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Hypothesis

Did Domestication Modify Neural Resilience? A Comparative Neurobiological Hypothesis Based on Wolves and Dogs

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Abstract

Canine Cognitive Dysfunction (CCD) is a naturally occurring neurodegenerative syndrome of aging dogs that shares important clinical, neuropathological, and molecular characteristics with Alzheimer's disease. Consequently, domestic dogs have become one of the most informative comparative models for investigating mechanisms of human cognitive aging and neurodegeneration. Surprisingly, far less attention has been devoted to their closest living relative, the gray wolf (Canis lupus), despite the unique evolutionary perspective that this species offers. Here, we propose the hypothesis that domestication has modified the environmental determinants of neural resilience by altering the lifelong ecological conditions and patterns of ecological exposure experienced by the canine brain. Rather than suggesting that wolves are intrinsically protected against neurodegeneration, we propose that wolves and domestic dogs may follow different trajectories of brain aging because of long-term differences in physical activity, cognitive demands, social organization, metabolic regulation, and environmental predictability. Current evidence is indirect but biologically coherent. Nevertheless, converging observations from comparative neurobiology, veterinary neurology, environmental enrichment, cognitive reserve theory, and evolutionary medicine provide a

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biologically plausible framework for its formulation. We integrate these independent lines of evidence into a conceptual model linking domestication, lifelong environmental complexity, neural resilience, and cognitive aging. The hypothesis generates explicit and experimentally testable predictions involving comparative behavioral studies, neuropathology, biomarkers, neuroimaging, and One Health approaches. If supported, this framework would expand the current understanding of domestication beyond its recognized effects on morphology and behavior, identifying it as a potential evolutionary modifier of brain aging. Comparative investigation of wolves and domestic dogs may therefore provide novel insights into the mechanisms governing neural resilience and age-related neurodegeneration across mammalian species, including humans.

Keywords
Brain aging; neural resilience; canine cognitive dysfunction; Alzheimer's disease; gray wolf; domestication; environmental complexity; cognitive reserve; comparative neurobiology; one health

1. Introduction

Age-related neurodegenerative diseases represent one of the greatest biomedical challenges of the twenty-first century. Although aging remains the strongest risk factor for disorders such as Alzheimer's disease, chronological age alone cannot explain the remarkable variability observed in cognitive trajectories among individuals or species. Increasing evidence indicates that brain aging results from complex interactions between genetic background, environmental exposures, metabolic regulation, vascular health, immune function, and lifelong neural plasticity rather than from aging itself [1-3].

Within this framework, the concept of neural resilience has emerged as a central paradigm in contemporary neuroscience. Neural resilience refers to the capacity of the brain to preserve cognitive function despite the progressive accumulation of age-related molecular and structural alterations. Although the concepts of cognitive reserve, brain reserve, and brain maintenance are not identical, they provide complementary theoretical frameworks for understanding individual differences in susceptibility to age-related cognitive decline [3]. This resilience is thought to arise through the interaction of multiple adaptive mechanisms—including cognitive reserve [4, 5], neuroplasticity, physical activity, environmental stimulation, social engagement, and metabolic homeostasis—which collectively determine the vulnerability of neural networks during aging [3, 4, 6].

Among naturally occurring animal models of neurodegeneration, the domestic dog (Canis lupus familiaris) occupies a unique position. Aging dogs spontaneously develop Canine Cognitive Dysfunction (CCD), a progressive syndrome characterized by memory impairment, spatial disorientation, altered sleep-wake cycles, changes in social interactions, and reduced learning capacity [7]. At the neuropathological level, CCD exhibits several similarities to Alzheimer's disease, including amyloid-β deposition, oxidative stress, chronic neuroinflammation, cerebrovascular alterations, and synaptic dysfunction [8]. Because domestic dogs share the human environment

throughout their lifespan while naturally developing cognitive decline, they are increasingly regarded as valuable translational models for studying human brain aging [9]. Importantly, however, normal cognitive aging and pathological cognitive dysfunction are not interchangeable phenotypes, and methodological differences in defining and measuring behavioral decline remain an important limitation in canine aging research [10].

Paradoxically, comparatively little attention has been devoted to the species that provides the closest evolutionary comparison: the gray wolf (Canis lupus). Wolves and domestic dogs diverged relatively recently and retain a remarkable degree of genetic similarity [11-13]. However, domestication altered the socio-ecological niche in which dogs live, including their relationships with humans, patterns of resource acquisition, social interactions, and behavioral opportunities [14, 15]. Whereas wolves continue to depend upon complex spatial navigation, cooperative hunting, territorial defense, environmental monitoring, and sophisticated social communication, domestic dogs occupy a broad spectrum of human-associated environments rather than a single standardized ecological niche.

These contrasting ecological histories raise an important but largely unexplored question: has domestication modified not only canine behavior and morphology, but also the biological mechanisms that determine neural resilience during aging? This question extends beyond veterinary medicine because domestication constitutes a profound evolutionary transition in which selection, developmental biology, and ecological niche construction interact [15, 16]. If long-term changes in ecological complexity influence the biological processes underlying brain maintenance, domestication itself may represent a natural experiment in comparative neurobiology.

The present hypothesis is motivated by two observations. First, wolves maintained in captivity or semi-captivity can attain substantial longevity, providing an opportunity for comparative aging research [17]. Second, despite increasing recognition of CCD in companion animals, published descriptions of dementia-like syndromes in aging wolves remain scarce. This disparity cannot be interpreted as evidence that wolves are resistant to neurodegeneration, because differences in sample size, surveillance, diagnostic practice, and opportunities for neuropathological examination may contribute to the evidence gap [18].

