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Natural or pathologic? Discrepancies in the study of behavioral and cognitive signs in aging family dogs

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ABSTRACT

In recent decades, typical and pathologic behavioral and mental aging in family dogs has received increased attention. This article reviews the literature and highlights methodological inconsistencies in this field. Most methodological concerns originate from disregarding the interaction of proximate and ultimate causes of this phenomenon. The literature review revealed several studies on family dogs that lack the methodological rigor needed for establishing a well-defined phenotype. The main issues include the chronological threshold accepted for aged dogs, the phenotypical features regarded as pathologic and the method applied to validate different behavioral scales. In addition, no baseline has been established for many studied behavioral and mental features by analyzing healthy adult population of dogs. In family or pet dog samples, the difference in the life expectancy of dog breeds is rarely taken into account, so it is not clear whether the observed changes are due to the normal aging process or are signs of an accelerated decline (senile dementia). We suggest that questionnaire studies should be complemented by behavior test batteries to validate data obtained from owners, and more attention should be given to the composition of the populations involved in the research. An effort should be made to discriminate normal or typical and pathologic aging in future work. Only by adopting a more rigorous approach can we identify risk and protective factors in dogs and reveal the aspects in which the family dog can provide a good animal model for human aging.

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Introduction

Behavioral changes associated with old age are highly relevant for veterinarians (Davies, 2012). Old dogs make up an increasing proportion of patients in part due to the growing awareness among owners. Associated problems include various signs from aggression to loss of house training, which can compromise both welfare and the human-animal bond for years, since these conditions are usually not considered life-threatening.

Aging provides a complex phenotype (throughout the text by phenotype we mean “the observable, measurable characteristics of organisms” as defined by Bergstrom and Dugatkin, 2012) that is rarely considered comprehensively. Aging can be summarized as

the deterioration of adjustment with adult age (Rose et al., 2012). Although aging affects every individual above a certain age, a subpopulation seems to suffer from more serious symptomatology. Some physical and behavioral deterioration, present in the vast majority of the population, is considered part of normal aging, while others (mostly involving only a small portion of the population) which severely impede the functioning of the organism is considered pathologic (Hedden and Gabrieli, 2004).

The first part of this review, which introduces some functional considerations related to dog aging, reflects on their specific evolutionary history because this aspect has not been highlighted previously. Other recent reviews discussing the identification and management of pathologic cognitive decline can be found in the literature (e.g., Landsberg et al., 2012; Cory, 2013). The second part critically reviews and compares some of the available psychometric tools and behavioral tests available with a focus on family dogs.

The huge variation of life span in dogs provides a good opportunity to discuss the inconsistencies in the methodology aimed at

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establishing a specific aging phenotype in dogs. Other problematic issues include the use of divergent tools for establishing behavioral measures, as well as a disregard for how intrinsic (e.g., sex) and extrinsic (e.g., social environment) factors may affect the aging phenotype and the outcome of comparative analyses. We suggest new ways of standardizing the classification of aging dogs and emphasize the importance of establishing validated aging phenotypes that also differentiate populations of dogs with different dynamics of aging.

The aging phenotype in dogs

Most reviews and experimental papers concentrate on a specific aspect of aging, that is, cognitive dysfunction syndrome (CDS), described as a pathology resulting in compromised behavior functioning in aged dogs. More specifically, [Head \(2001\)](#) and [Landsberg et al. \(2003\)](#) refer to a decreased capacity to obtain information, process it, retain it, and make decisions that can be detected in behavioral changes. Other similar terms are used describing a very similar phenotype, for example, canine cognitive dysfunction ([Salvin et al., 2010](#)), but we generally refer to CDS throughout this text. The changes most frequently reported in the literature involve anxiety (general fear from possible future events; [Bishop, 2007](#)), night walking, and vocalization ([Landsberg et al., 2012](#); [Fast et al., 2013](#)). Some of the changes seem to be minor (e.g., takes more time to learn new requests, increased daytime sleep), whereas others bear witness to severe deterioration (e.g., cannot navigate out from a corner; does not recognize owner returning after vacation) ([Landsberg et al., 2012](#)). Apart from naming issues, CDS may not be a well-defined phenotype or behavioral pathology for several reasons.

- (1) For their investigation, [Landsberg \(1995\)](#) compiled a checklist to help veterinarians rapidly and easily diagnose aging dogs and pinpoint specific problems that could be followed up by targeted medical investigations ([Landsberg et al., 2012](#)). Both in its original form and the different, but similar questionnaire used today, this checklist contains many items which may or may not relate to cognitive functioning.
- (2) Aging results in complex behavioral abnormalities that can be traced back to perceptual, mental, or motor problems. For example, urination in the house or flat can be the outcome of specific medical issues (e.g., bacterial infection), inability to control urinary function, disorientation, or discomfort during standing up or walking. This means that the reference to any cognitive function can only be sustained if the effect of medical, sensory, and motor dysfunction is excluded, for which explicit medical examination and testing is necessary ([Overall, 2013](#)).
- (3) If CDS is considered as a useful framework for describing the aging phenotype, then one would also need an estimate of how this phenotype changes over the whole life span. This characterization of age-dependent phenotype is critical because rather than determining the onset of old age arbitrarily in terms of years, one could use the rapid emergence of these phenotypic changes as markers for transition from adulthood to old age. This could also help in determining the difference for normal and pathologic age-related cognitive decline. For example, [Studzinski et al. \(2006\)](#) investigated the life-long variation of cognitive performance in a visuospatial delayed nonmatching to position task in laboratory beagle dogs. The most apparent changes occurred between adult (3–5 years) and middle-aged (6–8 years) dogs, although performance continued to decline further in old (8–10 years) and senior (10–12 years) dogs. In a related study, [Wallis et al. \(2014\)](#) investigated the life-long changes in attention and

sensory-motor abilities in border collies living in human families. Using a different type of grouping of late puppyhood (0.5–1 year), adolescence (1–2 years), early adulthood (2–3 years), middle aged (3–5 years), late adulthood (6–8 years), senior (8–10 years), and geriatric (over 10 years) they found that only dogs in the oldest group differed significantly from the middle-aged ones. Importantly, in this measure, adolescent dogs were very similar to geriatric dogs (they differed significantly in the same direction as geriatric dogs from middle-aged ones), and the study also showed the importance of making observations across the whole life span. The 2 types of groupings can be regarded as comparable, such as mean age for border collies and beagles is 13–15 and 13 years, respectively (see [Figure 1](#)), but the behavioral changes emerged at different phases during life. Environmental conditions and breed differences could be also playing a role in these cases. Nevertheless, only by obtaining this information can researchers determine the role of age in CDS in addition to other intrinsic (e.g., breed) and extrinsic (e.g., experience) factors.

During aging, changes in both directions can be a sign of cognitive impairment (e.g., apathy vs. restlessness, increased vs. decreased interest in owner), which makes evaluation of the signs challenging and raises the question whether the same underlying factor is responsible for the opposing behaviors.

Evolutionary and ecological considerations

Aging studies in dogs show huge divergence, partly because their starting points and focus are very different. Here, we emphasize that studying any aging phenotype should go hand in hand with understanding the aging process itself.

