Animal Models of Human Cognitive Aging

Edited by

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This book is dedicated to Jeanne Ryan, Ph.D., and Michela Gallagher, Ph.D.: true mentors and friends. It is also dedicated to our families, Costel Darie, Ph.D., Constantine Darie, Barry Setlow Ph.D., and Alexander and Anna Bizon-Setlow.

Preface

Because of significant improvements in health style and medical science, an increasingly large number of individuals are living to advanced ages in the United States and other developed nations. According to 2004 U.S. Census Bureau estimates, the number of people over 65 is expected to rise from 35 to 72 million by 2030, resulting in the elderly comprising one fifth of the population within the next 20 years. Many elderly people will develop cognitive decline ranging from severe dementia to mild impairment, in part due to diseases such as Alzheimer's disease and myocardial infarction, and in part as a consequence of the "normal" aging process. Importantly, however, cognitive loss associated with advanced age is not inevitable and, as such, modern society has placed new emphasis on "successful" cognitive aging. In addition to increasing the quality of life for elderly individuals, understanding the factors that impact cognitive aging and developing new treatments to combat age-related mnemonic decline also is advantageous from a societal standpoint. Health-care costs are substantial for those elderly who lose independence as a result of impaired cognition and can only be expected to rapidly escalate with the projected increase in life expectancy.

Animal models that accurately mimic age-related cognitive loss in humans are essential tools for understanding cognitive changes associated with the aging process and are necessary to developing novel and putatively more effective treatments to combat loss of function. While animal models for understanding human normal biological processes and disease states have long been used in scientific and medical research, models of cognition and aging are relatively new in accordance with the recent increase in human life expectancy. With the completion of the human genome project and other technical advances, significant work in the field of aging has focused on understanding changes of biological phenomena at the molecular and cellular levels across the life span. Solid animal models of cognitive aging remain essential to the interpretation of consequences of such findings. Human research, though clearly most directly relevant, presents barriers with regard to manipulation and also with understanding the temporal sequence of events that may have led to cognitive deficits and abilities. As such, translational research related to improving human health at advanced ages depends upon modeling age-related cognitive decline in rodents and nonhuman primates.

This book is designed to provide substantive background on some of the most widely used animal models in studies of cognition and aging. The goal is to present sufficient detail to aid neurobiological researchers in choosing and implementing appropriate animal models of cognitive aging, understanding the benefits and drawbacks of each. The authors also have related each of these cognitive models to human systems and circumstances.

Berchtold and Cotman start the book by discussing normal and pathological processes of brain aging in humans, relating these processes to animal models. The authors emphasize the role that lifestyle choices, such as exercise, may play in successful aging. Since primates are phylogenetically most similar to humans, use of nonhuman primate models is essential to many aging studies and can be critical when investigating complex neocortical-based cognitive functions that are difficult to model in rodents. Lecreuse and Herndon provide a comprehensive overview of the many such models currently used to study cognitive aging, and Baxter provides a comprehensive review of frontal cortical deficits and executive function in primates as related to not only humans but also rodents. Indeed, in many instances rodents provide an excellent model system for human cognitive aging, in part due to the wealth of background data available regarding the neuroanatomy, physiology, and behavior of this species. LaSarge and Nicole detail similarities and differences among different rat models most often used to model medial temporal lobe dysfunction related to nonpathological aging. A separate chapter by Calhoun describes important and often overlooked differences between using rat versus mouse models, while LaFerla and colleagues review the use of transgenic modulation in mice to model Alzheimer's and other age-related diseases. Sohrabji and Lewis continue an important discussion originally introduced by Berchtold and Cotman relating to sex differences in cognitive aging and the consequence of variations in hormones across the life span on cognition. Finally, Balci, Moore, and Brunner present a comprehensive review on the topic of "timing," which is well documented as altered in aging and may be related to impaired decision-making and other deleterious cognitive outcomes at advanced ages.

With the aging population steadily on the rise, studies focusing on cognitive decline both with normal aging and with age-related disease are a crucial focus of current research. New technologies, such as neuroimaging and molecular techniques, are helping to shed new light on how the brain changes across the life span, but animal models retain, and in many ways demand, an increasingly important role with respect to providing a necessary context by which to evaluate age-related neurobiological changes. It is in this spirit that we have put this book forth, as a collection of expert experience in animal models of cognitive aging. We thank the authors for their valuable contributions and hope that this volume will be of substantial value to neurobiological researchers in their understanding, selection, and implementation of appropriate animal models to aid in the translation of research from the bench to the betterment of human cognition well into advanced ages.