Relationship to our previous work and novelty of the present hypothesis. Our previous study provided a preliminary risk-factor comparison between domestic dogs and gray wolves maintained in captive or semi-captive conditions, focusing on factors relevant to canine cognitive dysfunction and human Alzheimer's disease, including aging, oxidative stress, inflammation, sleep disturbances, and periodontal disease [18]. That study suggested that domestic dogs may experience a greater burden of several recognized risk factors for cognitive dysfunction, while emphasizing the limited neuropathological and behavioral information available for aging wolves. The present manuscript addresses a different question. Rather than comparing individual risk factors or inferring relative vulnerability from their prevalence, we propose a broader neuroecological hypothesis in which lifelong ecological complexity and patterns of environmental exposure are considered potential integrative determinants of neural resilience. The present framework distinguishes species-level consequences of domestication from individual-level environmental exposure. It treats ecological complexity as a graded variable across free-ranging wolves, managed or captive wolves, and domestic dogs living in heterogeneous environments. It further incorporates candidate behavioral, physiological, molecular, epigenetic, and microbiome-related pathways and derives explicitly testable predictions that can be evaluated longitudinally and across ecological contexts. Thus, the

2025 study provides a preliminary comparative assessment of risk-factor profiles. In contrast, the present article develops a conceptual, mechanistically informed, and falsifiable framework for investigating how domestication and lifelong ecological exposure may jointly shape trajectories of neural aging. Importantly, the evidence supporting the present hypothesis is indirect at this stage. Evidence from canine cognitive aging and from experimental studies of environmental complexity provides biological plausibility. In contrast, direct longitudinal or neuropathological evidence linking ecological complexity to neural aging in wolves is currently lacking. The wolf-dog comparison therefore represents a testable comparative hypothesis rather than an established species difference.

Here, we propose the hypothesis that domestication may have altered the environmental determinants of neural resilience by changing the species-level socio-ecological context and, in turn, the patterns of lifelong ecological exposure experienced by individual dogs. Within this conceptual framework, wolves and domestic dogs are viewed not as healthy and pathological models, respectively, but as closely related evolutionary trajectories through which different environmental conditions may influence brain aging. This hypothesis integrates comparative neurobiology, environmental enrichment, cognitive reserve, evolutionary biology, and One Health, generating explicit and experimentally testable predictions that may advance our understanding of neurodegenerative vulnerability across mammalian species.

2. Current Evidence Supporting the Hypothesis

The hypothesis proposed here does not arise from a single observation but from the convergence of multiple independent lines of evidence derived from comparative neurobiology, veterinary neurology, evolutionary biology, environmental neuroscience, and aging research. Importantly, the first two lines of evidence below—canine cognitive aging and experimental studies of environmental complexity—provide biological plausibility but do not directly provide evidence of neural aging in wolves. Direct longitudinal or neuropathological evidence in wolves remains limited. Accordingly, none of these observations alone demonstrates that domestication has modified brain aging; together, however, they provide a biologically plausible framework that justifies the formulation of the present hypothesis.

The first line of evidence comes from studies of Canine Cognitive Dysfunction (CCD). CCD is now widely recognized as a naturally occurring neurodegenerative syndrome affecting aging dogs, characterized by progressive impairments in learning, memory, spatial orientation, sleep-wake regulation, and social behavior [7]. At the neuropathological level, CCD exhibits several features that parallel Alzheimer's disease, including β-amyloid accumulation, oxidative stress, mitochondrial dysfunction, chronic neuroinflammation, cerebrovascular alterations, and synaptic degeneration [8]. These similarities have established the domestic dog as one of the most informative spontaneous models for studying human cognitive aging and neurodegeneration [9].

A second line of evidence derives from the growing literature on brain resilience [19]. Contemporary neuroscience increasingly recognizes that cognitive aging cannot be explained solely by chronological age or neuropathological burden. Instead, the brain's capacity to maintain cognitive function throughout life depends on adaptive mechanisms—including neuroplasticity, cognitive reserve, vascular integrity, metabolic homeostasis, and immune regulation—that collectively determine resilience against age-related decline [3, 4]. Experimental studies in rodents

and humans demonstrate that environmental enrichment, sustained physical activity, and cognitively demanding experiences can enhance synaptic plasticity, stimulate adult hippocampal neurogenesis, improve vascular function, and delay cognitive deterioration [6, 20-23]. These findings support the idea that lifelong environmental conditions can influence the biological trajectory of brain aging, though they remain indirect with respect to wolves.

A third line of evidence comes from comparative behavioral ecology and recent wolf-dog research. Throughout their evolutionary history, gray wolves have depended on continuous interaction with complex and dynamic environments. Cooperative hunting, territorial defense, spatial navigation over extensive home ranges, social communication, and behavioral flexibility impose sustained cognitive demands that require integrating memory, executive function, sensory processing, and social cognition. Contemporary reviews emphasize that wolf-dog behavioral differences reflect adaptation to different socio-ecological niches rather than a simple hierarchy of cognitive abilities [14]. Evidence from another wild canid is also informative: captive coyotes show age-related declines in cognitive flexibility, demonstrating that age-related cognitive change is not unique to domestic dogs [24]. These findings do not establish a corresponding pattern in wolves, but they support the feasibility and importance of comparative aging research across canids.

