Brain Aging in Dogs: Parallels with Human Brain Aging and Alzheimer’s Disease*

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ABSTRACT

Differentiating normal from pathologic aging is a challenge to veterinarians treating geriatric patients and to clinicians diagnosing Alzheimer’s disease. Part of the difficulty stems from the lack of a biological marker. Dogs and humans develop similar cognitive dysfunction with age, and a subset of individuals develop severe impairments. Similar neuropathology also develops in the brains of elderly humans, individuals with Alzheimer’s disease, and dogs. Both species develop senile plaque neuropathology, with more extensive plaque accumulation associated with severe cognitive impairments. This article discusses similarities in the clinical features and development of neuropathology with age in both dogs and humans and provides a discussion of treatment options.

ANIMAL MODELS OF HUMAN AGING AND ALZHEIMER’S DISEASE

One of the challenges to researchers studying Alzheimer’s disease (AD) is to identify mechanisms underlying pathologic aging and then to develop therapeutics to prevent or slow disease progression. Animal models, including rodents and nonhuman primates, are critical to the success of this research. There are several advantages in using dogs to study human aging: Dogs exhibit a sophisticated repertoire of behaviors; aged dogs fall into one of three categories of cognitive function (successful agers, mildly impaired, and severely impaired); neuropathology in aged dogs is similar to that observed in humans; and neuropathology is significantly associated with cognitive decline.1–4 The primary goal of studies of canine aging is to identify brain mechanisms leading to cognitive dysfunction. This laboratory work should prove useful to veterinarians in practice, and researchers studying canine aging in the laboratory environment can benefit from information obtained in the veterinary clinic. This review focuses on the clinical features and neuropathology of AD in humans and highlights common issues regarding aging in dogs.

ALZHEIMER’S DISEASE IN HUMANS

Alzheimer’s disease, the most common cause of dementia in humans,5 is characterized by a progressive decline in cognitive function, leading to functional impairments and eventually death.6 The prevalence of AD in the elderly population ranges from 12% in people over 75 years of age to as high as 50% in people older than 85, although there is wide variability in

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*This review was sponsored by Pfizer Animal Health, New York, NY, and by research conducted under grant NIH/NIA AG12694 at the National Institute on Aging, Bethesda, MD.
these rates based on the populations studied.\textsuperscript{5} Alois Alzheimer was the first to describe the disease in 1907 when he published observations from a case study of a 51-year-old woman with memory loss, impaired language ability, paranoia, and delusions.\textsuperscript{7} Alzheimer also observed specific neurodegenerative features (neurofibrillary tangles [NFTs] and senile plaques [SPs]) in the brain of his patient. Neurofibrillary tangles and SPs are still considered to be hallmarks of AD and are required for a neuropathologic diagnosis.\textsuperscript{8–10}

**Clinical Features**

A thorough physical examination, blood biochemistry screens, neurologic examination, in vivo imaging (Figures 1A and 1B), and extensive neuropsychological testing are recommended for a clinical diagnosis of AD.\textsuperscript{6,11} The primary complaint of individuals thought to have AD, particularly early in the disease, is memory difficulties. Memory complaints are also a feature of a newly defined group of individuals with mild cognitive impairment (MCI), which includes individuals who are at a higher risk for developing AD.\textsuperscript{12–14} Presenting symptoms can be quite heterogeneous, however, and subtypes of AD probably exist.\textsuperscript{15–20} One of the first issues in the clinic is to rule out potential reversible dementias (e.g., metabolic disorders or infections).\textsuperscript{21} Other causes of dementia include Lewy body disease, Pick’s disease, Parkinson’s disease, and frontotemporal dementia (FTD).\textsuperscript{21} In addition to neuropsychological evaluations, other measures such as behavioral symptoms can also be helpful for differential diagnosis and for monitoring the progression of AD. Whereas neuropsychological tests measure language, visuospatial function, and

