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Title

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<https://escholarship.org/uc/item/54c8g8np>

Journal

Veterinary Clinics of North America Small Animal Practice, 44(6)

ISSN

0195-5616

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Publication Date

2014-11-01

DOI

10.1016/j.cvsm.2014.07.008

Peer reviewed



Published in final edited form as:

Vet Clin North Am Small Anim Pract. 2014 November ; 44(6): 1113–1129. doi:10.1016/j.cvsm.2014.07.008.

Aging in the Canine and Feline Brain

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Keywords

β-Amyloid; Cat; Dog; Cognitive dysfunction; Neuron loss; Tau

INTRODUCTION

This article reviews canine and feline brain aging. Several key features are discussed and compared, including general aging characteristics and neuropathology. Aging dogs and cats show many similarities in terms of brain changes but also some important differences. Several research groups have been working with aging dogs and cats to test various theories of aging and to develop therapeutics that will be beneficial to both species.

The median life span of dogs varies as a function of breed, with larger breeds typically having shorter life spans than smaller breeds.^{1–3} For the purposes of this article, several studies that are described have been collected in purpose-bred beagles and additional companion animals and clinical data are shared when available. Beagles have a median life span of 13.9 years, with no significant differences between males and females.⁴ A young beagle less than 5 years old is similar to humans who are less than 40 years old.³ Middle-aged beagles between 5 and 9 years are similar to humans between 40 and 60 years and beagles more than 9 years old are similar to humans more than 60 years old. However, the larger the breed of dog, the shorter the life span and thus biological age may vary across breeds given a specific age.¹

In a laboratory setting and in the veterinary clinic, studies of aging dogs report that some but not all aged dogs are impaired on different measures of learning and memory (see Refs.^{5–7}). Not all old dogs are impaired and not all types of learning and memory are equally affected. Neurobiological changes, as described later, can account for some, but not all, of the clinical signs of cognitive decline in aging dogs.

NEUROBIOLOGY OF AGING IN THE DOG

This article describes several neurobiological changes associated with aging in dogs (Table 1).

Brain Atrophy

Old dogs often show marked ventriculomegaly at postmortem examination associated with thinning of the cerebral cortex and the subcortical white matter.⁸ Magnetic resonance imaging (MRI) studies performed on aged beagle and German shepherd dogs show that cortical atrophy, identified as widened sulci, thinned parenchyma,⁹ and ventricular dilatation,^{9–11} progresses with age and is a consistent feature of canine brain aging. Furthermore, MRI studies suggest differential vulnerabilities of specific brain areas to aging. For example, in aging beagle dogs, the prefrontal cortex loses tissue volume at an earlier age (approximately 8–11 years) than does the hippocampus (after 11 years).¹² An MRI study by Hasegawa and colleagues¹³ (2005) suggested that although interthalamic adhesion thickness was smaller in older dogs, those showing age-related cognitive decline and a single dog with GM1 gangliosidosis also had a significant decrease in the thickness.

Periventricular white matter signal abnormalities are frequently seen in MRI of various dog breeds greater than 12 years of age that are evaluated for seizures, vestibular disease, or behavioral abnormalities. These bilaterally symmetric T2-weighted hyperintensities of the internal capsule are suspected to be caused by wallerian degeneration, demyelination, and accompanying gliosis.¹⁴

