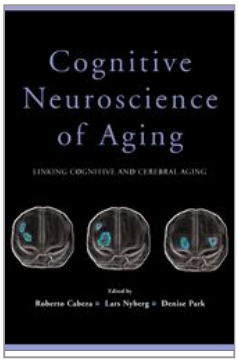

Cognitive Neuroscience of Aging: Linking cognitive and cerebral aging
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Cognitive Neuroscience of Aging

Emergence of a New Discipline

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Abstract and Keywords

This chapter begins with a brief discussion of the new discipline of cognitive neuroscience of aging (CNA). The main goal of CNA is to link the effects of aging on cognition to the effects of aging on the brain. An overview of the four main sections of the book and the subsequent chapters is presented.

Keywords: cognition, aging, brain, CNA

Until recently, the cognitive and neural mechanisms of age-related changes in cognition were usually studied independently of each other. On one hand, studies in the domain of *cognitive psychology of aging* investigated the effects of aging on behavioral measures of cognition and characterized a variety of age-related deficits in memory, attention, and the like. On the other hand, studies in the domain of *neuroscience of aging* investigated the effects of aging on the anatomy and physiology of the brain and described forms of age-related neural decline, such as cerebral atrophy and synaptic loss. Although it is reasonable to assume that cognitive aging is largely a consequence of cerebral aging, the relationships between these two phenomena are still largely unknown. Fortunately, this void is being rapidly resolved by studies focusing on the relationships between the effects of aging on the cognition and on the brain. This group of studies constitutes the new discipline of cognitive neuroscience of aging (CNA). Although CNA has a long past, only lately has it achieved the

critical mass to be considered an autonomous discipline. The main goal of this book is to provide an introduction to this exciting new field.

To describe the issues addressed by CNA, it is useful to start with a simple model that includes the basic components of the problem. In the model in figure 1.1, aging is assumed to affect structures and processes both in the brain and regarding cognition. Although artificial, the distinctions between brain and cognition and between structures and processes are useful for conceptual purposes. Likewise, even though any change in cognition implies a change in the brain, it is useful to distinguish between neurogenic and psychogenic effects. *Neurogenic effects* (solid arrows in figure 1.1) occur when a change in the brain causes a change in cognition. For example, age-related atrophy of prefrontal gray matter may lead to decline in working **(p.4)**

(p.5) memory function. *Psychogenic effects* (dashed arrows in figure 1.1) occur when a change in cognition causes a change in the brain. For instance, older adults who do not use certain cognitive processes may suffer greater cerebral atrophy in the brain regions that mediate these processes, or older adults who received a cognitive intervention may show improvements in cognitive function and changes in neural networks. As illustrated by figure 1.1, neurogenic effects may lead to psychogenic effects and vice versa. For instance, a decline in neural function may originate a compensatory change in cognitive strategies, which in turn may initiate a change in brain function.

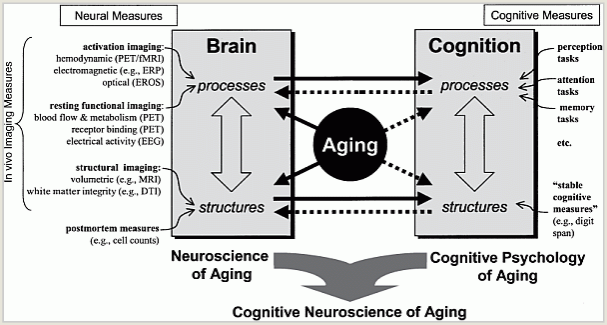

Figure 1.1. Model for the cognitive neuroscience of aging (DTI, diffusion tensor imaging; EEG, electroencephalogram; EROS, event-related optical signal; ERP, event-related potential; fMRI, functional magnetic resonance imaging; MRI, magnetic resonance imaging; PET, positron emission tomography).