By contrast, domestication has altered the ecological context in which most dogs live, although the resulting environments are highly heterogeneous. Companion dogs may experience predictable feeding schedules, reduced energetic demands, simplified spatial environments, continuous human protection, and substantially different daily activity patterns, whereas working, free-ranging, assistance, and village dogs may experience markedly different ecological demands. These environmental differences do not imply that domestic dogs receive less stimulation than wolves; rather, they suggest that the type, intensity, predictability, and ecological relevance of lifelong stimulation have been modified through domestication and subsequent human selection [14-16]. Consequently, wolves and dogs may experience distinct patterns of neural activation across the lifespan, potentially influencing mechanisms involved in neural maintenance and resilience.

A fourth line of evidence concerns comparative longevity and the choice of appropriate animal models for aging research. While few wolves survive to advanced age in natural ecosystems because of predation, disease, and environmental hazards, individuals maintained in captivity or semi-captivity may live much longer. Comparative gerontology emphasizes that the biological interpretation of aging trajectories depends strongly on species, ecological context, life history, and the distinction between proximate and evolutionary explanations [17]. Thus, wolves and domestic dogs should not be treated as automatically equivalent aging models simply because some individuals can attain similar chronological ages; rather, their contrasting life histories support carefully controlled comparative studies.

Finally, an intriguing observational gap remains largely unexplored. Despite the increasing recognition of CCD in companion animals, published reports describing dementia-like syndromes in aged wolves are remarkably scarce. Importantly, this absence of documented cases should not be interpreted as evidence that wolves do not experience neurodegeneration. Instead, it may reflect the limited number of aged wolves available for study, the absence of standardized cognitive assessments, the scarcity of longitudinal behavioral observations, and the limited availability of postmortem neuropathological investigations. Similar methodological difficulties in distinguishing normal from pathological cognitive aging have been documented in family dogs [10]. Nevertheless,

the discrepancy identifies a significant knowledge gap that warrants systematic comparative investigation [18].

Taken together, these independent observations do not establish a causal relationship between domestication and brain aging. However, they converge toward a coherent biological framework in which lifelong ecological conditions emerge as plausible modifiers of neural resilience. This convergence provides the foundation for the hypothesis proposed in the present article.

3. The Hypothesis

Based on the evidence summarized above, we propose that domestication may have altered the environmental determinants of neural resilience, thereby contributing to differences in the trajectory of brain aging between domestic dogs and gray wolves. The hypothesis concerns lifelong ecological exposure at the individual level, while recognizing that domestication changed the species-level socio-ecological niche and the selective regime under which dogs evolved.

This hypothesis does not suggest that wolves are intrinsically resistant to neurodegenerative disease, nor does it imply that domestication alone explains the development of Canine Cognitive Dysfunction. Rather, we propose that domestication altered the ecological conditions under which the canine brain develops and ages, producing lifelong differences in the balance between neural challenge and neural maintenance. Importantly, altered environmental complexity should not be equated with reduced welfare, nor should it be treated as synonymous with relaxed selection; these represent related but distinct ecological and evolutionary processes [14, 16].

More specifically, domestication and subsequent human-associated lifestyles may have influenced multiple biological systems known to participate in healthy brain aging. These include synaptic plasticity, hippocampal neurogenesis, cerebrovascular function, mitochondrial efficiency, sleep architecture, metabolic regulation, stress physiology, immune homeostasis, and neuroinflammatory responses [1, 2, 23]. Comparative genomic studies also indicate that domestication involved selection in brain-expressed genes and genes associated with neurological processes. At the same time, other domestication-associated regions are enriched for central nervous system development and neurological function [13, 25, 26]. Comparative domestication studies also indicate differences in brain gene-expression profiles and canine brain DNA methylation patterns associated with domestication and breed formation [27, 28]. Changes in microbiome composition and gut-immune-brain signaling have also been proposed as components of domestication-related biology [29]. These observations broaden the proposed mechanism beyond environmental stimulation alone, while remaining compatible with a multifactorial model of neural resilience. Importantly, these studies do not establish that canonical Alzheimer's disease genes such as APP, PSEN1, PSEN2, or APOE were direct targets of selection during dog domestication; rather, they support a broader possibility that domestication-related genetic changes in neural development, regulation, plasticity, and maintenance could interact with lifelong environmental exposure.

Within this framework, Canine Cognitive Dysfunction is interpreted not as the inevitable consequence of aging itself but as one possible neurobiological trajectory influenced by the interaction between genetic predisposition and lifelong environmental exposures. Wolves may follow a different trajectory because their evolutionary history and typical ecological niche differ from those of domestic dogs; however, captive wolves do not necessarily experience the ecological

conditions of free-ranging wolves. The hypothesis therefore predicts neither that all wolves will outperform all dogs nor that captivity preserves a uniquely protective wolf phenotype.

The hypothesis is conceptually consistent with contemporary theories of cognitive reserve, brain resilience, environmental enrichment, and evolutionary mismatch. These frameworks share the premise that biological systems evolved under particular ecological and developmental conditions and that deviations from those conditions may influence health across the lifespan [3, 30, 31]. At the ultimate evolutionary level, domestication altered selection pressures and the socio-ecological niche; at the proximate individual level, dogs experience diverse environmental exposures that can influence neural maintenance. Keeping these explanatory levels distinct is essential for testing the hypothesis [17].