Selective Neuron Loss

Atrophy may result from neuron loss or changes in neuronal density, as reported in normal human brain aging,^{15,16} although more extensive neuronal loss occurs in Alzheimer disease (AD).^{17,18} When neurons were counted using unbiased stereological methods within individual subfields of the hippocampus of young (3.4–4.5 years) and old (13.0–15.0 years) dogs, the aged dogs had significantly (~30%) fewer neurons in the hilus of the dentate gyrus.¹⁹ A study by Pugliese and colleagues²⁰ (2007) showed that cognitive deficits correlated with loss of Purkinje cells in the cerebellum. More recently, a study by Insua and colleagues²¹ (2010) examined noradrenergic neurons in the locus coeruleus of aged canines, a group of neurons that are implicated in AD in humans.^{22,23} Dogs that are cognitively impaired show a significant reduction in noradrenergic neurons. Reduced neurogenesis in the mature brain may also contribute to reduced neuron numbers and age-associated cognitive decline, resulting in slower replacement of dying neurons. In the hippocampus of beagles, a 90% to 95% decline in neurogenesis was measured in aged dogs.²⁴ Similar reductions in neurogenesis in aged dogs have been reported by other investigators.²⁵

Senile Plaques (β -Amyloid) in Dogs

A key feature of canine brain aging was the observation in 1956, by Braumühl, who reported Alzheimer-like senile plaques in aged dogs (reviewed in Ref.²⁶). Senile plaque accumulation in the aged canine brain has been well described.²⁶ Senile plaques are composed of β -amyloid (A β) protein, and are one of 2 key types of neurologic pathologies observed in the

AD brain.²⁷ The A β peptide is produced by the sequential cleavage of the amyloid precursor protein (APP) by beta-secretase and gamma-secretase.^{28,29} Cleavage by gamma-secretase results in differing lengths of A β , with the 42 amino acid form, A β 1-42 making up most of the insoluble deposits found in the AD brain.³⁰ One of the reasons why the canine brain has been examined extensively for A β neurologic disorder is that dogs and humans share an identical amino acid sequence of the protein.^{31,32} A β is thought to be a causative factor for AD in people.³³ The observation of brain A β first stimulated interest in the use of the dog to model human aging and disease.³⁴ Diffuse plaques are the predominant subtype of A β in the aging dog brain (Fig. 1).³⁵⁻⁴⁰ Specific brain regions are differentially vulnerable to A β .^{36,41-46} When cortical regions are sampled for A β deposition, each region shows a different age of A β onset.⁴³ In the dog, A β deposition occurs earliest in the prefrontal cortex (see Fig. 1C, D) and later in the temporal cortex, hippocampus (see Fig. 1A, B), and occipital cortex.⁴⁵

Beagles that show learning and memory impairments in a laboratory setting with systematic cognitive tests also show higher levels of A β plaques than those old dogs without cognitive impairments.⁴⁷⁻⁵⁰ For example, dogs with prefrontal cortex-dependent reversal learning deficits show significantly higher amounts of A β in this brain region.^{48,49} As in laboratory beagles, the extent of A β plaques varies as a function of age in companion dogs (including a wide variety of breeds and mixed breeds).⁵⁰⁻⁵² Further, the extent of A β plaques correlates with behavior changes and this association remains significant even if age is removed as a covariate.^{47,50} Case report 1 and Figs. 1 and 2 show a case study of cognitive decline and age-associated A β neurologic disorder in a border collie.

Case report 1

Martha was a female border collie that was a very competent farm dog with what her owner called “lots of sheep savvy.” She was also a fully integrated family member and companion to the family when hiking, skiing, and mountain biking. In addition, she successfully competed in sheep dog trials till the age of 10 years (see Fig. 1A). She and her handler worked their way through the succession of novice-level trials, winning several, and ultimately competing and placing in the highest level, the Open class, which attests to her skill (see Fig. 1B).

By the time Martha was 11 years old she was nearly deaf and slow enough that she could no longer trial. She started to show some confusion with commands at which she was expert. For example, one day her owner took her out in the field and gave her a command to go counter clockwise around the sheep and she went clockwise. Further, when her owner next said “OK, go clockwise” she reversed her direction, when she should have continued the clockwise direction (see Fig. 1C). The next time her owner was working with her, a normally benign ewe turned around to face Martha and stomped her foot. Martha, who would normally have politely stood her ground until the sheep backed down, promptly turned away and left the field. The owner at this time thought, “Well that is proof that Martha is fully retired now.” Not long after the incident with the ewe, the sheep began to act as if Martha did not even exist.