The main goal of CNA is to link the effects of aging on cognition to the effects of aging on the brain. The effects of aging on cognition are assessed with cognitive measures (right side of figure 1.1), such as accuracy and RT data from perceptual tasks, attention tasks, and the like. The effects of aging on the brain are assessed with neural measures (left side of figure 1.1), such as postmortem and in vivo imaging measures. Postmortem data provide much greater spatial resolution (e.g., dendrite morphology), but in vivo imaging measures can be more directly linked to cognitive performance in living human participants. This is the main reason why the development of imaging methods and their application to the study of aging were the main forces behind the birth of CNA. At present, imaging is the dominant CNA approach, which is a trend clearly

reflected in the contents of this first introduction to CNA. As CNA develops, future books are likely to cover other methodological approaches.

This book has four main sections. The first section describes the main imaging methods, including structural imaging (chapter 2 by Raz), resting functional imaging (chapter 3 by Bäckman and Farde), and activation imaging (chapter 4 by Fabiani and Gratton, chapter 5 by Gazzaley and D'Esposito, and chapter 6 by Rugg and Morcom). The second section reviews imaging findings about specific cognitive functions, including perception and attention (chapter 7 by Madden, Whiting, and Huettel), working memory (chapter 8 by Reuter-Lorenz and Sylvester), episodic memory (chapter 9 by Park and Gutchess), and prospective memory (chapter 10 by West). The third section focuses on clinical and applied issues, including causal mechanisms in healthy and pathological aging (chapter 11 by Buckner), functional connectivity in healthy and pathological aging (chapter 12 by Grady), and the combination of imaging and cognitive rehabilitation methods (chapter 13 by Nyberg). The last section of the book focuses on CNA models, including empirical models of the effects of aging on lateralization (chapter 14 by Daselaar and Cabeza) and a computational model of the effects of aging on the dopaminergic system (chapter 15 by Li). The contents of the four sections of the book are summarized and discussed next.

Imaging Measures

The chapters in the first section of the book describe the use in CNA of imaging measures, including structural, resting functional, and activation imaging. Structural imaging consists mainly of magnetic resonance imaging (MRI) measures of gray and white matter volume and integrity. Resting functional imaging measures include **(p.6)** positron emission tomography (PET) and MRI measures of blood flow and metabolism, scalp recordings of electrical brain activity (electroencephalogram, EEG), and PET measures of receptor binding. Activation imaging is comprised of measures taken while participants are actively engaged in performing a cognitive task; these measures include electromagnetic measures such as event-related potentials (ERPs), optical measures such as event-related optical signal (EROS), and hemodynamic measures such as PET and functional MRI (fMRI). The five chapters in the first section of the book focus on the use of different imaging techniques in CNA, including empirical findings and methodological issues.

The use of structural imaging in CNA is described by Raz in chapter 2, which reviews cross-sectional and longitudinal approaches in MRI studies of aging. These two approaches have different weaknesses: Cross-sectional data may be confounded by cohort effects, secular trends, and selection criteria differences, whereas longitudinal data may be contaminated by sampling bias caused by differences in mortality, morbidity, and mobility (the three *M*s of longitudinal research). These problems may be attenuated by combining both approaches.

The results of cross-sectional studies suggest that the volume of gray matter declines linearly with aging, whereas white matter increases during young age, plateaus during young adulthood and the middle age, and declines during old age (an inverted U function). The prefrontal cortex (PFC) is the region that shows greatest age-related differences, followed by the putamen and the hippocampus. There is substantial variability across studies because of differences in subject selection criteria, measurement methods, and definitions of regions of interest (ROIs). This kind of problem is attenuated by automated methods, such as voxel-based morphometry (VBM), but these methods have their own problems (e.g., sensitivity to fluctuations in MRI signal, partial-volume errors).

