# Canine Brain Ageing & Environmental Enrichment in the Geriatric Patient

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Improved nutrition and medical care have contributed to longer life spans in people and their pets. Longer pet life spans can result in an increase in the prevalence of age-related medical and behavioural conditions such as neoplasia, renal disease, heart disease and cognitive decline.[1]

Cognitive dysfunction syndrome or canine cognitive dysfunction (CCD) is a progressive neurodegenerative disorder of senior dogs characterised by gradual loss of memory and learning, and reduced problem-solving ability. The clinical signs are insidious and progressive and often not easily diagnosed at consultation. In fact, the behavioural changes associated with CCD may be more obvious to the pet owner at home than they are to the veterinarian.[2]

The brains of older dogs develop similar neuro-pathological features to the brains of elderly people.[2] Many of these features are associated with early pathology seen in normal human brain ageing, those with mild cognitive impairment and in Alzheimer's disease.[2] As in humans, the brains of older dogs accumulate senile plaques, which are thought to be neuro-toxic, between neurons. The primary constituent of these proteinaceous plaques is β-amyloid. Accumulation of these plaques has received a lot of attention as they are believed to play a causative role in development of Alzheimer's disease in elderly humans.[3] The extent of β-amyloid deposition in older canine brains is linked to the severity of cognitive deficits and behavioural changes.[4,5] Not all brain regions are equally vulnerable to β-amyloid associated pathological changes. Deposits of β-amyloid are evident in the prefrontal cortex at an earlier age and in a more consistent manner than in other cortical areas.[6] This pattern of deposition in older dogs parallels that seen in people.[6]

Accumulation of β-amyloid deposits occurs late in the disease process,[6] while the development of age-related oxidative damage may be one of the earlier pathological events. The free radical theory of ageing, first published in 1956,[7] proposed that as the body ages the mitochondria become less efficient at producing ATP, resulting in less efficient energy production and increased free radical generation. I.e. increased production of reactive oxygen species formed as by-products of cellular metabolism. The brain is particularly susceptible to free radical attack and oxidative damage because: [2]

- it has a high rate of metabolism requiring a high uptake of $O_2$
- it has a high polyunsaturated fat content, which makes it especially vulnerable to free radical attack
- it has limited antioxidant defences, and in the aged canine brain the activity of antioxidant enzymes is significantly reduced
- brain tissue has limited ability for repair.

There is increased oxidative damage to brain lipids prior to overt β-amyloid deposition, which provides evidence that oxidative damage is an early event.[8] Production of free radicals leads to oxidative damage to proteins, lipids and nucleotides, which may contribute substantially to neuronal dysfunction, and, ultimately, neuronal death. This results in an obvious reduction in the amount of functional brain tissue as evidenced by cortical atrophy and enlarged lateral ventricles, changes that are clearly visible on an MRI.[2,9] This loss of brain function in turn results in impaired learning and memory, and leads to certain behavioural changes.

The behavioural signs of cognitive dysfunction are identified by the acronym “DISH” –

**D**ISORIENTATION – Confusion, aimlessness, appears lost, decreased alertness, inability to recognise family members
**I**NTERACTION CHANGES – no longer greets family members, welcomes petting or asks for attention
**S**LEEP or ACTIVITY CHANGES – sleeps more during the day and/or less at night, wanders around the house at night, paces, pointless barking at night
**H**OUSE TRAINING LOST – doesn’t ask to go outside, frequent accidents, loss of bladder or bowel control

The signs are insidious and progressive. Early in the disease signs are subtle and may come and go, but as the disease progresses the signs become more apparent. The pet has ‘good days’ and ‘bad days’ but gradually worsens.[2]

A study of dog owners undertaken to determine the levels of DISH behaviour among dogs aged 7 or over[10] found that 75% of owners noticed at least one DISH sign, 37% observed one or more signs at least several times a week, and 32% reported three or more signs, but only 12% had discussed the signs with their veterinarian. The progressive nature of the syndrome is evidenced by the finding that older dogs with impairment in one behavioural category subsequently developed impairments in two or more categories within 12-18months.[11,12] Thus it appears that many owners can recognise the signs of CCD easily, but few do anything about it, believing that they are an inevitable part of normal ageing.

