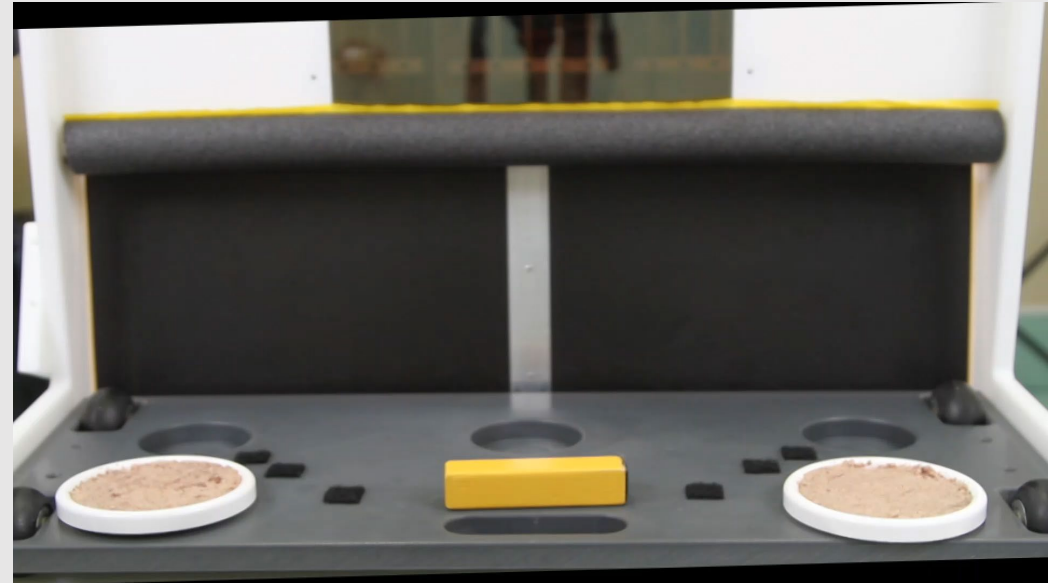
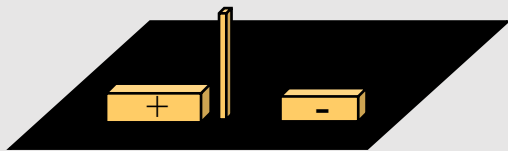


Visuospatial Learning - Landmark (Allocentric)

Land 0 - Landmark on object covering food well

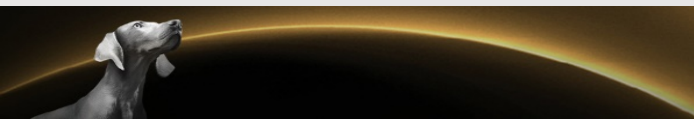


Land 1 - Landmark 1 cm from center of object



CDS - Recognition, Reporting and Screening

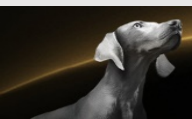
- Twice yearly senior veterinary visits – proactive, screen, counsel, diagnose
 - Early – Maintain / Improve / Slow / Resolve health, behavior, Q o L
 - Classes – attending class may mitigate progression and may prolong life
- 1. **Pet Owner** Reporting – Health and Behavior - **DISHAA screening**
 - 14.2% prevalence / 85% not diagnosed (Salvin et al, 2009) - Mild seldom reported
 - Owner education – resources / clinic website - history - questionnaire
- 2. **Veterinary** Senior Exam – oral, ophthalmic, otic, palpate
- 3. **Laboratory/Diagnostic** - Senior Screening – blood, urine, bp