The number of published longitudinal studies increased during the last three years. However, most of these studies covered relatively short intervals (e.g., 1–2 years), with only a few spanning intervals up to 5 years. In these studies, the expansion of cerebral ventricles with age is nonlinear, with little change in young adults, but rapid change in older adults. Cortical regions show a linear decline with age, and consistent with cross-sectional data, it is more pronounced in PFC. In contrast, medial temporal lobe (MTL) regions show a nonlinear decline, possibly reflecting cumulative pathological effects. MTL atrophy may provide important information for the diagnosis of Alzheimer's disease (AD), which is associated with a faster atrophy rate in these regions. In general, the results of longitudinal studies tend to agree with those of cross-sectional studies, but when they disagree it is usually because the latter underestimates the magnitude of true change.

chapter 2 reviews also a few recent studies using diffusion tensor and diffusion weighted imaging (DTI and DWI, respectively) to investigate age-related changes in white matter integrity. Finally, Raz considers modifiers of age-related neural decline, including those that bring bad news (hypertension), good news (aerobic exercise), and mixed news (hormone replacement therapy).

The use of resting functional imaging in CNA is described by Bäckman and Farde, whose chapter 3 reviews receptor imaging studies of dopamine (DA) function. There is abundant evidence that DA systems play an important role not only in **(p.7)** motor functions, but also in higher order cognitive functions. For example, cognitive functions are often impaired in patients (with Huntington's or Parkinson's disease) and animals with DA deficits and can be modulated by DA agonists and antagonists. The role of DA in cognition is also supported by computational models and by ontogenetic and phylogenetic evidence.

There are two main DA systems, nigrostriatal and mesolimbic, and two families of DA receptors, D_1 and D_2. Located in the presynaptic terminal, the DA transporter (DAT) protein regulates the synaptic DA concentration. DA function can be measured in vivo using PET and SPECT (single-photon emission

computed tomography) and special ligands. Different ligands have been developed for measuring D_1 and D_2 receptor binding, the synthesis of DA in presynaptic neurons, and the DAT. There is strong evidence of age-related losses in post- and presynaptic DA markers, which may reflect decreases in the number of neurons, the number of synapses per neurons, and/or the expression of receptor proteins in each neuron. D_1 and D_2 receptor binding declines from early adulthood at a rate of 4% to 10% per decade, and this decline is correlated with the decline of DAT, possibly reflecting a common causal mechanism.

From the point of view of CNA, the most important finding is that age-related DA decline is associated with age-related cognitive decline. Given the cognitive role of fronto-striatal loops, age-related striatal DA deficits could also account for age-related cognitive deficits associated with PFC dysfunction. Moreover, age-related DA binding deficits have been observed in PFC and in posterior cortical and hippocampal regions.

The use of activation imaging in CNA is described in chapter 4 by Fabiani and Gratton, chapter 5 by Gazzaley and D'Esposito, and chapter chapter 6 by Rugg and Morcom. chapter 4 by Fabiani and Gratton considers the advantages and disadvantages of different functional imaging methods, reviews the main findings of ERP studies of aging, and describes novel optical imaging methods and their application to aging research. Whereas hemodynamic imaging measures such as PET and fMRI have excellent spatial resolution but poor temporal resolution, electrophysiological measures such as ERPs have poor spatial resolution but excellent temporal resolution. Optical methods can provide good spatial and temporal resolution, but have limited penetration and a low signal-to-noise ratio.

Given that the strengths and weaknesses of these techniques are complementary, combining these methods is probably the best strategy to address their respective limitations. With their exquisite temporal resolution, ERPs are ideal to investigate one of the most prominent features of cognitive aging: the age-related slowing in information processing. Whereas in cognitive research the only direct measure of processing speed is reaction time (RT) and the duration of the various processing stages constituting the RT can only be inferred, ERPs provide a direct measure of these processing stages. For example, ERP studies have shown that age-related slowing affects the evaluation rather than the response stage, inconsistent with the notion of generalized slowing. ERPs can also assess the integrity of inhibitory processes by measuring neural responses to irrelevant and novel stimuli, and available results are consistent with the idea that aging impairs inhibitory control processes.