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Normal and Pathological Aging: From Animals to Humans

Nicole C. Berchtold* and Carl W. Cotman

Abstract While aging is associated with modest declines in certain aspects of cognitive function (memory, executive function, processing speed), many cognitive domains can remain relatively stable until late in life. In contrast to the mild decline observed in normal aging, pathological aging such as Alzheimer's disease (AD) affects global cognitive function – impairing memory, language, thinking, and reasoning, and interferes substantially with daily living capacity. Changes in the structural integrity of the brain underlie the cognitive declines that occur in both aging and AD, however different brain structures are affected. In healthy aging, mild functional changes are predominantly detected in the prefrontal cortex and basal ganglia, while in AD, pathology initially accumulates and disrupts function in the medial temporal lobe (disrupting memory), progresses to cortical structures, and eventually globally impacts the brain. Cognitive decline with normal and pathological aging is mediated by a complex interaction of multiple factors that include genetic and nongenetic risk factors that determine the age of onset as well as the rate of decline. Importantly, the progression and decline can be prevented or slowed by certain lifestyle factors (exercise participation, stress management) and pharmaceutical interventions (statins, hormone replacement therapy for postmenopausal women). While most individuals will experience some degree of cognitive decline with aging, conversion to MCI or AD is not an inevitable consequence of aging. It is likely that additional strategies to promote healthy brain aging will be uncovered in the next years that will further contribute to successful brain aging and will help to maintain a high quality of living through the last decades of life.

Keywords Alzheimer's disease • memory • executive function • risk factors • exercise

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Introduction

The structural integrity of the brain changes with age, and aging is associated with decline of some cognitive function, particularly executive function and mild memory decline. In contrast to what was once believed, dementia is not an inevitable consequence of aging. However aging is the main risk factor for Alzheimer's disease (AD), the most prevalent cause of dementia in the elderly. AD is a progressive neurodegenerative disorder that results in increasing loss of cognitive function, starting typically with memory loss, and proceeding to affect thinking, language, and global cognition to a severity that interferes with the individual's ability to function in daily life.

The declines in cognitive function that occur in aging and AD are due to changes in the structural integrity of the brain; however the changes that occur in aging versus AD are vastly different. The most notable change in healthy aging is due to declines in the prefrontal cortex (PFC) and basal ganglia, which correspond to executive function deficits and may contribute to the mild memory difficulties characteristic in aging. Through different mechanisms of decline, AD is characterized early in the disease by prominent change in the medial temporal lobe (MTL) which disrupts memory function, as well as by changes in cortical networks (including posterior cingulate and retrosplenial cortex) that occur even before clinical symptoms are recognized. While there is brain volume loss in both aging and AD, human and animal studies indicate that the atrophy in aging is primarily due to synaptic loss rather than cell loss, while both neuronal and synaptic loss are prominent in AD.

At the same time, compensatory strategies occur in the brain which counteract loss of function due to atrophy. For example, one compensation strategy relies on recruitment of more brain regions when challenged with a task. The degree of compensatory capacity has been called "cognitive reserve" and is emerging as an important factor determining who ages gracefully versus who undergoes significant cognitive decline. The capacity for cognitive reserve is determined by a complex interplay of aging with genetic risk factors and lifestyle factors that impact brain health and function, and that can initiate and propagate AD. In turn, there are lifestyle strategies that support brain health and help maintain cognitive reserve, that can prevent or delay age-related cognitive decline and even reduce the risk of AD. One lifestyle factor that is emerging as particularly significant for maintaining overall health and cognitive function with aging is exercise participation, based on both human epidemiological studies and basic science research using animal models.

"Healthy" Aging

Human aging, particularly after 60 years, is associated with decline of certain aspects of cognitive function, even in healthy "normal" aging of the brain. The cognitive abilities that are particularly sensitive to age-related decline include the ability to encode new memories of events or facts, working memory capacity, executive function, and processing speed, described in Table 1 (for reviews see (***1, 2***)). Working memory is a form of short-term memory, and requires the simulta-