Over the next 2 years, changes in Martha were subtle and included increasing hearing loss and stubbornness. She also stopped having interest in the sheep, and appeared most fixated with another dog (Ida) in the family. Several behaviors with the other dog appeared abnormal. For example, Martha would stare at Ida, the middle dog, whether they were inside or out walking, and then would stalk Ida, despite a lack of interest from Ida in interacting. The owners had to intervene frequently to prevent a snarling episode, although the two dogs never injured each other.

To her last day, Martha's social skills with human friends persisted. However, she began pacing, panting, and getting stuck under the bedside table at night. During the day when only 1 of the owners was home, Martha was frequently anxious and sometimes clingy, which never used to be the case. She showed signs of disorientation and during walks occasionally lost the younger dogs and her owner although the same daily route was followed. Martha was once found in a road looking up and down as if lost, although she had been walking that direction for years.

Throughout her life Martha had a great appetite and generally excellent health, although she had arthritis in almost every joint in her body and was on high doses of incontinence medication and Rimadyl (a nonsteroidal antiinflammatory drug) for arthritis. For the last year of her life, the owner was unable to get a photograph of Martha looking at her because she was no longer making eye contact (see Fig. 1D).

When Martha was 14 years old, the decision was made to euthanize her and the owner donated her brain to the University of Kentucky to determine whether neurologic disorder was present. A β neurologic disorder was extensive in Martha (see Fig. 2).

The focus in AD pathogenesis has recently shifted from A β plaques to considering smaller, soluble forms of A β assemblies called A β oligomers. Oligomers are highly toxic and impair synaptic function.⁵³ Furthermore, increased oligomer levels are strongly associated with cognitive dysfunction.^{53–55} A recent study by Pop and colleagues,⁵⁶ examined the accumulation of oligomeric A β in the temporal lobe of canines. This study provided evidence that canines, like humans, experience an increase in toxic oligomers with age.

Vascular Disorders, Cerebrovascular Amyloid Angiopathy

Cerebrovascular amyloid angiopathy (CAA) is the deposition of A β in association with the cerebrovasculature (see Fig. 1D). In dogs with CAA, the blood vessels of the brain typically contain the shorter, 40 amino acid–long species of A β .^{57–59} The occipital cortex seems to be particularly vulnerable to CAA in the aged dog brain. Vascular A β may compromise the blood-brain barrier, disrupt vessel wall viability,⁶⁰ and cause microhemorrhages.⁶¹

Aged dogs may also show lacunar infarcts of the caudate nucleus and thalamus with most dogs showing no causative metabolic, endocrine, or hypertensive disease.^{62,63} In a longitudinal study, these lesions were shown to increase in number with advancing age.⁶⁴ Lacunar infarcts of the caudate nucleus have been induced experimentally in beagle dogs by proximal middle cerebral artery occlusion.⁶⁵ The cause of naturally occurring lacunar infarcts in dogs remains unidentified.

Tau Neuropathology

Unlike humans but like many other animal species, canines do not develop full-blown neurofibrillary tangles,^{32,37,39,40} which is the second neuropathologic characteristic of AD. However, aged dogs show the accumulation of several phosphorylated tau epitopes that are consistent with AD in humans and observations in aged cats (described later).⁶⁶ In a study of cognitively impaired pet dogs that included a variety of breeds, intracellular phosphorylated tau was observed that was similar to the AD brain.⁶⁷

Oxidative Damage and Mitochondrial Dysfunction

Aging and the production of free radicals can lead to oxidative damage to proteins, lipids, and nucleotides that, in turn, may cause neuronal dysfunction and ultimately neuronal death. In the aging dog, the brain accumulates carbonyl groups, which are a measure of oxidative damage to proteins.^{68,69} Carbonyl groups are associated with reduced endogenous antioxidant enzyme activity or protein levels, including those of glutamine synthetase and superoxide dismutase (SOD).^{68,70–72} In addition, increased oxidative damage to proteins can be measured by the end products of lipid peroxidation (oxidative damage to lipids), including 4-hydroxynonenal,^{50,52,72,73} lipofuscin,⁵⁰ lipofuscinlike pigments,^{52,73} or malondialdehyde.⁶⁸ In addition, oxidative damage to DNA or RNA may be increased in the aged dog brain.^{5,50}

