Prevalence of behavioral changes associated with age-related cognitive impairment in dogs

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Objective—To determine the prevalence of age-related behavioral changes, namely impairment, in a randomly chosen population of dogs.

Design—Age-stratified cohort study.

Animals—97 spayed female and 83 castrated male dogs that were 11 to 16 years old.

Procedure—Data on possible impairment in 4 behavioral categories (ie, orientation in the home and yard, social interaction, house training, and sleep-wake cycle) linked to cognitive dysfunction were obtained from dog owners, using a structured telephone interview. Hospital records of dogs had been screened to exclude dogs with dysfunction in organ systems that may cause behavioral changes. Dogs with behavioral impairment were those with ≥ 2 signs of dysfunction within a category. Dogs with impairment in 1 category were considered mildly impaired and those with impairment in ≥ 2 categories were considered severely impaired.

Results—Age by sex interactions for dogs with impairment in any category were not significant, and, therefore, data on castrated males and spayed females were pooled for analyses across ages. The prevalence of age-related progressive impairment was significant in all categories. The percentage of 11- to 12-year-old dogs with impairment in ≥ 1 category was 28% (22/80), of which 10% (8/80) had impairment in ≥ 2 behavioral categories. Of 15- to 16-year-old dogs, 68% (23/34) had impairment in ≥ 1 category, of which 35% (12/34) had impairments in ≥ 2 categories. There were no significant effects of body weight on the prevalence of signs of dysfunction in the behavioral categories.

Conclusions and Clinical Relevance—Data collected provide estimates of the prevalence of various degrees of age-related behavioral changes associated with cognitive dysfunction in dogs. Age-related behavioral changes may be useful indicators for medical intervention for dogs with signs of cognitive impairment. (*J Am Vet Med Assoc* 2001;218:1787–1791)

Thanks to improvements in nutrition, medical care, and protection from accidental death, many companion dogs live well into their elderly stages of life. As of 1996, 14% (7.3 million) of all dogs in the United States were 11 years of age or older.[1] A longer life span brings with it age-related degenerative changes in a number of organ systems, including those of the cardiovascular, musculoskeletal, visual, auditory, renal, and endocrine systems. The brain also undergoes degenerative changes with age, resulting in noticeable impairment of memory and learning in dogs.[2,3] The growing interest in understanding the nature and prevalence of signs of dysfunction in dogs related to impairment of memory and learning was enhanced by the recent approval of the dopaminergic and neuroprotective drug selegiline hydrochloride[a] by the FDA Center for Veterinary Medicine for treatment of cognitive dysfunction syndrome in dogs.[4]

Because signs such as disorientation in the home, disturbance of house training, and reduced recognition of family members involve deficits in memory and learning, the terms cognitive dysfunction and cognitive impairment have been introduced into the literature dealing with aging dogs to refer to these behavioral changes.[2,3,5] Animal cognition usually refers to complex learned associations where the animal makes responses that appear to reflect abstractions from previously learned material; that is, a new response is made that was not the result of prior direct reinforcement.[6,7] Although such cognitive function would be difficult to assess clinically in companion dogs, this species, like many mammalian and avian species studied,[6,7] is undoubtedly capable of cognitive behavior. Loss of orientation in the home or yard, impaired recognition of family members, and loss of house training, although not necessarily manifestations of impairment in cognitive behavior, do reflect impairment of memory and learning and would be logically linked with impairment of cognitive function.

Use of the terms cognitive dysfunction or cognitive impairment is predicated on the assumption that these changes reflect neuronal, neurotransmitter, metabolic, cerebrovascular, or biochemical degenerative changes in the brain and are not primarily a reflection of dysfunction in other organ systems.[2,3] Aged dogs have been known for some time to accumulate β-amyloid deposits in the hippocampus and frontal cortex (areas especially involved in changes in cognitive behavior),[8,9] and results of recent research indicate that the deposits are similar to the primitive or early stage β-amyloid plaques in the brains of human Alzheimer's patients.[10,11] In humans with Alzheimer's disease, the plaques mature into discrete plaques that result in neuronal cell death.[12,13] Results of laboratory research on aging Beagles suggest that the degree of β-amyloid

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Supported in part by Friskies PetCare Residency Program in Clinical Animal Behavior at the University of California, Davis, the UC Davis Center for Companion Animal Health, and Deprenyl Animal Health, Overland Park, Kan.

