The Aged Dog as a Natural Model of Alzheimer's Disease Progression

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Alzheimer's disease is the most common cause of dementia in humans and is rapidly becoming an unmet medical need of epidemic proportions. More than 50 million people are expected to be diagnosed with Alzheimer's disease by 2050 unless efficacious disease-modifying treatments are developed. Although billions of dollars have been allocated to this cause, more than 190 putative Alzheimer's disease drugs have failed in the clinic, exemplifying the high risk to reward ratio of Alzheimer's disease therapeutic development. One factor implicated in this high failure rate is the limitation of animal models to accurately predict clinical outcomes.

Animal models are essential for demonstrating potential target relevance and target engagement of novel therapeutics. The fact that some of these models, such as transgenic mice, have a 100% failure rate for predicting clinical outcomes of putative drugs exemplifies their limitations and the need for additional models that better recapitulate the multifactorial nature of Alzheimer's disease progression.

Aged dogs naturally develop Alzheimer's-like neuropathological changes, as well as cognitive domain-specific impairments consistent with early stages of Alzheimer's disease progression. Moreover, cross-sectional data in differentially aged dogs suggests that Alzheimer's relevant biomarker changes are also found in dogs and could be used to monitor early-stage Alzheimer's-like disease progression. The naturalistic progression of these changes in canine aging has not been linked to a single target, which suggests aged dogs may be used as a confirmatory animal model for preclinically evaluating putative Alzheimer's therapeutics. In this respect, the aged dog model accurately predicted the clinical outcome of both the gold

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standard symptomatic Alzheimer's disease therapeutic, donepezil, and the failure of active fibrillary amyloid vaccination strategies.

The aged dog, therefore, provides a valuable preclinical animal model for assessing Alzheimer's disease therapeutics with demonstrable translational value for predicting clinical outcomes of both symptomatic and disease-modifying Alzheimer's disease interventions. Given the translational validity of the model, it is likely that Alzheimer's disease clinical research could also be used for improving care of senior dogs.

4.1   Introduction

Alzheimer's disease (AD) is a progressive and chronic neurodegenerative disease and the major cause of dementia in the elderly, accounting for 50–75% of all dementia cases (Alzheimer 1906; Grossman et al. 2006; Qiu et al. 2009; Selkoe 2001; Uzun et al. 2011). According to diagnostic criteria guidelines (McKhann et al. 1984), AD onset occurs between 40 and 90 years of age, with onset being highest in populations greater than 65 years of age; early-onset cases, associated with dominant familial gene mutations, represent less than 5% of all AD cases (Ott et al. 1995; Selkoe 2001). Current global estimates of AD prevalence range from 15 to 27.7 million cases in the general population, but are anticipated to rise to greater than 115 million cases by 2015, indicating there is unmet medical need of epidemic proportions (WHO 2012).

Longitudinal clinical studies aimed at characterizing the progression of AD in aged human populations suggest that neuropathological changes develop decades prior to clinical diagnosis, which can only be confirmed by postmortem confirmation of both pathological hallmarks of AD—senile plaques and neurofibrillary tangles. Therefore, it is increasingly accepted that there is a substantial prodromal phase of AD, and that disease progression, as well as therapeutic efficacy, could be monitored using pathophysiological biomarkers, which provide a paradigm for targeting patient populations during earlier, and presumably more responsive, stages of the disease.

Although an enormous amount of financial resource has been invested in developing AD therapeutics, more than 190 have failed in human clinical trials, and only four drugs have been approved (Becker and Greig 2012; Cummings et al. 2014). Therefore, there is a significant unmet need for novel, and efficacious, AD-modifying therapeutics that either halt or slow progression to clinical AD (Klafki et al. 2006). The failure to develop efficacious drugs for AD can be attributed in part to translational limitations of preclinical animal models to predict clinical outcomes. The current chapter aims to demonstrate that the aged dog model naturally models several characteristics of AD and can be used to evaluate the potential efficacy of putative therapeutics across varying stages of AD progression. Specifically, the aged dog is a translationally relevant preclinical animal model because the model accurately predicts outcomes of human clinical trials.

4.2   Alzheimer's Disease

Alzheimer's disease is a neurodegenerative disease originally described by Alois Alzheimer (Alzheimer 1906) in which patients present with progressive cognitive deficits across multiple cognitive domains that ultimately result in dementia and death. Although the cause of the disease is unknown, there are both distinguishing and associated neuropathological changes present in the disease. More recently, biomarkers of these pathophysiological changes are being investigated in the effort to diagnose disease in early stages of progression, and potentially to monitor disease-modifying interventions. The current section focuses on these three key features–neuropathology, cognitive deficits, and associated biomarkers of pathophysiological progression.