Table 1 Definitions

Working memory Also called short-term memory, working memory involves the simultaneous short-term maintenance and manipulation of information. A clinical test to assess working memory is the digit-span task.
Executive function General cognitive processes involved in attention, planning, multitasking, and capacity for switching among several tasks and sources of information. Executive function is needed to perform complex, goal-oriented tasks. A task that uses executive function is the Stroop test (defined below).
Stroop test In this test of executive function, the individual is presented with a series of names of colors that are written using different colors of ink. The color of ink used for the words does not match the name of the color itself. The individual must name the color of the ink rather than read the word, and the number of correct answers and the number of errors performed in 60 s is recorded. The active suppression of the urge to read the word itself requires executive function.
Declarative memory A form of long-term memory for information and facts. This contrasts to non-declarative memory (procedural memory) like skill sets, that can operate outside of awareness. Function of the hippocampus and related medial-temporal lobes is critical for declarative memory.
Medial temporal lobe (MTL) This neural system is important for encoding and consolidation of information, and is necessary for learning and memory function. In this chapter, the hippocampus is included in the definition of the MTL system.
Frontal-striatal neural system The neural system central for executive function. It consists of the prefrontal cortex (PFC) and PFC connections to the striatum. The striatum is important for the motor response, while the PFC is important in the executive processing of the decision-making for a motor output.

neous short-term maintenance and manipulation of information. For example, working memory is usually tested with the digit-span task, in which an ordered series of digits is heard and then repeated, with increasing numbers of digits presented in subsequent rounds of testing. Executive function is a high-order cognitive capacity that requires the domains of attention, planning, multitasking, and ability to switch among several tasks and sources of information. Older adults free from dementia often show difficulties on tasks that stress attention and executive function, such as the Stroop test, which is described in Table 1 (for review see ***(1)***).

These cognitive domains (encoding, working memory, executive function, and processing speed) constitute the basic mechanisms of the cognitive information processing architecture, and are the functions that are most sensitive to decline with aging. However, the decline in these cognitive capacities is not linear across the life span, in that they remain essentially stable until approximately age 60. For example, longitudinal studies demonstrate that processing speed, episodic memory, spatial ability, and reasoning show small or nonexistent age-related changes from ages 20–60, but then tend to show an approximate linear decline after 60 years ***(3–5)***. Similarly, short-term memory such as for the digit-span task, show only slight decline across the adult life span with sharper decline appearing after age 70 ***(6)***. This suggests that cognitive function remains largely intact until about the sixth decade of life, at which point declines in function can be detected.

While aging is associated with some decline in cognitive function, certain cognitive domains and memory forms are affected more than others. For example, memory

capacity is particularly sensitive to age-related decline, however not all aspects of memory are equally vulnerable. Both short-term (working memory) and long-term memory show relative decline in aging, while in contrast, measures of vocabulary and semantic knowledge are stable until late in life ***(3, 7)***. Aspects of memory that remain relatively stable over aging include short-term memory, autobiographical memory, semantic knowledge, and emotional processing ***(2)***. Clearly, different aspects of cognitive function are differentially vulnerable to decline with aging, indicating that aging does not affect the brain in an indiscriminate way (for good overviews see ***(2, 8)***).

The Brain's Structural and Functional Integrity Changes with Aging

Why do certain aspects of cognitive function decline with age? It is known that aging affects the structural and functional integrity of the brain, and these changes are thought to underlie the patterns of cognitive decline that occur with aging or AD. Recent research has provided insight into how particular neural systems are affected in aging, through both postmortem studies and in vivo imaging. Brain imaging studies have been key, allowing us to access the brain while individuals are still alive. Imaging studies have revealed volumetric changes with aging (atrophy) as well as the more subtle functional changes that occur, such as aging-related differences in brain activity when individuals are tasked with problem-solving. These studies have revealed structural changes at the gross anatomical and macroscopic levels, neurochemical changes, and functional changes in patterns of brain activation that occur in aging ***(9)***.

General Grey and White Matter Changes: Volume and Connections

On a gross anatomical view of the brain, postmortem and in vivo studies reveal that aging-related changes occur in both grey matter (neurons) and white matter (axons) of the brain. Brains of older adults tend to have lower volumes of grey matter than do the brains of younger adults ***(10***, ***11)***. Interestingly, the decreased brain volume is not a result of cell loss, but rather from cell shrinkage and from reduced synaptic densities ***(10–13)***. In fact, neocortical synapse density appears to decline steadily across the life span (ages 20–100) ***(12)***. While all cortical and subcortical regions show some level of atrophy with age, the atrophy is not uniform across the brain. Specifically, some brain regions like the prefrontal cortex and striatal regions are particularly affected in normal aging while other regions such as the occipital cortex are largely unaffected ***(2, 11, 14)***.

While grey matter has been the main focus of research on anatomical change, white matter fiber tracts are being increasingly studied to understand connectivity changes that occur between brain regions during the course of aging. MRI studies can assess the integrity of white matter fiber tracts *in vivo*, and have revealed that