The authors thank Dr. David Bruyette for technical assistance and Dr. Neil Willits for statistical assistance.

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deposition corresponds to degree of impairment in learning complex tasks.[14,15] Neuropathologic and behavioral changes described in some aging dogs are similar to behavioral changes in humans with dementia and suggest that canine dementia can serve as a model for human dementia.[5]

A further link between age-related behavioral changes in dogs and of humans with signs of Alzheimer's disease was profiled in 2 double-blind controlled studies with the drug selegiline, 1 revealing a slowing in the progression of degenerative changes in human Alzheimer's patients,[16] and the other revealing a significant improvement in aged dogs with cognitive dysfunction syndrome.[4]

Although dogs can be expected to have some aging of behavioral function, it could be that only a proportion of dogs at any age will have cerebral degeneration of the magnitude sufficient to cause severe impairments in memory and learning. Owners of older dogs may describe a variety of behavioral changes, and results of preliminary work indicated that aside from a reduction in activity, the signs could generally be grouped into the following 4 categories[2,3]: orientation in the immediate environment, social interactions with human family members, house training, and the sleep-wake cycle. Changes in the sleep-wake cycle are perhaps the most difficult to relate to deficits in memory or learning. However, the sleep-wake cycle is disturbed in humans with Alzheimer's, possibly as a reflection of disruption of the circadian rhythm.[13,17]

The purpose of the study presented here was to assess the age-related prevalence of behavioral changes in a randomly selected population of aging dogs receiving veterinary care. In addition to the behavioral changes, information was collected on visual and hearing impairment. It is known that dogs of larger body size physically age more rapidly than dogs of smaller body size.[18] Thus, we also set out to determine whether there was a correspondence between body weight and the age of onset of signs of failing learning and memory.

Materials and Methods

Selection of dogs—Dogs included in our study were receiving veterinary care and were chosen from the database of clients of the Veterinary Medical Teaching Hospital at the University of California, Davis. A computer program was used to randomly generate lists of case numbers of dogs that fell into targeted age groups.

Data collection—The hospital records were reviewed by a trained screener. Clients were then contacted by the screener to obtain information about whether their dogs were still alive and the willingness of the caregiver to participate in the study. Information was also sought about the existence of medical problems not apparent from the hospital record and a convenient time for a veterinary behaviorist (JCN) to call. The owner was then sent an information sheet about possible behavioral and physical changes in aging dogs, and approximately 2 weeks later, the behaviorist contacted the owner to conduct a structured telephone interview of approximately 30 minutes. An outside consultant on telephone interview techniques contributed to development of the interview methods to avoid biasing the responses of the interviewee.

Information was recorded on prepared data forms and organized onto a spreadsheet. Data collection forms dealt with the following 4 categories of behaviors: orientation in the home or yard, social interactions with human family members, house training, and the sleep-wake cycle. Prior to asking about signs of dysfunction in each category, there was an open-ended question for recording responses from each owner about signs displayed by their dogs. Following the open-ended question, the interviewer then asked about specific changes known to develop in older dogs associated with each category if these signs had not been previously mentioned by the owner. The initial part of the interview contained distractors to intentionally evoke comments of "no change" from the owner so they would not expect that questions should be answered in the affirmative.

During the interview, 3 to 4 specific questions were used that addressed signs of dysfunction in each behavioral category. The criterion for impairment in a category was that dogs had ≥ 2 distinct signs in that category that were not observed when they were younger (ie, 5 to 8 years of age). A dog had impairment in orientation if it had ≥ 2 of the following signs: staring into space, getting lost in the house or yard, getting stuck in corners, standing at the wrong door or wrong part of the door to go out, and any other sign that was logically attributable to disorientation. A dog had impairment in social interaction if it had ≥ 2 of the following signs: decrease in greeting owners, decrease in soliciting attention from the owners, and a change (increase or decrease) in following owners around the house. A dog had impairment in house training if it had the following 2 signs: started to urinate or defecate in the house with no other behavioral or medical explanation discernible such as urinary incontinence or separation anxiety, and a decrease in signaling to go out or a decrease in use of a dog door. If a dog was strictly an outdoor dog or never house trained, so that learned house training could not be evaluated, the dog was not included in our study. A dog had impairment in the sleep-wake cycle if it had ≥ 2 of the following signs: regularly waking up the owner at night by pacing or vocalizing, sleeping less at night, and sleeping noticeably more during the day.