Optical imaging methods provide greater spatial resolution and yield both hemodynamic measures (near-infrared spectroscopy, NIRS) and neuronal measures (EROS) **(p.8)** of brain activity. Optical imaging has already been

applied to investigate cognitive aging and could provide critical information concerning the effect of aging on the coupling between neuronal function and hemodynamic responses. This effect is one of the main topics of chapter 5 by Gazzaley and D'Esposito.

chapter 5 focuses on hemodynamic measures, particularly potential confounding factors in the interpretation of the blood oxygen level dependent (BOLD) signal in fMRI studies of cognitive aging. These studies generally attribute age-related changes in BOLD signal to age-related changes in neural activity, thereby assuming that the coupling between BOLD signal and neural activity is the same for young and older adults. However, this coupling may be altered by age-related changes in the neurovascular system and by comorbidities associated with aging. Age-related changes of the neurovascular system likely to affect the BOLD signal include changes in ultrastructure (e.g., sclerosis), resting cerebral blood flow (CBF), vascular reactivity, and cerebral metabolic rate of oxygen consumption. The BOLD signal may also be affected by comorbidities associated with aging, such as leukoariosis and small strokes, and by medications.

Given all of these potentially confounding factors, several fMRI studies directly investigated the coupling of BOLD signal and neural activity in young and older adults. These studies investigated simple sensory and motor tasks assumed to be unaffected by aging and measured the similarity of the hemodynamic response function (HRF) in younger and older adults. Overall, the results suggested that although the signal-to-noise ratio may be smaller in older adults, the overall shape, refractoriness, and summation of the HRF are similar in young and older adults. These findings are encouraging and support the feasibility of using fMRI to investigate age-related changes in neural activity. At the same time, differences in signal-to-noise ratio suggest caution when interpreting the results of studies in which the level of activity is generally weaker in the older group. Gazzaley and D'Esposito provide very useful recommendations on how to address potential confounds in imaging studies of cognitive aging.

Useful recommendations are also provided by Rugg and Morcom in chapter 6, which provides guidelines for avoiding potential confounds in fMRI and ERP studies of cognitive aging. After describing a series of general issues regarding brain activity measures and subject selection, Rugg and Morcom discuss a series of confounding variables when imaging the effects of aging on episodic memory encoding and retrieval. Regarding encoding, the authors emphasize the need for controlling study processing by using incidental study tasks that recruit qualitatively similar cognitive processes in young and older adults and measures of performance that allow the rejection of failed encoding trials. Another encoding-related issue is the potential confound between task-related and encoding-related activity, which can be partly addressed by analyzing encoding activity on the basis of later memory performance (subsequent memory paradigm). When using this method, it is also important to control for

differences in the type of memory measured by the subsequent memory task (e.g., recollection vs. familiarity). Even if the type of memory measured is controlled, there is a chance that age effects may be confounded with differences in item memorability. The authors illustrate the control of these various encoding-related issues by describing an fMRI study of encoding and aging.

(p.9) Regarding retrieval, Rugg and Morcom note that control over study processing is critical not only in encoding studies, but also in retrieval studies. They also emphasize the need for unconfounding the effects of aging on retrieval attempt and retrieval success; this can be accomplished by using event-related designs. Imaging studies should also make sure that young and older adults are using equivalent forms of memory, for example avoiding a greater implicit memory component in older adults. Finally, the authors underscore the need for distinguishing activations caused by age differences from activations caused by performance differences. If memory performance is lower in older adults, age-related activity will be confounded with differences in effort, differences in the proportion of guessing trials, differences in monitoring caused by lower confidence, and differences in the type of items retrieved (hard- vs. easy-to-retrieve items). Rugg and Morcom illustrate the control over some of these retrieval issues by describing an ERP study of retrieval and aging.