Healthy Dog Screening

41 senior based on size (4-9) / 59 geriatric (6-12+) Willems et al, JVIM 2017

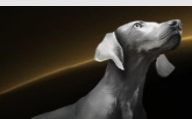
- Subcutaneous masses 56
 - ↑ Systolic blood pressure 53
 - Overweight 39
 - Heart murmurs 22
 - Severe dental calculus 21
 - ↑ creatinine 32
 - Proteinuria 31
 - ↑ alkaline phosphatase / ↑ ALT 27 / 25
 - Bladder infections 4
-
- Geriatric > orthopedic, subcu-masses, platelets - < temp, PCV, albumen, TT4



CDS Diagnosis – Screening and Reporting

- Owners must report signs arising or progressing from > 7 yrs
- CCDR: 13 items (Salvin 2013 Vet Rec)
 - 6 month change - pace, stare, stuck, drop food
- CADES (DISH): 17 items (Madari 2015, AABS)
 - Spatial, Social, Sleep, Housesoiling
 - 6 mos: 42% none to mild – 24 % mild to moderate
 - 1 yr: 71% none to mild – 50% mild to moderate
- DISHAA – 39 items to 19 (incl dropped food)
 - All / early signs – sensitivity – screening
 - 0-3 frequency / severity – Purina Institute (Landsberg)

D DISORIENTATION	<ul style="list-style-type: none">• Gets stuck, difficulty getting around objects, goes to hinge side of door• Stares blankly at walls, floor, or into space• Does not recognize familiar people/familiar pets• Gets lost in home or yard• Less reactive to visual (sights) or auditory (sounds) stimuli
I SOCIAL INTERACTIONS	<ul style="list-style-type: none">• More irritable/fearful/aggressive with visitors, family or other animals• Decreased interest in approaching, greeting or affection/petting
S SLEEP/WAKE CYCLES	<ul style="list-style-type: none">• Pacing/restless/sleeps less/waking at night• Vocalization at night
H HOUSESOILING, LEARNING AND MEMORY	<ul style="list-style-type: none">• Less able to learn new tasks or respond to previously learned commands/name/work• Indoor soiling of urine ___ or stool ___/decreased signaling to go out• Difficulty getting dog's attention/increased distraction/decreased focus
A ACTIVITY	<ul style="list-style-type: none">• Decrease in exploration or play with toys, family members, other pets• Increased activity including aimless pacing or wandering• Repetitive behaviors, e.g., circling ___ chewing ___ licking ___ star gazing ___
A ANXIETY	<ul style="list-style-type: none">• Increased anxiety when separated from owners• More reactive/fearful to visual (sights) or auditory (sounds) stimuli• Increased fear of places/locations (e.g., new environments/going outdoors)



CDS - Diagnosing Signs

- Diagnosis of Exclusion – based on signs
- Differentials – Medical, behavioral, drugs
 - Pain / neurologic / sensory / metabolic
- History: video – ALL signs – onset / progression
- Physical exam: r/o medical – *associated signs*
 - hearing, visual, tendency to smell, sway, tremors
- Diagnostics: based on screening, history/signs, exam
 - blood, urine, fecal, imaging, scope
 - Therapeutic response (e.g. analgesic)



“and if you’re the owner of a very old cat, this little baby comes with a speaker that amplifies the sound of the can being opened.”



