COGNITION IN AGING AND AGE-RELATED DISEASE
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Chapter Synopsis
Aging can have diverse effects on cognitive function. For many people, aging is associated with relatively little cognitive decline ( “healthy” or “successful” aging). For some, memory declines significantly with age, but does not prevent performance of daily activities ( “mild cognitive impairment”). For others, aging is associated with severe cognitive deficits that impede the ability to live independently (“dementia”). This chapter discusses the cognitive changes that accompany healthy aging and the theories put forth to explain them. These age-related declines are then contrasted with the ones that characterize mild cognitive impairment and dementia of the Alzheimer’s type.

Introduction
As the average age of the population increases, there is growing interest in understanding the cognitive and neural changes that accompany aging. It is now clear that significant cognitive decline is not an inevitable consequence of advancing age. This realization has spurred researchers to examine what separates high-performing older adults from lower-performing older adults, and to investigate how the changes with successful aging differ from those that result from age-related disease. Data acquired using behavioral testing, functional neuroimaging, and structural neuroimaging are beginning to inform these issues, although a number of open questions remain.

Cognitive Declines with Healthy Aging
Not all cognitive domains are affected equally by age, and not all cognitive processes show age-related decline. If an older adult were asked to list the cognitive declines that have been most notable to him or her, it is likely that at least one of the following would make the list: Problems paying attention to relevant information and ignoring irrelevant information in their environment; word-finding difficulties; problems remembering the context in which information was learned.

Much of the research within the field of cognitive aging is focused on understanding whether the pattern of age-related cognitive decline can be explained by
domain-general (or “core”) cognitive changes, or whether changes in domain-specific processes are required to describe the data.

Domain-General Theories of Cognitive Aging

Domain-general theories of aging are based on the hypothesis that there is a shared ability that cross-cuts all of the tasks on which older adults are impaired: These theories suggest that although aging affects a range of cognitive functions, there is one central or “core” deficit underlying the myriad changes. This chapter will focus on three “core” deficits that have been proposed to explain the pattern of age-related declines: changes in sensory perception, changes in inhibitory ability, and changes in speed of processing.

Sensory Deficits

The sensory deficit hypothesis of aging proposes that the cognitive changes with aging may be attributed to changes in sensation (i.e., deficits in vision and hearing). Indeed, aging is associated with dramatic sensory declines: By the eighth decade of life, the majority of older adults have significant hearing loss and a reduced ability to discriminate colors and luminance. Support for the hypothesis that these sensory deficits may underlie cognitive changes has come from two lines of research. First, across a wide range of cognitive tasks, older adults’ performance correlates strongly with their sensory abilities. Second, in young adults, cognitive impairments can arise when the to-be-processed stimuli are degraded. For example, when asked to remember words pronounced against a noisy background, or when asked to match digits and symbols written in low-contrast font, young adults perform comparably to older adults. Thus, it is plausible that age-related deficits on many cognitive tasks stem, at least in part, from reductions in sensory processing. For example, changes in audition may result in older adults’ slowed performance on tasks requiring auditory processing, and could explain older adults’ poorer memory for auditory information. It is also possible, however, that in at least some instances the correlation derives from a common influence underlying both the sensory and cognitive changes: For example, individuals who have greater brain atrophy or dysfunction may be more likely to have both sensory deficits and cognitive impairments. Regardless of the precise mechanism through which sensory deficits relate to cognitive ones, evidence of significant sensory changes with age underscores the importance of modifying testing procedures to minimize the influence of sensory deficits on older adults’ cognitive test performance (e.g., using louder or higher-contrast stimuli).

Inhibition

Lynn Hasher, Rose Zacks and colleagues have proposed that older adults’ cognitive deficits may relate to their inability to ignore irrelevant information in the environment while focusing attention on goal-relevant information. If an older adult is seated at a restaurant that has many tables in close proximity to one another, she may have difficulty paying attention to the conversation at her table while ignoring the conversations at nearby tables. In the laboratory, inhibitory deficits can result in responses to previous (but not current) targets. For example, after reading the sentence “Before going to bed, please turn off the STOVE,” older adults will be more likely than young adults to believe that the target word was LIGHT rather than STOVE. The age-
related increase in this type of error is thought to occur because older adults have a hard
time inhibiting the strong association present in the “garden path sentence” (e.g., between
the idea of going to bed and the idea of turning off the light”). Inhibitory deficits also
frequently emerge when older adults are required to task-switch or to set-shift. On these
tasks, older adults must first pay attention to one aspect of a stimulus (e.g., match items
based on their shape) and then another (e.g., match items based on their color). Older
adults often have a harder time than young adults when they must ignore the previously-
relevant dimension (e.g., the shape of the items) and instead focus their attention on
another stimulus attribute (e.g., the color of the items).