Evaluation system—To have impairment in a category, a dog had to have the signs of dysfunction in that category ≥ 1 time a week continuously for at least the previous month. The system was considered conservative. For example, it may be reasonable to assume that a dog had disorientation if it regularly stared into space, but a dog was not considered to have impairment in orientation unless there was ≥ 1 other marker of disorientation. Owners were asked about visual impairment and hearing impairment that was not noticeable earlier in the dog's life, and this information was considered during evaluation.

Owners were also asked about behavioral problems such as recent onset of separation anxiety, fears of inanimate stimuli, and aggression. If these problems could account for behavioral findings, the dog was not considered to have impairment in the related category.

The primary analysis dealt with each of the 4 behavioral categories. It was determined whether each dog had impairment in 0, ≥ 1, and ≥ 2 categories. Dogs with impairment in 1 category were arbitrarily considered to have mild impairment, whereas dogs with impairment in ≥ 2 categories were arbitrarily considered to have severe impairment.

Other methods of designating severity of impairment were considered, such as giving more weight to impairment in some categories than others (eg, requiring disorientation for a classification of severe impairment). Analysis of pilot data, however, revealed that the prevalence of dogs in each age group with impairments was not affected by whether data were weighted or not.

Statistical analysis—Analyses of changes in the proportion of dogs with impairments in the various categories as well as visual and hearing impairment across age groups included not only the possibility of sex differences but also the possibility of interaction between sex and age, which would complicate an analysis of the progression of signs of dysfunction across the age groups. The significance of such interactions was examined by logistic regression. Examination of age effects, after suppressing sex as a factor, was done with the Fisher exact test. The analysis of the degree of impairment as a function of body weight involved the possibility of interaction between body weight and age, which was also addressed by logistic regression. The effect of weight alone was examined after ruling out the age by weight interaction. Significance for all analyses was set at $P < 0.05$, using a 2-tailed t-test.

Results

Dogs—Data were obtained on 180 dogs, comprising 83 castrated males and 97 spayed females and representing 3 age groups, namely, 11 to 12 (n = 80), 13 to 14 (66), and 15 to 16 (34) years old. These were dogs for which there was no evidence in the hospital record that could provide an explanation for behavioral changes that could be attributed to dysfunction in ≥ 1 organ system other than the CNS.

Data were available for a somewhat larger number of dogs in the younger age groups than in the oldest group. Of the 11- to 12-year-old dogs, 56% (45/80) were females that were spayed at a mean age of 2.9 (± 2.6) years, and 44% (35/80) were males that were castrated at a mean age of 3.6 (± 3.1) years. Of the 13- to 14-year-old dogs, 53% (35/66) were females that were spayed at a mean age of 2.7 (± 2.6) years, and 47% (31/66) were males that were castrated at a mean age of 5.3 (± 4.1) years. Of the 15- to 16-year-old dogs, 50% (17/34) were females that were spayed at a mean age of 2.3 (± 2.6) years, and 50% (17/34) were males that were castrated at a mean age of 6.3 (± 4.2) years. Therefore, the percentage of each sex in each of 3 age groups was approximately the same. Overall, females were spayed at a mean age of 2.7 (± 2.6) years, and males were castrated at a mean age of 4.8 (± 3.8) years. Mean elapsed time from the last hospital visit indicated on the hospital record and the data-collection telephone call was 20.6 (± 22.5) months.

There was not a significant effect of age by sex interaction on the 4 categories and the 3 degrees of impairment represented by impairment in ≥ 1 or ≥ 2 categories (P values ranged from 0.26 to 0.85). To determine possible sex differences in proportion of dogs with impairments in the various categories and degrees of impairment, age groups were combined (**Fig 1**). Castrated male dogs were significantly more likely have impairment in orientation than spayed female dogs ($P = 0.03$). In the other 3 categories and 3 degrees of impairment, there were no significant sex differences (P values ranged from 0.06 to 0.35).