Medical Differentials

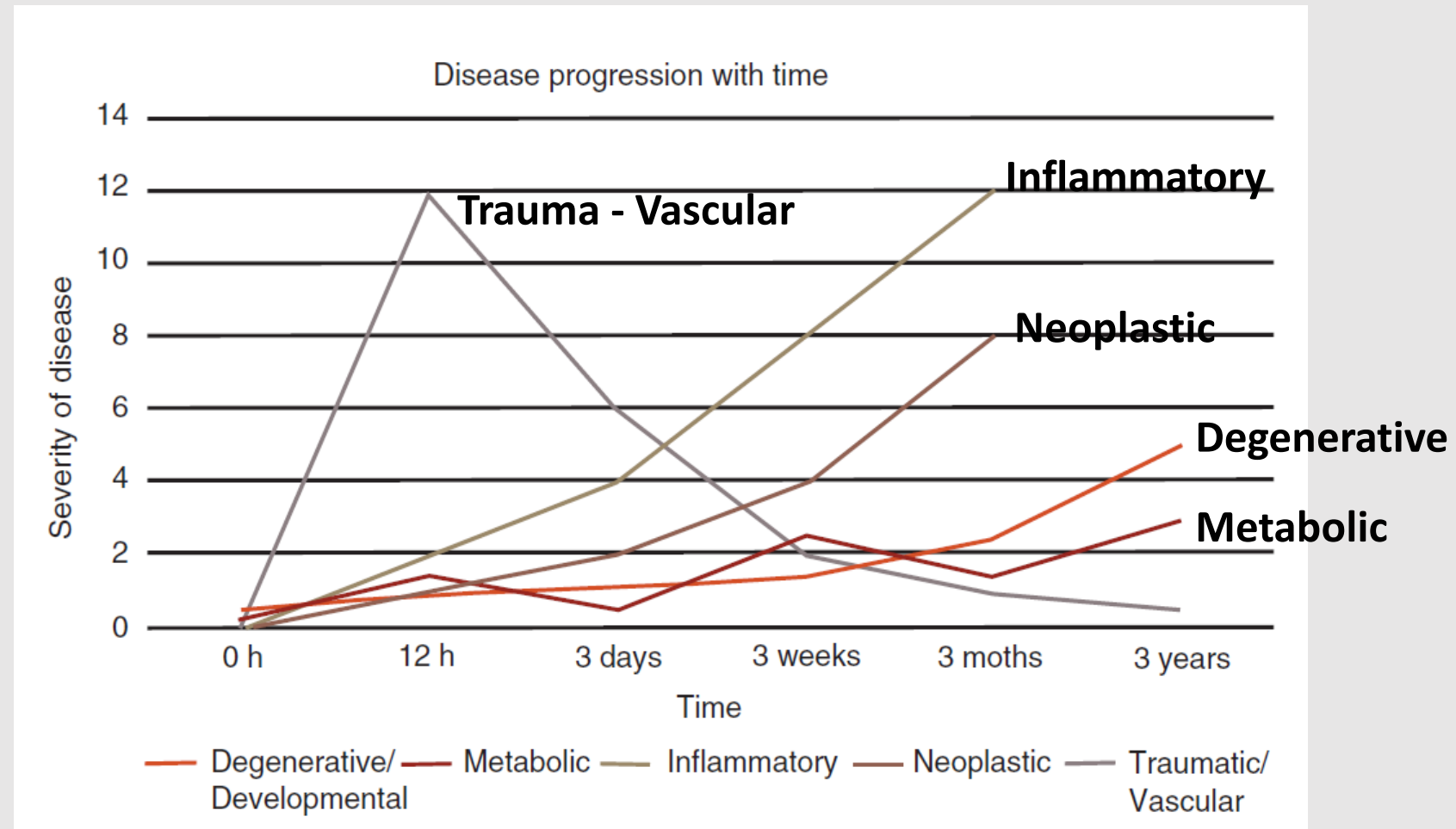
- CNS disease – intracranial and extracranial (e.g. toxins, perfusion) can directly alter mentation, response to stimuli, social interactions, learning and memory, demeanor (anxiety), activity and sleep
- Disease, degenerative, pain, sensory decline can lead to anxiety, withdrawal, avoidance, irritability, aggression, altered social interactions, soiling, and altered sleep.
- Sensory evaluation essential – owner / veterinary
- Pain evaluation essential – owner / veterinary
- Response to therapy

