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Review in Depth

Bridging the Gap: A Geroscience Primer for Neuroscientists With Potential Collaborative Applications

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Abstract

While neurodegenerative diseases can strike at any age, the majority of afflicted individuals are diagnosed at older ages. Due to the important impact of age in disease diagnosis, the field of neuroscience could greatly benefit from the many of the theories and ideas from the biology of aging—now commonly referred as geroscience. As discussed in our complementary perspective on the topic, there is often a "silo-ing" between geroscientists who work on understanding the mechanisms underlying aging and neuroscientists who are studying neurodegenerative diseases. While there have been some strong collaborations between the biology of aging and neuroscientists, there is still great potential for enhanced collaborative effort between the 2 fields. To this end, here, we review the state of the geroscience field, discuss how neuroscience could benefit from thinking from a geroscience perspective, and close with a brief discussion on some of the "missing links" between geroscience and neuroscience and how to remedy them. Notably, we have a corresponding, concurrent review from the neuroscience perspective. Our overall goal is to "bridge the gap" between geroscience and neuroscience such that more efficient, reproducible research with translational potential can be conducted.

Keywords: Cognitive decline, Frailty, Life-span–extending interventions, Resilience

Geroscience, Neuroscience, and the Hallmarks of Aging

As human longevity increases across the world, both in developed and developing countries, biomedical research has been forced to shift towards a greater understanding of age-related morbidities and causes of mortality (1). However, this research has disproportionately concentrated on specific diseases rather than the underlying aging process implicated across a host of pathologies. To this end, the field of "geroscience" has been proposed as a mediator between understanding the underlying molecular mechanisms of aging and developing human interventions. Over the last decade, the biology of aging field has been quick to incorporate the term geroscience and its underlying principles into their research and communication, even going so far as to rebrand the Journal of the American Aging Association to GeroScience in 2016. Geroscience encompasses aging at multiple physiological levels in both animals and humans,

from organelles to the entire organism. Furthermore, it incorporates studies at the population level, as well as translational interventions that can improve health and longevity in humans. As all age-related pathologies are influenced by the basic biology aging, they therefore can fall under the category of geroscience.

Geroscience is focused on understanding the basic biology of aging and its translational potential to humans. One of the most cited "foci" of geroscience is the "Hallmarks of aging" (2). These 9 molecular categories are broadly thought to be the overarching mechanisms that regulate aging and longevity, and these physiological processes potentially interact with each other and the environment to create individual variation in the aging phenotype. These 9 "hallmarks" include changes at various levels of organismal organization from molecules to whole organism changes. These hallmarks include: genomic instability, telomere attrition, epigenetic alterations, loss of proteostasis, mitochondrial dysfunction, stem cell exhaustion, cellular senescence, altered cellular communication, and dysregulated nutrient signaling (2). Numerous papers look at each factor individually, with more recent work investigating the parameters more holistically as well as their interactions. However, there are still large gaps in our knowledge about many of the direct effects and interactions of these hallmarks. In addition, there are still arguments in the field regarding if these 9 fully encompass all the mechanisms of aging, and the actual degree to which the hallmarks of aging are causative is still debatable (3).

These hallmarks of aging are pervasive in the geroscience field. While they have gained some traction among neuroscientists, the use of geroscience techniques and concepts has the potential to benefit neuroscientists in understanding age-related cognitive decline and neurodegeneration (4). Geroscience encompasses all biology of aging and the pathologies that it causes, this includes the majority of neurodegenerative disorders, and impaired brain function significantly increases with advancing age. Therefore, as we have relayed in our neuroscience perspective (5), the 2 fields of geroscience and neuroscience would greatly benefit from an increase in synergistic investigations on topics related to both fields. To do so, it is necessary that geroscientists have at least a basic understanding of the neurological changes that occur with age, and neuroscientists must undergo training in some of the fundamentals of geroscience. While the purpose of this review is not to define and explain the hallmarks of aging, there are many facets of the hallmarks that provide strong potential for collaborations between neuroscientists and geroscientists, and we believe areas of interest we discuss below are nicely intertwined with the hallmarks of aging (Figure 1). In addition, we wanted to bring to attention the idea of the hallmarks of aging, as many neuroscientists may work in these areas but not realize the conceptual framework from geroscience.