These data clearly indicate that inhibitory deficits can occur on a range of tasks
requiring the ability to selectively attend to information in the environment, or to inhibit a
strong association or response. However, inhibitory deficits may impair performance not
only on tasks that directly assess inhibitory ability, but also on assessments of working
memory capacity: If older adults have a hard time distinguishing relevant from irrelevant
information, this likely means that they store task-irrelevant information, reducing the
storage capacity available for task-relevant information.

Speed of Processing

Older adults have a slower speed of processing than young adults. This slowed
processing is noted at the motor level, but it also is apparent at a cognitive level. For
example, older adults will tend to be slightly slower than young adults when they must
slam on the break at a red light; this slowing may primarily be due to motor changes,
because the association of red = stop remains very strong with aging. The reaction time
differences between young and older adults will be exaggerated, however, if older adults
must decide whether to slam on the breaks or to hit the gas as they approach a light that
has just turned yellow. This additional slowing likely results because of the increased
cognitive processing that must occur before the appropriate action can be selected.

Salthouse and colleagues have suggested that this decline in processing speed
may underlie the age-related changes in cognitive function. It is apparent how slowed
speed of processing could be detrimental to performance on any type of timed task.
Importantly, however, a slower speed of processing could also manifest itself on non-
timed tasks. For example, imagine that I read aloud the following arithmetic problem,
and ask you to solve it in your head, with no time limit: “Jimmy walks up to a store
counter with 3 packs of gum, each costing 50 cents. He gives the sales clerk $5. Because
the clerk is out of dollar bills, she gives Jimmy his change in quarters. How many
quarters does Jimmy receive from the sales clerk?” On the face of it, this is a task of
working memory ability (the ability to store various pieces of information and to update
the information as you work through the problem) that might be thought of as being
independent from a measure of speed of processing, because there is no time limit for
solving the task. However, if it takes someone a little longer to process the phrase
“Jimmy walks up to a store counter with 3 packs of gum,” it is possible that they will
have a harder time attending to the phrase “costing 50 cents.” Similarly, if it takes
someone longer to multiply 3 by 50, it is possible that by the time that calculation is
completed they will have forgotten the amount of money that Jimmy gave to the clerk. In
other words, cognitive performance can suffer because the slowed mental operations
cannot be carried out within the necessary time frame, and because the increased time
between mental operations can make it more difficult to access previously processed information. Thus, a slower speed of processing may lead to a poorer encoding of information and a reduced ability to store information. In support of the hypothesis that processing speed changes may underlie much of the cognitive decline with aging, controlling for speed of processing often eliminates age differences on cognitive tasks, and longitudinal studies have shown a strong relation between changes in speed of processing and changes in performance on a large number of cognitive tasks.

Domain-Specific Theories of Cognitive Aging

In contrast to the domain-general theories of cognitive aging, domain-specific theories propose that some age-related declines may not be explained by core deficits that affect all aspects of cognition, but rather by changes that have a larger impact on one area of cognition than on another.

Word-Finding Difficulties and Transmission Deficits

Older adults often have difficulties retrieving the appropriate name for a person, place, or thing. These word-finding problems can be manifest in various ways: excessive use of pronouns (due to difficulty generating the proper nouns), decreased accuracy and increased reaction time when asked to name items, and increased tip of the tongue experiences. The tip-of-the-tongue state occurs when a person has access to a word’s meaning, but not the phonological features of the word. The word seems just out of reach. Older adults tend to have more tip-of-the-tongue experiences than young adults, particularly for proper names, and the accuracy of the phonological information available during a tip-of-the-tongue state (e.g., the first letter of the word, the number of syllables) tends to be more accurate for young adults than for older adults.