![Figure 1. Neuropathology of Alzheimer’s disease. Extensive brain atrophy can be detected using magnetic resonance imaging when comparing the normal elderly brain (A) with the brain in Alzheimer’s disease (AD) (B) (e.g., ventricular widening [black arrows], hippocampal atrophy [white arrows]). Neurofibrillary tangle formation is absent in normal elderly brain in the frontal cortex (C) but is extensive in AD (D). A higher magnification of immunostaining for neurofibrillary tangles illustrates that tangles fill the cytoplasm and the apical dendrites of pyramidal neurons (E, long arrow). Neuritic pathology also clusters in plaque regions [short arrows]. The normal elderly frontal cortex may show some senile plaque formation (F and G; arrows) but not as extensive as that observed in AD (H). Bars in C, D, F, G, and H = 100 µm; E = 20 µm.](image-url)
executive function, behavioral or functional measures detect difficulties in day-to-day tasks. These measures can be obtained using a checklist of behavioral problems, including such items as confusion, disorientation, loss of interest in activity or apathy, unusual sadness or depression, excessive or lack of appetite, awakening early, trouble sleeping or reversal of sleep/wake patterns, poor personal hygiene, pacing, aggression, and incontinence.22

Neuropathology

The final diagnosis of AD can only be made with a postmortem examination of the brain. The two diagnostic features that must be present for the diagnosis of AD are NFTs and SPs (Figures 1C to 1H). These two forms of neuropathology are not exclusive to AD and can be found in other forms of dementia as well as in normal aging.23–27

Neurofibrillary Tangles

As illustrated in Figure 1, one feature of the AD brain is the accumulation of NFTs. These are formed by the intracellular accumulation of tau protein that makes up the cytoskeleton of neurons.28 In AD, τ protein becomes hyperphosphorylated and forms paired helical filaments, which fill the cytoplasm and lead to neuronal dysfunction.29–31 New information suggests that mutations in the τ protein can lead to a distinct type of dementia named FTD and parkinsonism linked to chromosome 17 (FTDP-17).32

Senile Plaques

Extensive SP accumulation is the second hallmark of AD and can be visualized in human brain with a number of techniques, including silver stains, thioflavine-S fluorescence, or immunohistochemistry (Figures 1F to 1H). Senile plaques are extracellular proteinaceous deposits containing the β-amyloid (Aβ) protein. Aβ is enzymatically cleaved from a longer amyloid precursor protein (APP) to produce a 40-43 amino acid peptide.33–35 The longer, more toxic fragment (Aβx-42) is initially deposited in the human brain and is followed by the accumulation of the shorter, more soluble fragment (Aβx-40) in SPs and in blood vessel walls.36

β-amyloid pathology will receive the most attention in this review because of evidence suggesting that it plays a crucial role in the development of AD. Several families have been identified with early-onset AD that is linked to mutations on chromosomes 1 (presenilin 2 gene), 14 (presenilin 1 gene), and 21 (APP).34,35 All these genetic mutations lead to increased deposition of Aβ, specifically the longer, more toxic 42-amino-acid fragment Aβ1-42.37,38 Further, individuals with Down syndrome, who have a third copy of chromosome 21, overexpress APP and nearly always exhibit the characteristic neuropathology of AD after the age of 40 years.39–43 The recent development of transgenic mouse technology further supports the role of Aβ in AD; overexpressing human APP or mutant human APP leads to the development of SPs and cognitive dysfunction.44–49

Pathology and Behavior in Alzheimer’s Disease

A key issue is to identify neuropathology that has the greatest functional impact in AD. A role for tangle formation underlying cognitive dysfunction present in AD stems from clinicopathologic correlation studies. Several researchers demonstrate a strong correlation between higher numbers of tangles and dementia severity.50–56 An important link between the extent of Aβ deposition and cognitive dysfunction has also been established in AD.50,53,57–60 In direct comparisons, however, Aβ appears to be the best predictor of disease severity.61 Evidence from geriatric dogs helps
clarify this issue since dogs develop Aβ (but not NFTs) with age, allowing researchers the unique opportunity to study the role of Aβ in cognitive dysfunction.

**COGNITIVE DYSFUNCTION AND NEUROPATHOLOGY IN AGING DOGS**

There are several important features of canine aging, including the development of learning and memory deficits measured in a laboratory setting and clinical features of cognitive dysfunction syndrome (CDS). Neuropathology in the aged dog brain parallels that seen in the elderly human brain and individuals with AD.¹ The parallels in the development of cognitive dysfunction with increasing neuropathology suggest that these two features are linked, as they are in human aging.