Oxidative damage may also be associated with behavioral decline in dogs. Increased oxidative end products in the aged companion dog brain are correlated with more severe behavioral changes.^{50,52,69} In laboratory studies of aging beagles, higher protein oxidative damage (3-nitrotyrosine) and lower endogenous antioxidant capacity (SOD and glutathione-S-transferase activities) are associated with poorer prefrontal-dependent and spatial learning.⁷¹ Mitochondria are sources of free radicals that damage proteins, lipids, and DNA/RNA.⁷⁴ In a study of aged beagles, isolated mitochondria showed increased reactive oxygen species production in aged animals relative to young animals.⁷⁵ Thus, aged dogs show mitochondrial dysfunction and oxidative damage, consistent with humans with age-related neurologic dysfunction.

Correlates of Brain Aging Found in Lysosomal Storage Diseases

Cross-sectional studies of brain aging are negatively influenced by interindividual variations in brain size and structure, as well as by differing rates of atrophy. Longitudinal studies may be limited by repeated access to aged animals and to subject attrition.⁶⁴ Insight into mechanisms of brain aging can also be obtained through the study of breeding colonies of dogs with naturally occurring hereditary metabolic disorders, including mitochondrial disorders, lysosomal storage diseases, and leukodystrophies, which have clinical, neuropathologic, and biochemical changes similar to those found in old dogs. These disorders allow both cross-sectional and longitudinal studies of disease progression in related animals with short life spans.^{76,77} For example, more than 40 inherited lysosomal storage diseases (LSDs) have been identified, with many characterized by progressive cognitive decline, memory loss, brain atrophy, loss of myelin, and region-specific loss of neurons as are seen in aging.^{78,79} Two well-studied diseases are examples of what has been learned by studying affected dogs. The neuronal ceroid lipofuscinoses (NCLs) are

characterized by seizures, motor dysfunction, impaired vision, progressive cognitive decline, impaired memory, behavioral problems, brain degeneration, selective neuronal loss that is most severe in the cerebral cortex, white matter atrophy, neuronal accumulation of protein and lipid, and premature death.^{80,81} Both human patients and affected dogs show various ages of onset, disease course, and neuropathology.^{80–82} The juvenile-onset form of the disease, known as Batten disease, has naturally occurring analogous disease in English setters, Tibetan terriers, and border collies.⁸³ Biochemical analysis of the brain shows that storage of subunit c of the mitochondrial ATP synthase complex occurs; subunit c is an essential membrane component of the proton channel of the ATP synthase complex, which generates ATP by oxidative phosphorylation.⁸¹ Although not fully characterized, the neuronal loss seen in Batten disease is postulated to be caused by mitochondrial dysfunction and energy-linked excitotoxicity.⁸³ Synaptic loss and glial activation also occur in this disease, although the mechanism and contribution of these abnormalities to disease progression are not yet understood.⁸⁰

The T-maze reversal learning task has been used to evaluate progressive cognitive decline in the dachshund model of late-infantile NCL, which is caused by a mutation in the gene encoding the enzyme tripeptidyl-peptidase 1 (TTP1).⁸⁴ This model system is particularly interesting because intrathecal administration of TTP1 results in decreased lysosomal storage.⁸⁵ It is likely that a better understanding of how mitochondrial dysfunction and neuronal loss develop in the NCLs, as well as how they may be reversed with therapy, will shed light on similar mechanisms postulated to occur in brain aging.