Burke, MacKay, and colleagues have suggested that these word-finding difficulties result from the fact that, with age, the links connecting one unit to another within the memory system become weaker. Thus, more links must be active in order for older adults to generate the correct name for an object or a person. This transmission deficit will mean that older adults will be relatively good at generating words when there are lots of links converging onto the word, but will show larger impairments when trying to generate words that have fewer associated links. Most everyday objects have many semantic associations (e.g., individuals know that apples are red, of waxy texture, round, can be eaten raw, etc). This convergence onto the word “apple” (referred to by Burke and colleagues as “summation of priming”) makes it relatively easy to generate the name of the object. In contrast, proper names (with the exception of nicknames) are arbitrary and do not benefit from the same summation of priming (e.g., there is nothing that is required for someone to be a Jane versus a Linda). Consistent with a transmission deficit, older adults remain relatively good at generating words of everyday objects for which they know a lot of semantic information, but show larger impairments when asked to generate proper nouns.

Contextual Memory and Associative Binding Deficits

Episodic memory can be thought of as including memory for two different types of information: Memory for the item previously encountered (which typically can be based on familiarity), and memory for the contextual details in which that item was
encountered (which requires recollection). For example, when I pass by someone on the street, I might recognize that I have seen the person before (item memory). I also may remember that I met the person at a recent conference (an item-context association) or that the person is my colleague’s husband (an item-item association).

Older adults remain quite good at using familiarity to recognize previously encountered people or items. However, older adults are particularly impaired at using recollection to remember the contextual details of an event. They seem to have difficulties binding together multiple event details into one cohesive memory. These deficits arise both when trying to remember item-item associations and item-context associations (“source” memory). Naveh-Benjamin and colleagues have proposed that this associative memory deficit underlies older adults’ episodic memory difficulties.

Two broad types of memorial deficits may underlie this decreased ability to remember item-item or item-context associations. First, older adults have difficulties initiating effective encoding “strategies” that would promote memory for the associative details of an experience (as proposed by Craik, Jennings, and colleagues). When they are given a strategy to use as they learn information (e.g., if they are asked to tell a story that binds the item to its context), older adults often perform as well as young adults on tasks requiring associative or contextual memory. Thus, at least some of the age-related deficits in remembering contextual details seem to result from deficits at encoding. Second, older adults seem to have difficulties either forming a long-lasting “bond” between an item and its context, or in retrieving that bound representation. Thus, given retrieval support (e.g., an untimed recognition task), older adults will tend to perform better than when given little retrieval support (e.g., a recall task).

**Preserved Cognitive Function with Healthy Aging**

Although the sections above have focused on age-related declines, aging is not associated with across-the-board deficits in cognitive. In fact, some aspects of cognition remain markedly stable, or even improve, as individuals age.

**Crystallized Intelligence**

“Crystallized intelligence” refers to the ability to retrieve and use information that has been acquired throughout a lifetime. It often is contrasted with “fluid intelligence,” the ability to store and manipulate new information. As discussed above, “fluid intelligence” processes tend to be disrupted by healthy aging. “Crystallized intelligence,” in contrast, remains stable across the lifespan. Thus, older adults are very good (often better than young adults) at defining words, answering questions that rely on general world knowledge (e.g., “Who wrote the ‘Star Spangled Banner’?”), detecting spelling errors, or carrying out skills related to jobs that they have held for many years.

**Emotion Regulation**

Another important area of preservation (or enhancement) is within the realm of emotion regulation. After about the age of 60, the ability to regulate emotion seems to start to improve. Thus, older adults show lower rates of depression than young adults. Compared to young adults, their good moods last longer, and they are able to rebound more quickly from negative mood states. Older adults seem to focus more on positive
information in their environment, and to choose activities (e.g., spending time with close family or friends) based on their potential for emotional fulfillment.

At least some aspects of memory for emotional information also seem to be preserved with aging. While older adults tend to show overall poorer memory than young adults on a variety of tasks requiring retrieval of contextual information, studies of “flashbulb memories” (memories for a public event that was highly surprising and emotional) have suggested that older adults, like young adults, are more likely to remember contextual details if the event contains emotional relevance than if it does not. The emotional memory benefit for older adults may be particularly pronounced for positive information, although a number of studies have suggested that older adults receive a memory boost when asked to remember negative experiences as well.