**Laboratory Evidence**

Measuring deficits in learning and memory as a function of age in dogs has been the focus of a series of ongoing laboratory studies over the past 10 years. In these studies, dogs over 8 years of age are considered old based on evidence for reduced cerebrovascular function after this age.² However, this definition will vary somewhat depending on the breed of dog because larger breeds typically have shorter lifespans. Using a human neuropsychological approach, tasks sensitive to the function of specific cortical circuits and/or brain regions are selected. Each task is selected to measure several types of learning and memory abilities as is done in the AD clinic. All testing is conducted using food rewards, which sufficiently motivate dogs to learn each task. Deprivation protocols, which are particularly stressful for geriatric animals, are unnecessary. The two main conclusions that have evolved from these studies are that detecting cognitive dysfunction depends on the task used and that variability in the cognitive abilities of dogs increases with age.

In general, aged dogs are able to learn simple skills to the same extent as younger dogs.³ However, individual aged dogs can show pronounced impairments. Simple associative learning, such as visual discrimination (e.g., learning that one of two objects covers a food reward), typically remains intact with age, unless the discrimination is particularly difficult.³,⁶³,⁶⁴ Conversely, the ability to perform prefrontal-dependent tasks is consistently diminished in aged dogs.³ One of these tasks is the reversal-learning test in which dogs are first given a visual discrimination task. After reaching a preset criterion level of responding, the reward contingencies are reversed and dogs must shift from responding to one object to responding to the other. This problem involves response inhibition and the ability to shift strategies, functions that are mediated by the prefrontal cortex.⁶⁵,⁶⁶

Memory can be tested systematically in dogs using tasks developed for use in nonhuman primates and are analogous to those used for testing memory in humans. Two forms of memory that appear to be age-sensitive include spatial memory (the ability to remember the location of a food reward) and object recognition memory (the ability to recognize an object seen 10 to 120 seconds previously).²,⁶⁷–⁶⁹ Thus, systematic and controlled laboratory studies provide consistent evidence of impairments in aged dogs. However, it is interesting to note that in most of the studies described above, not all aged dogs are impaired. As mentioned earlier, aged dogs are similar to elderly humans in that they tend to fall into one of three categories: unimpaired (successful), age-impaired, or severely impaired agers. These categories of aged dogs may be analogous to normal aging, MCI, and AD in humans.

**Canine Cognitive Dysfunction Syndrome**

Clinical features of canine CDS have been measured using informant-based question-
Cognitive dysfunction syndrome in dogs is characterized by such signs as disorientation, disruptions in activity and sleep, changes in housetraining, and alterations in interactions with family members. In a survey of 26 owners of geriatric dogs, common complaints were destructive behaviors, inappropriate urination or defecation, and excessive vocalization in older animals. In another survey, up to 18% of 150 pet owners reported that their senior dogs (7 years of age or older) had exhibited at least one clinical sign of CDS. These behavioral signs were observed in dogs that were normal when younger and other medical conditions had been eliminated.

It is important to point out that CDS is identified based on several cognitive signs. Further, other potentially life-threatening disorders need to be ruled out and referral to a specialist in veterinary neurology or a related field is strongly recommended. It is critical to point out that similar to practice in the AD clinic, more than one cognitive domain (e.g., language, memory, visuospatial skills) must be affected and the observation of one sign is not a sufficient basis for implementing a pharmacologic intervention. However, the emergence of cognitive impairments in addition to worsening of existing signs illustrates that follow-up evaluations are critical.

In some cases, behavioral changes in CDS are the same indicators as those used in the clinical evaluation of functional disturbances in AD. The relationship between laboratory and clinical appraisals of age-associated cognitive decline in dogs has yet to be studied. The drawback to laboratory tests is that they are time consuming. Evaluation of a dog of average age undergoing even a simple associative learning task can take up to 2 weeks of testing. Memory testing requires even more time and can take up to 4 months to complete. Thus, the translation of laboratory-based tests to the clinic may be prohibitive. This is not true, however, of clinical evaluations in the laboratory and it would be worthwhile to explore the issue further.

Neuropathology

One of the first reports of age-associated neuropathology in dogs, published in 1914, described abnormal pyramidal neuron sprouting. It was not until the 1950s that other types of neuropathology were reported in aged-canine brains, including “Alzheimer-like” SPs. In 1971, Wisniewski and coworkers were among the first researchers to suggest that dogs would be a useful model of human brain aging. Similar to what has been observed in elderly human brains, aged-canine brains display a number of morphologic hallmarks, including cortical atrophy (Figures 2A and 2B), myelin degeneration in the white matter, accumulation of undegraded proteins, DNA damage, and possibly oxidative damage.

