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Perspective

Reuniting the Body "Neck Up and Neck Down" to Understand Cognitive Aging: The Nexus of Geroscience and Neuroscience

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The purpose of this *Perspective* is to propose a new, collaborative paradigm to study cognitive aging. The field of cognitive aging from the *neuroscience* perspective has focused on studying cognition over the life span from the "neck up," while fields studying the biology of aging/age-related diseases, known collectively as *geroscience*, have focused from the "neck down." However, it is abundantly clear that there is no discrete boundary at which the body ages independently of the brain, and the existing division between neuroscience and geroscience has led to an incomplete picture of the aging process. Processes affecting aging in one area often have profound effects in another, even when the timescales at which different organ systems age do not align perfectly. Thus, understanding the aging process by "reuniting the body" is an innovative approach and a new direction for both fields to conduct relevant research and translation toward improving the cognitive and physical health of older individuals.

Herein we discuss how this dissection does a disservice to both fields and how a merger between the two would powerfully enhance scientific knowledge to the benefit of the larger field of biomedical research (see Figure 1). We first address the dichotomy of individualized meetings and the reporting and publishing of data that maintains a physical separation preventing our sharing of scientific information and address the need for creating funding opportunities to meld these 2 fields. We then highlight areas of study where researchers are addressing this intersection to provide successful examples for moving forward. We conclude with a brief consideration of the historical usefulness of preclinical models that have dominated each of these fields to address cognitive aging.

Finally, this perspective will set the stage for 2 additional papers, one each from neuroscience and geroscience thought leaders. The goal of these 2 "primer" papers is to provide an understanding of essential knowledge

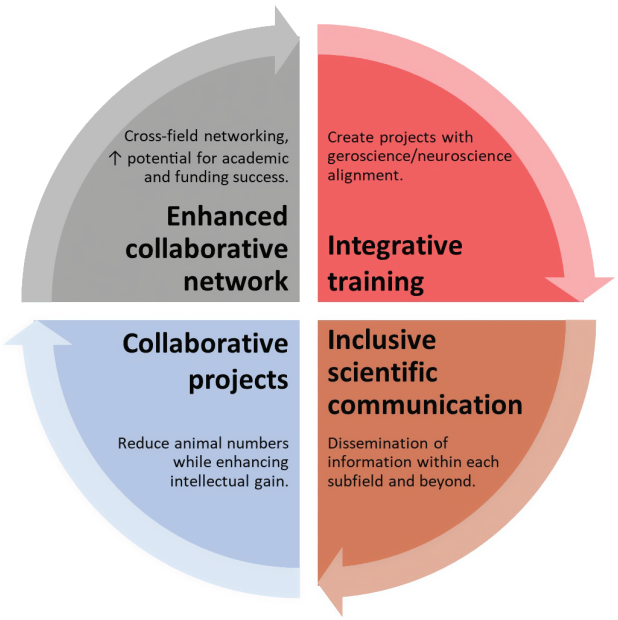

Figure 1. Proposed mechanisms through which collaborative efforts between geroscientists and neuroscientists will continue to propagate and enhance scientific gain. Enhanced training at the more junior levels will help to quickly actualize these concepts. Propagation at any level of the diagram will continue to have profound effects on the other elements, ultimately benefitting both fields.

that explores theoretical, biological, and state-of-the-art outcome measurements in each field. Our goal is to forge a new integrated aging science that synergistically provides a pathway to mitigate age-related cognitive decline and that will enhance our ability to "reunite the body" in doing so.