**Neural Changes with Healthy Aging**

Although healthy aging is associated with brain changes, not all regions are affected equally. To date, the vast majority of studies investigating the neural changes with healthy aging have used structural MRI (allowing examination of the volume of various brain regions) and functional MRI or PET (allowing indirect measurements of neural activity as individuals are performing a task). These studies have suggested that the largest changes in structure and function occur in the prefrontal cortex and in the medial temporal-lobe, while other cortical and subcortical regions remain relatively preserved across the lifespan. Current research also is focused on examining how the connections between regions are affected by aging: Diffusion tensor imaging studies are being conducted to examine age-related changes in white-matter tracks, and structural equation modeling of FMRI and PET data is being used to investigate age-related changes in the functional connections between brain regions. These methods may provide new insights into the neural changes that mediate older adults’ cognitive decline.

**Changes in Prefrontal Cortex**

The prefrontal cortex shows notable changes with aging. At a structural level, there is evidence of atrophy, both in the gray matter and in the white matter. The gray matter declines may reflect reductions in the number of cells (due to cell death) or may be a sign of neuronal shrinkage. The white matter changes reflect axonal abnormalities, and may result in slowed neurotransmission. It is plausible that these white matter changes may mediate the cognitive slowing that accompanies healthy aging.

Prefrontal function also is altered with aging. Across a range of working memory and episodic memory tasks, older adults seem to show a different pattern of prefrontal activity than young adults, with reduced activity in some prefrontal regions, and increased activity in other regions. As noted by Roberto Cabeza and colleagues, particularly in the prefrontal cortex, older adults often show a hemispheric asymmetry reduction. In other words, on tasks leading to unilateral prefrontal activity in young adults, older adults will tend to show bilateral recruitment. It is not yet clear whether this bilateral recruitment reflects compensatory activation, or whether it is a result of pathological changes (e.g., hemispheric release from inhibition). Some of the strongest evidence in favor of the compensatory view has come from studies comparing the pattern of neural recruitment in older adults who perform a task as well as young adults (high performers) and in older adults who perform the task more poorly (low performers).
These studies have found that the high performers tend to recruit the prefrontal cortex bilaterally, whereas the low performers show unilateral prefrontal activity. To the extent that the prefrontal activity underlies the initiation of goal-relevant task strategies, it would make sense that the older adults who recruit additional prefrontal regions would be those who would be best able to perform the tasks. Nevertheless, future studies are required to clarify whether this compensatory hypothesis can account for all of the findings of bilateral prefrontal recruitment with age.

Medial Temporal-Lobe Changes

The hippocampus proper is the other region that shows large age-related change. While there are structural changes in the hippocampus, it is not clear whether there is significant cell loss in the hippocampus with aging, or whether the structural changes are related more to neuronal atrophy (shrinkage). There also is ambiguity regarding the regions of the hippocampus that are most affected by aging. High-resolution MRI, allowing the distinction of the various hippocampal subfields (CA1, CA3, dentate gyrus, subiculum) may allow better assessment of the structure (and function) of these regions.

Functionally, the hippocampus tends to be under-recruited by older adults during both the encoding and retrieval phases of recollective or associative memory tasks, and these functional changes often correlate with the older adults’ reduced performance on the tasks. Given the critical role of the hippocampus in forming vivid and detailed memories, it makes sense that the functional and structural changes in this region would correspond with older adults’ difficulties in remembering the context in which information was learned.

Changes in Emotion Processing Regions

The fact that older adults show improved emotion regulation, and a memory enhancement for many types of emotional information, is consistent with the neural evidence indicating that emotion processing regions (particularly, the amygdala and orbitofrontal cortex) are relatively spared in healthy aging. The amygdala shows minimal atrophy with healthy aging; its atrophy is on par with the decline in whole-brain volume (with a 1-3% reduction in volume every decade). Similarly, the orbitofrontal cortex seems to undergo little volumetric decline with age, particularly as compared to other regions of the prefrontal cortex.