Dietary therapy has been shown to help combat signs of brain ageing and improve the learning ability of older dogs in a highly-controlled laboratory environment, in a less-controlled home environment, and in a multi-centre clinical study.[13, 15, 16] The principal behind dietary therapy for CCD is to protect against free radical damage to nervous tissue and to support efficient energy production by the mitochondria. This is achieved by inclusion of:

- high levels of the antioxidants vitamin E, vitamin C, beta-carotene and selenium to neutralise free radicals
- a combination of fruit and vegetable ingredients rich in carotenoids and flavonoids which reduces cell damage by inactivating free radicals
- mitochondrial co-factors L-carnitine and alpha lipoic acid which increase the efficiency of energy production by the mitochondria and decrease free radical production
- omega-3 fatty acids DHA & EPA which help strengthen neural cell membranes and protect them from free radical damage

Short term memory loss provides the first indication of cognitive dysfunction in humans; however methods of evaluating short-term memory loss in humans are typically neither applicable nor feasible in dogs. Neuropsychological tests were therefore developed to provide quantitative measures of cognitive function in dogs.[17]

To test the food’s ability to improve age-associated behavioural changes, a 2 year randomised, controlled clinical trial was performed using groups of old and young Beagles.[13] The dogs were fed either a base food (control) or base food supplemented with antioxidants including vitamins A and C, dl-lipoic acid, L-carnitine, and fruit and vegetable extracts. Each animal was trained in a series of learning tasks of increasing difficulty. As expected, the older animals learned more slowly and made more errors than the young dogs in all tasks and as the task became more difficult, the older animals had a harder time with it. However, the old dogs fed the test diet for 6 months made 58% fewer mistakes when learning a new task than those fed a control food. Older dogs fed the test diet also showed improved

alertness and increased attentiveness to problem-solving tasks. Learning ability was shown to be best preserved in older dogs by the use of a combined program of dietary fortification and behavioural enrichment. This combined program proved to be more effective than either dietary fortification or behavioural enrichment alone.[13]

The behavioural enrichment component included a program of cognitive enrichment, increased physical activity (exercise by hand walking on a leash for at least 30 minutes twice a week) and environmental enrichment such as being housed with another dog and the provision of toys that were rotated weekly.[13] The results of the study did not distinguish the relative importance of each of the behavioural interventions, however the researchers suspected that cognitive enrichment was particularly important. The cognitive enrichment program consisted of a broad range of tasks, all of which could be solved with a discrimination learning strategy,[13] but the mechanisms underlying the effect remain unknown. One possible explanation is that cognitive enrichment increases behavioural flexibility, and thereby modulates age-dependant cognitive decline. The second possibility is that cognitive enrichment affects brain structure, [13] a proposal supported by studies in which an increased number of synaptic contacts were found in the cerebellum of rats trained on a motor learning task.[14]

So, as the saying goes in people, and as it appears to apply in dogs, “if you don’t use it, you lose it” - mental exercises may help to delay the progression of senility and dogs are never too old to learn new tricks. Advising owners to add hand signals to commands may help a dog with hearing loss to understand, and the mental activity can improve overall cognitive function. Encouraging owners to implement behavioural enrichment by providing different and alternating toys, playing with their dog and continuing to stimulate their pet mentally are important components of CCD management.

The test diet described above was also evaluated in the home by owners of older dogs.[15] Two in-home use studies were conducted with dogs aged 7 years and older: the dogs were evaluated by their owners by comparing behaviour before and after feeding their current food or the test diet. In the first study, after only 30 days of feeding the test diet, owners reported significant improvements in all DISH signs. Results from the second study reported that enthusiasm in greeting family members increased in 61% of older dogs fed the test diet, and 74% of older dogs with a history of house-soiling ‘accidents’ experienced a reduction in accidents after consuming the test diet.

Finally, a 60-day, double-blinded, randomised, multi-centre clinical trial involving 125 dogs aged 7 years or older was published in 2003.[16] These dogs had a history of cognitive decline, with clinical signs in at least two of the DISH categories. A standardised questionnaire was completed by owners on day 1 & day 60. Dogs consuming the test diet showed significant improvements in 13 of 15 individual behavioural attributes across all DISH categories.

Drug therapies are also available for the management of cognitive dysfunction in the dog. Propentofylline is a selective inhibitor of adenosine transport and phosphodiesterase.[18] It has been shown to improve blood flow to the brain and other areas of the body in geriatric dogs.[19] In human medicine this pharmaceutical is at an advanced stage of clinical development for the long-term therapy of patients with Alzheimer's disease and vascular dementia. As discussed earlier, the neuropathological changes in the brains of senile dogs are similar to those seen in human patients suffering from Alzheimer's disease. Clinical studies in humans and experimental studies in animals have led to the adoption of this therapeutic approach in canine cognitive dysfunction.[20]

Another possible cause of canine cognitive dysfunction is depletion of dopamine, a chemical neurotransmitter vital to normal brain function. As such, medications that increase dopamine

or extend its activity can decrease the signs of senility in both animals and people. Selegiline (or L-deprenyl, Anipryl) prolongs the activity of dopamine in the brain by inhibiting monoamine oxidase (MAO), the enzyme responsible for dopamine metabolism. In addition, selegiline may be neuro-protective by reducing the damage to cellular DNA caused by free radicals, or oxidisers. In a non-comparative open-label study evaluating the effect of selegiline in a clinical setting, 77% of dogs showed an overall improvement after 60 days. [21] Whilst these results are very promising, the non-blinded nature of the protocol and the lack of a control group limit the usefulness of this study. The placebo effect in studies evaluating drugs for which response to therapy is measured by a behavioural change is relatively high. In the same study, possible adverse drug events were reported in 186 (out of 641) cases. The most frequently reported clinical signs included diarrhoea (4.2%), anorexia (3.6%), and vomiting/salivation (3.4%).[21] As all MAO inhibitors can have significant drug interactions, selegiline can be contra-indicated in some geriatric dogs that require other medications for concurrent health problems.

