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# Innovative approaches in cognitive aging

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ABSTRACT

Novel approaches to address cognitive aging and to delay or prevent cognitive decline in older individuals will require a better understanding of the biological and environmental factors that contribute to it. Studies in animal models—in particular, animals whose cognitive trajectory across their life span closely tracks that of humans—can provide important insights into the factors that contribute to the accumulation of reserve and ways in which it is preserved or depleted. A better understanding of the molecular processes that underlie these elements would enhance and guide not only research but also treatment approaches to these issues. These treatment approaches may include noninvasive brain stimulation and drug treatments to promote youthfulness or combat the aging process. It is important to realize, however, that these processes occur in the context of the human experience, and studies of them must consider the complexity and individuality of each person's life.



## 1. Introduction

The molecular mechanisms underlying cognitive function, reserve, and resilience are only beginning to be described. For all the gains that have been made in recent years in our understanding of the factors that influence cognitive aging, a tremendous unmet need remains for new approaches to delay or prevent dementia. These approaches may arise from a better understanding of the relationship between early- and mid-life experiences and the accumulation of reserve and resilience, how these mental capacities interact with ever-accumulating pathology in the aging brain, and the extent to which the brain retains plasticity and the ability to adapt in later life.

Research from both animal studies and human trials has identified physiologic factors and processes that influence higher-level functions of the brain. As has been seen in many other diseases (e.g., cardiovascular disease, obesity, diabetes, neurological disease, and cancer), chronic inflammation may play a role in cognitive decline and other neurological diseases. Identifying factors that contribute to cognitive decline—or, conversely, identifying factors that contribute to cognitive resilience—could represent new avenues of research and treatment. A better understanding of the causes of inflammation and ways to mitigate it could benefit many people. The impact of chronic inflammation on gene expression, possibly resulting in epigenetic modifications, may be of particular significance.

Some key questions could also be addressed through the development of better animal models of age-related cognitive decline. Although rodent studies have immeasurably improved our understanding of human disease, their applicability to humans is limited, particularly when considering higher-order cognitive domains. Studying cognitive decline in animals that are more similar to humans in terms of their social and cognitive abilities may be useful. Domestic dogs, which can learn and remember complex tasks for extended periods, socialize and interact well with humans, and seem to undergo cognitive decline as they age, could be a valuable model system in which the effects of aging are studied. In the end, research on cognition must be interpreted in the context of the whole individual, and studies of cognitive function will need to be performed and validated in older adults.

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Speakers in this session of the Cognitive Aging Summit III, chaired by Marilyn Albert, explored novel approaches and models that can be utilized to capture the many nuances of cognitive aging. The design and interpretation of experiments regarding cognitive function will require an appreciation of the complexity of the human cognitive experience across the life span as well as of the cognitive and neural response to interventions designed to improve function.

## 2. Cognitive aging: new and improved animal models

### 2.1. Steven N. Austad

Mammals that are commonly used in cognitive studies include mice, rats, dogs, and primates. It is important, however, to take into account the differences among strains and animals. Indeed, there is no such thing as "the" mouse or "the" primate; all animal strains have unique idiosyncrasies that can confound interpretation of experimental results. For example, the C57BL/6 mouse is the most commonly used inbred mouse strain for laboratory research. A study of mice with severe neurodegeneration identified a mutation in the *GTPBP2* gene (Ishimura et al., 2014). However, the phenotype was only observed in C57BL/6 mice obtained from the Jackson Laboratory and not in mice of the same strain that were obtained from other sources. Analysis revealed that the Jackson strain had a brain-specific mutation in one of its transfer RNA molecules that, in combination with the *GTPBP2* mutation, led to the observed phenotype only in this strain. This unexpected finding underscores the need to be vigilant for potential strain-specific idiosyncrasies when designing and interpreting studies of cognitive aging.

There is a need for better animal models of human physical and cognitive health assessment. This is especially important when one realizes that an individual's goal is often not to live a longer life but to live a healthier one, with mobility, cognition, and sensory function preserved for as long as possible. One of the more promising animals in which this "healthspan" is studied is the domestic dog.

Dogs offer several advantages over other animals in the study of human disease and health: they are diurnal (like humans) rather than nocturnal (like rodents); they show tremendous phenotypic variability; they have been selected for a wide range of physical traits and behaviors; and they are comfortable with and respond to humans. In addition, detailed genetic and genomic information about the dog is now being developed (Ostrander, 2012).

Dogs can be trained to perform cognitively complex tasks that are similar to those performed by humans. Service dogs, for example, are trained to remember specific routes, open doors, turn lights on and off, find and retrieve specific objects, and help people get dressed and undressed. Service dogs retire at various ages, perhaps because cognitive decline impairs their ability to carry out their service role. Retired service dogs could therefore represent an outstanding research resource for scientists studying aging and cognitive function. Different dog breeds cognitively age at different rates, or perform better or worse in different cognitive domains (Ostrander, 2012); research to uncover the mechanisms underlying these processes could be relevant to humans.