Theories of aging

Aging in humans and dogs from a biological perspective is associated with reduced fitness and fertility ([Kirkwood, 1997](#); [Borge et al., 2011](#)). Living beyond the time of active reproduction does not contribute directly to individual fitness, unless these older animals provide some indirect benefits to their relatives (inclusive fitness). This view is complemented by life-history theories suggesting that longevity may be correlated with ecological challenges. Animals in more risky environments live shorter lives and have many offspring, whereas species in a less risky environment live longer and have fewer offspring at reproduction ([Pianka, 1970](#)). The important insight of these functional approaches is that longevity

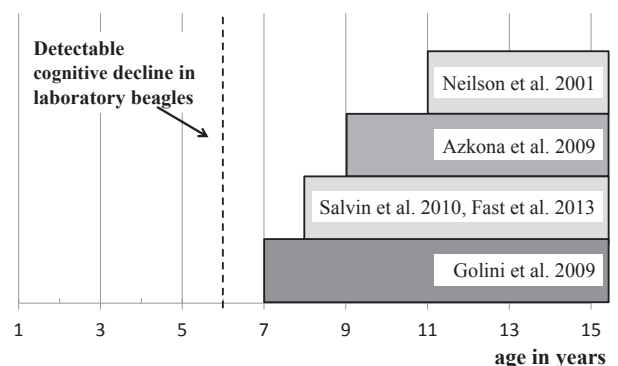


Figure 1. Different aging questionnaire studies on family dogs apply different inclusion criteria with regard to chronological age of dogs. In laboratory beagles, the first signs of cognitive decline already occur at 6 years of age ([Studzinski et al., 2006](#)).

(whether delayed aging or earlier death) can be selected for in nature. In contrast, most mechanistic theories of aging are focusing on the increasingly deteriorating function of the organism (error theories), which may come about by the accumulation of mutations, oxidative stress, or speed of metabolism.

To complicate matters, evolutionary and mechanistic theories have an additional meaning in aging research (Hughes and Reynolds, 2005). Instead of focusing on the proximal versus ultimate causes, both offer explanation for the ultimate cause. Evolutionary and program theories argue that there is an inherent, programmed mechanism underlying senescence while mechanistic and error theories explicitly deny the existence of such a mechanism and argue that destructive factors can be avoided (for a review, see Semsei, 2000).

Most reviews on aging in dogs share this latter mechanistic approach and investigate the advance of decline in perceptual, cognitive, and motor function affecting dogs' life. However, differentiating between cognitive changes (e.g., decline in memory function) and sensory-motoric or physical conditions (e.g., arthritis) is challenging in nonhuman animals. Thus, there is little known about the extent to which these changes are independent or interdependent.

Possible parallels between aging in humans and dogs (or other companion animals) have been extensively promoted, although it is not clear whether these species have been exposed to similar selection factors during their evolution. Neglecting such issues can be problematic if some concepts related to human aging (e.g., physical senescence, healthy aging, health span [the period of life during which an individual is free of chronic illness and substantial functional decrements sensu Martin et al., 2007]), are uncritically applied to dogs, despite the argument that mammals share basic processes of aging (de Magalhães and Toussaint, 2002).

The study of dog aging is significant from at least 2 applied perspectives. First, despite the growing number of aged dogs in present day populations, very little is known about the actual prevalence and risk factors of age-related changes in dogs (Neilson et al., 2001; Osella et al., 2007; Azkona et al., 2009; Salvin et al., 2010). Better evidence-based knowledge could facilitate the early recognition and treatment of specific age-related conditions, and provide for a predictive approach. Different life experiences (e.g., feeding, physical and mental exercises) might increase the chance of aging with less debility and improve dog welfare. Second, it has been argued (e.g., Milgram et al., 1999) that dogs provide a good animal model for human aging. However, there are actually many animal models of aging, and it is important to emphasize the specific limitations and advantages of the dog model.

Biological determination of life span in dogs and wolves

Environmental differences between wolf (*Canis lupus*) and dog populations support limited comparisons between the 2 species. Examples of environmental differences include that in the wild (but often not in captivity) wolves hunt, there is a supportive anthropogenic environment and veterinary care for pet dogs, and there is diversity in ecological conditions for stray dogs of pet origin. Nevertheless, comparing the species may help to understand the complexity of causal factors influencing aging in family dogs.

The maximum life span in wild wolf populations is estimated to be around 11–12 years (see Ausband et al., 2009 for 14–15 year old wild wolves), whereas in captivity a wolf may reach the age of 20 years (Mech, 1988). The mean life span of dogs living with humans is heavily breed dependent, but is estimated to be approximately 12 years (Michell, 1999; O'Neill et al., 2013), although the maximum life span recorded for family dogs is around 22–24 years (see data provided by Michell, 1999; Adams et al., 2010;

O'Neill et al., 2013). These data suggest similar maximum life spans for both species.

In the absence of quantitative data, most experts assume that the mean expected life span for wolves living on the Northern Hemisphere is between 5–7 years of age (see Mech, 2006). The population structure of family dogs suggests that there is a huge variability in maximum life span of this species if one considers dog breeds, mixed-breed dogs living with humans, and different populations of free-ranging dogs. In the case of pure breeds, mean life span may range from 5.5 to 14.5 years (Michell, 1999; O'Neill et al., 2013), for mixed-breed dogs the same value is 13.1 years. Such values are not available for free-ranging dogs, but a significantly shorter mean life span would be expected because of the risk environment, and this life span may be shorter than the mean expected life span for wolves. Dogs sharing their lives with humans may have gained considerably from this alliance by doubling their mean life span. Even most dog breeds associated with shorter life expectancies (Galís et al., 2006) reach an age approximating the mean life span of wolves in nature (5–7 years).

The relative early death of large sized dogs was often referred to as an opposing trend to the observation on wild species in which large size predicts longer life span (Rollo, 2002). On this basis, the reduction of size during domestication (Miklósi, 2014) was assumed to lead to reduced longevity in dogs. Studying the relationship between size and aging in other species showed that species level processes should be distinguished from within-species effects. Although the positive correlation between body size and longevity exists for major taxonomic clades, within species, smaller individuals live longer.

Dog breeds follow the trend which is characteristic for within-species variability, as do domesticated horses (Wolf, 2010). Selection for smaller size in laboratory mice has also increased life span, whereas selection for larger individuals has had the opposite effect (Rollo, 2002). Most researchers believe that the insulin-like growth factor-1 (IGF-1) plays a crucial role in this interaction. For example, Greer et al. (2011) reported a positive association between IGF-1 concentration in adult dogs and size (weight), and generally an opposite trend was found with age. Sutter et al. (2007) revealed that IGF-1 alleles may explain the large percentage of size variation in dog breeds. Thus, it is plausible that selection for greater size in dogs at the later stage of domestication (using smaller animals as the starting population) involved heavily the IGF-1 pathway, which apart from allowing for rapid early growth, has many side-effects (based on mammals studies), such as reduced investment in protein maintenance, more rapid rates of telomere abrasion, being more prone to developmental weaknesses (Metcalf and Monaghan, 2003), altered insulin signalling (Bartke et al., 2003; Reid et al., 2015), and higher risk of cancer (Gallagher and LeRoith, 2011), which led to truncated life span.

Importantly, selection for any trait is strongly related to the specific environment. Artificial selection for size or other traits in dogs could be achieved only in the protected anthropogenic niche in which the breeding stock has access to rich food sources. This may explain that breed selection could lead to longer (double) mean life span in many wolf-sized dog breeds (e.g., German shepherd dog, husky, and so forth) without affecting maximum longevity.