Tangles identical to those seen in the human brain are rare in other species. Dogs do not develop tangles. This is one of the limitations of the canine model as well as many other animal models, of human aging and dementia. However, it is possible that early tangles are present in the brains of aged dogs but they do not mature into the full phenotype. Tau phosphorylation is a feature of the aged-canine brain and can be classified into three stages ranging from weak to strong. One possible reason for the lack of development of tangles in dogs is that the sequence of the τ protein in dogs is different from that of humans; this in turn may affect the formation of paired helical filaments and subsequently NFTs (M. Hutton, personal communication, 2000). The advantage to the lack of tangle development in aged-dog brain is the opportunity to study the role of Aβ pathology on cognition in the absence of overt tangle formation.
Senile Plaques

The first reports of plaque formation in aged-canine brain were controversial. Early studies relied on standard silver stains or thioflavine-S fluorescence to visualize plaque pathology. However, canine plaques are diffuse and not reliably detected using these techniques. With the development of formic acid pretreatment protocols and sensitive immunohistochemical techniques, the question of canine Aβ could be more systematically studied. A number of commercially available antibodies against Aβ are available and are useful for visualizing Aβ pathology in the brains of geriatric dogs. Dogs naturally accumulate Aβ in the brain with age (Figures 2C to 2E). Some researchers did not observe a clear age dependency for Aβ deposition in dogs, but the inclusion of different breeds can confound the results because some breeds develop Aβ at an earlier age than others.

Not all brain regions are equally vulnerable; the prefrontal cortex develops Aβ pathology at an earlier age and more consistently than do areas such as the hippocampus or parietal cortex. The occipital cortex accumulates Aβ at a much later age than these other brain regions. This pattern of Aβ accumulation with age in dogs parallels that seen in humans. Within the prefrontal cortex, Aβ first appears in deep cortical layers; and at later ages, the superficial layers are increasingly affected. In studies of over 150 dog brains, Aβ deposition has not been observed in layer I, which is in contrast to that observed in the human brain. Conversely, a diffuse band of Aβ is observed in the outer molecular layer of the hippocampus where plaques are also found in the human brain in AD (Figures 2F and 2G). Another common characteristic between dogs and humans is that the predominant

Figure 2. Neuropathology in aged canine brain. Cross-sectional studies illustrate that, compared with the brain in young dogs (A), cortical atrophy and ventricular widening (black arrow) are features of aged canine brain (B). Hippocampal atrophy is not a clear age-dependent feature of aged dog brain (white arrow). A parallel between aged canine brains (C) and brains in AD (D) is the deposition of β-amyloid (Aβ) in the outer molecular layer of the hippocampus, which may be extensive in aged dogs (C, arrows) and in the brain in AD (D, arrows). Diffuse plaques develop with age in the dog brain and vary widely in extent. Young dogs do not show Aβ (E) but aged dogs (F and G) can show variable amounts of Aβ deposition. Some cognitively normal dogs show relatively minor Aβ pathology (F, arrow), but a subset of old dogs with learning deficits has extensive Aβ deposits (G). Bars in C to G = 100 µm.
species of Aβ is the longer, toxic fragment Aβ1-42. At later ages the shorter, more soluble fragment, Aβ1-40, accumulates in plaques and in blood vessel walls. Thus, the extent of Aβ detected in the brains of aged dogs is dependent on the detection antibody; anti–Aβ1-42 antibodies are the most sensitive. As with human brain aging, Aβ within the blood vessel walls of aged dogs, called amyloid angiopathy, suggests that they are a useful model to study this form of pathology.

The distribution of Aβ as a function of age in dogs, the sequence in which specific fragments of Aβ are deposited, and the fact that the protein itself is identical to the human protein are several reasons for the use of the dog model to understand human brain aging. Further, since Aβ deposits remain diffuse in the aged-canine brain, they are a good model for studying early AD prior to the appearance of other complex variables such as tangle formation.

Pathology and Behavior in Geriatric Dogs
What are the functional consequences of Aβ deposition? Several studies have demonstrated a significant association between the extent of Aβ deposition and the extent of cognitive dysfunction in dogs (Figures 2D to 2F). This association can be further refined on a brain region basis; for example, Aβ in the prefrontal cortex is correlated with frontal-dependent learning and memory deficits. A recent paper by Colle and coworkers showed a significant association between behavioral dysfunction in aged dogs and the extent of Aβ deposition. This recent publication, along with previous reports, supports an association between clinical measures of cognitive dysfunction and pathophysiology in the brains of aged dogs.