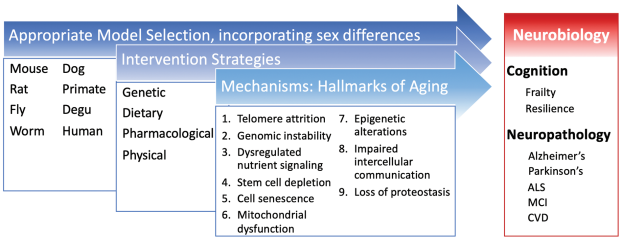

Figure 1. Framework of how geroscience experimental design and execution can be applied to the neurosciences. The ideal model organism for the question is chosen, and interventions are applied. Changes in the hallmarks of aging lead to improvements in cognition and decreases in neuropathology. ALS = amyotrophic lateral sclerosis; CVD = cerebrovascular disease; MCI = mild cognitive impairment.

Here, we give an overview of the field of geroscience and how these ideologies, methods, and applications may be of use to the neuroscience field. This is not meant to be an exhaustive review, nor do we discount the relationships that already exist between geroscientists and neuroscientists. Many advances in our understanding of neurodegenerative diseases have been championed by geroscientists. However, we hope to bring to light issues lacking exposure to neuroscientists, especially early career researchers. Our complimentary review takes the neuroscience approach to inform geroscientists of many of the neuroscience methods and applications that are not utilized highly in the biology of aging, see (6). Overall, our goal is to bridge the gap between geroscience and neuroscience to develop a more integrated approach to the study of aging, neurodegeneration, and cognitive decline.

Physical and Cognitive Frailty: Two Ends of the Same Beast?

Physical frailty in humans usually refers to a significant reduction in physical function and performance without any indicators of cognitive function (7). Physical frailty was clinically defined 2 decades ago by at least 2 different groups: a frailty scale based on activities of daily life and some clinical diagnoses by Rockwood et al. (8) and the more commonly used Fried scale (9). Geroscience research has devoted numerous resources to developing models of frailty in laboratory organisms that are based on what was originally seen in human populations. Thus, frailty has been reverse translated from humans to rodents with the end goal of translating experimental results back to humans. The ability to manipulate laboratory animals in multiple realms, combined with their short life span, enables us to develop markers of future frailty, as well as interventions to improve frailty on a significantly shorter timeline than clinical research alone.

Rodents are a potentially strong model of human frailty, as frailty in mice and humans measure equivalent types of physical function. Moreover, the relative frequency of frailty may be similar in humans and mice, though this has not been thoroughly investigated (10). The first large-scale frailty index in rodents was developed by the Howlett lab almost a decade ago; this scale, measuring 31 health-related parameters, involved several measurements that were quite invasive (11). As such, the frailty scale was later refined a couple years later to be less time consuming and stressful for the animal (12). This is more comparable to humans where frailty scoring involves fairly minimal effort by both the patient and doctor (8,9). Frailty scores have been calculated in dozens of aging mouse studies and have recently been used to determine if factors in the frailty score could be predictive of death of individual animals (13). A similar frailty index has been developed for rats (14); however, it has not been adapted to the degree seen in mice.

While frailty indices are important in aging research, they often fail to address the cognitive aspect that is often associated with frailty. We must note that some measures of human physical frailty include activities of daily living which do have a cognitive component, but it is often still the physical functions that are more closely analyzed. In humans, cognitive changes have been analyzed separately from physical frailty; however, more recently there has been a push to combine the 2 into a more integrated model termed "cognitive frailty" (15). Cognitive frailty refers to a significant decline in cognitive function, outside of clinical dementias; however, cognitive frailty could be an early indicator of future dementia development. In addition, the more recent definitions of cognitive frailty also include at least some reduction in physical function with cognitive

decline. Thus, there has been a significant push to better combine the physical and cognitive deficits that are seen with age, as it is likely that as physical frailty increases, so does cognitive frailty and vice versa. Therefore, geroscience tools may help us uncover the molecular changes that may synergistically lead to both cognitive and physical frailty. While cognitive frailty has been infrequently evaluated in geroscience research, the changes that occur in physical and cognitive parameters with age suggest that cognitive frailty does occur in laboratory models, specifically rodents, driven by strong declines in behavior and cognitive function in older ages (16–19).