Multiple factors in the evolution of dogs determine size and aging. These include adverse developmental growth pattern (e.g., increased postnatal growth rate [de Magalhães and Sandberg, 2005]), and/or the speed of aging (Kraus et al., 2013).

Apart from size, behavioral and personality traits may also affect life span of dogs but appear to do so in the opposite direction. Dog breeds with a more trainable character (Draper, 1995) tend to have a longer life span (Careau et al., 2010). However, one may argue, that

it is not trainability itself, but the docility achieved by reduced stress to anthropogenic factors which may play the key role.

In summary, life span of the dogs in general, and dog breeds, in particular, might have been affected by various (often opposing) selective factors either in parallel (e.g., decreasing size and increasing docility during early domestication) or sequentially in the course of domestication (e.g., a new selection for large body size). If so, particular attention should be paid to determine different parameters of aging in dogs (e.g., start of aging), how these values are compared across breeds, and how the different selective factors may have used different genetic, biochemical, and physiological pathways. It is possible that phenotypically similar aging processes may actually be controlled or driven by different biological mechanisms.

The diversity of aging and life span in dogs

Different dog populations (pure breeds, mixed breeds) living in human families show a huge variability in mean life span, and probably also in maximum life span (see Figure 2). Many factors such as size or weight (Galis et al., 2006), hybrid vigor (O'Neill et al., 2013), breed-specific behavioral tendencies (Careau et al., 2010) and predilection to particular diseases (Egenvall et al., 2005) can affect life span.

Even if the effect of these factors may be constant for a specific breed, researchers use different methods for the estimation of life span in dogs. This includes data from veterinary practices (e.g., Patronek et al., 1997), asking dog owners directly (Adams et al., 2010), or databases (often with uncontrolled origin of data) that can also lead to different estimates (Urfer, 2008).

Various authors also use different thresholds for numerically defining aging, independent of the cohort they investigate (see Figure 1) (Neilson et al., 2001; Studzinski et al., 2006; Azkona et al., 2009; Golini et al., 2009; Salvin et al., 2010; Fast et al., 2013). This means that in these studies the aged dog group is represented by different dog breeds. For example, based on median age from the 36 breeds listed by O'Neill et al. (2013), representatives of 32 breeds would have a high chance of being included if the threshold of old age is set at 7 years (e.g., Golini et al., 2009), an age commonly set for the end of adulthood among dog experts. In contrast, the median age of only 25 breeds is higher than 11 years, and that is also

referred to as the start of aging (e.g., Neilson et al., 2001). Note that all age boundaries between adult and aged dogs are set to be later than the start of objectively measured decline of cognitive performance in laboratory dogs (Studzinski et al., 2006 and Figure 1).

Relation between life span and senescence

Although there is no agreed way how to divide adult life in dogs into periods, Studzinski et al. (2006) introduced 5 periods for the beagle, for which median life span is estimated at 13.3 years (Michell, 1999). Assuming that a 1 year old beagle is sexually mature (Wildt et al., 1981; Studzinski et al., 2006) Studzinski et al. (2006) defined the groups young adult (1–3 years), adult (3–6 years), middle aged (6–8 years), old (8–10 years), and senior (≥ 11 years) individuals. The beagle life span seems to correspond well to the 11–12 years of age that was calculated for all pet dogs by Michell (1999); however, only 36% of dog breeds listed in O'Neill et al. (2013) reach this median age.

Shorter mean life span can be explained by different mechanisms including earlier onset of senescence, higher mortality, and increased rate of aging (Galis et al., 2006; Kraus et al., 2013). After analyzing aging data from a large set of dog breeds Kraus et al. (2013) argued that in larger dogs, faster aging is the main reason for the relative short life span. This means that these breeds are characterized by an abnormally shortened old and senior period.

If dogs in gerontology studies are categorized simply on the basis of age, then for the majority of dog breeds there are no representatives in the senior period, and a large number of breeds are missing from the “old” period as well. Unfortunately, this is commonly the case for surveys available in the literature.

One simple way around this problem is to use mean or median life span for each breed as a reference, and divide the actual age of the dog by this value. In this case, 0.5 means that the dog's current age is half of the expected life span for its breed, whereas a relative age of 1.1 means that the dog current age is 10% beyond that expected on average for the breed. For the means or medians, Michell (1999), Adams et al. (2010), or O'Neill et al. (2013) can be used as a source. Alternatively, the equation provided by Greer et al. (2007) can be used: $\text{life span/years} = 13.620 + (0.027638 \times \text{height/cm}) - (0.118609 \times \text{weight/kg})$. Using the relative age of individuals allows various breeds and crossbreeds to be placed in the same data set when one is investigating life-long changes in different phenotypic parameters. Note that this method assumes a linear relationship between all life periods in dog breeds that may not be the case according to Kraus et al. (2013). For a more accurate calculation, one would need the estimation of breed-specific age-period spans, but these are not available at present (see Figure 3).

Confounding medical conditions

Old age comes with a higher prevalence of various pathologic conditions. To diagnose an animal with CDS, one must exclude medical causes associated with similar signs (Landsberg et al., 2012). As mentioned earlier, sensory impairment can bias the behavioral measurements, including estimation of CDS prevalence. Although it is possible to exclude dogs that show impaired sensory skills in the case of laboratory studies (Cummings et al., 1996b), this is usually not a possibility in the case of surveys.

Data from aging human populations demonstrate a clear age-related increase in prevalence of impairment of eye-sight and loss in hearing that may have a profound influence on the behavioral phenotype (Lim et al., 2012; Yamasoba et al., 2013). Although aging dogs are exposed to similar processes, actual data are harder to find. For example, Urfer et al. (2011) reported that in dogs older than 5 years the incidence of cataract was 8.7%, in old dogs (7–10 years)

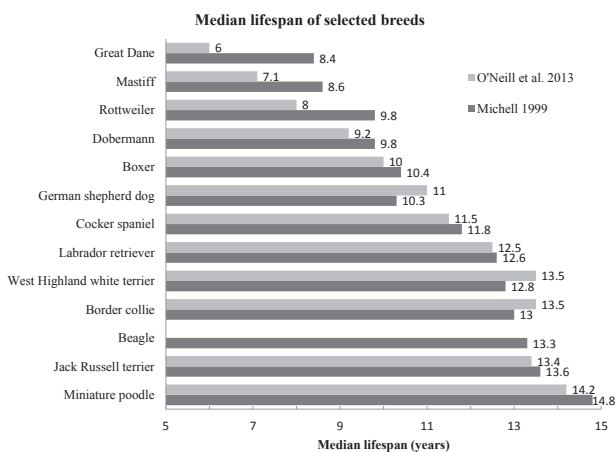


Figure 2. Comparison of different breeds' median life span based on 2 studies. Large and giant breeds tend to have shorter median life span and as a result are less likely to be included in the oldest age groups (e.g., 12–14 years), but they would be included in the old groups (e.g., 8–10 years) if it is defined by chronological age. Beagles were not represented in O'Neill et al. (2013). Although the source of data differed between the 2 studies, both of them reported median age at death and interquartile range.