Mucopolysaccharidosis type I (MPSI; Hurler syndrome) is another LSD characterized by progressive cognitive decline, including impaired memory and intelligence, in human patients.⁸⁶ Affected humans and dogs show progressive cortical atrophy, ventricular enlargement, and white matter loss.⁸⁷ Cardiovascular disease and accumulation of intracellular A β are also described in affected patients.^{88,89} In human patients with MPSI, MRI showed that corpus callosum volume and fractional anisotropy correlated with neuropsychological testing.⁸⁶ In dogs with MPSI, imaging studies showed corpus callosum volumes to be smaller in affected dogs compared with unaffected dogs; no cognitive studies have yet been performed. Similar to the late-infantile NCL, this disease is amenable to either whole-brain therapy by intrathecal enzyme replacement therapy or to regional gene therapy allowing for the assessment of therapeutic effect.^{90,91} When treated with intrathecal alpha-iduronidase, the enzyme that is deficient in MPSI, corpus callosum volumes in affected dogs were no longer distinguishable from those in unaffected dogs. These studies indicate the usefulness of quantitative imaging to study brain atrophy over time as well as the effectiveness of therapy in ameliorating the atrophy.

NEUROBIOLOGY OF AGING IN THE CAT

Cats are considered to be old, or senior, starting around the age of 7 to 10 years but consistently after 12 years, depending on the individual animal. Aging cats show several behavioral changes that can be of concern to a pet owner and that are not related to systemic illness or disease.⁹² Whether there is cognitive decline in aging cats as observed in dogs is still being studied but there are behavioral changes that have been reported clinically.⁹³

There are fewer studies of the aging cat brain compared with aging dogs in the literature, highlighting the significant gaps in knowledge regarding feline brain aging. Several reviews have been written describing feline age-associated neurologic disorder and some of those observations are summarized here.^{92,93}

Neuron Loss and Atrophy

There are several studies suggesting that the caudate nucleus of aging cats is affected by aging, including reduced neuronal numbers and reduction in the density of synapses.^{94–97} These losses may lead to impairments in motor function.⁹⁴ The locus coeruleus, a key nucleus responsible for producing the neurotransmitter acetylcholine, which is associated with learning and memory, also shows neuronal losses with age in cats.⁹⁸

A β

A β is typically observed in cats more than the age of 10 years,^{99–103} although there is a report of 7.5-year-old animal showing A β disorder.¹⁰² Feline A β deposition seems to be different from that of dogs and humans in several respects. Unlike human and dog brain, plaques in the cat brain are primarily made up of A β 1-42 without A β 1-40 and the peptide is not posttranslationally modified (suggesting a more rapid turnover) in cats compared with dogs and humans.^{66,99} Further, truncated A β (A β pN3) was absent in aged cat brain.¹⁰⁴ Blood vessels in aging cat brains are positive for A β 1-40, the shorter more soluble form of A β .⁶⁶ To our knowledge, there are few reports of the link between behavioral dysfunction and the extent of A β disorder as reported in dogs. Although cats that show signs of behavioral dysfunction tend to also have A β plaques,¹⁰⁰ the severity of behavioral changes does not seem to correlate well with the extent of A β disorder.⁶⁶

Tau Phosphorylation

An interesting feature of the aging cat brain is the detection of phosphorylated tau protein, which is consistent with reports in human AD.^{105,106} Cats show multiple isoforms of tau protein, as do humans.¹⁰⁷ Not all studies consistently observe tau neuropathology in cats^{101,108,109} and this may be because of methodological challenges. In addition, when using sensitive immunohistochemical methods, phosphorylated tau is not as frequently observed as A β plaques, but the epitopes on tau that are phosphorylated overlap with those observed in dogs and humans.⁶⁶ The morphology of neurons that show an accumulation of intracellular phosphorylated tau suggests a sprouting response, which is also similar to human brain.⁶⁶ Tau phosphorylation is also more frequently associated with the presence of seizures in aging cats.¹⁰⁰