The opposite of frailty is often referred to as "resilience," though declines in resilience occur significantly before frailty manifests. However, similar to frailty, resilience in geroscience is different than cognitive resilience. In the biology of aging field, resilience refers to the ability of an individual to "bounce back" from some physical stressor. This includes, but is not limited to, injuries, infections, and environmental stressors. A decline in physical resilience is seen significantly earlier than the onset of frailty, and thus, many older adults may have a decreased resilience but are not frail (20). While the concept of physical resilience has been around for years, actual experimental research on the factors and interventions that lead to improved or decreased resilience are still scarce (21). In the neurosciences, cognitive resilience refers to the ability of an individual to withstand insult from some mental stressor. These are often thought of as environmental factors that can lead to significant mental pressure, and resilience is the ability to combat these mental pressures. For example, individuals dealing with grief, lower socioeconomic status, or abuse will all be under mental strain, and those that are able to healthily deal with these stressors are thought to have strong cognitive resilience. In addition, cognitive resilience may also be seen in individuals that show pathological biomarkers of neurocognitive disorders, like plaques and tangles in Alzheimer's disease (AD), but fail to show any symptoms or negative effects of the pathology (eg, Negash et al. (22)). While both physical and cognitive resilience measure the ability of an individual to cope with a stressor, these 2 are most often investigated individually, even though it is conceivable that many physical stressors would have significant mental impacts. Geroscience studies of resilience frequently fail to consider the cognitive aspect, and in our view, this is detrimental to the aging field. Similarly, cognitive neuroscientists do not frequently assess physical peripheral health and its role on cognitive outcomes in aged animal models.

While it appears that physical and cognitive declines are correlated with each other (eg, Black and Rush (23) and Ishizaki et al. (24)), work in both animal models and humans has only just begun to look at actual relationships between physical and cognitive frailty and much less so physical and cognitive resilience. In addition, while physical frailty increases the risk for cognitive decline (25), cognitive decline may also precede physical disability (26). Thus, there may be individual variation in the onset of cognitive frailty as compared to physical frailty that could be well addressed tighter integration of geroscience and neuroscience. Neuroscientists may want to consider these declines in physical function when measuring any age-related cognitive decline and neurodegenerative disorders, and geroscientists likely need to make a stronger push to measure more direct values of cognition in addition to physical frailty.

Healthspan, Life Span, and Life-Span–Extending Interventions

For decades, life span/longevity, or the length of time an individual lived, was the main "outcome" of research on the biology of aging. Life span is very easy to measure in the laboratory, and while much more difficult, it is also possible in the wild. A primary assumption of these longevity studies was that there was a direct correlation between the longevity of an individual and their health; therefore, if researchers could develop interventions that increased life span, they would by default also improve health. However, more recent research has suggested that life span and health are not necessarily correlated (27,28), leading to the development of stronger research in the area of "healthspan." While life span refers to the number of years (or day/months) an individual lives, healthspan refers to the period of time in which that individual remains "healthy." Not surprisingly, healthspan is much harder to define, as there are no individual measures that would deem an individual healthy one day and unhealthy the next. Frailty itself has been described as a potential biomarker of healthspan (29). However, healthspan potentially ends before the onset of frailty, as resilience declines well before frailty starts to increase, but to test this, more discrete endpoints of resilience and healthspan must be determined. To this end, geroscience researchers are now putting increased effort into defining healthspan, how it relates to life span, and developing interventions that increase life span that also make a discernable difference on health. An intervention capable of increasing longevity, while simultaneously improving health, would be of great importance to neuroscientists, as such an intervention may demonstrate potential for preventing age-related declines in cognitive function as well (Figure 1). In the next section, we review 4 "modes" of life-span–extending interventions and how they may help alleviate cognitive declines and neurodegeneration.