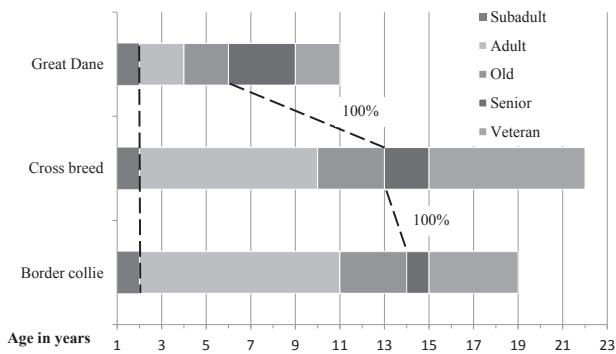


Figure 3. Comparison and possible categorization of aging dogs based on data from O'Neill et al. (2013). The median life expectancy for breeds or population (in bold and also indicated by 100%) is taken as the border between old and senior dogs. Lower interquartile range is used to separate adult and old aged dogs, and upper range is indicating a separation of senior and veteran dogs. The end values of the scales refer to the maximum life expectancy reported in O'Neill et al. (2013). Changes in the phenotype may not reflect these borders which should be revised accordingly if data become available. Using this framework, dogs having the same biological age could be categorized differently. The scheme could be refined by calculating the relative age of the dog in percentages (see also main text).

14.1% of the population was affected, and that the rate is probably even higher in senior dogs. This condition seemed to be more typical for large and giant dog breeds. Few similar reports are available for other age-related malformations of the eye, for example, myopia (short-sightedness), which is a relatively prevalent condition in many breeds (e.g., poodles, spaniels, and collies) (Williams et al., 2011). Although adult age was not included as a variable in the latter report, Kubai et al. (2008) found a significant increase of myopia in aged dogs regardless of breeds. Similarly, there are only scarce data for loss of hearing, but research studies usually show impairment in middle aged or older dogs compared to younger ones (e.g., Ter Haar et al., 2010).

Although some experimental studies report that they exclude dogs with impaired sensory function (Rosado et al., 2012a), routine veterinary examinations do not usually include specific testing for myopia or reduced hearing range. The narrowing of perceptual skills (affecting in parallel multiple senses) can lead to reduced behavioral performance in many situations by making the older individual less active, more weary, or less able to perform well in cognitive tasks relying on vision or hearing. In dogs described as cognitively more impaired, it is entirely possible that sensory impairments may account for some of the behavioral differences compared to the unimpaired individuals (Rosado et al., 2012b). For example, dogs with narrower sensory function may show disoriented exploration in novel places (open-field test).

In conclusion, neglected sensory impairment could be a profound confounding factor in detecting CDS in aged dogs, especially because some of these malfunctions also have a genetic component.

Next to sensory impairment, various medical conditions such as tumors, seizures, endocrine, and metabolic disorders can also result in signs which are generally associated with CDS. For a detailed summary of such not exclusively aging specific conditions consult Landsberg et al. (2012).

Mental decline in aged dogs

With regard to age-related changes of mental processing, Head (2013) discriminates 3 types of dogs. Dogs aging successfully diverge by a small amount (<2 SD) from young adults in performance on some cognitive tasks. Cognitively impaired dogs differ by

a moderate amount (at least 2 SD) on these tasks, and severely impaired dogs are unable to learn to solve the same problems. Although the category of "impaired dogs" may seem to be defined arbitrarily, the categorization presents an objective description of performance in aged dogs, and it also reveals that significant mental decline is not universal for dogs as time passes by.

Unfortunately, no similar objective framework exists at present for pet dogs living in human families (see point 1 in section 6). This is problematic because the methodology used by these studies does not allow for the separation of aging from mental dysfunction that correlates at the population level but may or may not affect individuals. Research on family dogs refers to the term CDS for which only a broad definition exists (see above). CDS has been developed on the assumption that aging dogs become gradually less compatible with their actual environment, without specifying what kind of perceptual, mental, and motor processes are affected. In spite of this, CDS is often portrayed (and its name also implies) as an abnormal mental process, analogous to Alzheimer's disease.

In the next section, we review previous studies which used behavior for measuring cognitive aging in family dogs. Some studies rely on indirect measurements (behavior as perceived by the owner), whereas others use direct observations. Both approaches have their advantages. Direct observations are more objective, but the duration of observation is very limited, and some relevant behaviors may occur only infrequently.

Using questionnaires for estimating behavioral changes

Questionnaires completed by the owners provide a useful tool for researchers to get an initial estimate about the behavior of family dogs. Questionnaires are less labor intensive for the researcher, but the power of this approach is often overestimated, especially in the absence of validation.

In the last decades, many different questionnaires have been created to assess cognitive decline; however, the questionnaire items changed dynamically across studies. The oldest publication we could find (Ruehl et al., 1994), lists the following 15 behavior items: house training, interest in food, attention and activity, awareness of surroundings, recognition, response to requests, hearing, climbing stairs, tolerance to being alone, compulsive behaviors, circling, tremors, changes of sleep patterns, stiffness or weakness, and inappropriate vocalizations. Although this checklist (and its antecedents) was mainly developed as a tool to aid veterinary evaluation, researchers started to use it as a measurement tool for cognitive decline in dogs. The evaluated categories usually include questions about alternations in spatial orientation, social interactions, house soiling, sleep-wake cycles, and activity level. Among these, house soiling is the topic consistently mentioned in the different questionnaires (see Table for a detailed comparison).

Our subjective review of several articles (see Table) revealed the following problematic issues.

- (1) Variation in questionnaire items included: Although all authors aim to measure a standardized syndrome, the phenotype which falls into this category differs among the scales. For example, most of the questionnaires include a subset of the original items along with additional items. Bain et al. (2001) included 4 categories with 3-5 items in each, without a corresponding description explaining why and how the items were selected. Fast et al. (2013) used the questionnaire from Rofina et al. (2006), but added 6 additional questions from the domains of anxiety and learning or memory. It is not clear whether these additional items included in the questionnaire were used for the evaluation.

Table

Subjective review of several papers regarding questionnaires measuring cognitive dysfunction syndrome in dogs

Domain	Kiatipattanasakul et al. 1996	Colle et al. 2000	Neilson et al. 2001	Rofina et al. 2006	Osella et al. 2007	Azkona et al. 2009	Golini et al. 2009	Salvin et al. 2011a	Landsberg et al. 2012	Rosado et al. 2012b	Fast et al. 2013
Activity	No	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Aggression	No	Yes	No	Yes	Yes	No	Yes	No	Yes	No	Yes
Aimless pacing	Yes	No	No	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes
Anxiety	No	No	No	No	Yes	No	Yes	No	No	Yes	Yes
Appetite	Yes	Yes	No	Yes	Yes	No	Yes	No	Yes	No	Yes
Auto stimulatory behavior	No	Yes	No	No	Yes	No	Yes	No	Yes	No	No
Difficulty to find dropped food	No	No	No	No	No	No	No	Yes	Yes	No	No
Disorientation (objects)	No	No	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Disorientation (routes)	No	No	Yes	Yes	Yes	Yes	No	No	Yes	Yes	No
Drinking	No	Yes	No	Yes	No	No	No	No	No	No	Yes
House soiling	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Sleep/wake cycles	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes
Social behavior-toward animals	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No
Social behavior-toward humans	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Work, tasks, commands	No	Yes	No	No	Yes	Yes	Yes	No	Yes	Yes	Yes

As shown, different authors include and exclude different domains from their evaluation. Yes: the questionnaire contains at least one item regarding the respective category, No: the questionnaire does not contain any indicative item for the respective category. Disorientation (objects) refers to questions like “Collides into furniture” which indicate difficulties with avoiding or navigating around objects. Disorientation (routes) refers to items like “Gets lost in familiar locations” which indicate difficulties with memory and large scale spatial orientation skills. Work, tasks, commands refers to items regarding responding to previously learnt commands, carrying them out correctly or learning new ones.