Neuronal Loss in Feline Niemann-Pick Type C Disease and Similarities to AD

Niemann-Pick type C (NPC) disease is another example of how LSDs may contribute to the understanding of neuronal loss, oxidative stress, A β deposition, and tau neuropathology in the aging brain. NPC disease is caused by dysfunction of either of 2 proteins, NPC1 or NPC2, which result in lysosomal storage of cholesterol and glycosphingolipids.¹¹⁰ How dysfunction of these proteins results in the dementia and neuronal loss associated with disease has been difficult to determine. A feline model of NPC1 disease exists and has been

critical for understanding disease pathogenesis and evaluating therapy.^{110–115} As disease-modifying therapies are evaluated, clinicians hope to gain insight into the relative contributions of each of the following factors in causing cognitive decline and brain atrophy.

Autophagy, the degradation or recycling of damaged intracellular organelles and aggregated-proteins, is necessary for cellular homeostasis. NPC1 has been implicated in mediating membrane-tethering events between autophagosomes and late endosomes that subsequently fuse with lysosomes to degrade their contents.¹¹⁶ When NPC1 is defective, autophagy is impaired. Because impaired basal autophagy has been found to cause neurodegeneration,^{117,118} it is postulated that impaired autophagy in NPC1 disease may contribute to the observed neuronal loss as a consequence of the buildup of dysfunctional mitochondria and the accumulation of misfolded proteins, resulting in cell death. Altered autophagosomal-lysosomal function has similarly been implicated in brain aging.^{119,120}

Oxidative stress and the generation of reactive oxygen species have also been proposed as contributing factors for neuronal loss in NPC disease.¹²¹ In vitro studies showed increased oxidative stress in cultured neurons and fibroblasts.¹²² Evaluation of serum from patients with NPC showed decreased fractions of reduced coenzyme Q10 and decreased Trolox-equivalent antioxidant capacity.¹²¹ Evaluation of plasma and cerebrospinal fluid from patients and affected cats showed accumulation of cholesterol oxidation products, and, in cats, these oxysterols decreased in response to a disease-modifying therapy.¹²²

In addition, both NPC1 disease and AD are marked by dementia and abnormal cholesterol metabolism; however, they also share abnormalities in A β processing and the presence of neurofibrillary tangles.^{110,123} First, in both affected humans and cats, relative A β peptide distributions differ from those found in unaffected individuals, with lower relative levels of A β 1-37, A β 1-38 and A β 1-39 in cats with NPC1 compared with controls.¹²⁴ Second, neurofibrillary tangles composed of paired helical filaments of phosphorylated microtubular protein accumulate in NPC disease as they do in AD.¹¹⁰ Third, apolipoprotein E4, the isoform associated with increased risk for developing AD, has also been found to be associated with early onset of disease and with increased NPC1 disease severity.¹²³ Other deficits seen in NPC1 disease, including peroxisomal dysfunction,¹²⁵ abnormal sphingosine metabolism,¹²⁶ neuroinflammation,¹²⁷ and induction of apoptosis,¹²⁸ may also contribute to changes seen in the aging brain.¹²⁹

CLINICAL IMPLICATIONS OF BRAIN AGING IN DOGS AND CATS

Laboratory-based studies of cognition in beagles suggest that there are age-dependent functional changes related to brain disorders. In the clinic, owners of geriatric dogs frequently report behavioral changes.^{130–132} Some of these behavioral changes may be linked to systemic illness or other health issues (including sensory decline). When ruled out, a subset of older dogs shows evidence of behavioral changes that are now considered to be signs of canine cognitive dysfunction (CCD). The original reports of CCD were by Ruehl and colleagues¹³³ in the mid 1990s and several reports followed, along with the development of new tools to detect CCD in pet dogs.^{6,7,93,134,135} CCD has been linked to brain pathology in pet dogs.^{20,136,137} There are reports that CCD can be reduced in aging

dogs through treatment with various pharmaceuticals (eg, Anipryl),¹³⁴ by dietary intervention using a prescription diet (B/D diet Hills Pet Nutrition¹³⁴; the same diet used in laboratory studies showing a benefit to cognition and neuropathology¹³⁸), and to immunotherapy using anti-A β approaches.¹³⁹ In cats, there is less evidence of a form of feline cognitive dysfunction syndrome but evidence is accumulating that a similar phenomenon can occur.^{66,92,93,100,140}