4.2.1   Neuropathological Features

The hallmark neuropathological features of AD are extracellular senile, or neuritic, plaques and intracellular neurofibrillary tangles (NFT) in the neocortex and temporal lobe structures (Hyman and Trojanowski 1997). The senile plaque pathology is a result of extracellular focal deposition of amyloid beta (Aβ) protein, and the NFT pathology is comprised of intracellular paired helical filaments and straight filaments of abnormally, or hyper-, phosphorylated tau protein (Markesbery 2010). These two pathologies can occur decades prior to clinical manifestation of the disease, and are accompanied by extensive neurodegenerative processes that include neuronal and synaptic dysfunction and loss, leading to widespread cortical atrophy and alterations in multiple neurotransmitter systems and neural networks (Jack et al. 2010).

In addition to these hallmark pathological features, several other neuropathological changes are associated with AD, including decline in neurotransmitter systems, particularly the cholinergic system (Bartus 2000; Bartus et al. 1982; Norbury et al. 2005; Picciotto and Zoli 2002; Reinikainen et al. 1987, 1990; Rossor and Iversen 1986), extensive cortical and/or brain region-specific atrophy measured by both postmortem evaluation and in vivo magnetic resonance imaging (MRI) (Double et al. 1996; Fox and Freeborough 1997; Jack et al. 2005), and increased oxidative stress (Markesbery 1997; Smith et al. 2000). Thus, the two neuropathological diagnostic criteria for an AD diagnosis represent only a part of the neuropathological processes occurring in AD progression.

4.2.2   Cognitive Decline

The clinical diagnosis of AD is based on a progressive dementia with cognitive impairment in multiple independent cognitive domains and behavioral (neuropsychiatric) changes (Albert 2011; Marin et al. 1997; McKhann et al. 1984, 2011) that ultimately result in death (Cummings 2000). In the majority of cases, deficits in

episodic memory occur in conjunction with changes in at least one other cognitive domain, although other variations of cognitive deficits are described (Albert 2011; McKhann et al. 2011). Moreover, episodic memory deficits are reported in sub-populations with mild cognitive impairment (MCI) who are at risk for development of AD; however, this subgroup does not differ cognitively from normal aged-matched controls on other cognitive measures, which suggests that deficits in epi-sodic memory may precede clinical diagnosis of AD (Sperling et al. 2011).

The most devastating feature of AD is perhaps the progression of cognitive decline leading to overt dementia, in which multiple cognitive domains are affected over several years until individuals are no longer able to live independently (Albert 2011). Cognitive domains most commonly affected in the pathophysiological pro-gression of AD include memory, executive function/attention, visuospatial skills, and language (Albert et al. 2011). The majority of AD patients show a relatively consistent pattern of cognitive decline, which is referred to as progressive amnestic disorder, and is generally characterized by early impairments in episodic memory (Albert 2011; Backman et al. 2000; Grober et al. 1999; Linn et al. 1995; Perry et al. 2000; Petersen 1998; Petersen et al. 1994) consistent with early neuropathological changes in the entorhinal cortex and hippocampal formation (Braak and Braak 1991; Jack et al. 1992, 1997). Executive function deficits precede language and visuospatial deficits in a majority of AD cases (Amieva et al. 2004; Foldi et al. 2002; Grady et al. 1988; Lafleche and Albert 1995; Perry et al. 2000; Reid et al. 1996), although some report that visuospatial deficits also occur early in the course of AD progression (Becker et al. 1988; Johnson et al. 2009). Based on performance across various cognitive tasks, it is suggested that AD progression can be divided into amnestic cases, in which declarative memory deficits are most evident; non-memory or dysexecutive cases, in which deficits on executive function tasks are most evident with sparing of declarative memory; or multi-domain, or mixed, cases in which deficits across multiple cognitive domains are evident, including combined memory and language deficits (Delano-Wood et al. 2009; Eppig et al. 2012; Libon et al. 2010, 2011; Petersen 2004; Petersen and Morris 2005; Ritchie and Touchon 2000).

4.2.3   Pathophysiological Biomarkers of Progression

It is increasingly accepted that pathophysiological biomarkers can provide diagnos-tic and prognostic information for improved clinical management of patients in early stages of AD progression (Buerger et al. 2006; Hampel et al. 2008; Jack et al. 2010; Shaw et al. 2007). To a large extent, this has been facilitated by large longitu-dinal clinical trials such as the Alzheimer's Disease Neuroimaging Initiative (ADNI) and the Dominantly Inherited Alzheimer's Network (DIAN), which collect longitu-dinal data in patients with AD, mild cognitive impairment, and elderly controls with the aim of understanding disease progression (Jack et al. 2008; Morris et al. 2012; Moulder et al. 2013; Weiner et al. 2013). The emerging data indicate that AD pro-cesses begin decades before clinical manifestation, and to this end, Jack et al. (2010) propose a trajectory of neuropathological events progressing through cerebral