System	Possible causes	Possible behavioural signs
Sensory	Cataracts/lenticular sclerosis	Fear/anxiety
	Loss of vision	Disorientation
	Loss of hearing	Decreased response to stimuli
		Reduced learning ability
	Aggression	
	Avoidance	
	Vocalisation	
Pain/musculoskeletal	Degenerative diseases	Avoidance
	Arthritis	Reduced interest in exercise or play
	Muscular dystrophy	Altered response to stimuli; aggression
Reduced self-hygiene		
Increased vocalisation		
Cardiovascular	Mitral insufficiency	Disorientation
	Hypertension	Tiredness or reduced interest in play and activity
		Withdrawal/avoidance
	Cardiomyopathy	Irritability
		Fear/anxiety
Changes in appetite		
	Vocalisation	
Endocrine	Diabetes mellitus	All signs of cognitive dysfunction
	Insulinoma	House soiling/urine marking
	Diabetes insipidus	Appetite – increased/decreased
	Hypothyroidism	Activity – increased/decreased/apathy
	Hyperthyroidism	Irritability
	Hyperadrenocorticism	Aggression
	Hypoadrenocorticism	Sleep-wake cycle
Stereotypic – licking		
Restlessness – pacing		
Vocalisation		
Digestive	Dental diseases	Reduced appetite
	Hepatic diseases	Aggression/irritability
	Infectious/inflammatory	Avoidance/withdrawal
	Constipation	House soiling
	Nutritional imbalances	Night-time waking
	Pain	Stereotypic – pacing/licking
Coprophagia		
Urinary	Renal diseases	House soiling/markings
	Urinary tract infection	Aggression
	Idiopathic cystitis	Withdrawal/avoidance
	Urolithiasis	Pacing
	Urinary incontinence	Sleep-wake changes



Behavioral diagnosis

- Signs / description
- Onset
- Progression
- History
 - Social / environment
- Owner response
- Video



Molly – 12 yr F(s) - Schnoodle

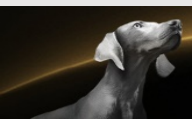
- Physical health - mild decline hearing / vision - mild hip OA
- NAF – blood / urine – stable on thyroid meds
- Confusion: Lays down to eat – drops food / not retrieve
- Social / Activity: Less interactive / playful
- Anxiety: Follows (up / down steps)
- Will not go into yard without coaxing





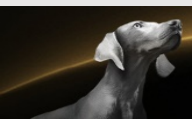
Management and Treatment of CDS

- Improve signs – slow / prevent progression
 - Improve neuronal health and neurotransmission
 - Reduce oxidative stress
 - Correct metabolic changes
 - Improve mitochondrial function
 - Improve oxygenation to the brain
- Physical / behavioral health – welfare - Limits
- Behavioral needs – Enrichment
- Functional Foods / Supplements / Medication



Enrichment / Nutrition

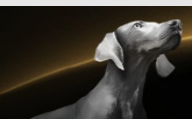
- Reduce risk / improve signs / slow progression
- Human: Nutrition + Enrichment - mental / physical / social
 - Enrichment - Social / exercise and ↓ ROS
 - Nutrition – Mediterranean diet (fruits, veg, nuts, fish) – omega 3 + B vitamins
- Pet Nutrition + enrichment
 - **Enrichment** - Mental / Social / Physical – pet needs / limitations
 - B/D plus enrichment > diet or enrichment alone
 - Work for physical / mental enrich – train/learn, agility, food puzzles, search
 - Sensory – visual, sound, odor – sniff, tactile
 - **Nutrition** - Addressing risk factors - Sole vs. combined / blend





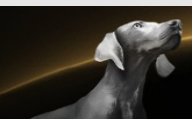
Drugs for CDS

- Selegiline^{CT,L} - MAOB inhibition - Enhance catecholamine transmission - Anti-oxidant
- Propentofylline - Xanthine derivative - Increase blood flow - decrease thrombus
- Nicergoline - alpha adrenergic antagonist - ↑ cerebral blood flow; neurotransmission
- Memantine – NMDA antagonist - block glutamate which may induce neurotoxicity
- Cholinergic decline – avoid anticholinergics
 - Acetyl (butyryl) cholinesterase inhibitors^L – phenserine, galantamine, donepezil
- Crisdesalazine^{CT} – reduce inflammation - inhibit antioxidant activity
- Stem cell implant / Immunotherapy
- Adjunctive medication for clinical signs / anxiety / sleep – health, compatibility