In summary, there is today a wealth of neuroimaging methods available to CNA researchers; these methods include structural imaging, resting functional imaging, and activation imaging techniques. These various imaging techniques have complementary strengths and weaknesses, which are partly a consequence of the level of neural phenomena they measure. As illustrated by figure 1.2, neural structure is a prerequisite for resting neural function, and resting neural function is a prerequisite for cognition-related neural activity. Thus, the three types of imaging measures provide access to different but interconnected aspects of the neural bases of cognitive aging. Structural imaging measures have the advantage being closer to the original neurobiological mechanisms of cognitive aging and being primarily sensitive to neurogenic effects (e.g., it is more likely that atrophy causes cognitive deficits than the other way around). On the other hand, structural imaging measures are only indirectly related to behavior and cannot easily identify compensatory changes in the aging brain.

The advantages and disadvantages of activation imaging are a virtual mirror image of those of structural imaging. Activation imaging measures are directly related

(p.10) behavior and are ideally suited for investigating reorganization of function and possible compensatory changes in the aging brain. On the other hand, activation imaging measures are removed from the original neurobiological mechanisms of aging and cannot easily distinguish between neurogenic and psychogenic effects (Do older adults perform differently because their brain activity is dissimilar, or is their brain activity dissimilar because they perform differently?). Finally, the strengths and weaknesses of resting functional imaging fall somewhere between those of structural and activation imaging. Thus, the three imaging techniques provide different and complementary information; hence, an exciting challenge for CNA researchers is to combine these techniques and integrate their findings to achieve a clearer picture of the neural correlates of cognitive aging.

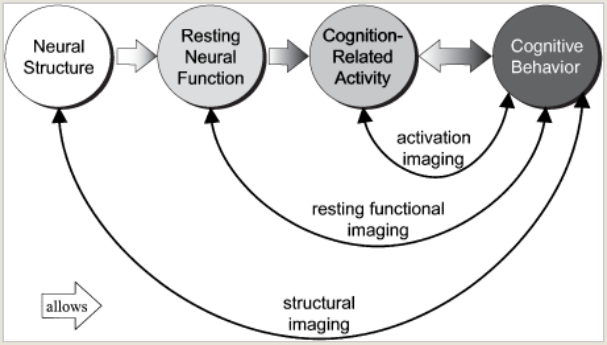

Figure 1.2. Imaging techniques link behavior to different kinds of neural phenomena.

Basic Cognitive Processes

There has been rapid growth in linkage between cognitive processes and neural function in older adults, and the integration of these domains has provided stunning insight into the dynamic interplay between neurobiological and cognitive processes across the life span. It is clear that, with age, frontal and hippocampal structures that are central structures to higher order cognition show a decrease in volume, particularly in frontal areas. It appears, however, that these decreases in volume do not map directly onto decreases in attention and memory function. Based on early findings in the CNA, it appears that, in response to these neural insults, the brain retains a certain amount of residual plasticity and may remodel or reorganize activation patterns and neural networks to partially mitigate the effects of the decreasing integrity of the aging brain. Thus, a key question in the CNA regards the extent that differences in neural activity between young and old reflect adaptive neural activations compensatory for decreased volume. Other questions focus on the nature of neural activations that underlie areas of preserved cognitive function with age and, as the field develops, the specific nature of remodeled neural networks. In this section, we include chapter reviews of visual perception and attention, working memory, longterm memory, and prospective memory.

In chapter 7 by Madden, Whiting, and Huettel on visual perception and attention, the authors provide a comprehensive overview of age-related changes in sensory systems that alter the identification of objects and events in the environment. A thorough review of the behavioral literature on perception and attention is provided, documenting decreases in sensory function with age and

the centrality of theories of decreased speed of processing in accounting for many age differences in perception and attention. This is followed by a discussion of age differences in attention, as well as the instances when some types of attentional processes remain age invariant. Then there is a review of the neurobiological underpinnings of attention and perception in young adults. This sets the stage for a detailed discussion of what has been learned about age differences in neural activation and pathways for object recognition and attention. The picture presented is one of decreased efficiency and less differentiation of neural pathways mediating object recognition and higher order visual processes, along with instances of compensatory activation. The authors discuss **(p.11)** the importance of understanding the nature of age differences in the hemodynamic response, assessing criteria for evaluating whether data are supportive of compensatory recruitment with age, and the authors also suggest that there may be age differences in baseline neural activity that color the interpretation in subtraction analyses of attention and perception.