Communication Opportunities and Scientific Funding

Historically, the dissection of studies focusing either above or below the neck was represented nationally by funding opportunities supported separately by the National Institute on Aging (NIA) divisions, by meetings attended and journals supported by researchers focusing on either area. The division created by separate academic meetings between the 2 fields may prevent the generation of a more collaborative environment for investigators and their trainees, creating an active "group think" and stymieing integration of research opportunities and funding. While specialty meetings are important for transmission of data and career development, individuals are often limited in the number of meetings they can attend annually and thus stick to meetings closely related to their own work. For individuals in the geroscience community, both the Gerontological Society of America (GSA) and American Aging Association (AGE) meetings are key conferences, whereas the annual Society for Neuroscience meeting attracts neuroscientists studying aging and age-related disease neurological states. Furthering this meeting-based division is the abundance of smaller, more targeted meetings including disease-specific meetings, such as the Conference on Alzheimer's Disease and Dementia and the Geroscience Summit, targeting neuroscientists and geroscientists, respectively. More recently, some larger entities are working to bridge this divide such as the Federation of American Societies for Experimental Biology (FASEB), representing more than 130 000 researchers from around the world, encompassing scientific societies that share a common vision for the advancement of research and education in biological and biomedical sciences. In 2016, AGE became a member and is currently advocating a specific biology of aging symposium featuring cognitive aging. In addition to traditional networking, an added benefit for a targeted cognitive aging symposium would be creating mentoring opportunities for junior faculty and upcoming trainees interested in embracing this new integrated scientific approach.

The outcomes of geroscience and neuroscience-focused studies often remain segregated in the dissemination of information as well, which can be seen through the journals where data are often published. Many geroscience studies tend to publish in Geroscience, Journals of Gerontology: Biological/Medical Sciences, and Aging Cell, while neuroscience-focused research is often targeted toward Neurobiology of Aging, Nature Neuroscience, Neuron, and Journal of Neuroscience. While it is sensible to target an audience most likely to benefit from one's work and maximizing field-specific recognition for career advancement, this strategy also limits the potential to influence fields even narrowly beyond the scope of your subdivision and impairs collaborative potential. Thus, special or joint issues that feature the intersection of these 2 fields, which are currently limited in number, represent advancement to bridge across these divides and bring together experts in these 2 fields.

Funding support for biomedical research within the United States is primarily through the National Institutes of Health (NIH). While both areas are broadly contained within the NIA, the NIA further subdivides into divisions with minimal overlap across fields. For example, the majority of primarily geroscience-focused applications are submitted through either the Division of Aging Biology or Division of Geriatrics and Clinical Gerontology. Conversely, applications focused on neuroscience outcomes are typically included within the Division of Neuroscience. While there are certainly exceptions, such as the Division of Behavioral and Social Research portfolio, this separation can hinder collaborative funding opportunities for individuals seeking to bridge the divide between peripheral and nervous system health. Importantly, the NIA has begun to take these important steps through efforts like the initiation of Successful Trajectories of Aging: Reserve and Resilience in RatS (STARRS). Future shared workshops and joint funding opportunities from other NIH institutes representing both Neuroscience and Geroscience (NIA, National Institute of Mental Health, National Institute of Alcohol Abuse and Alcoholism, National Institute on Drug Abuse) would help catalyze collaborations for research teams working on the interaction between the periphery and the central nervous system (CNS).

Theories and Definitions

Differences in aging theory, subfields of study, definitions, and common verbiage enhance the division between geroscience and neuroscience. In particular, vocabulary often used to refer to cognition, learning, and memory is inconsistent, despite the fact that cognitive outcomes are relevant for both fields. If dissimilar vernacular is used across the 2 fields, this disparity can lead to replication issues and misinterpretation. For example, within the neuroscience field, there has been an enhanced focus on defining "resilience" and "reserve," including a 3-year NIA-supported Collaboratory on Research Definitions with the goal of developing operational definitions for reserve and resiliency (1) and a whitepaper addressing this lack of consensus (2). Conversely, the geroscience field has long-established working definition of biological resilience: the capacity to respond or recover from insult (3,4).

Differences in vernacular likely stem from isolated subfields, including the division between neuroscience and geroscience. This

separation begins early within a trainee's career as graduate training often focuses on a specific subfield, which may bias individuals to view concepts in a specific way. For example, there are several schools of thought within neuroscience regarding learning and memory, ranging from theoretical and computational neuroscience to behavioral outcomes observable in a human population. Each of these subjects is often isolated from one another through specific programs like neuroengineering or psychology. These subdivisions are further separated from programs and curricula that focus on the biology of aging. Earlier exposure and cross talk across these fields would help to foster better, more robust scientific investigations.