BIOMARKERS OF PATHOLOGIC AGING
Detection of pathologic aging in both the AD field and in veterinary clinics is hampered by the absence of a biomarker. A consensus report of the Working Group on Molecular and Biochemical Markers of Alzheimer's Disease suggested a number of criteria for a satisfactory biomarker to detect AD; however, at this time no biomarkers have been identified.

The two markers that have received the most attention are Aβ in cerebrospinal fluid (CSF) or serum and tau levels in CSF. Both measures are promising; decreased Aβ1-42 in CSF and increased τ levels are associated with AD and are significantly different from age-matched controls. However, neither of these markers differentiates AD from other types of dementia with similar neuropathologies and clinical signs. This is also true of in vivo imaging techniques; cortical atrophy cannot be used to differentiate normal from pathologic aging. However, some studies suggest that measuring the rate of atrophy in asymptomatic individuals may be a better predictor than a single scan.

This area of research is essential for developing therapeutics to treat AD at a point early enough in the disease to prevent progression. This same area of research can benefit from studies in aged dogs; and the inclusion of measures of serum Aβ levels or longitudinal imaging studies may clarify the issue for both canine and human pathologic aging.

TREATING COGNITIVE DYSFUNCTION SYNDROME
Currently, there are three approved drugs that utilize the cholinesterase inhibitors tacrine, donepezil, and rivastigmine for treating AD. All these pharmaceuticals prolong the availability of acetylcholine at neuronal synapses. The use of anticholinesterases stems from postmortem studies demonstrating a reduction in cholinergic cells of origin in the basal forebrain in AD. The cognitive status of individuals with AD is significantly im-
proved with cholinesterase inhibitors, although overall the effects are modest.\textsuperscript{113} In addition, not all individuals respond favorably and the ability to enhance quality of life can be questionable.\textsuperscript{114} Pharmacologic manipulation of the monoaminergic system using selegiline in AD has also been beneficial in delaying the need for institutionalization\textsuperscript{115} and improves clinical signs of CDS in dogs.\textsuperscript{68,116–118} Thus, the currently available treatments for AD can provide some symptomatic relief but have little or no effect on disease progression. Treatments for AD that would have the most benefit should prevent or slow the development of neuropathology. Two potential interventions will be discussed in detail, but other interventions that may promote successful aging in humans and dogs are also being explored.

Over the past 10 to 15 years research has focused on the role of antioxidants and nonsteroidal antiinflammatory drugs (NSAIDs) in the development and progression of AD. Both of these drug types play a significant mechanistic role in AD neuropathology. Inflammatory processes are a characteristic feature of the AD brain and are closely associated with SP formation.\textsuperscript{119} Individuals using NSAIDs are at a reduced risk for developing AD,\textsuperscript{120} but NSAIDs may have other beneficial effects. For example, ibuprofen can reduce Aβ accumulation in transgenic mice,\textsuperscript{121} and it would be interesting to determine whether companion animals receiving the antiinflammatory drug carprofen (Rimadyl\textsuperscript{®}, Pfizer Animal Health, Exton, PA) are at a reduced risk for developing CDS.

Oxidative damage may play an important role in the development of brain pathology associated with AD.\textsuperscript{122,123} A growing body of literature strongly supports a role for oxidative damage to proteins, lipids, and DNA/RNA in the development of neuronal dysfunction in human brain aging.\textsuperscript{124–126} Recent evidence suggests that this form of neuronal damage may precede the development of SPs in transgenic mice.\textsuperscript{127} Although not as well understood, antioxidant enzymes are significantly reduced with age in the aged-canine brain,\textsuperscript{86} and studies of markers of oxidative damage to proteins, lipids and DNA/RNA are currently under way.\textsuperscript{128} Preliminary studies suggest that oxidative damage in the canine brain parallels that seen in the human brain. Vitamin supplementation in humans\textsuperscript{129,130} or nutritional interventions in rodent models\textsuperscript{131} may improve cognitive function or reduce age-associated cognitive decline. It may not be entirely surprising that oxidative damage may be important for CDS and for AD because one of the strongest risk factors for both conditions is age. However, systematic intervention studies are required to test the hypothesis that oxidative damage is a major contributor to AD and CDS. Clinical trials in AD are currently under way, but one study conducted in moderately to severely demented individuals yielded modest effects\textsuperscript{115}; vitamin E supplementation delayed the need for institutionalization. In dogs, a 4-year study using a diet rich in a broad spectrum of antioxidants is currently under way. The results have been dramatic: Antioxidants are significantly improving learning and memory ability in aged dogs.\textsuperscript{132} These results may provide some insight into the clinical efficacy of selegiline (Anipryl\textsuperscript{®}, Pfizer Animal Health) because in addition to improving monaminergic function it can also function as an antioxidant and can promote neuron survival after trauma.\textsuperscript{133–135} Thus in theory, selegiline administered for a short period of time can improve monoamine function and potentially reduce oxidative damage and promote neuron survival over the long term.