amyloidosis, neuronal injury and synaptic dysfunction, and neurodegeneration, with memory impairment occurring prior to clinically diagnosed dementia. Specifically, markers of amyloidosis including increased amyloid positron emission tomography (PET) tracer retention and reduced cerebrospinal fluid (CSF) $A\beta_{42}$ are detected early in the disease process in patients that are clinically normal (de Leon et al. 2001; Jagust et al. 2006; Petrie et al. 2009). Neuronal and synaptic dysfunction can be monitored by increased CSF tau and decreased fluorodeoxyglucose uptake on PET imaging, respectively. Neurodegeneration can be identified by magnetic resonance imaging (MRI) measures of cerebral atrophy (Bobinski et al. 1999; Frisoni et al. 2010; Ramani et al. 2006; Scheltens et al. 2002). Moreover, combinations of biomarkers demonstrate improved ability to predict conversion to AD better than one marker alone (Vemuri et al. 2009a, b, 2010). Ultimately, biomarkers may serve as a method to track the in vivo efficacy of AD-modifying treatments in patient populations that are presymptomatic (Jack et al. 2010).

In addition to the abovementioned biomarkers, there are several other in vivo imaging, CSF, and blood-based biomarkers currently being explored. For example, metabolic markers of neuronal health can be measured by proton magnetic resonance spectroscopy (H-MRS). In patients with MCI or AD, levels of n-acetylaspartate (NAA) and myoinositol (INS) are of particular interest. NAA is an amino acid made in the mitochondria, which are located in neuronal cell bodies, axons, and dendrites (Birken and Oldendorf 1989; Simmons et al. 1991). Thus, NAA is thought to be a biomarker for neuronal loss. H-MRS studies have shown decreased NAA in MCI and AD patients (Kantarci et al. 2000; Rose et al. 1999). By contrast, INS is a glial metabolite. Kantarci et al. (2000) reported that INS levels are increased in MCI and AD patients. Given the large-scale longitudinal trials and the intensity of interest in novel biomarker of AD progression, it is likely that key biomarkers will be identified and validated in the near future.

4.3 The Aged Dog Model of Alzheimer's Disease Progression

Canine aging is associated with behavioral and neuropathological changes that parallel the progressive nature of human AD. Recent data examining in vivo imaging and CSF pathophysiological biomarkers in canine aging also demonstrate parallels to the biomarker changes observed in AD progression. The current section compares these three features of canine aging to AD progression to demonstrate the parallels of this naturally occurring disease process in dogs and humans.

4.3.1 Neuropathological Changes

Like AD patients, aged dogs also demonstrate amyloid plaques, and numerous studies have examined the composition and accumulation pattern of senile plaques in the aged canine brain (Cummings et al. 1996a, c; Mirra et al. 1991). This research is

driven largely by the popularity of the amyloid hypothesis of AD that proposes that Aβ is a causative factor in disease progression (Hardy 2006). Mirra et al. (1991) found that senile plaques are composed of Aβ protein, which is identical in sequence between dogs and humans (Johnstone et al. 1991; Selkoe et al. 1987). The Aβ peptide is produced by the sequential cleavage of amyloid precursor protein (APP) by beta-secretase and gamma-secretase in both humans and dogs (Borghys et al. 2012; Murphy et al. 2010; Selkoe 1996), resulting in similar isoforms in both species (Portelius et al. 2010). In both dog and human, the 42-amino acid isoform (Aβ$_{42}$) is the predominant isoform found in the insoluble plaque deposits (Selkoe 2001; Wisniewski et al. 1990). The regional and temporal pattern of Aβ deposition in the human brain is well characterized (Braak and Braak 1991; Braak et al. 1993; Wisniewski et al. 1970). Similar to humans, Aβ deposition occurs earliest in the prefrontal cortex, and later in the temporal cortex, hippocampus, and occipital cortex of beagles (Giaccone et al. 1990; Head et al. 2000; Ishihara et al. 1991; Thal et al. 2002) and other breeds of dogs (Rofina et al. 2003, 2004, 2006; Smolek et al. 2016). In contrast to human plaque pathology, which includes both diffuse and dense core plaque, canine amyloid plaques are mainly of the diffuse subtype (Cummings et al. 1993; Giaccone et al. 1990; Morys et al. 1994; Okuda et al. 1994; Russell et al. 1992; Uchida et al. 1992). In the cerebrovasculature, the deposition of the 40-amino acid isoform of Aβ occurs in both dogs and humans, resulting in cerebrovascular amyloid angiopathy (Attems 2005; Attems et al. 2005; Herzig et al. 2006). Vascular Aβ deposits can result in disruption of the blood-brain barrier and vessel wall viability (Prior et al. 1996), as well as microhemorrhages (Uchida et al. 1991).