Age-related prevalence of impairment in behavioral categories—Because there were no significant sex by age interactions, subsequent analyses used combined data from female and male dogs across age groups (**Fig 2**). There was a progressive and significant age-related prevalence of dogs with impairment in each category and proportion of dogs with impairments in ≥ 1 and ≥ 2 categories (P values ranged from 0.001 to 0.004). The proportion of dogs with impairment in just

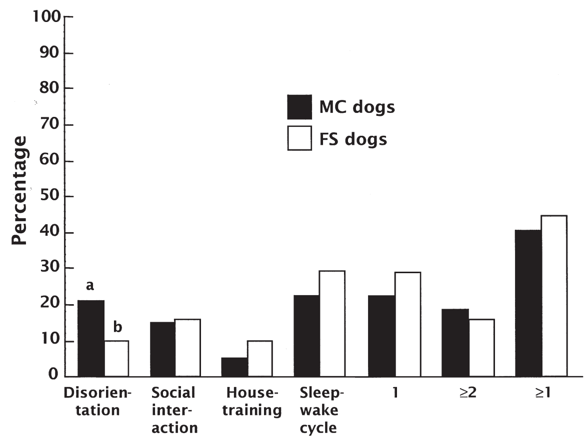

Figure 1—Percentage of male castrated (MC; n = 83) and female spayed (FS; 97) dogs that had impairments in each of 4 behavioral categories and in 1 category, ≥ 2 categories, and ≥ 1 category. [a,b]Different letters within a set of bar graphs (ie, 2 bars) indicate a significant difference ($P < 0.05$) between sexes.

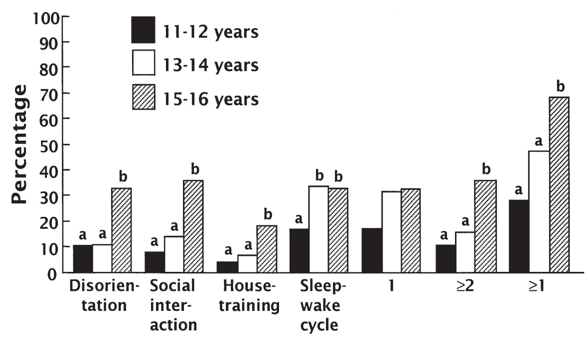

Figure 2—Percentage of 11- to 12-year-old (n = 80), 13- to 14-year-old (66), and 15- to 16-year-old (34) dogs that had impairments in each of 4 behavioral categories and in 1 category, ≥ 2 categories, and ≥ 1 category. [a,b]Different letters within a set of bar graphs indicate significant differences ($P < 0.05$) among age groups.

1 category was not expected to be significantly different between age groups, because further impairment with advancing age would be expressed as impairment in ≥ 2 categories. The percentage of 11- to 12-year-old dogs with impairment in ≥ 1 category was 28% (22/80), of which 10% (8/80) had impairment in ≥ 2 categories. Among 15- to 16-year-old dogs, 68% (23/34) had impairment in ≥ 1 category, of which 35% (12/34) had impairments in ≥ 2 categories. There was no indication of a chronologic progression of impairment such that dogs would have impairment in any particular category prior to developing impairment in other categories.

Impairment of vision and hearing—Visual and hearing impairment was described by the owner and not necessarily evaluated by a veterinarian. There were no sex by age interactions for visual or hearing impairment ($P = 0.39$ and 0.45, respectively). Combining data from males and females for further analysis revealed a significant age-related increase in prevalence of visual and hearing impairment ($P = 0.03$ and $P < 0.001$, respectively). Visual impairment progressed from 41% (33/80) of 11- to 12-year-old dogs to 68% (23/34) of 15- to 16-year-old dogs. Hearing impairment progressed from 48% (38/80) of 11- to 12-year-old dogs to > 97% (33/34) of 15- to 16-year-old dogs.

Body weight and signs of dysfunction—The issue of body weight and predisposition for behavioral impairment was addressed by testing for interactions between age and weight for dogs with impairment in ≥ 2 categories. The interaction was not significant, and the analysis conducted without the age by weight interaction revealed no significant weight effect ($P = 0.36$).