SUMMARY

Aging dogs and cats show features of brain disorders that can be similar to human aging and AD. Neuropathologic changes with age may be linked to signs of cognitive dysfunction both in the laboratory and in a clinic setting. Less is known about cat brain aging and cognition and this represents an area for further study. Neurodegenerative diseases such as LSDs in dogs and cats also show similar features of aging, suggesting some common underlying pathogenic mechanisms and also suggesting pathways that can be modified to promote healthy brain aging.

Acknowledgments

The authors are grateful to Virginia Price, DVM, and her stories of Martha and donation of her tissue for research. We thank Judianne Davis-Van Nostrand and Dr William Van Nostrand at Stony Brook University in New York for help with collecting tissue for the study. Ms Katie McCarty collected the A β immunostaining data for Martha.

Research reported in this publication was supported by the National Institute on Aging of the National Institutes of Health under award number R01AG031764 (E. Head) and R01NS073661 and P40-02512 (C.H. Vite, Mark Haskins), and the Ara Parseghian Medical Research Foundation (C.H. Vite). The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

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KEY POINTS

- Brain atrophy, neuron loss, decreased neurogenesis, and oxidative stress but few tau-associated disorders are observed in aging dog brains.
- Cerebrovascular pathology can be extensive in canine brain aging.
- β -Amyloid protein, associated with Alzheimer disease in humans, is increased with age in the dog brain and is linked to signs of learning and memory impairments.
- Lysosomal storage diseases in dogs are associated with similar types of neuropathology as are observed with aging and Alzheimer disease.
- Few studies describe the neurobiology of aging in cats but interesting similarities and differences from dogs have been reported.
- Feline Niemann-Pick type C disease has several neuropathologic and clinical similarities to Alzheimer disease.

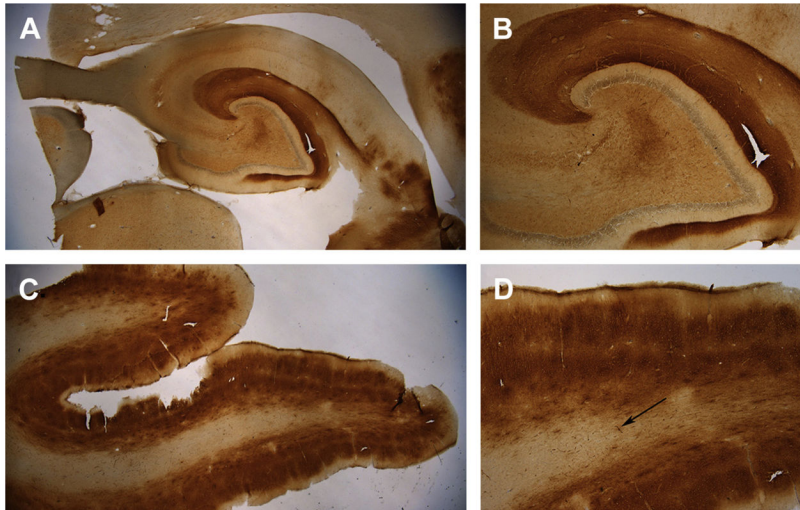


Fig. 1.