Neilson et al. (2001) relied on 4 main categories of behavioral focus (orientation, social interaction with humans, sleep-wake cycle, and house training), whereas Golini et al. (2009) used 8 categories. The problem is obvious if we consider that the quantitative data involve the number of impaired categories. If the intensity and frequency or number of different behaviors is disregarded, then the number of included or excluded categories becomes a central issue if one wants to compare results across studies.

Another problem across questionnaires is a lack of item stability within categories. For instance, the item “Decreased recognition of/Does not recognise familiar people” has been placed in the category “Disorientation” (Osella et al., 2007), “Social interactions” (Azkona et al., 2009), and “Learning and memory: work, tasks, commands” (Golini et al., 2009). Because the evaluation is often done out at the level of categories rather than contributory items, outcome of the evaluation may differ. Such approaches risk reducing categories to arbitrary groupings devoid of stable definition with questionable validity.

The number of evaluated items varies between 15 (Azkona et al., 2009) and 39 (Osella et al., 2007). A shortened version may lead to limited sensitivity and precision, and researchers should make sure that they cover the most essential aspects of the investigated behavioral changes. Theoretically, the more diverse—but relevant—items included in a questionnaire, the more accurate is the measurement of the underlying construct. The advantages of a longer questionnaire must be balanced with the fact that dog owners are more likely to complete a shorter questionnaire.

- (2) Scoring of questionnaire items: Some studies simply rely on the recent occurrence of certain behaviors (yes/no), while others pair this with frequency and continuity of the signs. Frequency-based categories differ (Osella et al., 2007; Salvin et al., 2011a), as do criteria (e.g., “at least once a week continuously for at least the previous month”; Neilson et al., 2001). Some authors score the severity of the impairments by severity scales (e.g., 0–non impaired, 4–severely impaired; Rosado et al., 2012b) while others weigh the more extreme behaviors with higher scores (Kiatipattanasakul et al., 1996).

Some authors make it explicit that the owners should compare their dog’s behavior to when it was younger. “Younger” may not be

qualified (Azkona et al., 2009). In extreme cases, owners were required to remember how the dog behaved 12 years prior (before 7 years of age, Osella et al., 2007). In contrast, Salvin et al. (2011a) set a more realistic expectation with a 6 months’ time-span. In general, however, reliance on the owner’s memory as part of the evaluation process is likely to introduce additional error variance.

- (3) Categorization of cognitive decline: Questionnaires have been used to categorize dogs, alone, or with some other measure (e.g., behavior test, neural examination) for validation of content. In both cases, the dogs were grouped based on the questionnaire scores. Some authors apply weights to some items, often without a clear rationale that could be replicated (Kiatipattanasakul et al., 1996; Colle et al., 2000; Salvin et al., 2011a). This approach is problematic because it gives rise to poorly defined categories that are impossible to compare objectively, such as “predementia” (Kiatipattanasakul et al., 1996), “border-line” (Fast et al., 2013), “mildly impaired” (e.g., Neilson et al., 2001), etc. Hence, the severity of cognitive decline (or the specific category) of a dog can depend less on the dog and more on the questionnaire used. The specificity and sensitivity of the different questionnaires should be compared by using different questionnaires on the same sample of dogs (within-subject design) (similarly to Rofina et al., 2006).

The distinction between normal dogs and dogs with pathologic mental decline may rely on whether the dog shows impairment across multiple categories (Neilson et al., 2001; Osella et al., 2007; Azkona et al., 2009) or one sign/category (e.g., Rosado et al., 2012b). Some researchers set diagnostic criteria based on summed scores (Kiatipattanasakul et al., 1996; Salvin et al., 2011a; Rosado et al., 2012b; Fast et al., 2013) but threshold criteria vary. Threshold criteria may not be specified (Kiatipattanasakul et al., 1996; Rosado et al., 2012b), may be subjective (Fast et al., 2013), or may be based on the lowest score achieved within a small sample of dogs diagnosed with dementia by a veterinarian (Salvin et al., 2011a). These results suggest that distinction between categories is elastic, at best.

Authors also do not agree on the number or type of severity categories. In some cases, severity classification is not used for questionnaires (e.g., Golini et al., 2009). Mild cognitive impairment

is sometimes used within the CDS group (e.g., Azkona et al., 2009; Rosado et al., 2012b), but Fast et al. (2013) argues against this usage and applies a distinct group called “borderline canine cognitive dysfunction.” Whether this intermediate state is seen as pathologic or within the range of normal aging is not clear. This hesitance can be observed in behavioral studies as well, in which authors report findings with the 2 groups both pooled and treated separately (Rosado et al., 2012b).

Beyond mild impairment, some papers use only the category of “severe” (Neilson et al., 2001; Rosado et al., 2012b), although Azkona et al. (2009) makes a further distinction between moderate and severe impairment. Whether these categories can be justified by physiological correlates in any qualitative or quantitative sense and whether mild cognitive impairment indicates extant pathology or is simply a reliable early marker/preclinical stage are questions for future research. These methodological differences prevent further comparison between different studies.

- (4) Correlating CDS with age: Many authors aim to validate these questionnaires by showing that there is a positive correlation between the scores and dogs' age. Older dogs obtain higher scores, which reflects stronger decline with age. Unfortunately, many studies use a very small sample size, and the results may depend on whether younger dogs are in the sample. If younger animals are included, then the positive correlation is expected on the basis of aging independent of whether the aged dogs are unimpaired (“normal aging”) or impaired (“abnormal aging—cognitive dysfunction syndrome”) (see Head, 2013 previously mentioned). Thus, such positive correlation provides no evidence that the questionnaire actually measures CDS. It is not surprising that when the sample contained only old dogs, no specific validity emerged. Using one variant of the questionnaires, Golini et al. (2009) found that from the dogs “diagnosed” with CDS by the questionnaire, only 6 showed any concurrent neurological signs, while 8 animals did not.
- (5) Validation by behavioral and neural measures: Attempts have also been made to validate the questionnaires by observing the dogs' performance in various behavior tests and/or obtaining physiological data in parallel. The inclusion of young dogs in these samples distorts the results because this age effect is usually much stronger than the effect of abnormal mental decline. For example, Rofina et al. (2006) correlated brain pathology with the scores of 3 questionnaires (Kiatipattanasakul et al., 1996; Colle et al., 2000; Rofina et al., 2006). Although the scores across questionnaires highly correlated with each other ($r \geq 0.9$), most of the measured physiological variables (including amyloid beta [A β]) correlated more strongly with age ($r = 0.9$ for A β) than with any of the questionnaire scales ($r = 0.5$ and 0.6 for A β).
- (6) Inclusion of perceptual and motor decline: Questionnaire studies imply that data are collected on mental dysfunction, nevertheless, little effort is taken to control for dogs displaying perceptual and motor impairment. For example, in Salvin et al. (2010), from the 957 dogs enrolled in their study, 518 dogs were reported to suffer from arthritis, 290 from deafness, and 226 dogs from blindness. The authors concluded that dogs suffering from dementia showed an increased prevalence of blindness. The lack of any external standard by which to assess dogs with sensory impairment may have interfered with questions like “difficulty to find dropped food” and “dog walking into doors/getting stuck”.
- (7) Using secondary phenotypes for validation: Questionnaires may reveal some background variables that may show a stronger correlation with physiological and/or behavior measures than individual items or their arbitrary combinations.