Mechanisms of Interaction and Influence Between the Brain and the Periphery

While the focus of this perspective is shed light on how geroscientists and neuroscientists working together would better serve scientific advancement, that is not to say that there have not already been pioneers leading the way in this regard. The following section provides a nonexhaustive list of examples of research areas whereby our groups are studying the intersection of geroscience and neuroscience, and where we see existing gaps (see additional "primer" papers in each subject area for additional details).

Metabolism

Metabolic health is known to be a significant risk factor for several neurodegenerative disease states, but the mechanisms by which impaired peripheral metabolism hinders neuronal function are lacking. Furthermore, while there is a strong, reciprocal link between peripheral and CNS function, the degree to which strategies targeting metabolic health in late life can reverse cognitive decline is unknown. It is imperative that the bidirectional relationship between peripheral metabolic health and the CNS be investigated, as >25% of individuals in the United States over 65 have diabetes (5) and >36% are obese (6).

The profoundly high incidence of impaired metabolism in aged people may be due, in part, to the typical Western diet. While there is certainly evidence that dietary composition can influence both cognitive (7–9) and peripheral (10–12) health in aged individuals, how these factors influence one another requires further elucidation. In addition to investigating the effects of nontraditional diets, such as the Mediterranean and ketogenic diets, there is also great interest in altered patterns of consumption such as caloric restriction (CR) or time-restricted eating. Notably, CR has been broadly investigated in the longevity field (13). However, investigations into CR and longevity by investigators focused on the biology of aging do not frequently incorporate the potential outcomes on CNS function and cognition, even though we know CR influences CNS function through preservation of white matter (14), changing neurotransmitter receptor expression within the brain (15,16) and many other potential mechanisms (17). Moreover, the process of aging animals to investigate longevity and aging is lengthy and costly. Thus, there is great potential for synergistic investigations incorporating gero- and neuroscientists that would serve to reduce the number of animals required while still gaining maximal scientific progress.

While the multitude of benefits from exercising throughout the life span is widely accepted, the mechanism by which physical activity influences cognitive outcomes remains widely debated and reasonably unknown (18,19). This knowledge gap is perhaps due to the very separation of neuroscience and geroscience discussed within this article. Researchers within our group are working to bridge this divide.

Lastly, there is strong potential for the reverse situation, as the CNS greatly influences peripheral metabolic function through the neuroendocrine system (20). Given that neural circuitry directly influences peripheral metabolism (21,22), degradation or impairment to these systems may exert negative influence on peripheral metabolic functioning (23).

Gut–Brain Axis

Gut health can also profoundly affect cognitive aging, and alterations in brain health are often accompanied by impaired intestinal function. Several aspects of gut health are impaired with age. Firstly, gut dysbiosis, or an unfavorable perturbation in the diversity or density of intestinal microbial flora, is prevalent in aged populations (24,25). Altered gut microbiota have not only been linked to bowel diseases (26,27), but also to metabolic problems (eg, diabetes and obesity; 28), inflammation (29,30), musculoskeletal conditions (eg, osteoporosis; 31), and notably, neurodegenerative diseases (32–34). Microbiome ablation with antibiotics leads to impaired cognition in rodent studies (35,36), demonstrating a correlation between altered gut microbiota and cognitive outcomes (37). Secondly, intestinal permeability increases with several age-related factors, leading to a host of other physiological problems (38). Together, the altered gut microbiome and increased permeability may compound neurological and cognitive impairments through multisystem immune function impairment. Enhanced inflammation and peripheral immune activity may influence brain health through enhanced microglial activation, leading to Aβ aggregation.

It should not be overlooked that changes in activities of daily living are often altered in aged individuals, providing a diverse area of research that would benefit from cross talk among geroscientists and neuroscientists, as well as psychologists and health care workers. Aged individuals are not as active as younger adults, which has important implications for both brain and gut health (39–41). Additionally, older adults tend to eat a less diverse diet than younger adults (42), and are exposed to fewer new places, resulting in altered gut microbiome composition. Antibiotics are overprescribed in residential aged care facilities, further contributing to altered gut health, microbiome composition, and related physiological processes (43). As gut health is likely a modifiable factor mediating cognitive resilience, several potential mechanisms of the bidirectional interactions across the gut–brain axis warrant further investigation.