Importantly, the hypothesis remains fully falsifiable. Comparative studies demonstrating no meaningful behavioral, neuropathological, biomarker, or neuroimaging differences between aged wolves and domestic dogs would argue against the proposed model. Conversely, consistent differences in these domains would support the view that domestication has influenced the biology of brain aging through mechanisms related to lifelong environmental complexity. The value of the present hypothesis therefore lies not in asserting a definitive explanation but in providing a coherent conceptual framework that can generate experimentally testable predictions.

4. Conceptual Model

The hypothesis proposed here is summarized in a conceptual framework in which domestication is viewed as a long-term modifier of the socio-ecological conditions relevant to neural resilience rather than merely a process of artificial selection affecting morphology and behavior (Figure 1). The model distinguishes species-level evolutionary change from individual-level lifelong environmental exposure.

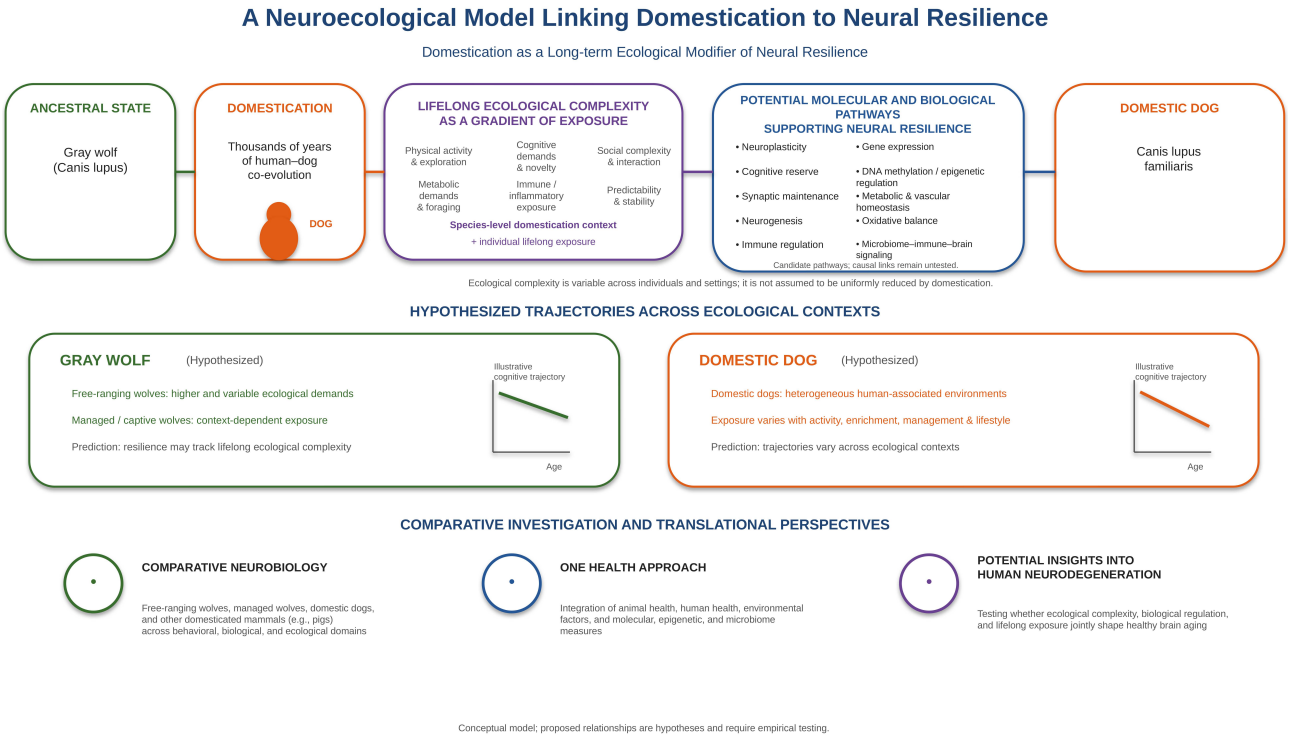


Figure 1 Proposed neuroecological model linking domestication, lifelong ecological exposure, and neural resilience. The model conceptualizes domestication as an evolutionary transition that may have altered the species-level socio-ecological context while producing heterogeneous patterns of lifelong ecological exposure among individuals. Environmental complexity is treated as a graded variable encompassing physical activity and exploration, cognitive demands and novelty, social complexity and interaction, metabolic and foraging demands, immune and inflammatory exposure, and environmental predictability and stability. These factors are hypothesized to interact with candidate biological pathways supporting neural resilience, including neuroplasticity, cognitive reserve, synaptic maintenance, neurogenesis, gene expression, DNA methylation and other epigenetic regulation, metabolic and vascular homeostasis, oxidative balance, immune regulation, and microbiome-immune-brain signaling. The framework distinguishes free-ranging wolves, managed or captive wolves, and domestic dogs rather than assuming a simple wolf-dog dichotomy or that all domestic dogs experience reduced ecological complexity. The proposed molecular, epigenetic, and microbiome-related pathways are candidate mechanisms within the hypothesis and are not presented as established causal explanations of aging or neurodegeneration in wolves or dogs. The model is intended to generate testable comparative predictions across ecological contexts and, where appropriate, other domesticated mammals.