Mild Cognitive Impairment (MCI)

As discussed above, some cognitive impairment is a natural part of the aging process. For some adults, however, advancing age is associated with fairly severe impairments in recent memory. Although the deficits do not impair their ability to function in daily life (and thus they do not meet the criteria for dementia), these individuals have cognitive impairments that exceed those that typically accompany healthy or successful aging. “Benign senescent forgetfulness” was the first term used (by Kral and colleagues) to describe these individuals’ impairments, although there were no strict diagnostic criteria associated with the concept. “Age-associated memory impairment” (proposed by Crook and colleagues) was the first attempt at a standardized definition, requiring an individual to have subjective memory complaints and to perform at least 1 standard deviation below the mean for young adults on a standardized memory
task. This concept was criticized by a number of researchers, who believed that the concept was too restrictive. “Mild cognitive impairment” (MCI; defined by the Mayo clinic Alzheimer’s Disease Research Center) is the most recent in a series of attempts to characterize these individuals who straddle the boundary between healthy aging and dementia. A diagnosis of mild cognitive impairment requires subjective memory complaints, and impairment in one area of cognition (scores must be more than 1.5 standard deviations below age-scaled norms), but with deficits not severe enough to interfere with activities of daily living or to result in a diagnosis of dementia.

There has been tremendous interest in defining this group of individuals, because as treatments that slow or reverse the development of Alzheimer’s disease (AD) become available, it will be critical to have a method for diagnosing individuals at risk for, or in the prodromal stages of, the disease. Individuals with MCI seem to be an excellent population to be the targets of such treatments, because they are at increased risk for development of dementia, and of AD in particular. In fact, by some estimates, the vast majority of patients with MCI will eventually meet the diagnostic criteria for dementia.

The link between MCI and AD is supported not only by the high conversion rate, but also by the overlapping neuropathological and genetic features. Like AD patients, those with MCI have significant structural and functional changes in the medial temporal- lobe. They also have alterations in the concentration of amyloid-beta protein, the protein associated with neuritic plaque formation in AD. Moreover, the ε4 allele of the apolipoprotein E, associated with an increased risk of developing AD, also is over- represented among individuals with MCI.

Alzheimer’s Disease (AD)

Alzheimer’s disease was first described by Alois Alzheimer in 1907. In the landmark publication, Alzheimer reported a case study of a woman with severe psychiatric symptoms and memory deficits. An autopsy conducted upon her death revealed a large quantity of intracellular neuritic plaques and extracellular neurofibrillary tangles, now recognized as the pathologic hallmarks of AD.

Cognitive Changes in Alzheimer’s Disease

Although dementia (a loss of intellectual function severe enough to interfere with daily activities) can result from a variety of etiologies, AD is by far the most common cause, accounting for an estimated two-thirds of all cases of dementia. Because AD can only be confirmed at autopsy, its clinical diagnosis must be an exclusionary one. Thus, the clinical profile of AD requires memory impairment plus decline in one other area of cognition (language, motor function, attention, executive function, personality, or object recognition). The deficits must have a gradual onset, and they must progress continually and irreversibly. When these criteria are met, a diagnosis of “probable” AD is given. When made by a trained clinician, this diagnosis will be accurate in the vast majority (80-90%) of cases.

Episodic Memory

In contrast to healthy older adults, who remain able to successfully remember previously-encountered information (though perhaps not the context in which it was encountered), the most notable deficit for patients with mild AD is an inability to
remember information encountered in the recent past. This deficit extends across different types of encoding tasks (e.g., incidental or intentional; deep or shallow processing), and exists regardless of the stimulus materials (e.g., pictures, words, faces, autobiographical events, emotional stimuli) or the task’s retrieval demands (e.g., recall, forced-choice recognition, yes-no recognition). In fact, deficits in episodic memory tend to be the best way of distinguishing people with AD from healthy older adults.

**Semantic Memory**
In contrast to episodic memory, semantic memory (general world knowledge) is relatively spared with mild AD. As the disease progresses, however, significant semantic deficits arise. The deficits are particularly pronounced on word-finding tasks, with the extent of such deficits being useful for tracking the severity of AD. Current research is examining the extent to which the breakdown in semantic memory is due to changes in the structure of the memory networks (i.e., to a problem with the storage of such knowledge) or to difficulties retrieving the stored information (i.e., a problem with access).