Dietary Interventions

Over one hundred years ago, fruit flies that were raised on a low-nutrient diet were shown to live longer than those on a more "standard" diet (30), and less than 2 decades later, rats that were calorically restricted were found to also live longer than those fed ad libitum (31). This might be considered the beginning of the "biology of aging" field, and from this point forward caloric restriction (CR) has been the most robust and reproducible method to extend life span across organisms. Simply defined, CR consists of a reduction in calories of 10%–40% compared to animals fed ad libitum diets, and CR has been shown to increase life span in numerous different invertebrate and vertebrate species (32). CR has since been extrapolated to other forms of dietary restriction, most notably protein restriction and different fasting regimes. Protein restriction has been shown to increase life span and improve health, both with total protein reduction or specific amino acids (33), and a high-fat/ketogenic diet, that is simultaneously low in protein and carbohydrates, has also been shown to improve median life span and health (both physical and cognitive) in mice (34,35) as well as improved cognition in rats (36). In addition, multiple forms of fasting have been shown to improve health with potential effects on longevity (37); these range from fasting for set periods of time within a day to every-other-day fasting. While physical health parameters have been measured most frequently, CR in rodent models also improves cognition both in naturally aging animals and models of AD (eg, Halagappa et al. (38) and Kuhla et al. (39)). More recently, these interventions have been applied to human populations where both mild CR and time-restricted feeding appear to improve markers of health (reviewed in Dorling et al. (40)). Moreover, mild CR in normal weight adults may have mild effects on improving working memory (41), though other studies suggest little effect on cognition with short-term CR (42). However, the effects of most dietary interventions have not

been well examined in older populations, yet there is evidence that short-term CR, even at older ages, may improve cognitive function (43). Overall, there is an unfortunate dearth of long-term studies of CR in middle-aged and older adults that include cognitive outcomes, despite the enhanced potential to provide the most benefit in this population.

Physical Interventions

Extensive research both in animal models and humans supports the benefits of exercise on health. Interestingly, exercise, while having large benefits on healthspan, does not appear to significantly influence life span in mice (44) or rats (45). However, exercise interventions do appear to improve both physical and cognitive health. For example, aged mice that are given the opportunity to exercise demonstrate enhanced learning ability and spatial memory on the Morris Water Maze (MWM) (46). Additionally, the majority of studies that have looked at the impact of exercise on mouse models of neurodegenerative diseases (eg, AD and Parkinson's disease) have found significant cognitive benefits of exercise (eg, Nichol et al. (47), Zhang et al. (48), and Zhou et al. (49)). Moreover, blood taken from exercised animals has rejuvenating properties, as transfer of blood of old exercised mice into old sedentary mice improves the health of the sedentary mice (50). Surprisingly, these health benefits were the strongest in relation to improved cognition of the sedentary mice. Thus, exercise causes biochemical changes that have the potential to directly affect brain chemistry. Work in humans also suggests that individuals who exercise regularly are at decreased risk for AD, and exercise may improve or delay declines in cognition in those diagnosed with AD (reviewed in Cass (51)). In addition, exercise itself has been shown to improve cognitive function in healthy adults (52); however, the majority of exercise and cognition studies are focused on younger adults, and the long-term effects of exercise, aging, and cognition are still unknown.

Pharmacological Interventions

One of the most promising routes for life-span- and healthspan-extending interventions in humans is with the supplementation of either natural or synthetic pharmacological compounds. Dozens of drugs have been supplemented in the diets of worms and fruit flies to extend their life span (53), and many of these have moved into trials in mammalian species. Almost 20 years ago, the National Institute on Aging started the Interventions Testing Program (ITP) with the goal of developing pharmacological interventions that would increase longevity and improve health in mice (54), with the first completed study in 2008 (55). Perhaps not unexpectedly, the majority of compounds tested in the ITP thus far have failed to show significant life-span extension, and for those that do, the majority only work in males (56). Interestingly, for those drugs that do confer increased life span, the majority also improved physical performance throughout the life span (29), with preliminary data suggesting cognitive benefits. For example, rapamycin, arguably the most robust pharmacological intervention to increase life span in both sexes, has been shown to improve learning in the MWM, independent of swimming speed, as well as improve other markers of brain function (57). However, with the exception of rapamycin, most pharmacological interventions have not been studied deeply in relation to effects of cognitive declines with age. We believe that this is a greatly untapped area for geroscientists and neuroscientists to combine research to determine potential drug interventions that improve both physical and cognitive function with age.

Genetic Interventions

Discovering genes that can extend life span have been of great interest to geroscientists for over 30 years. In 1989, the first gene was discovered, that, when mutated, could lead to increased life span in worms, aptly named *age-1* (58). Since then, over 100 genes have been uncovered that when either knocked down or overexpressed lead to increased longevity in worms and flies, and dozens have been discovered in mice (59). Arguably, the most robust genetic intervention to increase health and longevity in mammalian systems is disruption of the growth hormone (GH) axis (60). Down regulation of GH, leading to increased lifespan was first discovered over two decades ago in the Ames dwarf mouse. Since then, multiple different mutations that lead to downregulation of GH have been discovered that also cause a corresponding increase in life span. Mice with dysregulated GH are much smaller in size than their wild-type littermates, and unexpectedly, they appear to have much higher adiposity levels, both in white and brown adipose tissue (61). In addition to being longer lived, GH mutant mice have improved physical function throughout their lives, suggesting GH downregulation improves health in conjunction with longevity.