Several studies in beagle dogs indicate a positive correlation between cognitive impairments and increasing brain Aβ plaque load in addition to increasing age (Colle et al. 2000; Cummings et al. 1996a, c; Head et al. 1998; Rofina et al. 2006). In this respect, standardized neuropsychological tests (described in the subsequent section) have been useful for determining the impact of brain region-specific amyloid burden on cognitive domain-specific function independently of age. High levels of Aβ in the prefrontal cortex, for instance, are associated with reversal learning and complex working memory deficits, whereas high levels of Aβ in the entorhinal cortex are associated with impairments in size discrimination and reward- and object-approach learning (Cummings et al. 1996a; Head et al. 1998; Tapp et al. 2004); the prefrontal pathology-linked impairment is consistent with the known dependency of executive processes to prefrontal integrity. In pet dogs, the extent of Aβ plaque load also correlates significantly with behavioral changes independently of age (Colle et al. 2000; Rofina et al. 2006). On the other hand, impairments in complex working memory (measured by the delayed non-matching to position task (DNMP)) occur early in canine aging and likely precede amyloid plaque deposition (Studzinski et al. 2006). This pre-plaque impairment may be attributable to soluble amyloid oligomeric species, which are highly toxic, impair synaptic function, and correlate with cognitive dysfunction in humans (Lacor et al. 2004; Selkoe 2008; Tomic et al. 2009). Oligomeric amyloid also is increased with age in beagle dogs (Pop et al. 2012) and may serve as a target for AD-modifying therapeutics early in the disease process.

The second neuropathological hallmark of AD is NFT neuropathology, which generally is absent in aged animals, including dogs (Morys et al. 1994; Russell et al. 1992; Selkoe et al. 1987; Uchida et al. 1992); however, others report the presence of NFTs in aged dogs, albeit to a lesser extent than humans (Papaioannou et al. 2001; Schmidt et al. 2015). Regardless, several phosphorylated tau epitopes, as well as neuropil threads that are consistent with AD pathology in humans are found in the aged canine brain and may be linked to behavioral changes associated with cognitive dysfunction syndrome (Pugliese et al. 2006, Schmidt et al. 2015; Smolek et al. 2016; Yu et al. 2011). Therefore, it is unclear if tauopathy in dogs leads to synaptic and cell loss. Aged dogs often also show marked ventriculomegaly, thinning of the cerebral cortex, and reduced white matter (Gonzalez-Soriano et al. 2001; Kimotsuki et al. 2005; Su et al. 1998; Vandevelde et al. 2012). Moreover, brain atrophy varies by region; for example, prefrontal cortical volume decreases prior to hippocampal volume (Tapp et al. 2004). Significantly fewer neurons are found in the hilus of the dentate gyrus of aged dogs, and fewer Purkinje cells are found in the cerebellum of impaired dogs (Pugliese et al. 2007; Siwak-Tapp et al. 2008), which is consistent with the extensive neuronal loss in AD (Bobinski et al. 1997; West 1993). These reductions may reflect decreased neurogenesis in aged dogs (Pekcec et al. 2008; Siwak-Tapp et al. 2007). Another potential source of neurodegeneration is the increase in oxidative stress and reduced antioxidant capacity in canine aging, which is linked to cognitive deficits (Head et al. 2002; Hwang et al. 2008; Kiatipattanasakul et al. 1997; Opii et al. 2008; Papaioannou et al. 2001; Rofina et al. 2004, 2006; Skoumalova et al. 2003) and may be a result of age-related mitochondrial dysfunction (Head et al. 2009).

Although age-related modification in neurotransmitter systems has not been extensively investigated in the dog, there is growing evidence that alterations in neurotransmitter systems may be a cause of cognitive dysfunction and may be a result or cause of other AD-like neuropathological changes. Like humans, aged dogs are more sensitive to cognitive disruption caused by scopolamine than young dogs, which may be due in part to reduced muscarinic receptor numbers across multiple brain regions except the cerebellum (Araujo et al. 2011b; Reinikainen et al. 1987, 1990). Complex working memory performance is particularly susceptible to cholinergic disruption and is improved using cholinesterase inhibitors in both dogs and humans (Araujo et al. 2004, 2011a; Drachman and Leavitt 1974). Cognitively impaired dogs also show a significant reduction in the noradrenergic neurons in the locus coeruleus, which are also implicated in AD (Dringenberg 2000; Grudzien et al. 2007; Insua et al. 2010).

4.3.2   Cognitive Decline

Consistent with AD-like cognitive impairments, cognitive function tasks can be used to demonstrate that domain-specific cognitive decline which also occurs in canine aging (Araujo et al. 2008; Chan et al. 2002; Landsberg et al. 2012; Rofina et al. 2006; Siwak et al. 2001; Snigdha et al. 2012; Studzinski et al. 2006; Tapp et al. 2003). For

example, memory and executive functions are impaired relatively early in the aging process (Studzinski et al. 2006; Tapp et al. 2001), and these impairments are positively correlated with brain region-specific amyloid burden and atrophy (Cummings et al. 1996c; Head et al. 1998; Rofina et al. 2006; Tapp et al. 2004). To objectively assess cognitive function across multiple cognitive domains in dogs, a number of validated laboratory-based neuropsychological tasks have been developed (Landsberg et al. 2012). These tasks are tester administered and utilize food rewards to reinforce correct responses.