Chapter 8, authored by Reuter-Lorenz and Sylvester, reviews what is known about working memory and aging and the neural underpinnings of working memory as revealed by functional neuroimaging studies. The chapter is organized with an initial section on behavioral work that isolates the structure and function of working memory in young adults. This is followed by a review of the literature on aging, which suggests that although maintenance functions are relatively preserved in working memory with age, executive processing components exhibit substantial declines in late adulthood. From this point, the chapter addresses the neural circuitry of working memory with an initial focus on findings in young adults, followed by what is known about aging. There is a thorough discussion of the meaning of increased frontal activations in older adults and an evaluation of arguments suggesting that the increased activation is compensatory; there are suggestions for directions and questions that future research should address.

Park and Gutchess address in chapter 9 the topic of the cognitive neuroscience of long-term memory. They review findings from the behavioral literature that indicate that long-term memory declines with age, although there are also areas of preserved function, such as that observed for recognition of complex pictures. In this chapter, neuroimaging findings are organized around the hypothesis that increased activation in frontal areas with age during encoding of long-term memory is observed in response to decreased hippocampal activations. A lengthy section on the encoding of information addresses age differences in neural activations associated with intentional versus incidental memory, pictures compared to words, and differences in neural activations associated with remembered compared to forgotten items. Contextual manipulations, as well as neural activations associated with retrieval, are also studied, with evidence that patterns of neural differences with age are larger for encoding in comparison to retrieval manipulations. The final section of the chapter examines patterns of

neural activations as a function of individual differences, such as for high versus low performers. The results from these studies do not provide convincing evidence at this time regarding the compensatory value of increased frontal activations with age. The authors nevertheless conclude that the study of individual differences and aging has the potential to resolve arguments about the compensatory value of increased neural activation in older adults.

The final chapter in this section is authored by West and focuses on neural activations associated with prospective memory, that is, remembering to carry out planned intentions or actions. There is a large body of behavioral literature on age differences in prospective memory, and important distinctions are made between event-based and time-based prospective memories. Models of prospective memory are compared in chapter 10, including the multicomponent model, the automatic associative model, and the controlled attention model. Functional imaging and ERP studies have revealed a distributed network of structures that support prospective memory, including the frontal and parietal lobes, as well as the thalamus and hippocampus. Nevertheless, **(p.12)** research in this domain is limited; at the time of this writing, there were only two functional imaging studies and three ERP studies on prospective memory. Decreases in prospective memory with age are isolated because of inefficient encoding of intentions and the inability to maintain those intentions over time, with these functions residing primarily in the frontal lobes, brain structures that show decreased integrity in late adulthood.

The four chapters in this section provide a complete overview of behavioral findings on age differences in perception and attention, working memory, long-term memory, and prospective memory, along with a thorough integration of the neural mechanisms governing these fundamental aspects of cognitive function. Perhaps the single most consistent theme throughout these chapters is the meaning of increased neural activation in frontal areas with age, along with the great promise that larger studies that examine individual differences hold for resolving this issue. The chapters in this section represent the most complete integration of behavioral data with neuroscientific findings on basic cognitive processes and aging that presently exist.

Clinical and Applied Issues

As noted at the beginning of this chapter, the main goal of CNA is to link the effects of aging on cognition to the effects of aging on the brain. If the knowledge generated by studies within this field can help us understand the basis for the cognitive problems that often accompany normal aging as well as pathological forms of aging (notably Alzheimer's disease), then it may in turn have relevance for attempts at developing means by which age-related cognitive deficits can be compensated for. In particular, it is possible that knowledge about age-related brain changes can inform us about the constraints we may be facing in trying to boost the memory performance of older and demented adults.