The effect of GH on cognitive function with age is still a disputed subject (62). Early developmental studies suggested that downregulation of GH leads to cognitive impairments and disabilities; however, work in mouse models suggests that GH mutant mice have delayed cognitive aging as measured by the MWM (63). Notably, Laron syndrome in humans leads to dysregulated GH and results in many of the same phenotypes observed in mice including small stature and high adiposity. Like the mouse models, these individuals appear to be protected from many age-related diseases, as well as having better cognitive performance (64). These data suggest that downregulation of GH in humans might be a potential healthspan/life-span extender. While the translatability of genetic interventions to human populations is by far the furthest away from clinical use (relative to dietary, exercise, or pharmacological interventions), the discovery of specific genes capable of increasing life span or healthspan may provide us with specific pathways to utilize as targets. As an example, a drug that can knockdown GH signaling may prove beneficial to both life- and healthspan. However, genetic interventions may have temporal effects, such as a more robust response during development, which are more difficult to translate out of the laboratory.

GH has predominately been shown to work by activating insulin-like growth factor-1 (IGF-I) in the liver, and therefore, it was assumed that similar to knockdown of GH, knockdown of IGF-I would also lead to increased life span and improved health. However, results have been conflicting, with some studies suggesting decreases in IGF-I do lead to increased life span (65) while others found no effect (66). More recent research suggests that modulation of IGF-I may work in a sex-specific manner with female mice showing a greater benefit (67). With regards to cognition, the effects of IGF-I have also been mixed. Lower IGF-I protects against age-related brain pathologies like AD, while also potentially causing other cognitive deficits (68). In addition, male mice with higher IGF-I in the brain show mild behavioral improvements compared to IGF-I knockdowns, but overall cognitive decline with age remains the same (69). Combined, the roles of GH and IGF-I on age-related cognitive decline are still not fully known.

Collectively, we believe that the use of geroscience supported life-span- and healthspan-extending interventions have the potential to make large improvements in age-related cognitive decline.

It should be noted that the timing of each of these interventions can have significant impacts on the effects of the intervention. Many interventions may need to be completed longer term than is feasible in human studies to reap the full benefits that are seen in animal models, and some interventions may have negative effects if continued too long. However, overall, the majority of interventions are completed by geroscientists focusing more on physical function, and these have not been fully leveraged by neuroscientists. The integration of geroscience and neuroscience will enable us to better determine those interventions that have the strongest promise to translate into human populations, and we look forward to seeing these collaborations on interventions coming to fruition.

Sex Differences as a Major Geroscience Factor

In humans, females live longer than males in every population across the globe, and females die at lower rates of almost all age-related diseases (70) with the exception of AD and other dementias (71). It should be noted though that females will spend a larger proportion of their lives in a lower health or frail state (72); thus, females have a longer life span but shorter healthspan on average than males. This is an important factor in both geroscience and neuroscience as it suggests the underlying physiology is different between the sexes, leading to differences in health and longevity. A similar longevity trend is seen in animals, where in both captive and wild populations, females tend to be longer lived (73,74). Interestingly, in rodent models, which are predominately used for both geroscience and neuroscience studies, sex effects are more minor, with the longer-lived sex appearing to be affected by genetic background and laboratory environment (73). In addition, female rodents do no undergo a traditional menopause, and they can continue to cycle much longer in their life than seen in humans (18), though this appears to be species and strain specific (75,76). Thus, overall, rodents are not necessarily ideal models to study sex differences in humans, and neuroscientists and geroscientists may need to look outside rodents for more ideal models of sex differences in aging.

For decades, the majority of geroscience (and neuroscience for that matter) research was completed in male rodents, due to scientists' lack of incentive to address the hormonal fluctuations that occur in female animals, under the assumption that males and females would respond similarly to the aging process, including interventions to improve health and longevity. However, as stated above, sex is obviously an important factor in the regulation of aging, health, and life span. Moreover, there is evidence that male rodents actually demonstrate larger variations in hormones following stressful events than their female counterparts (eg, Radley et al. (77)). Yet, it is only since 2015 that the National Institutes of Health has required the use of both sexes in laboratory research, much later than was required in human research.