Perhaps the strongest link between physical and cognitive health in older adults is the correlation between cognitive and physical frailty (44). Physical frailty is not only one of the main predictors of dementia (45,46), cognitive frailty is a strong indicator of future functional disability (47) and it may be the result of altered gut health (48). Additionally, one of the earliest symptoms of Parkinson's disease, a disorder primarily affecting the CNS, is impaired gut health (49), and patients demonstrate specific alterations in gut microbiome (50).

Muscle–Brain Axis

Skeletal muscle has been proposed as a central regulator of organismal metabolism, communicating metabolic and proteostatic stress to distant tissues via secretion of circulating "myokines" (51). Multiple epidemiological studies suggest that skeletal muscle aging is a risk factor for the development of age-associated disease (51,52), including those of the CNS (53,54). Skeletal muscle

undergoes prominent remodeling during aging (55–57), and exercise powerfully opposes these local deleterious effects of aging, engaging metabolic (52,58) and proteostatic pathways to accommodate increased bioenergetic demands (59). Exercise also increases secretion of specific CNS-targeting myokines ("exerkines") into circulation, including brain-derived neurotrophic factor (60), irisin (61), and cathepsin B (62), which very likely contribute to the exercise-associated benefits on cognition (59). Indeed, shared circulation and plasma injection experiments demonstrate that circulating myokines can promote functional rejuvenation of the aging neurogenic niche (63,64). Consistent with this hypothesis, circulating blood factors in plasma from exercised aged mice are sufficient to transfer the effects of exercise on adult neurogenesis and cognition to sedentary aged mice (65). Furthermore, conditioned media from activated muscle cells induces differentiation of adult neural stem cells in vitro (66), directly linking muscle-originating secreted factors to the function of the aging CNS.

Exercise contributes to the health and functioning of not only muscle, but also the CNS. The CNS also undergoes a progressive functional decline during aging, including increased neuroinflammation and impaired proteostasis and mitochondrial systems (63,67), which contribute to the development of age-associated neurodegenerative disease, including Alzheimer's disease (AD). Regular exercise plays an essential role in maintaining healthy neurocognitive function and immuno-metabolism in the aging CNS, benefitting cognition and memory during healthy aging (68) and reducing the risk of age-associated neurodegenerative disease (26). Indeed, exercise powerfully stimulates adult hippocampal neurogenesis in animal models (60,69,70) and increases brain-derived neurotrophic factor levels in the aging hippocampus (60,70,71), implicating exercise as a highly relevant behavioral strategy for preventing age-related cognitive decline (68–70). Moreover, there is substantial evidence to support that physical activity decreases the risk of developing AD (71–74), is associated with better AD prognosis (75), and positively affects cognitive function in AD patients (76,77). Similar benefits have been reported in AD transgenic mice, where exercise rescues impaired neurogenesis, enhances synaptic plasticity, and attenuates neuropathology (78–82). However, the precise mechanisms responsible for this exercise-dependent rejuvenation of the aging and/or AD CNS remain largely unexplored.

Circadian Rhythms, Central Clocks, and Peripheral Clocks

One area of research in which there is great potential for the unification of these 2 fields is circadian clocks, as it integrates both the central and peripheral systems to maintain homeostatic and cognitive bodily functions. Virtually every cell has a clock and every tissue/organ is a circadian system. At the molecular level, the circadian clock in individual cells is based on a highly conserved transcriptional/translational negative feedback mechanism controlling rhythmic gene expression (83).