In turn, this could put focus on the avenues by which various forms of compensation are most likely to have an impact. The chapters in the section on clinical and applied issues speak to these significant issues.

Chapter 11 by Buckner begins by asking the fundamental question of why there is so much variability in the age of onset of prominent cognitive decline. Buckner presents a thought-stimulating discussion of possible answers to this question. The discussion is organized around three basic principles. The first principle holds that multiple, co-occurring causal mechanisms contribute to cognitive decline in aging. The second principle states that variability exists in the expression of causal mechanisms across individuals and in the responses of individuals to them. This principle is of critical importance to various attempts at supporting impaired cognition as it stresses the role of the active mechanisms of compensation and responses that individuals adopt. The third and final principle is that causal mechanisms should be studied within integrative theories that span different levels of organization, from the genetic to the behavioral. This final principle not only is relevant in this particular section, but also is closely related to issues discussed in the following section on CNA models.

In chapter 12, Grady presents a review of functional neuroimaging studies of memory in young adults, older adults, and patients with dementia. A special focus is on changes involving the PFC and the hippocampus as these areas have been suggested **(p.13)** as particularly vulnerable to aging, and much of the neuroimaging literature on memory has indeed focused on these particular regions. The first review section is concerned with studies using the traditional univariate subtraction approach to identify brain regions in which age-related differences in the magnitude of activation changes exist.

In the next section of chapter 12, Grady introduces another important approach to the analysis of functional neuroimaging data: connectivity analyses. One form of connectivity analysis is referred to as *functional connectivity* and involves assessing how activity in a given region covaries with activity in other areas of the brain during a task. Another form of connectivity analysis, *effective connectivity*, models the way brain areas influence one another and tests whether the model fits the data at hand. It is illustrated in the chapter how connectivity analyses can be useful in identifying between-group differences not seen with univariate approaches.

Nyberg is concerned in chapter 13 with the topic of *plasticity*, defined as withinperson variability designating the potential for various forms of behavior or development. A selective literature review is presented to address four related issues: (1) the potential for plasticity in older age, (2) limitations of plasticity in older age, (3) cognitive explanations of reduced plasticity in older age, and (4) neuroanatomical correlates of reduced plasticity in older age. Based on this review, the chapter concludes that there is indeed substantial potential

for plasticity in older age. Nonetheless, there is much evidence to suggest that younger adults benefit more from training than older adults, and the reduction in plasticity in older age seems to reflect both a processing and a production deficit. Imaging studies provide some indication that the processing deficit can be linked to age-related changes in the frontal cortex, whereas the neural correlates of production deficits seem to be task specific. It is tentatively proposed that training aimed at overcoming production deficits in specific cognitive domains is the most fruitful strategy for attempts at improving the performance of older adults.

Taken together, the chapters in this and other sections demonstrate that today there is some knowledge about the basis for impaired cognitive performance in older age. The chapters also suggest that future CNA studies, using imaging techniques as well as other methodological approaches, can yield additional important information. The transformation of knowledge about brain–cognition relations in adulthood and aging into various compensatory actions for age-associated cognitive impairment is still a relatively little examined area, but an area that holds promise for the future.

Models in Cognitive Neuroscience of Aging

Perhaps the most salient aspect of the discipline of CNA is its integrative nature (see figure 1.1). That is, we strongly emphasize the need to consider changes at multiple levels of examination (see also chapter 11). Naturally, in a specific study, it is not realistic to think that all the relevant theoretical and methodological aspects of a problem can be considered. Instead, cross-level integration will typically be realized in efforts to link related findings from multiple studies. The section on CNA models presents two such efforts.