The majority of pharmacological interventions that improve life span in mice only do so in males (56), suggesting that the physiological processes that drive aging are, to a large extent, sex specific. As female humans are at a higher risk of AD as well as some other dementias (78,79), the use of both sexes in neuroscience studies is imperative, including in the development of neurodegenerative models that reflect these sex differences in age-related cognitive decline. However, too many studies in both geroscience and neuroscience currently rely entirely on one sex.

Animal Models of Geroscience for Neuroscience

Invertebrates

One could argue that invertebrate laboratory models, most often *Caenorhabditis elegans* and *Drosophila melanogaster*, are still the cornerstone of geroscience research. The costs are low, life spans are short, and health measurements are possible in both species. Therefore, it often makes sense to begin the discovery of novel interventions in these 2 species. In addition, the molecular tools available make invertebrate models ideal for dissecting the intricate genetic, protein, and metabolic mechanisms that affect aging and longevity. And while not nearly as sophisticated as seen in mammalian species, cognitive function can be assayed in worms and flies in the laboratory, though more so in the latter. We know cognitive function declines with age in flies (80), and transgenic fly AD models have become highly studied in the field as insertion of human transgenes in the fly leads to neurodegeneration and cognitive impairment (81). Similarly, AD transgenes in worms have become a model of protein aggregation, which is a defining factor of plaques and tangles, allowing researchers to understand the exact molecular mechanisms that lead to aggregation and develop novel interventions to prevent or reverse it (82). While some neurobiology of aging studies use invertebrate models, they are significantly fewer. However, we believe that the adoption of invertebrates may allow neuroscientists to more quickly develop hypotheses and interventions that can then be tested in rodent models. In addition, using the molecular tools available in invertebrates may allow neuroscientists to more quickly understand molecular mechanisms of neurodegeneration, thus again jumpstarting potential interventions with translatability.

Rodents

In both geroscience and neuroscience, not surprisingly, rodents are the most common mammalian models used in the laboratory. However, geroscience has traditionally utilized mice more frequently than rats, while neuroscientists have embraced the rat model to a higher degree. Mice are less expensive to rear which makes them more cost-effective for geroscientists conducting years-long life-span experiments. However, there has been a push more recently to use the rat in geroscience research, due to the potential higher translatability and more easily measured cognitive changes that occur in the animals (83). In addition, the costs of aging rodents have become less of an issue as the National Institute on Aging now allows the investigators to receive already aged mice and rats; though we must note, the genetic backgrounds and number of animals researchers are allowed to receive are limited. In addition, many geroscience studies are interested in the long-term changes that occur under different interventions as described above, so rodents must be aged in their own laboratory at great expense. As neurodegeneration is most often age-related, the use of "old" rodent models is necessary to really understand the nuances of brain aging, yet many studies of neurodegeneration are done on disease models that develop pathologies at younger ages (described more below). And for those neuroscience laboratories that do study natural age-related cognitive decline, there is often a lack of communication with geroscientists. If the 2 fields could work together on the same individual animals, we could reduce animal costs and develop more integrated theories of cognition and aging.

While age-related cognitive decline is significant in both rats and mice, they do not naturally develop most of the age-related neuropathologies seen in humans, especially AD. Dozens of different

models of AD exist between mice and rats combined, yet they are all genetic modifications that do not *completely* recapitulate the diseases present in humans. For example, rodent models of AD develop pathologies and cognitive deficits at relatively young age, and just small shifts in the environment, including adding extra behavioral enrichment items to the animals, can remove many of the AD phenotypes (eg, Griñán-Ferré et al. (84) and Herring et al. (85)). Thus, they fail to mimic the actual human condition, though some rat models are getting closer (eg, Cohen et al. (86)). To this end, geroscientists have been highly involved with the development of new models of neurodegeneration, the most promising rodent of which is the degu. The degu, *Octodon degus*, is a small rodent from South America that naturally develops many age-related morbidities (87), including many of the protein pathologies and corresponding cognitive declines seen in naturally occurring AD (88), though more studies have not been able to replicate this development of brain pathologies (89,90). Thus, the use of the degu as a model of age-related neurodegenerative disease is still debatable. Overall, we are still lacking a laboratory rodent model that naturally replicates the neuropathologies seen in human age-related cognitive disorders.