This would be logical because most items actually refer to a specific context in which the behavior of the dog is expected to have changed. In contrast, neural alterations (e.g., atrophy of neural tissue or plaque formation) may have a more general effect on behavior. Although such methods, e.g., factor analysis, are widespread in personality research, only a single study (Salvin et al., 2010) attempted to apply this statistical tool to the questionnaire on CDS, in which a single underlying component (“factor”) for cognitive decline was reported (Salvin et al., 2011a).

In conclusion, questionnaires can be a very useful tool for researchers, but a more cautious approach is needed. There is little validation of such tools, and changes in assessed behavior may be due to the physical rather than the cognitive effects of aging. A better approach would be to develop a questionnaire by which secondary measures (such as co-occurrences or order of occurrence) could be revealed. This tool should then also be used for phenotyping the dogs for the whole life span (similarly to Salvin et al. (2011b)), by also distinguishing breeds and dog populations (e.g., working lines vs. show lines). The time course of various behavioral features should differ as pathology progresses, based on survey studies, and repeated questionnaire assays should reveal this.

Observing behavioral changes in aged and/or cognitively impaired dogs

Behavioral studies fall mainly into 2 different categories. One approach evaluates the effect of age-related changes in general, by comparing healthy young adults to healthy aged dogs. Another approach uses questionnaires with observed and quantified performance variables to reveal categorical parallels.

Age-related changes

Activity is expected to decrease in older dogs. Independent owner-based questionnaire studies of family dogs seem to support this (Vas et al., 2007; Salvin et al., 2011b). Some of the activity changes will be due to malfunction of sensory and motor systems independently from cognitive function. Experiments show that the situation is more complicated, which could also explain why low-level correlations between questionnaire scales and neural parameters are reported. Rosado et al. (2012a, 2012b) investigated locomotor and exploratory behavior and problem solving in dogs of various ages. In an open-field test, cognitively impaired old (from 9 years) dogs visited the door less often, visited the corner of the room more often and were more restless than unimpaired dogs of the same age, whereas little behavioral difference was apparent for middle aged (5–8 years) and unimpaired old dogs. Similar experiments on laboratory beagles revealed no significant differences with respect to locomotion in old dogs, and cognitive state (based on learning performance) had no effect in open-field tests (Head et al., 1997; Siwak et al., 2001). Young laboratory dogs had higher inactivity scores than old dogs (Head et al., 1997), suggesting that cognitively impaired old dogs may be more anxious in novel places. Age may also have a context-specific effect on activity in old family dogs, similar to that of laboratory beagles (Siwak et al., 2002), that could be measured by specific behavioral tests. Extant questionnaires are not sensitive enough to detect such differences.

Several studies looked at specific aspects of cognitive performance, including spatial orientation, flexibility in learning, and social attention. Salvin et al. (2011b) compared the performance of young (1–4 years) and normally aging old dogs (over 8 years) in a sand maze using a simple visuospatial memory paradigm. There were 4 doors in the arena, and dogs entered from different sides in

subsequent trials. This design prevented the dogs from using an egocentric search strategy. There was no difference between the 2 groups with respect to latency during the acquisition trials (reward fully buried in the sand), but it took longer for the aged group to reach the target quadrant in the control trial (half-buried reward). Aged dogs also took longer to reach the target after a 90-minute delay in the retention trial. Aged humans also show impaired performance in a long-term memory task (Goh et al., 2012).

In a different spatial learning task, dogs needed to navigate out from a 3 × 3 m T-maze in order to get to their owner (Mongillo et al., 2013a). They found that while there was no difference between young (3–7 years) and old (8–13 years) dogs' performance in the initial learning and retention phase, the older dogs committed twice as many errors in the following reversal learning task, which took place 2 weeks later in the same maze. The impaired reversal learning of aged dogs indicates decreased cognitive flexibility. Similar results were reported in senior (older than 12 years) laboratory beagle dogs (Christie et al., 2005). Cognitive flexibility has been described to show age-related decline in humans as well (Peltz et al., 2011).

Mongillo et al. (2010) reported that older dogs (more than 7 years) were as attentive toward their owners as young dogs (1.5–7 years) while their owners stayed in the room, but they paid less attention to the door once their human companions left. When the dogs were allowed to go to the doors, old dogs were just as likely to successfully track the door where they saw the owner disappear as younger dogs. This shows that age-related differences observed in behavior do not necessarily mean impaired functioning in everyday life. Old dogs were just as successful in tracking the doors where their owner disappeared as young dogs, even when they looked at their owner for a shorter period of time. More experimental studies on the social aspect of cognitive aging are clearly needed.

A recent single-breed (border collie) study by Wallis et al. (2014) measured attentiveness of dogs throughout their life span in a cross-sectional design. No signs of age-dependent decline were found with respect to latency of orientation (attentional capture). Although an overall decrease in looking time (sustained attention) was found, this turned out to be context specific. The looking time toward nonsocial stimuli decreased with age, but no such decline was found in relation to social stimuli (human), which shows the preserved capacity for sustained attention in aged dogs. In a selective attention task (training to establish eye contact), both the latency to establish eye contact and to find the dropped food was shortest among 3–6 years old dogs, which the authors concluded suggests a quadratic relationship between age and performance in this task. The idea that different traits can show different (not necessary linear) trajectories across the life span is well known for humans, but so far only Wallis et al. (2014) and Salvin et al. (2011b) have applied this approach in dog aging research.

CDS-related changes

In a series of experimental studies, Rosado et al. (2012a, 2012b) used a sample in which dogs were labeled as cognitively unimpaired, mildly impaired, or severely impaired based on their own questionnaire. A dog was considered impaired if showed signs in at least 2 categories (from a total of 4 categories), and severity was evaluated by sum scores (each item was scored on a 5-point scale). No difference was found between impaired and unimpaired dogs in a human interaction test for frequency of active interactions or for a mirror test measuring time spent in front of the mirror. The authors did not report the correlation between the observed behavior and the achieved questionnaire score, which could have provided further insights into the sensitivity of the questionnaire. A study on laboratory beagles (Siwak et al., 2001) found that impaired old dogs

(categorized by learning performance) spent more time interacting with the mirror than unimpaired old dogs and that they spent less time beside the human in the human interaction test. There was no difference between impaired old dog and young dogs in this respect.

Using the same group of dogs as Rosado et al. (2012a, 2012b), González-Martínez et al. (2013) found that older dogs (from 9 years) performed worse in a food searching (finding food 15 seconds after seeing it hidden) and in a problem solving task (turn a plastic container over with owner encouragement). No difference was found between unimpaired old dogs and cognitively impaired subjects, based on a prior categorization by the means of the previously described CDS questionnaire.

The lack of differences could have resulted from a number of factors, including insufficient sensitivity of the questionnaire to detect CDS in dogs. Insufficient sensitivity of the test instrument could also explain the lack of replication for the findings of the mirror test with laboratory beagles (Siwak et al., 2001). Differential rates of aging for different breeds could also be a consideration. There was a moderate correlation between the score received in the food search task and the score of the Rosado et al. (2012b) questionnaire, but the analysis also included the young dogs.