In summary, canine cognitive dysfunction is a common problem of ageing dogs, and its clinical manifestations can have a dramatic impact on the human animal bond. Veterinary health care professionals should evaluate their senior canine patients for this disorder, perhaps by including behavioural checklists in their clinical assessments. Incorporating one or more of the management options described above in their treatment programs for patients with evidence of cognitive changes may help to prolong the extent and quality of their lives.

## References


1. Epstein M, Kuehn NF, Lascelles BDX et al. AAHA Senior Care Guidelines for Dogs and Cats. *J Am Anim Hosp Assoc* 2005;41: 81-91.
2. Roudebush P, Zicker SC, Cotman CW et al. Nutritional management of brain aging in dogs. *J Am Vet Med Assoc* 2005; 227: 722-728.
3. Selkoe DJ. Amyloid beta protein and the genetics of Alzheimer's disease. *J Biol Chem* 1996:271:18295
4. Cummings BJ, Head E, Afagh AJet al. Beta-amyloid accumulation correlates with cognitive dysfunction in the aged canine. *Neurobiol Learn Mem* 1996:66:11
5. Colle MA, Hauw JJ, Crespeau F et al. Vascular and parenchymal Abeta deposition in the aging dog: correlation with behavior. *Neurobiol Aging* 2000:21:695
6. Head E, McCleary R, Hahn FF et al. Region-specific age at onset of beta-amyloid in dogs. *Neurobiol Aging* 2000:21:89
7. Harman D. Aging: a theory based on free radical and radiation chemistry. *J Gerontol* 1956;11:298-300.
8. Pratico D, Uryu K, Leight S et al. Increased lipid peroxidation precedes amyloid plaque formation in an animal model of Alzheimer amyloidosis. *J Neurosci* 2001;21:4183-4187.
9. Cotman CW, Head E. The neuropathology of Alzheimer's Disease. *Hill's European Symposium on Canine Brain Ageing*, 2002.
10. U.S. Marketing Research Summary. Omnibus Study on Aging Pets. November, 2000. Data on File. Hill's Pet Nutrition, Inc.
11. Neilson JC, Hart BL, Cliff KD, Ruehl WW. Prevalence of behavioral changes associated with age-related cognitive impairment in dogs. *J Am Vet Med Assoc* 2001:218:1787
12. Bain MJ, Hart BL, Cliff KD, Ruehl WW. Predicting behavioral changes associated with age-related cognitive impairment in dogs. *J Am Vet Med Assoc* 2001:218:1792-1795.
13. Milgram NW, Head E, Zicker SC et al. Learning ability in aged beagle dogs is preserved by behavioural enrichment and dietary fortification: a 2 year longitudinal study. *Neurobiol Aging* 2005;26:77
14. Anderson BJ, Alcantara AA, Greenough WT. Motor-skill learning: changes in synaptic organisation of the rat cerebellar cortex. *Neurobiol Learning and Memory*, 1996: 66: 221-229
15. Hill's Prescription Diet b/d Canine In-Home Use Tests I & II. Data on file. Hill's Pet Nutrition Inc. 2001
16. Dodd CE, Zicker SC, Jewell DE et al. Can a fortified food affect the behavioral manifestations of age-related cognitive decline in dogs? *Vet Med* 2003;98:396
17. Milgram NW, Head E, Weiner E, Thomas E. Cognitive functions and aging in the dog: acquisition of nonspatial visual tasks. *Behav Neurosci* 1994;108:57-68.
18. Scaramuzzi RJ and Baker DJ. Possible therapeutic benefits of adenosine-potentiating drugs in reducing age-related degenerative disease in dogs and cats - 2003 *J Vet Pharm Therapeutics* 26:327-335
19. Hudlicka O, Komarek J and Wright AJ. The effect of a xanthine derivative, 1-(5' oxohexyl)-3-methyl-7-propylxanthine (HWA 285), on heart performance and regional blood flow in dogs and rabbits (1981) Br *J Pharmacol* 72(4):723-730.
20. Kapl D and Rudolphi KA. New pharmacological aspects in the neurological profile of Propentofylline. Tierarztliche Praxis Ausgabe K: *Kleintiere - Heimtiere* 1998 26:317-321
21. Campbell S, Kozan B, Trettien A. A Noncomparative Open-Label Study Evaluating the Effect of Selegiline Hydrochloride in a Clinical Setting* 2001 *Vet Therapeutics* • Vol. 2, No. 1, Winter 2001




 