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**UNDERSTANDING THE DISEASE**

Cognitive dysfunction syndrome is a diagnosis of exclusion, and clinical treatment options
are limited. The link between clinical measures of CDS and systematic laboratory cognitive tests is not clear, and results from the latter do not directly translate to the clinic. It is important to make this distinction because it remains to be determined whether tests of spatial memory and the cognitive processing involved with laboratory tasks are the same brain circuits engaged in clinical signs of CDS, such as disorientation. Another key issue is the development of sensitive biomarkers or more systematic clinical criteria for CDS because many of the signs currently identified can have many causes, as reported in the human literature. Dementia can be caused by issues such as polypharmacy or metabolic disorders in addition to specific brain pathologies. To further complicate diagnosis in the human clinic, there are a number of different dementias and it is highly likely that the pathology reflects these differences. It remains questionable whether dogs show similar dissociable dementias. For example, FTD in humans is associated with non-AD-type pathologies and has been linked to mutations in chromosome 17. Both FTD and AD include memory loss, but behavioral signs can be particularly useful for differentiating the two disorders. It is helpful in diagnosing AD to include a component that will assay how rapidly symptoms are appearing as well as to measure the rate of decline. Alzheimer’s disease is a gradual and progressive disorder in contrast to, for example, vascular dementia, which typically occurs in increments. Thus a careful clinical study measuring the progression of CDS over time is necessary, and two recent studies indicate that old dogs with impairments in one category were later found to have impairments in two or more categories. It is also as important in dogs to obtain a medical history as it is in humans; head trauma with a loss of consciousness is as much a risk factor as is a family history of AD. As such, the veterinary clinic can benefit from consensus criteria such as that developed for AD to identify the important elements necessary for a diagnosis of CDS and to list and eliminate other potential contributing factors.

Further, there is a gap in the current literature regarding whether dogs with CDS show more extensive brain pathology than do non-CDS dogs. Studying this issue will be critical for determining differences in markers of pathology that discriminate normal from pathologic aging in dogs. Indeed, we need to more fully understand what constitutes normal aging in both humans and dogs. Considering the potential role for genetics in the development of AD, this is an area of research in which studying dogs provides potentially unique insights. Are different breeds more susceptible to CDS than others, and do familial forms of CDS exist? This is a distinct possibility because there is a high concordance rate in the extent of Aβ within littermates in beagles. Are some dogs affected by CDS at a very early age as is reported in early-onset AD that is typically linked to genetic mutations? It would not be surprising to find that dogs are vulnerable to genetic mutations that predispose them to CDS, as is the case with AD.

Selegiline as a treatment for CDS provides additional benefits over conventional treatment with anti-cholinesterases in AD in that in addition to improving monoaminergic function, it has the potential to reduce oxidative damage. Clinical studies with selegiline to treat CDS in geriatric dogs have proven beneficial with minimal adverse side effects. Much less is known about neurotransmitter deficits as a function of age in the canine brain. However, whether this is the most promising avenue of research to develop treatments for CDS is debatable. It is more likely that understanding the mechanisms underlying brain pathology associated with CDS will lead to more promising interventions for senior and geriatric dogs.
ACKNOWLEDGMENTS

The author appreciates the critical review and comments from Dr. Julene Johnson and Dr. Carl Cotman at the Institute for Brain Aging and Dementia Alzheimer's Disease Research Center, University of California, Davis, CA, and Dr. N.W. Milgram at the University of Toronto, Canada. The author would like to thank Dr. Patrick J. Kesslak at the Institute for Brain Aging and Dementia for providing magnetic resonance images of human brain and Dr. Lydia Suh at the Department of Radiology, University of California, Davis for providing magnetic resonance images from dogs.

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