Physiological measurements

Aging can cause several physiological changes that directly or indirectly affect behavior. For example, Horváth et al. (2007) found that a threatening approach by a human experimenter resulted in significant elevation of salivary cortisol among old (8–11 years) male German shepherd working police dogs, whereas no such change was detected among young dogs (2–7 years). This observation was reinforced by a study of Mongillo et al. (2013b) in which young (1.5–7 years) and old (older than 7 years) dogs of both sexes and various breeds were compared in a strange situation test (Ainsworth, 1969). Consistent with the results of the previous study, the baseline level of salivary cortisol did not differ among the age-groups tested, but old dogs showed an elevated level of cortisol in response to the strange situation test compared to the younger dogs. Aged dogs may have a lower tolerance for social stress, like humans (Lazarus and Folkman, 1984), but we lack data on how such stress tolerance may be influenced by CDS.

Several studies have been carried out to reveal more specific alterations at the neural level that could be related to mental decline in dogs. In a detailed descriptive study, Borrás et al. (1999) found various age-related changes in dogs' brain, involving a wide variety of tissue types in the central nervous system (e.g., neurons, glia cells, vascular endothelial cells). Changes included retraction of the cerebral gyri, cerebral hemorrhages, and lipofuscin accumulation. No age effect was found for cerebrovascular amyloidosis.

The correlation between different CDS questionnaire scales and various physiological measurements has been investigated with moderate positive outcomes. Pugliese et al. (2005) evaluated the cognitive state of dogs with their own specific questionnaire, which was based on Kiatipattanasakul et al. (1996), Colle et al. (2000), and on mental checklists designed for humans. This questionnaire, unlike others, did not include the domain "activity" and "spatial orientation." In their sample, all dogs over 8 years were classified as suffering from cognitive deficit. They reported an increase in the concentration of lactate, potassium, and pyruvate in the cerebral spinal fluid of severely impaired dogs, but as severely impaired dogs were significantly older than the mildly impaired group, a nonspecific age effect cannot be excluded.

Hasegawa et al. (2005) proposed a method to quantify brain atrophy, using magnetic resonance image to evaluate interthalamic adhesion. Cognitively normal and "demented" old dogs (defined as suffering from a principal complaint of dementia) were compared.

Smaller and demented dogs had thinner adhesions, using a criterion of 5.0 mm or less interthalamic thickness as an indication of brain atrophy in dogs. The demented group was older and smaller, whereas the younger group was more diverse.

It is not decided whether brain pathology or a selected behavioral profile should serve as the basis of categorization in the future. Both have their advantages and disadvantages, as the same behavior could result from different neural changes, and the same level of brain alternation can lead to conspicuous deterioration in one individual and go unnoticed in the other.

Golini et al. (2009) studied the relationship between behavioral signs measured by a questionnaire and neurologic abnormalities. Dogs with CDS were 1.89 times more likely to have neurologic abnormalities (e.g., tremors), which shows an increased likelihood of co-occurrence. No causal link has been established.

Although A β deposition has been often tied to cognitive dysfunction (Cummings et al., 1996a; Borras et al., 1999; Landsberg et al., 2003), a recent postmortem study on laboratory beagles by Pop et al. (2010) found no correlation between A β measures and performance in any of the evaluated cognitive task (but see Cummings et al., 1996a). Similarly, Colle et al. (2000) found no correlation between the environment-specific behaviors (learned behaviors and adaptive capabilities) as assessed by their questionnaire and A β deposition in the family dogs' brain.

González-Martínez et al. (2011) measured 2 types of plasma A β levels (A β 1–42 and A β 1–40) from blood of hospitalized dogs. The severity evaluation of CDS was based on a questionnaire designed by the authors and partially based on Colle et al. (2000) and Azkona et al. (2009). The questionnaire operated with the 5 (of 8) most commonly evaluated domains (see above section 3.1, and Table). Young dogs had higher levels of A β than healthy old dogs, but the mildly impaired group showed the highest level of A β 42 and A β 42/A β 40 ratio. The authors suggest using the increased level of A β 42 and the A β 42/A β 40 ratio as biomarkers for CDS, although the individual values overlapped between cognitively impaired and normal old dogs, and the serum levels did not correlate with the dementia scores among old dogs.

Badino et al. (2013) investigated changes in various markers (e.g., muscarinic receptors) from blood. The cognitive status of the animals was evaluated using the questionnaire from Osella et al. (2007). Although they found age sensitive markers, no CDS specific markers were revealed.

None of the previously mentioned markers has proved to reliably differentiate between dogs on the basis of the presence or severity of cognitive impairment in a blind study, although the interthalamic measurement proposed by Hasegawa et al. (2005) may have potential.

The development of reliable biomarkers from blood or saliva would be beneficial, but reliable assessment tools (e.g., specific indicators of brain pathology, behavioral profiles) need to be identified.

Putative risk and protective factors

The prevalence of cognitive decline increases with age (Neilson et al., 2001; Azkona et al., 2009), and one assumes that its occurrence is associated positively with individual longevity (an animal which died without displaying any signs may have shown them later if it lived longer), but the mental state of dogs is usually not investigated in life span studies.

In the case of humans, several intrinsic and extrinsic factors have been identified that influence mental decline. Regarding dogs, relatively small samples sizes and episodic studies, complex interactions between factors like age and breed and mental decline may prevent the detection of potential risk factors.

Azkona et al. (2009) found an increased prevalence of CDS among female dogs, whereas others (Neilson et al., 2001; Yalcin et al., 2010; Salvin et al., 2011a; Fast et al., 2013) disclaimed sex as a risk factor. Similarly, sex may not have a strong effect in humans (Feinson, 1987; Ruitenberget al., 2001). The canine findings may be confounded by the longer mean life span of females (e.g., Waters et al., 2009), a pattern shared with humans (e.g., Kruger and Nesse, 2006).

Azkona et al. (2009) reported a higher risk of CDS prevalence among neutered dogs. Hart (2001) also concluded that the risk of progression is higher among neutered dogs but used a small sample that did not include intact females. Fast et al. (2013) found no evidence for a detrimental effect of neutering, but the sample size in all groups was also small (e.g., $n = 3$ in case of non-CDS or intact females). Since neutered dogs seem to live longer (Hoffman et al., 2013), we cannot exclude the confounding effect of differential life span.

The effect of size, breed, or longevity on cognitive status has been investigated in a heterogeneous manner. "Size" is sometimes based on height (Salvin et al., 2010), whereas others use weight (Neilson et al., 2001; Azkona et al., 2009; Fast et al., 2013). In the Azkona et al. (2009) and Fast et al. (2013) studies, dogs below and above 15 kg were distinguished. Neilson et al. (2001) did not report the weight criteria used to categorize dogs as "small." Smaller dogs showed a higher prevalence of CDS in the sample reported by Azkona et al. (2009), but the authors did not consider weight as a predictor variable. Neilson et al. (2001), Salvin et al. (2010), and Fast et al. (2013) found no evidence of a size effect, whereas Salvin et al. (2012) found a relationship between body size of the breed and some items of the CDS questionnaire. Regardless, no significant overall pattern for size effects was identified.

Environmental effects on aging in dogs have been neglected. Roles for husbandry (indoor vs. outdoor dogs) and diet (dry vs. moist vs. homemade food) have been investigated, but results are inconclusive (Yalcin et al., 2010). One study (Calderón-Garcidueñas et al., 2008) has suggested that air pollution may play a significant role advancing mental decline in dogs.