It is becoming increasingly clear that aging is associated with a decline in the function and systemic coordination of circadian rhythms (84–88). Circadian disruption, either through genetic models or through environmental perturbations (eg, chronic jet lag), has systemic outcomes and tissue-specific outcomes that mimic what is seen with aging (86,89–93). This includes altered metabolism leading to insulin resistance, increased inflammation, and muscle weakness. Conversely, analysis of the circadian clock systems in different organisms as well as across different tissues with age has shown that all levels of the hierarchy are affected (85,93–95). It is well established that aging leads to a diminished ability of the central superchiasmatic nuclei (SCN) clock to entrain to light:dark cycles and electrophysiology studies document altered SCN output with age, including sleep/wake states and physical activity. In general, older people do not sleep as well as young people (96), likely compromising the body's ability to appropriately respond to metabolic and physiological challenges. While the circadian clocks are functional with age, the output is dampened and, across several animal models, all tissues undergo an age-associated reprogramming of the circadian transcriptome (95). It is clear that all clock systems are altered with age but how changes within the CNS affect the periphery and vice versa remains to be determined.

However, pathways that regulate the circadian clock and those implicated in aging share significant overlap. Several of the key signaling pathways that contribute to aging have been shown to also regulate the clock mechanism, for example, the nutrient/energy sensing (ie, insulin/insulin-like growth factor 1, AMP-activated protein kinase, mechanistic target of rapamycin [previously known as mammalian target of rapamycin], autophagy), epigenetic regulation (SIRT1), and systemic and chronic inflammation (97). Given that circadian decline is detrimental to healthy aging, detailed mechanistic dissection of how the circadian clocks change in the SCN, other CNS regions, and within peripheral tissues with age promises to offer new insights and hopefully strategies to improve healthy aging and treat age-related diseases and chronic conditions. Therefore, it is imperative that geroscientists and neuroscientists investigating these mechanisms incorporate both fields into their research.

Choice of Preclinical Models

An additional disconnect between the 2 fields is differences in animal models utilized in preclinical investigations, requiring an alignment in communication between thought leaders regarding preclinical models to best serve our understanding of the interaction between the body and brain. Therefore, it is imperative that the choice of animal model is appropriate for both gerontological and neuroscientific investigations. Both fields embraced the use of mice in the early 1990s to study the genetic basis of neurodegeneration and diseases related to aging. However, in the context of functional outcomes, rats have been the "powerhouse" model to study cognitive behavior and our group has advocated to "Bring Back the Rat" to geroscience research (98). However, most geroscientists trained within the last 2 decades have had a mouse-centric focus, and may particularly benefit from working with a second mammalian model that not only more closely resembles humans in many aspects, but has more genetic diversity even among the same strain (98).

Among the work done in rat models, most work investigating longevity by the geroscience community has utilized Fischer 344 × Brown Norway (FBN) hybrid rats. Conversely, Fischer 344 or Long Evans rats have long been the cognitive model of choice for many investigators in neuroscience. Indeed, a recent request for applixations (RFA) espoused the need to study the biology of aging and longevity in the Long Evans model. However; there is no mirror RFA to study the impact of the FBN model in the context of age-related cognitive decline, even though there is an enormous literature regarding their pathology, longevity, and behavioral characteristics across the life span (99–101). Fortunately, recent work within the cognitive aging field, by our groups as well as others, has begun to utilize the F1 generation of FBNs (7,102–104) for complex cognitive behaviors

investigating the impact of peripheral biological contributions, contributing to the better alignment of these 2 fields.

Regarding cognitive behavioral testing, there is a large imbalance across fields along this mouse/rat divide. When geroscientists do incorporate cognitive testing into their work, there is an unfortunate trend to utilize mice in behaviors designed for the more complex rat organism, confounding interpretations and translatability to humans (see (98) for details).

In addition to the discussion of differing rodent models, there are several other animal models utilized for aging preclinical research across fields. Nonhuman primate (NHP) models in geroscience and neuroscience have a number of key advantages and disadvantages. Strong advantages of research with NHPs include greater physiological and neuroanatomical similarity to humans owing to their more recent evolutionary divergence, which should increase translatability (105,106). This is particularly important in understanding the impact of aging on brain regions, such as the dorsolateral prefrontal cortex, that are implicated in human cognitive aging and do not have clear homologs in rodent models (107,108). There has also been growing interest in the extent to which NHPs can be used to understand the biology of neurodegenerative diseases for which age is a risk factor in humans, such as AD. Some species of NHPs have natural age-related pathology that resembles AD (109) leading to an interest in developing inducible models of neurodegenerative disease in NHPs that may provide greater translatability than rodent models (110).