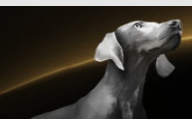
Nutrition –Supplements and Diets

- Hills b/d diet ^{CT,L} - mitochondrial cofactors, antioxidant, EFA
- Purina Medium chain triglyceride (MCT) diet ^L
- Purina – MCT + Brain protection blend ^{CT}
- S-adenosylmethionine (Novifit) ^{CT,L} - methyl donor
- Senilife ^{CT,L} - Phosphatidylserine (PPS), antioxidants – trial + laboratory
- Aktivait ^{CT} – PPS, l-carnitine/alpha-lipoic, EFA, antioxidants - trial
- DHA^L, alpha-lipoic/l-carnitine^L, Huperzine A, cholidin, curcumin
- Homotaurine ^L - ↓ beta-amyloid
- Um-Palmitoylethynolamide (PEA) - neuroinflammation,
- DiSenior – spatial navigation + cell culture – Krill oil, Gingko biloba, Co-Q, vit E ...



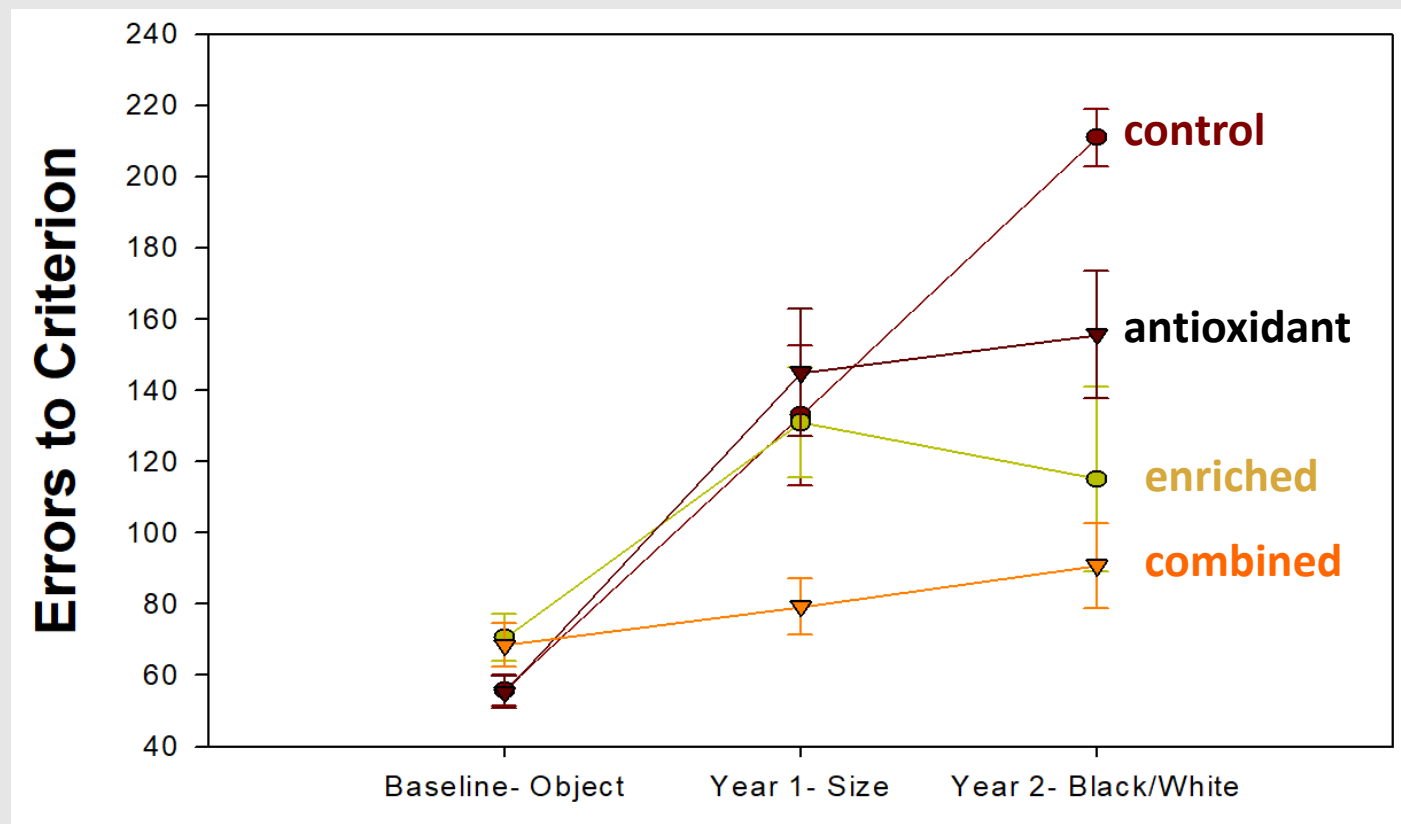
Canine Prescription B/D

- Senior formulated – restricted sodium / phosphorus
- Antioxidants: Vit. E, C, Selenium, beta-carotene, flavonoids, carotenoids
- Omega-3 FA
- Mitochondrial efficacy - α -lipoic acid / l-carnitine
- Neuropsychological (3 year) + Clinical Trials (DISHA)
 - 24 Control diet - 12 enriched environment
 - 24 Enriched diet – 12 enriched environment
 - Effect of diet 8 weeks (Landmark); 6 months (Attention)
 - Annual all dogs 1 / 2 years all dogs



Discrimination Reversal Learning

- Diet
 - Improved mitochondrial function
 - Reduced oxidative damage
 - Reduced beta-amyloid pathology
- Enrichment
 - Protect against neuronal loss



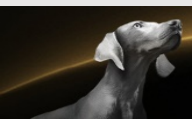