Although the behavioral changes associated with canine cognitive dysfunction (CDS) are presumably due to brain neuropathology and impaired cognitive function (Landsberg et al. 2012, see Chaps. 1 and 5), early and subtle cognitive deficits may be difficult to identify in the home or clinical environment. Moreover, the behavioral changes associated with CDS generally occur later in life than the cognitive impairments detected using neuropsychological testing. In fact, impaired spatial working memory performance predicts behavioral changes that include altered sleep-wake cycles and decreased exploration and interaction (Siwak et al. 2001, 2003).

The test apparatus and neuropsychological tasks have been described extensively elsewhere (Landsberg et al. 2012), but here we describe a subset of tasks that are sensitive to both aging and therapeutic intervention. Importantly, these tasks can be used to examine therapeutic interventions both as a model for AD progression and as a preclinical model for CDS.

Delayed Non-matching to Position Task (DNMP): The DNMP task can be used to assess both complex visuospatial learning and short-term visuospatial working memory (Chan et al. 2002; Studzinski et al. 2006), although the former can only truly be tested once, limiting its use in assessing interventions. On each trial of the task, the dog is presented initially with a single object (e.g., white block) over one of the three possible locations and then is required to displace the object to obtain a food reward (Fig. 4.1a). The tray is then removed from the dog's sight, and a delay is initiated. Following the delay, the animal is then presented with two objects identical to that used in the original presentation. The dog is required to displace the object in the new location and receives a reward for responding correctly (see Fig. 4.1b).

The delay between the first and second presentations may be varied to modify the memory demands of the task. Old dogs can be separated into three groups based on DNMP performance—unimpaired, impaired, and severely impaired—which may be analogous to the various cognitive stages of AD progression (Adams et al. 2000). Also, learning and memory impairments on the DNMP can be detected as early as middle age (Studzinski et al. 2006). In terms of assessing learning, this is a particularly useful task because performance varies directly with age: young dogs learn the task rapidly, older dogs learn more slowly, and very old dogs may be unable to learn even with extensive training (Studzinski et al. 2006); specifically, age predicted 48.2% of the variability in learning the DNMP task. Beagle dogs ranging from 1 to 11.99 years generally made more errors with increasing age, and mild visuospatial deficits were detected by 6 years, which precedes the typical onset of Aβ accumulation in the dog brain by approximately 2 years. This suggests the DNMP task can serve as an early marker for cognitive decline in the dog, and that age-related
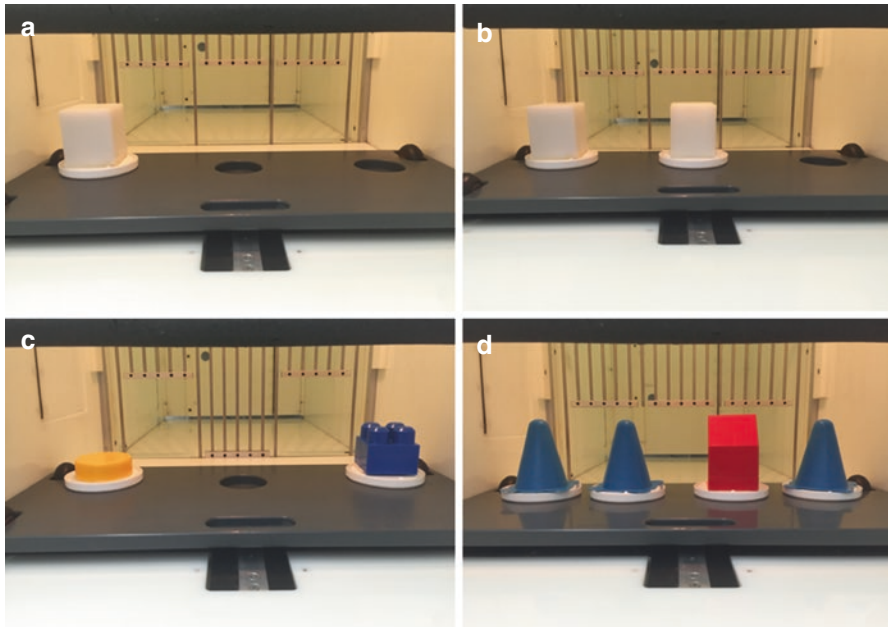
Fig. 4.1 (**a**) Sample phase of the DNMP task. The dog is required to displace a single block in one of the three positions to obtain a food reward. (**b**) Choice phase of the DNMP task. Following sample presentation and a predetermined delay, the dog must select the block in the new (non-match) position to obtain a food reward. (**c**) Simple discrimination learning and reversal task. During learning, the dog is required to continually select one of the two objects until learning criteria are reached. Subsequently, the reward contingency is reversed during reversal learning discrimination. (**d**) Selective attention task. The animal is required to select a single object and not a distractor; however, the number of distractors (i.e., negative stimuli) can vary from 0 to 3 during each trial

changes in visuospatial function in the dog models are seen in humans (Studzinski et al. 2006), possibly due to the influence of the cholinergic system on its performance (Araujo et al. 2004, 2011a, b).