Scientists who might collaborate in studies of aging in dogs could include cognitive scientists, dog behaviorists, dog service trainers, and canine geneticists. The Dog Aging Study (dogagingproject.com) at the University of Washington aims to enroll 10,000 dogs in a long-term study of aging. Interested researchers could access this resource to collaborate and generate a registry of people with specific dog breeds who are interested in participating in a research study. An additional resource might be people who are already participating in aging studies and are interested in enrolling their dogs in the study.

## 3. Circadian gene regulation by histone deacetylation contributes to age-related impairments in memory and synaptic plasticity

### 3.1. Marcelo A. Wood

Our laboratory is working to understand the mechanisms underlying long-term memory processes in the young adult and aging brain. Most of our work is at the level of the epigenome—the chemical modifications to histone proteins and DNA that modify and regulate chromatin structure. The epigenome represents a powerful signal transduction platform reflecting the interaction of the genome and experience/environment and how this interaction ultimately produces a phenotype. Our overall hypothesis is that enzymes that modify chromatin play a role in controlling gene expression required for stable changes in neuronal function that give rise to long-term changes in behavior.

Histone acetylation is a classic epigenetic modification of chromatin. This process has been implicated in hippocampal memory formation (Levenson et al., 2004) and synaptic plasticity (Vecsey et al., 2007). Histone acetylation is a dynamic process, with the addition of acetyl groups to histones balanced by their removal via histone deacetylases, or HDACs. One HDAC, HDAC3, has been identified as a critical negative regulator of long-term memory formation (McQuown et al., 2011). Deletion or inhibition of HDAC3 can transform a subthreshold learning event that would not normally lead to a short- or long-term memory into a robust long-term memory that persists past the point at which normal memory would fail. HDAC3 inhibition can gate the information that is processed into long-term memory and affect the specificity and strength of memory, and potentially even the number of neurons recruited for memory representation (Bieszczad et al., 2015; Campbell and Wood, 2019).

These observations led us to examine the possibility that the impaired ability to form new memories in the aging brain might be a consequence of dysregulated chromatin modification resulting in a more repressive chromatin structure that impedes gene expression. This hypothesis was originally put forth by Sweatt and Barnes (Penner et al., 2010). Evidence for this hypothesis comes from observations that gene transcription is disrupted in normal aging (Berchtold et al., 2008; Rowe et al., 2007); that age-related memory problems seem to be dependent on hippocampal function (Driscoll and Sutherland, 2005); and that the epigenome is altered in aged neurons, resulting in a repressive chromatin structure that prevents normal gene expression required for long-term memory formation (Peleg et al., 2010; Snigdha et al., 2016).

We have found that young adult mice (2–4 months) perform better on an object location memory task than aging mice (18–20 months), but older animals lacking *HDAC3* perform like younger animals (Kwapis et al., 2018). Focal genetic deletion of *HDAC3* ameliorates both synaptic plasticity as well as long-term memory impairments observed in aging mice. HDAC3 may therefore act as a molecular "brake pad," constraining the formation of new long-term memories in the aging brain.

In trying to identify possible mediators of this effect, we identified 4 genes whose expression was increased in younger mice during memory consolidation, failed to increase in older mice, and was restored in older mice after *HDAC3* disruption (Kwapis et al., 2018). One of these encodes a core component of the circadian molecular machinery. Additional experiments demonstrated how HDAC3 may be regulating this circadian gene in the hippocampus during memory formation. Overall, the results suggest that circadian gene regulation represents a potential mechanism to link aberrant epigenetic repression to memory impairments in aging brain and that circadian genes may have an autonomous role in the

hippocampus for memory function beyond their role in circadian rhythm function in the suprachiasmatic nucleus.

## 4. Mechanisms of brain aging and rejuvenation

### 4.1. Saul A. Villeda

Our group is addressing the questions of whether the effects of aging—in particular, its effects on regeneration and cognitive aging—can be reversed. We are examining the features of the young brain (~20s) with its adaptive, resilient properties and asking whether there is a way to restore these functions in the older brain (>65). If this approach could be realized, it would represent a transformative way of thinking about aging and addressing its effects on cognition in later life. Our ultimate goal is to extend the number of cognitive healthy years in the life span.

We use mouse models to explore the potential for animals to repair and restore lost cognitive function in old age. To examine these processes, we administer tasks that are associated with regenerative capacity and age-related impairment—one of them being a test of spatial learning and memory. We measure the ability of mice to find a hidden platform in a pool of water based on its location with respect to surrounding visual cues. A young animal can learn this task quickly, but an older animal takes longer to learn the task and makes many more errors while doing so (Villeda et al., 2011, 2014).