Diet + Enrichment > Enrichment > Diet > Control



Medium Chain Triglycerides (MCT)



- Brain glucose metabolism decreases with age which may contribute to cognitive impairment in dogs and to MCI and AD in humans
- Brain uses ketones as alternative (backup) source of energy to glucose
- Dietary MCT metabolized to ketone body β -hydroxybutyrate (BHB) by liver
- In humans, MCT improved cognitive performance in mild AD
- 5.5% MCT diet laboratory trial compared to control diet – n=24
 - 7 months – Improved Landmark 1 & 2, egocentric reversal, attention
 - Increased levels of ketones (BHB)



Brain Protection Blend - BPB – Nutritional Risk Factors

Risk factors	Proposed nutritional solution	Benefit
Oxidative stress	Antioxidants - Vitamins E, C, and Se)	Protect brain against oxidative stress
Chronic Inflammation	EPA and DHA	Reduce chronic inflammation
DHA deficiency	DHA	Support brain structure & function
Hypertension	Arginine - Nitric oxide-releasing compound	Support circulation, blood pressure, cognition
High homocysteine	B vitamins	Prevent high homocysteine
Low B6, B12, folate	B vitamins	Energy metabolism, biosynthesis of neurotransmitters

Elderly humans – 2 yrs - B Vitamins reduced mean atrophy by 40% in high omega 3 group

Dogs — 6 months - BPB diet improved more difficult tasks - landmark 1, egocentric reversal

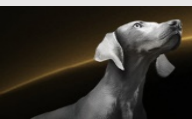
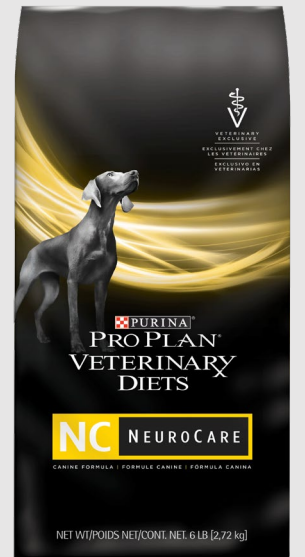