The model proposes that the ancestral wolf lineage evolved under ecological conditions characterized by sustained environmental complexity. Throughout life, wolves depend on spatial navigation, cooperative hunting, territorial defense, social communication, environmental monitoring, and persistent physical activity. These ecological demands require the coordinated activation of neural systems involved in memory, executive function, sensory integration, motor

control, and social cognition. However, the intensity of these demands varies among individuals and habitats, so the wolf-dog comparison should be treated as a gradient rather than a simple binary contrast [14, 15].

Accumulating evidence from experimental neuroscience indicates that sustained cognitive engagement and environmental complexity promote biological mechanisms associated with healthy brain aging, including synaptic plasticity, adult hippocampal neurogenesis, angiogenesis, mitochondrial efficiency, neurotrophic signaling, and adaptive regulation of neuroimmune function [6, 20, 21, 23]. These processes contribute to neural resilience, defined as the brain's capacity to preserve function despite progressive molecular and structural changes associated with aging [3, 19].

Domestication altered this ecological context, but not uniformly across all dogs. At the species level, dogs evolved within a human-associated socio-ecological niche; at the individual level, environmental complexity ranges from highly managed companion-dog lifestyles to working, free-ranging, and other more demanding contexts [14, 15]. These environmental differences should not be interpreted as reductions in animal welfare. Rather, they represent differences in ecological demands, predictability, physical activity, and opportunities for species-typical behavior. Consequently, lifelong activation of biological pathways supporting neural maintenance may differ quantitatively or qualitatively among canids.

Within this framework, domestication is not proposed as a direct cause of neurodegeneration. Rather, it is considered an evolutionary modifier that may influence multiple interacting determinants of brain aging. Environmental complexity may interact with genetic and epigenetic changes associated with domestication, including altered brain gene expression and DNA methylation, as well as microbiome-related immune and metabolic pathways [27-29]. Thus, the proposed environmental pathway is not intended to exclude genetic or developmental mechanisms; instead, the hypothesis predicts interaction among these levels of explanation.

The conceptual model therefore predicts that brain aging reflects the cumulative interaction between inherited biology, domestication-related evolutionary change, and lifelong ecological experience. Wolves and domestic dogs are interpreted not as examples of healthy and pathological aging, respectively, but as closely related populations that may differ in the biological mechanisms supporting neural resilience. Comparative investigation across free-ranging wolves, managed wolves, and diverse dog populations can help determine how much of any observed difference is attributable to species history, individual environment, genetic background, or their interaction.

More broadly, this framework extends beyond canid biology. If supported, it would suggest that ecological transitions—including domestication—can influence the trajectory of brain aging through interacting mechanisms operating across the lifespan. This perspective aligns with contemporary concepts in evolutionary medicine, comparative gerontology, and One Health, including recent work emphasizing links among domestication, shared environments, neural plasticity, and cognitive aging [32].

5. Testable Predictions

The principal value of a scientific hypothesis lies in its ability to generate explicit predictions that can be evaluated empirically. The present framework therefore proposes several testable

predictions spanning behavioral neuroscience, neuropathology, neuroimaging, biomarker research, and comparative biology.

5.1 Prediction 1: Comparative Behavioral Trajectories

If domestication has modified the environmental determinants of neural resilience, aged wolves maintained under comparable veterinary conditions should exhibit behavioral aging trajectories that differ from those of age-matched domestic dogs. Longitudinal observations should assess domains commonly affected in Canine Cognitive Dysfunction, including spatial orientation, social behavior, exploratory activity, learning performance, responsiveness to environmental stimuli, and sleep-wake organization [33]. The hypothesis predicts differences in the onset, progression, or expression of cognitive decline, not the complete absence of age-related impairment. Importantly, it does not predict a simple ranking in which captive wolves must perform worse than dogs and free-ranging wolves must perform best. Instead, comparisons among free-ranging wolves, managed wolves, and dogs living under different environmental conditions should test whether ecological complexity predicts variation within and across species.

5.2 Prediction 2: Comparative Neuropathology

Compare naturally deceased wolves and domestic dogs reaching similar chronological ages, using standardized neuropathological protocols. Quantitative assessment of amyloid-β deposition, synaptic density, microglial activation, astrocytosis, cerebrovascular pathology, mitochondrial alterations, and oxidative damage may reveal species-specific patterns of brain aging. Importantly, opportunistic postmortem studies provide an ethically appropriate strategy that respects current standards of animal welfare while maximizing scientific value.

5.3 Prediction 3: Biomarkers of Neural Aging

Emerging biomarkers—including neurofilament light chain (NfL), glial fibrillary acidic protein (GFAP), inflammatory cytokines, markers of oxidative stress, and extracellular vesicle-associated proteins—could reveal distinct trajectories of neural aging in wolves and dogs if collected opportunistically during routine veterinary procedures or clinical interventions [34]. Such studies would bridge behavioral observations and neuropathological findings.

5.4 Prediction 4: Comparative Neuroimaging

Advanced magnetic resonance imaging techniques, including structural MRI, diffusion tensor imaging, and functional connectivity analyses, may identify differences in age-related changes affecting hippocampal, frontal, and limbic networks. These approaches could determine whether prolonged exposure to distinct ecological environments is associated with differences in brain atrophy, white matter integrity, or network organization during aging.

5.5 Prediction 5: Environmental Complexity as a Graded Ecological Variable

The hypothesis predicts that environmental complexity should influence cognitive aging along a continuum rather than as a simple wolf-versus-dog dichotomy. Comparative studies involving free-

ranging wolves, captive wolves, working dogs, assistance dogs, free-roaming village dogs, and companion dogs may therefore reveal graded relationships between lifelong ecological stimulation and markers of neural resilience. This prediction matters because it recognizes that domestication encompasses a broad spectrum of environmental conditions rather than a single lifestyle.