We explored systemic factors that might influence brain function. We looked for factors in the blood, because it touches all organs and systems. We used parabiosis (i.e., the anatomic joining of 2 animals so that they share a common blood supply) to test whether there are systemic factors present in old animals that dispose them toward cognitive decline or whether there are factors present in young animals that protect them from cognitive decline. In other words, we asked whether cognitive decline was the consequence of loss of a protective factor or the gain of a deleterious one.

Using this approach, we conducted a targeted proteomic screen and identified several immune factors that were especially prominent in "old blood" (Villeda et al., 2011). This finding suggested that inflammation at a systemic level may be an important contributor to cognitive decline. We looked more closely at beta-2 microglobulin (B2M), whose levels increase in blood during aging in mice and humans. Genetic studies of B2M knockout mice show that young animals are normal but older animals have more regenerative capacity. Conversely, young mice who received injections of systemic B2M performed more poorly on tests of cognitive function, but this effect was reversible if B2M was discontinued (Smith et al., 2015).

Our ongoing studies are exploring whether there are "pro-youthful" factors that can help rejuvenate neural regeneration and restore cognitive function. Ultimately, we hope to better understand the mechanisms by which cognitive function can be preserved and to identify factors that may mediate this ability to rejuvenate neural functioning and plasticity.

## 5. Evidence needed to validate noninvasive brain stimulation for neurocognitive modulation

### 5.1. Joel L. Voss

In recent years, there has been an explosion of researchers trying to find ways to influence the brain using noninvasive methods, including methods such as noninvasive brain stimulation (i.e., transcranial magnetic stimulation, transcranial direct current stimulation, transcranial alternating current stimulation) and activities such as cognitive training. Current methods to evaluate the effectiveness of these approaches are limited and may not differentiate placebo from treatment. This is because the interventions themselves are complex and involve a variety of subjective experiences that limit the ability to blind participants and researchers to experimental conditions and to control various nonspecific factors that could mediate the response of outcomes variables. Because of this complexity and of the relative lack of information regarding potential mechanisms of action on brain and cognitive function, special precautions must be taken to validate these interventions.

Our laboratory is evaluating the utility of transcranial magnetic stimulation to influence the human hippocampal brain network and thereby to alter memory function. This is an important target because, with age, connections between the hippocampus and its cortical networks decrease, a phenomenon that is associated with age-related memory impairment (Salami et al., 2014). Our studies exemplify the approach we advocate for validating neural stimulation and other putative interventions for cognition. This approach includes the following 3 requirements: (1) We must show that the putative neural target of the intervention is engaged by the stimulation regimen, that is, that the targeted brain network responsible for the cognitive function of interest changes in response to the intervention. (2) We must use within-experiment control and comparison conditions to validate the effects of stimulation on cognition and brain function, because this effectively guards against nonspecific factors. (3) The experimental design and statistical analysis methods must guard against nonspecific or placebo effects and statistical false-positive results. In addition to standard considerations regarding factors such as sample size, statistical power, and experimental design, we must avoid post hoc data analysis decisions, such as splitting research subjects into groups based on positive versus negative treatment responses, because this is a form of "p hacking" that amplifies the likelihood of false-positive results (Head et al., 2015).

In young adults, we found that stimulation increased functional connectivity among cortical-hippocampal network regions and improved associative memory performance (Wang et al., 2014). Thus, the putative neural target, the hippocampal network, was engaged by stimulation, satisfying the first requirement that we propose for validation. In a follow-up experiment using spatial memory testing, we measured subjects' general ability to remember the location of an object (i.e., success) and also the precision of that memory. Previous findings have indicated that the hippocampus is more critical for memory precision than it is for general success (Kolarik et al., 2017). We found selective effects of stimulation on precision as well as on its neural correlates, with no effects on success (Nilakantan et al., 2017). The selectivity of the effect on precision but not general success provides a within-experiment control, guarding against possible nonspecific factors of stimulation and thereby meeting our proposed second requirement for validation. Furthermore, stimulation affected the specific aspect of cognition that we hypothesized would respond to stimulation based on previous neuroanatomical findings, thereby showing further evidence for target engagement and further satisfying the first requirement for validation. By applying these rigorous methods in older adults, we found that stimulation selectively improved recollection memory and increased activity within the hippocampal network, thereby validating the effects of stimulation on the specific behavioral and neural hallmarks of age-related memory decline (Nilakantan et al., 2019).