Object Discrimination and Reversal Learning Tasks: Discrimination learning requires the animal to select one of the two different objects to obtain a food reward (Milgram et al. 1994). Objects may vary in color, shape, size, or a combination of the three (see Fig. 4.1c). Discrimination learning performance typically remains intact with age, possibly because an associative learning strategy can be used (Cotman et al. 2002). However, increasing difficulty of the task (by using more similar objects) exacerbates age-related deficits (Tapp et al. 2003). Once the task is learned, reversal learning can be tested by modifying the reward contingency such that the previously non-rewarded object is rewarded. Reversal learning is highly age sensitive in dogs, as the task predominately relies on executive function, requiring the subject to inhibit previously rewarded actions and shift responses to a new stimulus (Mongillo et al. 2013; Tapp et al. 2003). Specifically, both delayed learning and perseverative responding increase with increasing age.

Selective Attention Task: The selective attention task, or variable object discrimination task, is similar to discrimination learning in that the dog is required to select a single object for a reward; however, in this task, rather than one negative stimulus, there is a variable number of distractor objects (0 to 3) on any given trial (see Fig. 4.1d). With increasing distractor number, accuracy decreases significantly, and latency to respond increases across dogs of all ages (Snigdha et al. 2014), which is consistent with human selective attention impairments on tasks such as the visual search task (Parasuraman et al. 1995; Snigdha et al. 2012). Senior dogs are significantly impaired compared to both young and old dogs, and old dogs are intermediate in performance between young and senior age groups (Snigdha et al. 2014). These results suggest that aging impairs the ability of canines to discriminate between task-relevant and task-irrelevant stimuli, likely due to impairments in attentional processes related to inhibitory control and engagement.

The selective attention task employs a previously learned object to permit repeated testing in longitudinal aging or therapeutic intervention studies. A similar paradigm, oddity discrimination learning, examines learning when the incorrect object is present in duplicate and in which difficulty can be increased by using objects that are more similar (Milgram et al. 2002b; Tapp et al. 2003). On the oddity discrimination task, performance declines with both increasing age and task difficulty (Milgram et al. 2002b), presumably due to the increased attentional demands associated with increased distractor number (Araujo et al. 2008).

4.3.3 Pathophysiological Biomarkers

The longitudinal pattern of AD-relevant biomarker changes has not been well studied in the dog, but there is increasing evidence from cross-sectional studies suggesting biomarkers of brain amyloidosis, neuronal and synaptic dysfunction, and neurodegeneration, which parallel those seen in AD progression, are also evident in canine aging. Head et al. (2008) demonstrated that percent $A\beta_{42}$ CSF levels decline from middle to senior age in dogs, and that this decline is inversely correlated with increasing brain amyloid burden. This parallels the findings in humans that decreasing levels of $A\beta_{42}$ in CSF correlate with increased brain amyloid burden measured using amyloid-binding ligands with PET imaging (Fagan et al. 2006; Grimmer et al. 2009; Jagust et al. 2009; Sperling et al. 2011; Tolboom et al. 2009). However, the amyloid-binding ligands currently used for clinical or research purposes have not demonstrated specific amyloid binding of canine plaques, which may be due to the diffuse nature of the canine amyloid plaques (Cummings et al. 1996b; Czasch et al. 2006; Rofina et al. 2004; Torp et al. 2000a, b; Yoshino et al. 1996; Verhoeff et al. 2003).

More recently, we investigated changes in CSF levels of amyloid in 130 beagle dogs divided into four age groups (young, *n* = 17, 2.00–2.58 years; middle age, *n* = 21, 6.33–7.25 years; old, *n* = 57, 8.00–11.92 years; and senior, *n* = 35, 12.00–17.33 years) (Araujo et al. 2013a). A significant effect of age on percent $A\beta_{42}$ was found, which reflected significantly higher levels in middle-aged dogs compared to all other age groups. This finding supports the hypothesis that a threshold

concentration of $A\beta_{42}$ is achieved during middle age prior to brain amyloid deposition (Sutphen et al. 2015). Percent $A\beta_{42}$ was significantly lower in senior dogs compared to old dogs, which is consistent with the findings of Head et al. (2008). We also examined CSF levels of total tau in a subset of these dogs and found a significant age-dependent effect on CSF total tau levels, which increased from middle age to old and from old to senior, analogously to findings in human AD (Buerger et al. 2006). The mean within-subject coefficient of variance was 9.9% for $A\beta_{42}$, 10.8% for $A\beta_{40}$, and 9.7% for total tau, suggesting CSF $A\beta_{42}$ and total tau levels may serve as reliable and translational biomarkers for preclinical aged canine studies investigating AD progression and possibly for predicting CDS.