5.6 Prediction 6: Extension to Other Domesticated Species

Finally, if the proposed mechanism reflects a general biological principle, comparable relationships between domestication, environmental complexity, and neural resilience may be detectable in other domesticated mammals. Pigs and wild boar offer a useful comparison because domestication has produced major changes in ecology, behavior, physiology, and human-associated living conditions. Cross-species comparative analyses should determine whether similar relationships between domestication, environmental complexity, and cognitive aging occur beyond canids or whether the proposed pattern is canid-specific [27].

These predictions are intentionally falsifiable. Failure to identify meaningful behavioral, neuropathological, biomarker, or neuroimaging differences between wolves and domestic dogs would argue against the proposed framework or indicate that environmental complexity contributes less to brain aging than hypothesized. Conversely, convergent evidence across these domains would support the view that domestication has influenced neural resilience through long-term modification of ecological conditions experienced throughout life.

6. Alternative Explanations

Several alternative explanations warrant careful consideration before attributing potential differences in cognitive aging to domestication itself.

The most immediate explanation is methodological. Dementia-like syndromes may simply be under-recognized in gray wolves because relatively few individuals survive to advanced age, standardized cognitive assessments have rarely been implemented, and opportunities for systematic neuropathological examination remain limited. Consequently, the apparent scarcity of published cases may primarily reflect under-detection rather than genuine biological differences.

A second possibility is that wolves develop age-related neuropathological changes comparable to those observed in domestic dogs but express them through different behavioral phenotypes. Species-specific ecological adaptations, social organization, and behavioral repertoires may mask or modify clinical manifestations that companion dogs really recognize as Canine Cognitive Dysfunction (CCD). Establishing standardized behavioral criteria applicable to wolves therefore represents an essential prerequisite for meaningful comparisons.

Genetic and evolutionary factors also warrant consideration. Although domestic dogs and gray wolves remain closely related, domestication involved artificial selection affecting behavior, endocrine regulation, metabolism, stress responsiveness, reproduction, and immune function [11, 13, 16]. Comparative genomic analyses have identified positive-selection signatures in neurological processes and brain-expressed genes, as well as domestication-associated regions enriched for genes involved in central nervous system development and neurological function [13, 25, 26]. Such findings support the possibility that inherited differences in neural development, regulation, plasticity, or maintenance could influence susceptibility to age-related cognitive change independently of environmental complexity or in interaction with it. However, current evidence

does not establish that canonical Alzheimer's disease genes such as APP, PSEN1, PSEN2, or APOE were direct targets of selection during dog domestication. The present hypothesis should therefore not be interpreted as a purely environmental explanation, nor as a claim of direct domestication-driven selection on specific Alzheimer's disease genes; instead, it predicts interaction among evolutionary change, genotype, and lifelong environment.

Similarly, lifespan itself may represent an important confounding factor. Even under managed conditions, captive wolves and companion dogs may differ in nutrition, veterinary care, reproductive history, body composition, chronic disease burden, and causes of mortality. These variables may influence both longevity and brain aging, complicating direct interspecies comparisons.

Finally, environmental complexity constitutes only one component of healthy cognitive aging. Sleep quality, metabolic health, vascular function, microbiome composition, chronic inflammation, and lifelong social interactions all contribute to neural resilience and are themselves influenced by both genetic and environmental factors [1, 2, 29]. In addition, differences in selection regime, developmental history, breed formation, and individual management may contribute to observed wolf-dog differences. The present hypothesis therefore proposes a multifactorial framework in which environmental complexity is one interacting determinant, not a sufficient or exclusive cause of brain aging.

Recognition of these alternative explanations does not weaken the hypothesis. On the contrary, it identifies the critical variables that future comparative studies must evaluate to determine the relative contribution of environmental complexity within the broader biology of aging.

7. Future Directions

Testing this hypothesis will require a multidisciplinary and comparative research strategy integrating comparative neurobiology, veterinary medicine, wildlife biology, evolutionary biology, comparative gerontology, and One Health.

Because invasive experimentation in wolves is ethically inappropriate and logistically challenging, future investigations should prioritize non-invasive and opportunistic methodologies. Longitudinal behavioral monitoring of aging wolves maintained in zoological institutions, conservation centers, and semi-captive populations represents one of the most feasible initial approaches. Standardized assessments of spatial orientation, exploratory behavior, social interactions, learning capacity, and circadian activity could establish the first comparative datasets describing cognitive aging in wolves.

Complementary neuropathological investigations should focus on naturally deceased individuals. Collaborative biobanks involving zoological institutions, wildlife rehabilitation centers, veterinary hospitals, and academic laboratories would facilitate systematic collection of brain tissue and biological samples while fully respecting animal welfare principles. Comparative histopathological analyses could evaluate amyloid deposition, tau pathology, synaptic integrity, neuroinflammation, cerebrovascular alterations, and mitochondrial dysfunction using standardized, cross-species protocols.