Regarding the third requirement for validation, the appropriate design and analysis of any experiment related to cognition is of key importance. While all researchers are conscious of the current focus on rigor and reproducibility as it relates to factors such as sample size and statistical corrections for multiple comparisons, there are additional factors to consider in analyzing experiments utilizing

complex interventions. For instance, experiments must include appropriate control conditions, including "positive" and "negative" intervention controls. For instance, in our experiments, we deliver full-intensity stimulation to regions that are not within the hippocampal-cortical network, such as the motor cortex, to guard against nonspecific effects of stimulation. Furthermore, it is a common practice to divide study participants into intervention "responder" and "nonresponder" groups post hoc and then look for differences between these groups. This practice is problematic because nonspecific differences almost inevitably exist between such groupings, and therefore the likelihood of falsely identifying effects related to intervention is artificially inflated. Finally, in studies of brain stimulation, it is important to incorporate adequate measurement of pain, discomfort, and other subjective states that could amplify nonspecific or placebo effects. By following these principles, researchers can increase the likelihood that any effects they observe in their studies are valid, reproducible, and meaningful.

## 6. Hippocampal neurogenesis throughout adulthood and aging

### 6.1. Amar Sahay

The adult brain continues to generate new neurons throughout life in the dentate gyrus region of the hippocampus; however, neurogenesis does decline with age (Altman and Das, 1965; Eriksson et al., 1998; Spalding et al., 2013). Recent evidence suggests that adult-born neurons play a critical role in decreasing interference between similar memories and may support pattern separation (Clelland et al., 2009; Knierim and Neunuebel, 2016; McAvoy et al., 2016; Nakashiba et al., 2012; Sahay et al., 2011). Understanding the mechanisms that regulate adult neurogenesis may identify strategies to promote continued neurogenesis into older age, which could represent an attractive strategy to mitigate cognitive decline.

Genetic studies that modulated levels of neurogenesis in the dentate gyrus of adult mice showed that changes in neurogenesis influenced the ability of mice to distinguish between similar contextual representations (McAvoy et al., 2016). In particular, aged mice that were manipulated to produce more adult-born neurons (by manipulating competition between old and new neurons) were better able to discriminate between 2 similar contexts compared with aged controls (McAvoy et al., 2016; McAvoy and Sahay, 2017). Researchers are now working to better understand the mechanistic underpinnings of these findings and to identify molecules that could safely produce a similar therapeutic effect, which may improve cognition in aging humans.

## 7. Discussion

Animal models of human disease are just that—models—but they can yield important insights into disease processes that would be difficult to discover in studies of people. Therefore, animal models represent important systems in which biology can be manipulated and studied in ways and over life course intervals that are impractical in humans. Not all animal models are equally relevant for investigating human disease processes. One particularly overlooked issue is the nature of the environment in which studies are performed. For example, rodent studies are typically conducted in environments deficient in cognitive stimulation. Simple environmental enrichment is well-known to affect neuroanatomy and physiology, cognitive performance, as well as multiple diseases processes (Mustroph et al., 2012). Cognizance of this fact could be crucial in interpreting laboratory experiments. For example, interventions such as exercise in a laboratory environment could have their cognitive impact not only because of the cardiovascular or other effects but also simply because an exercise wheel provides a source of environmental enrichment. Humans live in phenomenally enriched environments compared with laboratory animals. One advantage of using companion animals such as dogs in cognitive research is that they share the complex human environment.

Research into human cognitive function in old age must consider changes in the human body that occur both within the brain and in the larger physiological context. Even if the human mind is more than the sum of its parts, a better understanding of these parts—and how they work together, both inside and outside the brain—could lead to significant insights into the ways that cognitive function is preserved in some people. Because of the complexity of human cognition and age-related cognitive decline, it is likely that combination treatment approaches may be the most effective long-term strategy. However, not enough is known about the mechanisms of cognitive decline to select the appropriate combinations for testing.

Moving forward, our understanding of human cognitive function will be improved by a better understanding of the molecular mechanisms that give rise to it. It is important to ensure that these studies are well-designed and free of bias. Given the complexity of neural pathways, a key consideration is ensuring that an intervention is indeed acting on the pathway that is targeted.

Current research into human cognitive function and the search for ways to preserve or improve it face the same problems as the blind men who were asked to describe an elephant: there is a risk that any one element of cognition—no matter how well characterized—may not represent the whole picture. The challenge for researchers is to integrate their findings into a unified model of brain function and resilience to understand the sources of reserve and the factors that lead to cognitive decline as well as interventions that might influence either of them. The guiding principle of biomedical research is to improve health and reduce suffering—if not by adding more years to life, then by adding more life to one's years. These tenets should serve as important guideposts in designing and interpreting experiments to ensure broad applicability of any observed effects of interventions.

## Disclosure

SAV is on the scientific advisory board for Alkahest, a company developing commercial products targeting geronic blood factors. The other authors report no conflicts of interest.

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## Appendix A. Supplementary data

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