Discussion

Our cross-sectional analysis of data from dogs ranging in age from 11 to 16 years provides information on the prevalence of age-related behavioral changes associated with cognitive dysfunction. These signs were the result of impairment in the behavioral categories of orientation in the house and yard, social interactions with human family members, house training, and the sleep-wake cycle. Impairment in 1 category was arbitrarily designated as mild impairment, and impairment in ≥ 2 categories was designated as severe impairment. As discussed, signs of dysfunction in all the behavioral categories except the sleep-wake cycle can be related, at least in part, to disturbances of learning and memory. Although the behavioral patterns affected may not represent cognitive function as studied by animal behaviorists or neuroscientists, the changes in dogs correspond with neuropathologic changes, especially the deposition of diffuse β-amyloid plaques,[14,15] and share similarities with Alzheimer's disease in humans, which is also characterized by β-amyloid deposition.[12,13,17]

Behavioral impairments in some dogs in our study may have actually been a reflection of an organ system abnormality (other than brain degeneration). More likely, perhaps, is the possibility that hypothyroidism, arthritis, and cardiovascular disease may have intensified some signs that also reflected loss of memory and learning. In fact, most old dogs have ≥ 1 major organ system disorder, so it would be unusual to find a 15- to 16-year-old dog with impairment in ≥ 2 behavioral categories without any substantial impairment in any nonbrain organ system. Data from the clinical trial with selegiline,[4] involving 199 dogs that had an extensive physical examination with a routine neurologic examination, hematologic analysis, blood biochemical analysis (including T_4 analysis), and urinalysis to rule out medical disorders as causal factors in the signs of cognitive dysfunction, provided evidence that the signs of dysfunction in the categories of orientation, social interaction, house training, and sleep-wake cycle were not typically a consequence of a medical disorder (other than brain degeneration). We believe that our demographic study is a fair approximation of the age-related prevalence of the signs associated with cognitive dysfunction in dogs.

Further confirmation of the legitimacy of our demographic study as a guide to age-related prevalence of this syndrome comes from the longitudinal study[19] from this institution focusing on the short-term progression of impairment in a subset of dogs of our study presented here. Results of that study indicate that almost all dogs that initially had impairment in a category continued to have impairment in the category, and many progressed to a more severe degree of impairment, because they developed impairment in ≥ 1 additional category during a subsequent 6- to 18-month period. If the signs used to define impairments in our study presented here had reflected disturbances in the environment, interactions with the owner, or transient medical problems, rather than age-related pathologic changes in the brain, one would expect a reversal in many of the signs, and this would have invalidated the particular behavioral measures used.

Results from the longitudinal study[19] also indicate that the onset of visual impairment, hearing impairment, or both accounted for only a small proportion of dogs that developed disorientation during the same period. Thus, although some disorientation developed or was intensified by visual or hearing impairment, most instances of disorientation were independent of impairment in these organ systems.

In this study, 23% (22/80 of 11- to 12-year olds and 68% (23/34) of 15- to 16-year-olds had impairment in ≥ 1 category. Ten percent (8/80) of 11- to 12-year-olds and 35% (12/34) of 15- to 16-year-olds had impairment that was designated as severe in ≥ 2 categories. The only significant difference between male and female dogs was a higher proportion of castrated male than spayed female dogs with impairment in orientation. Visual and hearing impairment also increased with age; 68% (23/34) of 15- to 16-year-old dogs had visual impairment, and 97% (33/34) had hearing impairment. The age-related increase in impairment in dogs for all behavioral categories was significant, as was the increase in impairment in visual and hearing function with advancing age.

Although it is established that dogs of large body size die at a younger age, presumably as a function of more rapid aging in the cardiovascular, musculoskeletal, and endocrine systems,[18] findings of our study suggest that the processes in the brain responsible for age-related behavioral changes do not progress more rapidly in larger dogs. At any given age, small dogs are as likely to have impairment in ≥ 2 categories as large dogs. This means that because small dogs often live longer, one would predict they would be more likely to have signs associated with cognitive dysfunction during their lifetime than dogs of larger body size.