Some extrinsic factors may protect against rapid cognitive decline, improving the welfare of dogs. Longitudinal studies have revealed the positive effects of cognitive experience, cognitive enrichment, and antioxidant fortified food in laboratory beagles (Milgram, 2003; Milgram et al., 2005). Groups of aged laboratory beagles undergoing an enrichment program (increased exercise, environmental enrichment, and cognitive enrichment) performed better in a discrimination task than a control group, an effect superior to that attributable to antioxidant fortified food. Araujo et al. (2005) found that dogs fed an antioxidant and mitochondrial cofactor combination diet for 2 years performed better in a delayed nonmatching to sample task than did control dogs, even without the positive effect of additional enrichment. Milgram (2003) provided some evidence that younger dogs benefit more from early, related cognitive experience in a size discrimination paradigm than older animals. All these studies were done on laboratory dogs. No comparable research exists for family dogs.

Factors potential related to brain aging investigated in humans but not yet examined in dogs, include personality (Terracciano et al., 2014), restricted daily activity (James et al., 2011), genetic factors (Xing et al., 2013; Karch and Goate, 2014), general cognitive experience (Summers et al., 2013), environmental hazard (Moulton and Yang, 2012), and obesity (Kivipelto et al., 2005).

Dogs may provide a useful system for examining long-term (anthropogenic) environmental effects on behavior and cognitive performance; however, sufficient sample sizes are needed to reveal meaningful relationships between lifestyle or medical history,

genetic background, and age-related cognitive decline. Considerations for breed, weight, height, and sex remain.

Dog as a model for aging in humans

Dogs may provide another useful animal model for human aging (Waters, 2011), in addition to the models for targeted molecular research developed using *Caenorhabditis elegans*, *Mus musculus*, and so forth. Separate from the laboratory dog model which has been influential in studying the effect of aging processes on cognitive performance (e.g., Adams et al., 2000; Waters, 2011; Head, 2013), family dogs are unique to offer a natural model (Overall, 2000) that has unprecedented advantages in terms of general validity to the human case.

It is important to note, however, that the aging of family dogs also has to be studied for its own sake, because their increased life span is likely a direct consequence of sharing their life with humans. We recommend 2 approaches for the future study of aging in dogs. The first is a naturalistic study of aging in family dogs, with sufficient numbers and power to address potential effects of breed, size, sex, neutering, and all applicable aspects of sensory, motor, and mental decline. For example, exceptionally long-lived female Rottweiler dogs had intact ovaries for longer (“life time ovary exposure”) than females in the “average life span” group (Waters et al., 2009). Researchers hypothesize that hormonal influence may protect against malfunctions emerging with age. Unfortunately, no similar study has been performed with regard to mental decline.

The second approach should focus on whether, in general, aging family dogs, their cognitive skills and their brains are good models of aging humans. Uncritical acceptance of mental decline in dogs as a model for human Alzheimer’s disease is a concern. Alzheimer’s disease is one of the most common forms of dementia, which starts with mild cognitive impairment (Sperling et al., 2011). Clinical signs of Alzheimer’s disease overlap also with other senile dementias, so neuroanatomic and neuromolecular changes are required for diagnosis. Recent investigations stress the difference between the manifestations of these attributes between dogs and humans. Head (2013) notes that while the sequence and location of the emerging amyloid plaques (first in frontal cortex, then in occipital cortex) parallels in dogs and humans, the pathology documented in dogs reflects better the early phases of the human disease.

Use of sensitive and standardized behavior tests could benefit both the welfare of aging dogs and any proposed canine models of brain aging.

Open questions and future trends

Suites of behavioral traits change with age. Dogs’ behavior is likely affected by changes in emotional and motivational processes [e.g., decreased processing of negative emotional stimuli (Kasznik and Menchola, 2012), possible change in incentive value of food reward (Yu et al., 2006), response to stress (Horváth et al., 2007)], which are currently not assessed in pathologic cognitive decline.

Mental impairment in aged dogs represents a heterogeneous category for which “severity” is likely only one dimension. In humans, different types of dementias with differing pathologies are recognized (Perri et al., 2014). A similar situation may also exist for the age-related cognitive decline in dogs.

The main issues that should receive more focus in research on aging dogs include the following.

- (1) Acknowledgment of the dynamics of the aging process in dogs: Demographic and evolutionary studies aim to reveal specific

aging patterns in different dog populations to reveal underlying biological processes. This approach is seldom considered for brain aging in dogs. There is no standardized age or developmental intervals at which any standardized cognitive assessments are performed. Standardized terminology, with well-defined diagnostic and inclusion or exclusion criteria would help to distinguish dogs with “healthy” (successful) aging from those with significant pathology. Such approach has been successfully applied in humans (Rowe and Kahn, 1997).

- (2) Defining the behaviors underlying CDS Questionnaires have advantages that are clear when the patient is nonverbal. Better understanding of brain aging could benefit from well designed, reliable, and valid behavior test batteries. Such test batteries could validate different scales or questionnaires.
- (3) Establishing a more robust questionnaire scale: We do not know whether questionnaires used for characterizing CDS can detect general underlying mental features. We do not know how signs of CDS covary with each other or with any measure of behavioral domains (e.g., learning skills in specific cognitive tests).
- (4) Validation and cross-validation of different aspects of the aging phenotype: The efforts devoted to (2) and (3) may facilitate validation (external, construct, and face validity in particular) of batteries of behavior tests, questionnaires, and physiological measurements in an age-specific manner.
- (5) Noncognitive impairment: We need clear evaluation criteria and procedures to assess sensory and motor impairment in dogs as they age.
- (6) Increasing ability for predicting the process of aging for individuals: Both questionnaires and behavioral tests should be designed to include measures that aim to also have predictive value for decline in cognitive function. Behavioral markers can be extremely informative in preclinical stages (for humans see Sperling et al., 2011).
- (7) Research for prevention: Future research should identify any protective factors that could improve the well-being of older dogs and lengthen their health span.

Conclusion

It is encouraging to reflect on the quantity and variety of research on CDS. Dogs are integral members of human households and a fuller appreciation of how their age should lead to improvements in their lives. During the last few decades, we have learned that, as for humans, part of the aging dog population suffers from some form of pathologic mental decline which affects their day-to-day life. The common signs have been described, the neurologic changes associated with impaired cognitive functions have been studied in great detail (Osella et al., 2007; Head, 2011; Bosch et al., 2012) and therapeutic agents became available (Overall, 2013). If a diagnosis is made, there are available medications which can alleviate some of the signs and which may slow further decline. By gaining a better understanding of the canine aging process, we may enhance our understanding of similar phenomena in humans. As we gain a better insight into brain aging and work to forestall deleterious effects aging on our dogs, we also begin to develop opportunities for improved human-animal interactions by better addressing the dogs’ needs. The value of the CDS research done to date is diminished by conflicting methodologies, inconsistent definitions, and, in general, the absence of a broad overview of the ways in which elements such as sensory and motor impairment associated with age interact with pathologic cognitive decline. A clear opportunity exists for meaningful improvements in our understanding of CDS using research models with improved designs,

reliable, valid, and standardized tools, that builds on the work done thus far.

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Conflict of interest

The authors declare no conflict of interest.

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