Many in vivo imaging studies have been conducted in dogs, and several results parallel human AD findings. A pilot study examining fluorodeoxyglucose uptake on PET imaging in six adult and six senior dogs revealed significantly decreased fluorodeoxyglucose uptake across multiple brain regions consistent with the hypometabolism reported in AD patients (Araujo et al. 2013c). When cognitive tasks of varying difficulty were administered prior to imaging, brain region-specific engagement and disengagement were seen in adult, but not senior dogs, which suggests impairments in synaptic function and cortical processing (Horwitz et al. 1999). Magnetic resonance imaging studies demonstrate age-related ventriculomegaly as well as tissue volume loss of the frontal lobe, which occurs prior to atrophy of the hippocampus (Dimakopoulos and Mayer 2002; Su et al. 1998, 2005; Tapp et al. 2004). Moreover, a longitudinal MRI study in 47 dogs ranging from 8 to 11 years of age at the start of the 4-year study indicated that ventricular volume increased significantly over the last 2 years of the study and that the increase in ventricular volume was greater in older dogs than younger dogs; a 2.8% compared to 1.1% increase in ventricular volume was seen in dogs that were 11 compared to 8 years old at the start of the study, respectively (Su et al. 2005). Imaging studies using H-MRS also indicate an age-dependent reduction in NAA levels in dogs, which also is reported in AD patients (Adalsteinsson et al. 2000; de Rivera et al. 2007).

Therefore, biomarker patterns seen in AD progression are also found in canine aging, albeit the temporal sequence of these events has not been well studied in canine longitudinal studies. The same biomarkers may also prove valuable for predicting likely progression to CDS in pet dogs; however, the cost and invasiveness currently limit their use in the clinical setting. Regardless, biomarkers can be incorporated into laboratory canine studies designed to understand the progression of neuropathological events, their impact on cognitive function, and evaluation of novel therapeutics for AD-modifying drugs.

4.4 Predictive Validity of the Aged Dog Model

The validity of an animal model or test can be evaluated using various criteria which are beyond the scope of the current chapter. Rather, the ability of animal model to accurately predict clinical outcomes, or predictive validity, is the focus of the current section, which is pertinent given the absence of available AD-modifying

therapeutic agents. In this respect, (pharmacological) predictive validity can be evaluated by determining how accurately an animal model predicts the results of human therapeutic clinical trials. While several animal models accurately predicted the symptomatic benefits of cholinesterase inhibitors on AD-like memory deficits, more than 190 compounds that were positive in animal models of AD have failed in clinical trials. This high number of false positives demonstrates a general lack of pharmacological validity in the most commonly used animal models, and transgenic mouse models, for example, have failed to accurately predict a positive result (Zahs and Ashe 2010). Although the absence of a gold standard AD-modifying therapeutics limits the ability to evaluate predictive validity for disease-modifying therapeutics, the dog has demonstrated ability to detect both true positives and false negatives (Studzinski et al. 2005) and also shows predictive value in non-pharmacological studies.

4.4.1   Symptomatic Treatment

The current gold standard for treatment of AD is donepezil hydrochloride (Aricept®), a cholinesterase inhibitor, which works by inhibiting the breakdown of acetylcholine in the brain. The rationale for this drug class is to compensate for the cholinergic deficits that are consistently reported in AD by increasing cholinergic neurotransmission (Bartus 2000; Bartus et al. 1982). Two cholinesterase inhibitors have been evaluated in the canine model: the first was the gold standard, donepezil, and the second was phenserine tartrate (Araujo et al. 2011a). Donepezil (1.5 mg/kg, PO) improved memory performance on the DNMP at the longer delays during treatment compared to both baseline and washout. By contrast, phenserine (0.5 mg/kg, PO) significantly improved DNMP performance at the longest delay compared to washout, and improved learning on a difficult version of the oddity discrimination task compared to placebo. In a study replicating the effects of donepezil in which the pharmacokinetic profile was also examined, DNMP improvement corresponded with plasma levels of donepezil consistent with those reported in humans (Araujo et al. 2013b; Matsui et al. 1999). Similarly, the canine model has accurately predicted symptomatic treatments that failed human clinical trials (i.e., false positives), such as the ampakines (Studzinski et al. 2005). Collectively, these data support the predictive validity of the aged dog model for future screening of symptomatic therapeutics for AD, as well as for investigating the links among cholinergic function, Aβ pathology, and cognitive decline in both AD and CDS.