Nonhuman Primates

The use of nonhuman primates in the geroscience field has grown over recent years, as laboratory rodent models are unable to accurately mimic many human age-related conditions, and the rhesus macaque has been the primary laboratory primate model to study aging and longevity. Living up to 40 years, macaques show many of the same age-related deficits as humans including type II diabetes and cognitive dysfunction (91). In addition, dietary interventions, such as CR, performed in laboratory macaques, demonstrate the potential of these interventions to improve health in larger mammalian species (92).

The macaque has been the workhorse of the primate aging field, but recently other primates have been proposed as more "ideal" models. The long life span of the macaque makes the study of interventions and longevity lengthy and extremely costly. Moreover, the large size of the animals makes the ability to rear large populations difficult in limited space. These issues have led to the common marmoset, *Callithrix jacchus*, being put forward as a translational model of human aging. Weighing less than 1 kg with a life span of 15–20 years, the marmoset is much easier to raise in captivity. Though it is not as phylogenetically related to humans as the macaque, the marmoset does develop many age-related pathologies, such as cancer, diabetes, and amyloidosis similar to humans (93), as well as showing cognitive decline with age (94).

While there are researchers that combine neuroscience and geroscience in primate models, many studies in the 2 fields work independently. The geroscientists tend to focus on the physical and molecular decline, with only rudimentary cognitive appreciation, while neuroscientists frequently look specifically at neck up, not the entire organism. Overall, there is great potential for collaborations between geroscientists and neuroscientists to develop primate models that mimic the human aging condition.

Nonmodel Species

While the majority of geroscience research is focused on laboratory model organisms, there are an increasing number of researchers taking a comparative approach, as well as trying to develop nonmodel species for aging research (95). While rodents are able to teach us about the individual genes and interventions that might prolong life, they do not naturally develop many of the same age-related pathologies as humans. With the exception of some cancers, most age-related disease models in mice are either genetically or pharmacologically induced. In addition, laboratory models are kept in constant environments that do not represent the diverse environmental conditions that humans are exposed to. Therefore, there is a need in the field to develop nonmodel species that naturally age in a pattern more similar to humans. However, for these nonmodel organisms, brain aging is often only used in reference to the ability of the organism to be a model for AD, and little thought is given to other age-related neurocognitive disorders. To this end, melding the geroscience comparative approach with a more full-scale repertoire of age-related neurodegenerative conditions has the potential to make great strides in the translatability of both fields.

For example, work in the companion dog has recently shown that dogs die of many of the same causes of death as humans, with the exception of cardiovascular disease (96), and 25 years ago the dog was put forward as a model of AD (97). Not unexpectedly, cognition declines with age in the dog (98), and dogs also spontaneously develop canine cognitive dysfunction with age. This dementia-like phenotype has several pathological changes similar to AD (99), but it is still not an exact representation of the human condition. As veterinarian researchers have been examining aging canines for years, great potential exists for fostering collaborations between veterinary medicine, geroscience, and neuroscience to understand peripheral and brain aging in an enriched canine model that has a profound capacity for human translation.

Conclusions

Overall, geroscience encompasses the overall study of the biology of aging with a focus on developing translational interventions to delay or reduce age-related morbidities and mortalities. We believe that integrating geroscience thinking into the neurosciences has the potential to allow rapid research development within both fields. However, the level of interaction between geroscientists and neuroscientists has been less than ideally possible, as we discussed in our perspective (5). Even for those in the geroscience field who work on brain aging, they do not communicate extensively with classically trained neuroscientists, as we present in our neuroscience primer for geroscientists (6). This leaves many geroscientists unable to utilize the most up-to-date methods in neuroscience, especially with regards to the measurement of cognitive impairment in model organisms and many imaging techniques (see Hernandez et al. (6)).

In summation, we believe that enhanced collaborations between geroscience and neuroscience are necessary to pin down the molecular mechanisms and potential interventions to improve age-related cognitive decline and neurodegenerative diseases. In addition, these interactions have the potential to more rapidly discover, test, and translate interventions into the human population. We are excited to see these collaborations fostered, and their ensuing research results, develop over the next decade.

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Conflict of Interest

None declared.

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Author Contributions

All authors contributed to the manuscript conceptualization. J.M.H. wrote the first draft of the manuscript with input from all authors. J.M.H. and A.R.H. created the figure, and all authors approved the final manuscript.

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