(p.14) chapter 14 by Daselaar and Cabeza relates recent behavioral and neuroimaging findings on hemispheric lateralization and aging to general ideas about hemispheric organization. The chapter has three sections. In the first section, anatomical differences between the left and right hemispheres and various accounts of hemispheric specialization are introduced together with three models of hemispheric interaction (insulation, inhibition, and cooperation). In the second section, two models of age-related changes in hemispheric lateralization are presented: the right hemi-aging model and the hemispheric asymmetry reduction in older adults (HAROLD) model. The former model states that the right hemisphere is most sensitive to the harmful effects of aging, resulting in a greater dependence on left hemisphere processing in elderly adults. By contrast, the HAROLD model states that elderly are more likely to rely on both hemispheres in conditions in which unilateral recruitment is sufficient in young adults. In the final section, three different accounts of age-related asymmetry reductions are discussed in relation to the different hemispheric

interaction models addressed at the beginning of chapter 14 (dedifferentiation, competition, and compensation).

Chapter 15 by Li is concerned with neurocomputational approaches that examine the relation between cognitive aging deficits and aging-related attenuation of neuromodulation that can have effects on neural representations and information transfer within and between cortical regions. A selective review of recent computational approaches to neuromodulation and their applications in cognitive aging research is presented. It is proposed that cognitive aging may be related to declines in dopaminergic modulation in the PFC and in various subcortical regions. A cross-level integrative theoretical link is highlighted: Deficient neuromodulation leads to noisy neural information processing, which in turn might result in less-distinctive cortical representation and various subsequent behavioral manifestations of commonly observed cognitive aging deficits. It is emphasized that the brain is an open system, and life span cognitive development is a dynamic, cumulative process that shapes the neurocognitive representations of ongoing interactions with the environment and sociocultural contexts through experiences. From this position, it follows that not only feed-upward effects from neural mechanisms to cognition and behavior must be considered, but also downward contextual and experiential influences on neurocognitive processing.

These chapters jointly span the levels from neurochemical modulation to evolutionary and cultural influences. It may strike the reader as an overwhelming task to consider data from such a multitude of sources. However, given the complexity of the substantive issues, a full understanding of how brain–cognition relationships are affected by aging will most likely require that (directly or indirectly) happenings at the molecular level are interrelated with changes that take place at the societal level.

Conclusion

This volume is designed as a handbook to represent state-of-the-art knowledge about the CNA. Leading researchers have provided detailed and thoughtful consideration of the theoretical, methodological, and empirical knowledge and challenges facing the emerging discipline of the CNA. It is likely that progress in this field will be **(p.15)** rapid and, 5 years from now when a new edition of this volume will likely be available, that many of the puzzles raised in this book will have been solved. We feel relatively certain that a central question raised in this volume—whether increased frontal activations in older adults that occur across a range of demanding cognitive tasks are compensatory—will have been answered. The theoretical and methodological tools to address the compensation issue empirically are available. All that remains is for a large, carefully controlled and executed study to be conducted to address this issue across fundamental domains of attention, working memory, and long-term memory.

Even as we see that a deeper understanding of compensatory neural mechanisms is within reach, we recognize as well that unlocking this puzzle will lead to many new questions. We expect that new techniques and methodologies will evolve at a rapid rate, resulting in a new set of issues and challenges facing researchers in the CNA. If we were to guess, we would expect that studies of tensor imaging, connectivity analyses, and transcranial magnetic stimulation (TMS) will play a more prominent role in the next volume than in this present version. We also believe that imaging techniques will provide a gold standard for evaluating the efficacy of cognitive interventions, both pharmacological and behavioral. Moreover, we expect that the study of individual differences with age will move beyond behavioral measures of performance into the dynamic field of neurogenetics, resulting in an important new subdiscipline within the CNA.

In closing, we have high hopes for the promise of the CNA to provide the framework necessary for understanding both neurological health and disease as it unfolds across the human life span. We are hopeful that the research and ideas contained in this volume serve as an important springboard for better understanding of the aging mind, as well as provide the information needed to further the maintenance of health and vitality into the later years of our older citizens. **(p.16)**