Clinical Trial – MCT + BPB

Diet with 6.5% and 9% MCT + BPB compared to control diet – 90 days

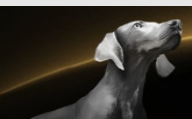
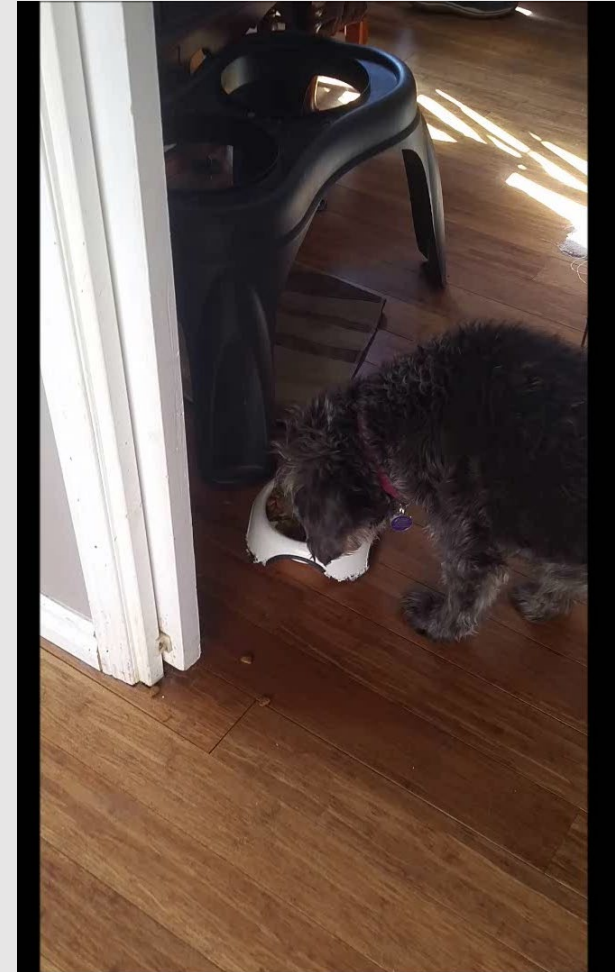
- 100 screened – 29 per group - 24 clinics - >8 years – 2 DISHAA signs
- Exclusion: medical, marked OA, marked sensory decline
- 6.5% - Significantly improved 6/6 categories – 5/6 at 30 days
- Control – Significantly improved 4/6 categories - 3/6 at 30 days
 - Not disorientation, social
 - Placebo vs. Diet Effect (B vitamins, Se, Arginine above AAFCO)
- 9 % MCT diet - Lack of improvement – palatability and compliance

Pan Y et al. Front Nutr, 2018, doi.org/10.3389/fnut.2018.00127



Molly - 90 days

- Improvement - 4/6 categories day 30 – 6/6 day 90
- Greatest improvement disorientation / anxiety / social
- On & Off couch / up & down stairs more readily
- Stands to eat - ↑interest in food – retrieves if dropped
- More playful - Less following / clingy
- More aware – can determine which treats have pills





Thank You

Veterinary Resources – Purina Institute

<https://www.purinainstitute.com/science-of-nutrition/advancing-brain-health/cognitive-dysfunction-syndrome>

<https://www.purinainstitute.com/sites/g/files/auxxlc381/files/2018-08/DISHAA.pdf>

Pet Parent Resources

https://indoorpet.osu.edu/dogs/aging_pets/cds

<https://www.purina.com/articles/dogs/health/canine-cognitive-dysfunction-syndrome>

<https://fearfreehappyhomes.com/anxiety-often-accompanies-cognitive-dysfunction/>