A β immunostaining (brown) in the brain of a 14-year-old border collie (Martha) with signs of cognitive dysfunction syndrome. A β was detected using the 6E10 antibody that binds A β 1 to 16. (A) Low-power magnification (1.5 \times) of extensive A β deposition in the hippocampus. (B) A β is primarily found in the outer molecular layer of the dentate gyrus, which contains neuron terminals originating from the entorhinal cortex (4 \times). (C) The prefrontal cortex also shows extensive A β deposition that appears most dense in layers II and V of the cortex and is less apparent in the white matter (1.5 \times). (D) At high magnification (4 \times), the differential deposition of A β in the 6 cortical layers can be seen as well as extensive white matter cerebral amyloid angiopathy (*arrow*). Sections have been counterstained with cresyl violet (*blue*).

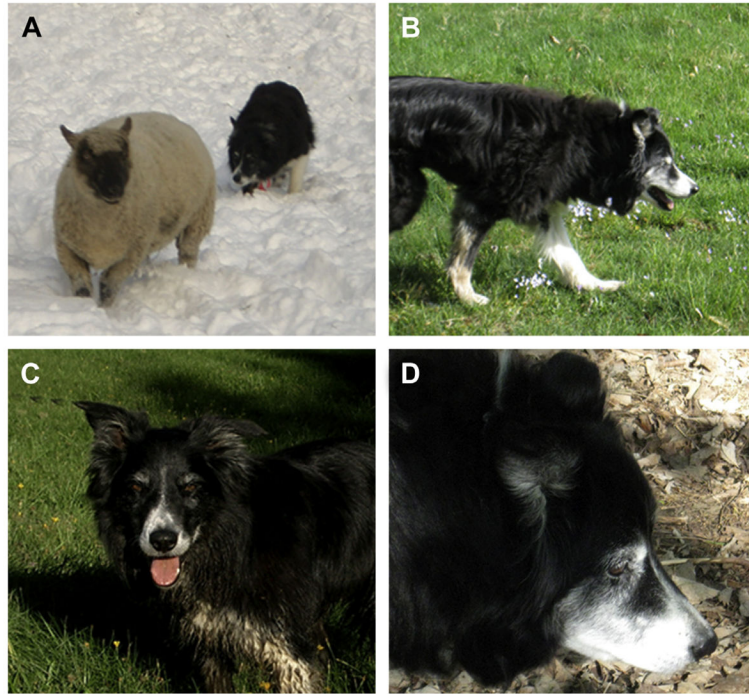


Fig. 2. Aging and canine cognitive dysfunction in a border collie (Martha). (A) Martha competing in sheep dog trials when she was young, and (B) still active around the age of 10 years. As she reached 11 years of age she struggled to complete commands issued by her owner (C). At 14 years of age, Martha was generally in good health except for arthritis but would not make eye contact with her owner (D).

Table 1

Comparison of dog and cat neurologic neurodegenerative features

Neurobiological Outcome Measures	Canine	Feline	NCL or MPSI	NPC Disease
Brain atrophy	Yes	NA	Yes	Yes
β -Amyloid	Yes	Yes	Yes	Yes
Tau	Yes	Yes	NA	Yes
Cerebral amyloid angiopathy	Yes	Yes	NA	NA
Infarcts	Yes	NA	NA	NA
Vascular disease	Yes	NA	Yes	NA
Lipofuscin accumulation	Yes	Yes	Yes	NA
Caspase activation	Yes	NA	Yes	Yes
DNA fragmentation	Yes	NA	NA	NA
Neuron loss: hippocampus	Yes	NA	Yes	Yes
Neuron loss: caudate	NA	Yes	Yes	Yes
Neuron loss: locus coeruleus	Yes	Yes	NA	NA
Neuron loss: Purkinje cerebellar cells	Yes	NA	Yes	Yes
White matter degeneration	Yes	NA	Yes	Yes
Inflammation	Yes	NA	Yes	Yes
Oxidative damage	Yes	NA	Yes	Yes
Gliosis	Yes	NA	Yes	Yes

Abbreviations: MPSI, mucopolysaccharidosis type I; NA, not available; NCL, neuronal ceroid lipofuscinoses; NPC, Niemann-Pick type C.