4.4.2   Disease-Modifying Treatments

The prevailing theory in AD is that Aβ is toxic and that its accumulation in the brain is one of the leading causes of cognitive dysfunction (Hardy 2006). Consequently, eliminating the accumulation of Aβ in the brain has been a major research and drug development focus since the development of the amyloid cascade hypothesis. For

example, amyloid vaccines resulted in plaque clearance as well as cognitive benefits in several transgenic mouse lines (Janus and Westaway 2001; Schenk et al. 1999; Sigurdsson et al. 2001); however, the vaccination approach has repeatedly failed in phase 3 human clinical trials (Alves et al. 2014; Holmes et al. 2008).

In contrast to transgenic mouse models, the aged dog predicted the clinical outcome of active vaccine trials, thereby identifying a false-positive finding in transgenic mice (Head et al. 2008). In both old and young dogs, immunization with fibrillar $A\beta_{42}$ and a Th1 adjuvant (TiterMax Gold) resulted in primarily IgG2 and IgM antibody responses, and also caused a nonsignificant increase in CSF $A\beta_{40}$ and decrease in cortical $A\beta_{40/42}$, which was consistent with findings in transgenic models and humans (Head et al. 2006). In a subsequent 2.4-year vaccination study investigating both $A\beta$ pathology and effect on cognitive dysfunction in aged dogs, no improvement on measures of learning, spatial attention, or spatial memory was found; however, after extended treatment, maintenance of prefrontal-dependent reversal learning ability was found (Head et al. 2008). Moreover, levels of soluble and insoluble $A\beta_{40}$ and $A\beta_{42}$ and the extent of diffuse plaque accumulation in the brain were significantly decreased in several cortical regions, with largest reductions in the prefrontal cortex. This predicted the outcome of similar human clinical vaccination trials and also suggests that reducing total $A\beta$ may be of limited therapeutic benefit, particularly late in AD progression (Head et al. 2008; Holmes et al. 2008).

Current research extending beyond vaccination strategies includes beta- and gamma-secretase inhibitors and modulators, as well as numerous approaches targeting tau pathology. While the dog has been utilized to evaluate biomarker changes (i.e., CSF amyloid markers) following administration of secretase modulators (Borghys et al. 2012), the absence of canine studies aimed at predicting clinical trials, as well as the lack of a gold standard, limits the ability to further evaluate predictive validity of the canine model for accurately identifying successful (true-positive) disease-modifying drugs.

4.4.3   Non-pharmacological Studies

Non-pharmacological intervention studies in humans have focused primarily on lifestyle changes to see if these may improve or ameliorate the clinical signs associated with the early stages of Alzheimer's disease. Two lines of research have shown efficacious results in humans: moderate exercise and dietary modification. In humans, moderate exercise has been shown to promote brain health via changes in specific brain mechanisms (Dao et al. 2013; Radák et al. 2001; van Praag et al. 1999; Liu et al. 2011). These changes have been shown to delay the onset of cognitive delay associated with AD (e.g., Rolland et al. 2007). Aged dogs trained to run on a treadmill for 10 min daily were tested on three different memory tasks: a concurrent discrimination task, a novel object recognition task, and a novel object location task (Snigdha et al. 2014). Acute exercise was able to improve performance on both the concurrent discrimination task and the novel object location task on a 24-h retest, and chronic

exercise improved performance on the object location memory task. Interestingly, one of the brain changes reported after exercise in humans is a reduction of reactive oxygen species (ROS). Alternate methods to reduce ROS are via consumption of a diet rich with antioxidants. In a large prospective study held in the Netherlands called the Rotterdam Study, it was reported that a diet high in antioxidants vitamins C and E may lower the risk for Alzheimer's disease (Engelhart et al. 2002). By comparison, a diet enriched with antioxidants alone and when combined with environmental enrichment improves cognitive function and prevents cognitive decline in aged dogs (Cotman et al. 2002; Milgram et al. 2002a, b; 2004). It is important to note that the general absence of phase 3 clinical trial data for non-pharmacological interventions impacts the ability to robustly evaluate predictive validity.

4.5 Summary

Aging dogs show AD-like cognitive domain-specific deficits and associated neuro-pathology that result in biomarker patterns consistent with those seen in AD progression. Therefore, the dog provides a natural model of AD progression that can be used to evaluate novel therapeutics or potentially be used to learn more about human disease progression and the sequential pathological events associated with disease progress. Moreover, aged dogs demonstrate the ability to accurately predict clinical outcomes and have successfully predicted symptomatic drugs that were approved and disease-modifying drugs that failed, such as active vaccine approaches. Consequently, the aged dog is a unique model of sporadic AD in which the progression of disease can be monitored using CSF and in vivo imaging biomarkers currently used in AD clinical research and drug development. On the other hand, developments in the AD field may also prove valuable for improved diagnosis, monitoring, and treatment of CDS.

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