**Working Memory and Executive Function**
In addition to deficits in long-term memory, Alzheimer’s patients also show deficits in the on-line processing of information (“working memory”). Deficits are particularly pronounced on tasks requiring dual-task performance, suggesting that a primary deficit in AD may be in “executive functions,” the ability to flexibly shift attention and to attend to goal-relevant information.

**Neural Changes in Alzheimer’s Disease**
Although plaques and tangles often are apparent throughout the brain in the later stages of Alzheimer’s disease, early in the course of the disease, the medial temporal-lobe regions are those most affected. Even early in the disease, the hippocampal formation shows marked atrophy, and a volumetric reduction in the entorhinal cortex (which serves as the site of input to the hippocampus) is one of the best indicators that an individual has early Alzheimer’s disease. Given the essential role of the hippocampus for memory formation and retrieval (as demonstrated by the link between hippocampal damage and amnesia), it makes sense that patients with mild AD would be best identified by their difficulties remembering recently learned information (as discussed above).

The amygdala is another region of the medial temporal-lobe that is affected early in the disease process. This region, through its interactions with other medial temporal-lobe structures, is thought to be essential for enhancing individuals’ memories for highly emotional events. It is likely because of the amygdalar damage that patients with AD do not show a memory benefit for emotional information.

In addition to the medial temporal-lobe changes, the nucleus basalis also shows significant cell loss in mild AD. This region of the ventral forebrain contains many of the brain’s cholinergic neurons; thus, the damage to this region impedes cholinergic neurotransmission. Many of the first approved therapies for AD have been aimed at increasing the amount of acetylcholine in the brain, by blocking the function of acetylcholine esterase (the enzyme that breaks down the neurotransmitter acetylcholine). The minimal effectiveness of these acetylcholine esterase inhibitors in affecting cognitive
function in AD patients suggests that the acetylcholine deficiency is not the only cause of the cognitive dysfunction in AD (and, indeed, at least by late-stage AD, there is marked depletion of other neurotransmitters, including norepinephrine, dopamine, and serotonin). The underwhelming effect of the cholinesterase inhibitors has led to continued research on alternate therapeutic options for AD, which may prove to be more effective in altering the progression of the disease.

Neural Changes in Later-stage Alzheimer’s Disease

In later stages of the disease, there is increased atrophy throughout the medial temporal-lobe, and the cellular abnormalities also become apparent in the frontal lobe and throughout the temporal lobe. Because the frontal lobe is essential for higher-level executive functions, and the temporal neocortex is critical for the ability to retrieve semantic information, the advancing neuropathology in these regions clearly is linked to the cognitive deficits that arise in moderate AD. By the very late stages of AD, neuropathology is abundant throughout the cortical and subcortical structures, even within primary sensory regions (e.g., auditory, visual, and motor cortex).

Individuals Differences in Aging

Unlike many diseases or illnesses that can be linked to a specific cause, MCI and AD appear to arise due to a combination of many factors, both environmental and biological. Research has begun to elucidate some of the traits that can increase the likelihood of disease development (“risk factors” such as prior head injury, mutations in the apolipoprotein, presenilin-1 and presenilin-2 genes, or having the ε4 allele of apolipoprotein E) or that seem to reduce the probability of disease (“protective factors” such as high education level, intake of antioxidants, or having the ε2 allele of apolipoprotein E). Research continues to investigate the reliability of these factors in predicting disease development, and to examine whether any of the protective factors can alter disease progression once the pathological hallmarks of disease are present.

More broadly, researchers are beginning to recognize the necessity of taking an individual-differences approach to understanding the cognitive and neural changes that accompany aging. Research is now exploring the potential differences between high-performing and low-performing older adults. It is plausible that a better understanding of what differentiates the most successful agers from those who age less gracefully will lead to ideas for behavioral or neurobiological interventions that can boost the performance of individuals who experience significant age-related cognitive decline.

Bibliography


**Suggested Cross-References to Other Articles**

Learning and memory in normal aging
Aging of the brain
Aging of the brain and Alzheimer’s Disease
Aging and memory: Humans
Alzheimer’s disease: Overview
Mild cognitive impairment