Despite the importance of these models, an important and significant limitation to working with NHPs is the significant constraint in the supply of aged NHPs that are suitable for geroscience and neuroscience investigations. Therefore, it is imperative that the 2 fields work harmoniously to best utilize NHP cohorts to their fullest extent. Unlike rhesus monkeys, marmosets have a shorter life span and reproduce more rapidly and so may be more tractable for aging research, but this smaller NHP species has a more constrained behavioral repertoire which may constrain their utility for understanding the neurobiology of cognitive aging (106).

In addition to mammalian models, invertebrate laboratory organisms, mainly the fruit fly, *Drosophila melanogaster*, and the worm, *Caenorhabditis elegans*, play a large role in overall biomedical research, especially in geroscience. Both of these organisms have been used to study a variety of human diseases despite the gross differences in morphological and cellular features. This is because many of the molecular mechanisms governing development and orchestrating the organismal cellular and physiological processes are highly conserved between invertebrates and humans. Indeed, the fly genome is 60% homologous to the human genome and as many as 75% of human disease genes are conserved in *Drosophila* (111). Similarly, over 80% of the translated proteins in *C elegans* share a human homologue (112). These genomic similarities combined with low maintenance cost, fast reproduction, ability to model complex disorders, high-throughput screening capabilities, and the enormous repertoire of genetic tools available for research make worms and flies ideal models to study the many aspects of organismal functional deterioration with age.

With regards to cognition, assays exist to measure cognition in both worms (113) and flies (114), though they are more numerous and sophisticated for *D melanogaster*, and both species show an age-related decline in these cognitive behaviors (eg, (115,116)). In addition to age-related cognitive decline, *D melanogaster* and *C elegans* have proved to be a powerful model to further our understanding of individual pathologies including AD (117,118). AD fly models have provided insights into the genetic architecture of AD and have identified genetic and environmental modifiers of neuropathological outcomes (119). A more holistic approach may be better suited to elucidate common mechanisms and/or shared genetic architecture that underlie age-associated decline in function accompanying the neurodegeneration associated with disorders like AD (120). Furthermore, direct links between longevity and cognition have been found in flies, as selection studies on *Drosophila* have shown that flies selected for improved memory at a young age will have a reduced life span (121). Likewise, flies selected for a longer life span and delayed reproductive senescence develop cognitive deficits at a young age (121). Such trade-offs are not exclusive to cognitive and life-history traits but extend to other facets of organismal function, including body weight and energy metabolism traits (122). Overall, the ease of care coupled with the sophisticated genetic tools available for invertebrate models make them ideal study systems for understanding the specific molecular mechanisms that cause age-related declines in cognition.

Conclusions

Together, the authors of this manuscript are promoting collaborative efforts between neuroscientists and geroscientists that investigate health at the organism level, as opposed to the traditional isolation of a specific organ system. While this review is not meant to be an all-encompassing look across either of the 2 fields, we have pointed out several areas in which the 2 fields could intersect to form synergy and advance understanding. Additional details regarding the current topics and trends in both the neuroscience and geroscience fields will be subsequently published as individual primers.

Biomedical research greatly benefits when scientists can work together and learn from one another. To do so, it is imperative that future workshops, meetings, and funding mechanisms emphasize the importance of bridging this divide, which may be done through broader inclusivity in meeting symposia, which would allow for stronger interactions between the 2 fields, with the hope of enhancing team science.

Furthermore, it is imperative that bridging this divide be supported at the more junior levels of training and conducting of science. Currently, graduate training is largely divided between these 2 areas. This is exacerbated by separate training aspects of T32 funding mechanisms, separated laboratories and/or principal investigators as well as divisions between departments within universities. Therefore, a focus on incorporating the bidirectional relationship between the periphery and the nervous system, as outlined herein, is imperative for all students undergoing biomedical training.

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Conflict of Interest

None declared.

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