If impairment in ≥ 1 category is an indication for medical intervention, results of our study indicate that almost 30% of dogs 11 to 12 years of age would be candidates for such treatment, as would about 70% of dogs 15 to 16 years of age. On the assumption that dogs often progress in severity of signs of impairment in behavioral categories with advancing age, some clinicians may wish to recommend treatment when a dog has 1 sign of dysfunction in a behavioral category, as long as an extensive medical evaluation precludes an organ system disorder as the causal factor (other than brain degeneration). It should also be emphasized that there are undoubtedly other behavioral changes associated with aging that were not included in our study, which could be used as indications for medical interventions.

[a]Anipryl, Pfizer Animal Health, Exton, Pa.

References

1. American Veterinary Medical Association. *US pet ownership and demographics sourcebook*. Schaumburg, Ill: Center for Information Management, American Veterinary Medical Association, 1997.

2. Ruehl WW, Hart BL. Canine cognitive dysfunction. In: Dodman N, Shuster L, eds. *Psychopharmacology of animal behavior disorders.* Malden, Mass: Blackwell Scientific Publications, 1998;283–304.

3. Ruehl WW, Bruyette DS, De Paoli A, et al. Canine cognitive dysfunction as a model for human age-related cognitive decline, dementia and Alzheimer's disease: clinical presentation, cognitive testing, pathology and response to l-deprenyl therapy. *Prog Brain Res* 1995;106:217–225.

4. FDA. *Freedom of information summary*, *Anipryl (selegiline hydrochloride)*, *Pfizer, Inc*, *Groton, CT.* Washington, DC: US FDA, 1998.

5. Cummings BJ, Head E, Ruehl WW, et al. The canine as an animal model of human aging and dementia. *Neurobiol Aging* 1996;17:259–268.

6. Shettleworth SJ. *Cognition, evolution and behavior.* New York: Oxford University Press, 1998;3–48.

7. Czeschi T. Animal cognition—the phylogeny of cognitive abilities. *Anim Cogn* 1998;1:1–2.

8. Wisniewski H, Johnson AB, Raine CS, et al. Senile plaques and cerebral amyloidosis in aged dogs. A histochemical and ultrastructural study. *Lab Invest* 1970;23:287–296.

9. Uchida K, Miyauchi Y, Kakayama H, et al. Amyloid angiopathy with cerebral hemorrhage and senile plaques in aged dogs. *Jpn J Vet Sci* 1990;52:605–611.

10. Cummings B, Su JH, Cotman CW, et al. β-Amyloid accumulation in aged canine brain. A model of early plaque formation in Alzheimer's disease. *Neurobiol Aging* 1993;14:547–560.

11. Cummings BJ, Satou T, Head E, et al. Diffuse plaques contain C-terminal $A\beta_{42}$ and not $A\beta_{40}$: evidence from cats and dogs. *Neurobiol Aging* 1996;17:653–659.

12. Cummings BJ, Cotman DW. Image analysis of β-amyloid load in Alzheimer's disease and relation to dementia severity. *Lancet* 1995;346:1524–1528.

13. Ashford JW, Schmitt F, Kumar V. Diagnosis of Alzheimer's disease. In: Kumar V, Eisdorfer C, eds. *Advances in the diagnosis and treatment of Alzheimer's disease*. New York: Springer Publishing Co, 1998;111–136.

14. Cummings BJ, Head E, Afagh AJ, et al. β-Amyloid accumulation correlates with cognitive dysfunction in the aged canine. *Neurobiol Learn Mem* 1996;66:11–23.

15. Head E, Callahan H, Muggenburg BA, et al. Visual-discrimination learning ability and β-amyloid accumulation in the dog. *Neurobiol Aging* 1998;19:415–425.

16. Sano M, Ernesto C, Thomas RG, et al. A controlled trial of selegiline, alpha-tocopherol, or both as treatment for Alzheimer's disease. *N Engl J Med* 1997;336:1216–1222.

17. American Psychiatric Association. *Diagnostic and statistical manual of mental disorders*. 4th ed. Washington, DC: American Psychiatric Association, 1994:133–155.

18. Patronek GJ, Waters DJ, Glickman LT. Comparison longevity of pet dogs and humans: implications for gerontology research. *J Gerontol A Biol Sci Med Sci* 1997;52:B171–B178.

19. Bain MJ, Hart BL, Cliff, KD, et al. Predicting behavioral changes associated with age-related cognitive impairment in dogs. *J Am Vet Med Assoc* 2001;218:1792–1795.