Advances in minimally invasive biomarkers also provide promising opportunities. Circulating neurofilament light chain (NfL), glial fibrillary acidic protein (GFAP), inflammatory mediators, extracellular vesicles, and emerging plasma biomarkers associated with neurodegeneration could be incorporated opportunistically into routine veterinary procedures, providing valuable

longitudinal information without additional animal handling [34]. Emerging technologies—including wearable sensors, automated behavioral tracking, machine learning-assisted video analysis, and minimally invasive biomarker approaches—may substantially improve comparative studies of aging wolves while minimizing disturbance. These innovations could facilitate the collection of longitudinal behavioral and physiological data under conditions that fully respect contemporary standards of wildlife welfare, helping bridge one of the principal methodological limitations identified in this hypothesis.

Future research should also move beyond the simple comparison between wolves and companion dogs. Free-ranging village dogs, working dogs, assistance dogs, livestock-guarding breeds, and other populations experiencing markedly different levels of environmental complexity may offer a valuable continuum for investigating how ecological conditions influence trajectories of brain aging. Parallel measurement of genetic, epigenetic, microbiome, behavioral, and physiological variables will be essential for distinguishing environmental effects from domestication-related inherited differences [27-29].

More broadly, this hypothesis invites integration within the One Health framework. Domestic animals and humans increasingly share nutritional patterns, physical inactivity, artificial environments, altered sleep cycles, and prolonged longevity. Understanding how these shared environmental conditions influence neural resilience may therefore provide insights extending beyond veterinary medicine. Recent One Health perspectives have emphasized the potential value of integrating domestication, shared environments, neural plasticity, and cognitive aging across dogs and humans [32]. Comparative studies of wolves and domestic dogs may ultimately help identify general biological principles governing healthy brain aging across mammals.

8. Conclusions

The hypothesis presented here proposes that domestication may have influenced brain aging not only through genetic selection but also by altering the environmental and socio-ecological conditions under which the canine brain develops, functions, and ages. Rather than suggesting that gray wolves are inherently protected against neurodegenerative disease, we propose that wolves and domestic dogs may represent closely related yet biologically distinct trajectories of cognitive aging, shaped by interactions among evolutionary history, lifelong ecological experience, and mechanisms that sustain neural resilience.

Current evidence remains indirect, and definitive conclusions about comparative susceptibility to age-related cognitive decline in wolves are lacking. Evidence from comparative neurobiology, environmental enrichment, cognitive reserve, evolutionary biology, dog aging research, and domestication studies provides a biologically plausible framework that justifies systematic investigation of this hypothesis. The framework also incorporates the possibility that domestication is associated with genetic, epigenetic, and molecular changes relevant to neural biology, while recognizing that these mechanisms may interact with, rather than substitute for, lifelong environmental exposure.

Importantly, the proposed model is explicitly falsifiable. Comparative behavioral studies, neuroimaging, biomarker analyses, and neuropathological investigations can support or refute the predicted relationship between lifelong environmental complexity and neural resilience. The principal contribution of this hypothesis therefore lies not in claiming a definitive explanation but in

providing a coherent conceptual framework that can generate experimentally testable research questions.

More broadly, domestication may represent one of nature's largest unplanned experiments in evolutionary neuroscience. By profoundly reshaping ecological conditions over thousands of years, it may have altered not only behavior and morphology but also the biological processes governing brain maintenance across the lifespan. If environmental complexity is a significant determinant of neural resilience, comparative investigation of wolves and domestic dogs could illuminate fundamental mechanisms underlying neurodegenerative vulnerability in many mammalian species, including humans.

Ultimately, this perspective encourages a shift in how we conceptualize brain aging. Rather than viewing neurodegeneration exclusively through molecular or genetic mechanisms, it highlights the possibility that lifelong ecological experience constitutes an integral component of brain biology. Whether this hypothesis ultimately proves correct, it emphasizes that domestication itself may represent one of the largest natural experiments ever performed on mammalian brain aging.

Author Contributions

Rafael Castro-Fuentes: Conceptualization, data acquisition, methodology, figures, and original draft preparation. Rosy Socas-Pérez: Methodology, table, review, and editing. Both authors have approved the final version.

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Competing Interests

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AI-Assisted Technologies Statement

During the preparation of this manuscript, ChatGPT (OpenAI) was used as an AI-assisted tool for language editing, refinement of scientific phrasing, organization of the manuscript, and improvement of clarity and consistency. All AI-assisted content was critically reviewed and edited by the authors, who verified the scientific accuracy and integrity of the manuscript and take full responsibility for the final content of the manuscript.

References

1. Franceschi C, Garagnani P, Parini P, Giuliani C, Santoro A. Inflammaging: A new immune-metabolic viewpoint for age-related diseases. Nat Rev Endocrinol. 2018; 14: 576-590.
2. López-Otín C, Blasco MA, Partridge L, Serrano M, Kroemer G. Hallmarks of aging: An expanding universe. Cell. 2023; 186: 243-278.

