Aging Pathobiology and Therapeutics 2025; 7(2): 83-84 ***83***
DOI: 10.31491/APT.2025.06.171

EDITORIAL

The neuropathology of aging and Alzheimer's disease in domestic cats

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Abstract

Current animal models for Alzheimer's disease (AD) research face significant translational challenges, with many promising preclinical findings failing to yield effective human therapies. Interestingly, aging pet cats naturally develop neuropathology-like lesions representing amyloid beta plaques and neurofibrillary tangles containing hyperphosphorylated tau, in contrast to most other AD animal models that primarily exhibit amyloid plaques. Pet cats share environmental exposures with humans, develop similar age-associated comorbidities, and exhibit behavioral changes that correspond to neuropsychiatric disorders in humans that often precede AD dementia. Clearly, domestic cats represent an underutilized but superior model for investigating AD pathogenesis and gerotherapeutic interventions, but extensive funding will be needed to develop networks of pet cat owners and referring veterinarians to take advantage of these translational characteristics.

Keywords: Alzheimer's disease, domestic cats, aging, neuropathology, translational animal model, research funding

Changes in brain structure and function continue throughout life, and studies at multiple levels of analysis in model organisms and humans are helping to define the normal trajectory of changes in the brain over the adult lifespan. Human and animal studies suggest that adaptive or resilient processes may be needed for maintenance of brain structure and function during normal aging. At the molecular and cellular level of analysis in animal models, brain aging is associated with changes in gene and epigenetic expression, mitochondrial and energy metabolism, protein homeostasis, neural plasticity, and synaptic function. What remains unclear is when these aging changes transition to pathological aging and disease phenotypes. Complicating the understanding of the role of aging in AD is the fact that most animal studies employ adult but not aged genetic models of disease. Integration of research at various levels of analysis, from cells to neural networks, in older adults and in appropriate animal models is needed to reach a global understanding of brain aging and its contribution to, and promotion of, pathological processes underlying AD.

AD is the most common neurodegenerative disease in humans, affecting millions of people worldwide and accounting for nearly two thirds of dementia cases. The disease is characterized by pathologic accumulations of two types of protein aggregates in specific brain regions, which include plaques composed of amyloid beta (Aβ) peptide, and neurofibrillary tangles (NFTs) composed of hyperphosphorylated tau protein formed intracellularly in neurons. These accumulations contribute to progressive neuronal loss and cognitive dysfunction. Transgenic rodent models historically have been used to investigate pathophysiologic mechanisms and identify candidate drugs for early preclinical studies, however, candidate drugs validated in these models have generally failed in human clinical trials. A better understanding of the mechanisms and pathogenesis of AD in an animal model that naturally develops similar pathologies of AD would be invaluable for developing new translational therapeutic strategies targeting the disease.

Several animal species have been shown to develop one or more age-related lesions that are comparable to AD. In general, nonhuman primates and dogs develop spontaneous A deposition with age, but do not reliably recapitulate tau pathology. Wild-type rodents also do not spontaneously form plaques or NFTs, but genetically engineered mice have been developed that have single, double or multiple mutations in genes responsible for the production of A and/or tau proteins. It is now becoming clear that do-

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Received: 17 June 2025
Accepted: 18 June 2025/Published: 27 June 2025

mestic cats can spontaneously develop both Aβ deposition and NFTs, as well as associated neuronal loss, in a pattern of distribution similar to humans, and which develop with increasing age [1]. Concurrently with the progression of neuropathology, cats develop behavioral and cognitive dysfunction.

Aβ deposition can be seen in the brains of adult pet cats predominantly as plaques composed of Aβ1-42. They are most commonly found in the cerebral cortex, with extension to the hippocampus and basal ganglia. Adult cats also express 6 tau isoforms, including hyperphosphorylated 3R and 4R isoforms, which can form aggregates in the presence of Aβ in the form of pretangles, threads, dystrophic neurites, NFTs or ghost tangles. These features of feline NFTs, accompanied by neuronal loss and occurring with intracellular oligomers in the same brain region, distinguish the cat from dogs and nonhuman primates.

The aging pet cat is therefore an innovative model to study AD because of the development of naturally occurring AD-like lesions, with similar comorbidities as older people, sharing the same environment, and with the development of behavioral changes with increasing age. In addition, pet cats have not been studied with the explicit intent of using a scientifically valid translational animal model for brain aging and AD. The concept of a cat brain infrastructure based on neuropathology is highly innovative and will provide access to a model of brain aging and AD that will allow in-depth investigation into causes and mechanisms not available in other animal models.

The impact the domestic cat AD model can have on human health is highly significant because new information gathered regarding brain aging as a risk factor for the development of AD-like neuropathology can reveal targets for gerotherapeutic treatment and intervention. The fact that cats can be challenging to determine levels of cognitive impairment does not diminish the value of the model since a number of abnormal neuropsychiatric behaviors are seen in both cats and humans, which in humans can be associated with increased risk for AD. This neuropsychiatric aspect of AD is less studied because there are no well characterized animal models. Early onset of neuropsychiatric problems in pet cats based on owner history and veterinary clinical records can be used as predictive phenotypes in preclinical therapeutic trials. The domestic pet cat thus has unique advantages as a naturally occurring model of AD that can provide the translational relevance needed to advance the successful treatment and prevention of AD. But funding for the development of networks of pet cat owners and referring veterinarians will be needed to take full advantage of this model.

Declarations

Availability of data and materials: Not applicable.

Financial support and sponsorship: Referenced studies were supported in part by NIH grant R01 AG067193 (Ladiges- PI).

Conflicts of interest: Warren Ladiges is a member of the editorial board of *Aging Pathobiology and Therapeutics*. The authors declare that they have no conflicts and were not involved in the journal's review or decision regarding this manuscript.

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Cite this article as: Sharma A, & Ladiges W. The neuropathology of aging and Alzheimer's disease in domestic cats. *Aging Pathobiol Ther*, 2025, 7(2): 83-84. doi: 10.31491/APT.2025.06.171