3. Stern Y, Arenaza-Urquijo EM, Bartrés-Faz D, Belleville S, Cantilon M, Chetelat G, et al. Whitepaper: Defining and investigating cognitive reserve, brain reserve, and brain maintenance. Alzheimers Dement. 2020; 16: 1305-1311.
4. Stern Y. What is cognitive reserve? Theory and research application of the reserve concept. J Int Neuropsychol Soc. 2002; 8: 448-460.
5. Stern Y. Cognitive reserve in ageing and Alzheimer's disease. Lancet Neurol. 2012; 11: 1006-1012.
6. Kempermann G, Fabel K, Ehninger D, Babu H, Leal-Galicia P, Garthe A, et al. Why and how physical activity promotes experience-induced brain plasticity. Front Neurosci. 2010; 4: 189.
7. Dewey CW, Davies ES, Xie H, Wakshlag JJ. Canine cognitive dysfunction: Pathophysiology, diagnosis, and treatment. Vet Clin Small Anim Pract. 2019; 49: 477-499.
8. Prpar Mihevc S, Majdič G. Canine cognitive dysfunction and Alzheimer's disease-Two facets of the same disease? Front Neurosci. 2019; 13: 604.
9. Ruple A, MacLean E, Snyder-Mackler N, Creevy KE, Promislow D. Dog models of aging. Annu Rev Anim Biosci. 2022; 10: 419-439.
10. Szabó D, Gee NR, Miklósi Á. Natural or pathologic? Discrepancies in the study of behavioral and cognitive signs in aging family dogs. J Vet Behav. 2016; 11: 86-98.
11. Freedman AH, Gronau I, Schweizer RM, Ortega-Del Vecchyo D, Han E, Silva PM, et al. Genome sequencing highlights the dynamic early history of dogs. PLoS Genet. 2014; 10: e1004016.
12. Frantz LA, Mullin VE, Pionnier-Capitan M, Lebrasseur O, Ollivier M, Perri A, et al. Genomic and archaeological evidence suggest a dual origin of domestic dogs. Science. 2016; 352: 1228-1231.
13. Pendleton AL, Shen F, Taravella AM, Emery S, Veeramah KR, Boyko AR, et al. Comparison of village dog and wolf genomes highlights the role of the neural crest in dog domestication. BMC Biol. 2018; 16: 64.
14. Range F, Marshall-Pescini S. Comparing wolves and dogs: Current status and implications for human 'self-domestication'. Trends Cogn Sci. 2022; 26: 337-349.
15. Hecht EE, Barton SA, Flattery CN, Meza AM. The evolutionary neuroscience of domestication. Trends Cogn Sci. 2023; 27: 553-567.
16. Jensen P. Behavior genetics and the domestication of animals. Annu Rev Anim Biosci. 2014; 2: 85-104.
17. Kubinyi E. Biologia futura: Four questions about ageing and the future of relevant animal models. Biol Futur. 2022; 73: 385-391.
18. Castro-Fuentes R, Socas-Pérez R. Unveiling the significance of dog domestication in cognitive dysfunction: Are wolves protected? Open Vet J. 2025; 15: 6126-6145.
19. Stern Y, Albert M, Barnes CA, Cabeza R, Pascual-Leone A, Rapp PR. A framework for concepts of reserve and resilience in aging. Neurobiol Aging. 2023; 124: 100-103.
20. Van Praag H, Kempermann G, Gage FH. Neural consequences of enviromental enrichment. Nat Rev Neurosci. 2000; 1: 191-198.
21. Nithianantharajah J, Hannan AJ. Enriched environments, experience-dependent plasticity and disorders of the nervous system. Nat Rev Neurosci. 2006; 7: 697-709.
22. Kempermann G. Environmental enrichment, new neurons and the neurobiology of individuality. Nat Rev Neurosci. 2019; 20: 235-245.
23. Erickson KI, Voss MW, Prakash RS, Basak C, Szabo A, Chaddock L, et al. Exercise training increases size of hippocampus and improves memory. Proc Natl Acad Sci. 2011; 108: 3017-3022.

24. Van Bourg J, Young JK, Alkhalifah R, Brummer S, Johansson E, Morton J, et al. Cognitive flexibility and aging in coyotes (*Canis latrans*). J Comp Psychol. 2022; 136: 54-67.
25. Li Y, Vonholdt BM, Reynolds A, Boyko AR, Wayne RK, Wu DD, et al. Artificial selection on brain-expressed genes during the domestication of dog. Mol Biol Evol. 2013; 30: 1867-1876.
26. Wang GD, Zhai W, Yang HC, Fan RX, Cao X, Zhong L, et al. The genomics of selection in dogs and the parallel evolution between dogs and humans. Nat Commun. 2013; 4: 1860.
27. Albert FW, Somel M, Carneiro M, Aximu-Petri A, Halbwax M, Thalmann O, et al. A comparison of brain gene expression levels in domesticated and wild animals. PLoS Genet. 2012; 8: e1002962.
28. Sundman AS, Pértille F, Lehmann Coutinho L, Jazin E, Guerrero-Bosagna C, Jensen P. DNA methylation in canine brains is related to domestication and dog-breed formation. PLoS One. 2020; 15: e0240787.
29. Glazko VI, Zybaylov BL, Kosovsky YG, Glazko GV, Glazko TT. Domestication and microbiome. Holocene. 2021; 31: 1635-1645.
30. Gluckman P, Hanson M. Mismatch: Why our world no longer fits our bodies. Oxford, UK: Oxford University Press; 2006.
31. Nesse RM, Williams GC. Why we get sick: The new science of Darwinian medicine. New York, NY: Times Books; 1994.
32. Quadalti C. One health, two species: Linking domestication to cognitive aging in dogs and humans. Animals. 2025; 15: 2851.
33. Fast R, Schütt T, Toft N, Møller A, Berendt M. An observational study with long-term follow-up of canine cognitive dysfunction: Clinical characteristics, survival, and risk factors. J Vet Intern Med. 2013; 27: 822-829.
34. Sung J, Chae Y, Yun T, Koo Y, Lee D, Kim H, et al. Use of neurofilament light chain to identify structural brain diseases in dogs. J Vet Intern Med. 2024; 38: 2196-2203.