In America today, there are 46 million people over the age of 65 and there will be over 98 million by 2060. With aging, there are many neurological diseases that can adversely affect the brain, such as Alzheimer’s disease, Lewy body dementia, and Parkinson’s disease. These diseases are common and a major cause of disability and suffering. Although, in a small percentage of patients, these diseases can be related to a genetic defect, for the most part we do not fully understand their causes. Perhaps that is why they are called “degenerative diseases.” Several decades ago, the diagnosis of Alzheimer’s disease was made only in those who were below the age of 65 and had signs of progressive dementia. If a person had cognitive deterioration and was above the age of 65, their disorder was called “senile dementia.” One of the reasons this term was used is that many clinicians thought memory loss and cognitive decline were part of normal aging. Fortunately, we have learned that disorders such as Alzheimer’s disease are associated with specific pathological changes in the brain, such as neurofibrillary tangles, and that normal aging does not cause this disease. Although the origins of these degenerative brain diseases are still unclear, much progress has been made in understanding their pathophysiology, thereby helping to pave the way for preventative, ameliorative, and curative treatments.

In the absence of any brain disease, from the time we are born until the time we die, our brains are continuously changing. These changes alter many brain functions such that with maturation there is growth and with aging deterioration. Neuroscientists and clinicians who treat brain disorders have three interrogative pronouns they often use in approaching such matters: how, why, and what? How does the brain change with aging and how do these changes affect us? Why does it change? What can be done about these changes? The goal of this book is to try to address these how, why, and what questions.

The word “cognition” comes from the Latin verb *cognosco*, which is a cognate of the Greek verb γινώσκω, gi(g)nósko, meaning, “I know.” This book is about the effects of aging on cognition, but it is not limited to our ability to know and learn. It also about the influence of aging on sensory perception, creativity, emotions and moods, action programming, and executive functions such as planning, initiating, monitoring, controlling, and completing.

There are many different organizing principles of cognitive function, and in the last two centuries we have learned much about them. One of the most basic principles is that brain processes are organized in a modular fashion. The concept of modularity or localization of specialized functions dates back to the early part of the nineteenth century. Franz Joseph Gall, the founder of phrenology, proposed that different regions of the brain are important for mediating different cognitive functions. Gall also proposed that the larger and more developed a module, the better the performance. Although Gall’s postulates generated the pseudoscience of phrenology, in which the shape and size of the skull, quantified through caliper measurements, were thought to indicate an individual’s personality and mental abilities, his postulates of modularity and size have received scientific support.

Support for the modularity hypothesis first came from Paul Broca, a French physician and anthropologist, who was strongly influenced by a lecture given by Ernest Aubertin. Aubertin and his father-in-law, Jean-Baptiste Bouillard, were students of Gall. Aubertin believed that speech is mediated by the frontal lobes. After hearing that lecture, Paul Broca reported the case of Louis Victor Leborgne, a patient who had a history of speech loss and a right hemiplegia [1]. Broca noted that, although Leborgne was unable to speak or write, he was able to understand spoken language, a
dissociation of two language–speech functions. Leborgne died and a postmortem examination revealed that he had a discrete lesion localized in his left hemisphere, primarily in the inferior portion of the frontal lobe, but also extending to the anterior temporal lobe and deep into the cerebral white matter. The inability of this patient to speak, according to Broca, caused by a disorder of the special faculty of articulated language [1]. In a subsequent paper published in 1865, Broca described several other patients who had an aphasia associated with a right hemiplegia [2]. Based on these observations of laterality, Broca concluded that in humans, the left hemisphere primarily mediates speech. These observations provided additional evidence of brain modularity.

Double dissociations provide even greater evidence of modularity. In 1864, Carl Wernicke wrote “Der Aphatische Symptomencomplex,” describing patients who, unlike the nonfluent patients Broca described, were fluent. In addition, unlike patients with Broca’s aphasia, those that Wernicke described exhibited a severe comprehension disorder [3]. Furthermore, whereas patients with Broca’s aphasia have anterior perisylvian lesions maximally involving the frontal lobe, patients with Wernicke’s aphasia have posterior perisylvian lesions that extensively involve the superior temporal lobe. In Wernicke’s important paper, in addition to describing a form of aphasia and its localization, he also introduced the concept of an information-processing network. He suggested that the area that contains the memories of how words sound, located in the left posterior temporal lobe (now called Wernicke’s area), is connected to and provides information to the area where the articulation of words is programmed (now called Broca’s area).

The second part of Gall’s hypothesis, bigger is better, was supported by a study by Geschwind and Levitsky [4]. They reported that the posterior superior temporal lobe, which includes Wernicke’s area, is often larger in the left than in the right hemisphere. In addition, Foundas et al. [5] reported that righthanded people with left hemisphere dominance for speech also have a larger left pars triangularis, which is part of Broca’s area.

The reasons why certain areas of the cerebral cortex store different forms of information and perform different mental operations are now fairly well understood. By far the most important reason is patterns of connectivity. This can be illustrated with some examples. The daily business of neurons in auditory association cortices is the processing of acoustic input. In the left hemisphere, to a greater extent than in the right, the daily business of neurons in Broca’s area is to translate input into spoken words. The network of connections between auditory association cortex and Broca’s area, including Wernicke’s area and the supramarginal gyrus, in the course of language learning, acquires knowledge of the orderly relationships between acoustic phonological sequences and spoken articulatory sequences. Unimodal and polymodal association cortices acquire knowledge of the world and the objects within it through the repeated sensory input that underlies perception. Connectivity between both unimodal and polymodal association cortices and the perisylvian phonological cortex entrains phonological processing to semantic knowledge. Analogous principles of cortical connectivity apply to all components of language function, including syntax and grammatical morphology. The connectivity principle extends to other regions of the brain. The major inputs to the frontal lobes are sensory (relayed from postcentral association cortices to dorsolateral frontal cortex) and limbic (relayed from limbic structures to the orbito-frontal cortex). The major output of the frontal lobes is to the motor cortex. Thus, prefrontal cortex is predestined by its connectivity patterns to acquire knowledge that enables the translation of sensory and limbic input into orderly plans for action. The fact that frontal-postcentral connectivity is bidirectional conveys additional capacities for working memory and volitional attention that are essential to optimization of information processing and to thinking.

In the preceding paragraph, we spoke of the daily business of neurons in auditory association cortex being the processing of acoustic input. This leads us to another way of understanding regional cortical function – in terms of the position of a region in a trajectory of sensory or motor projections. Thus, primary auditory cortex (Heschl’s gyrus) projects to primary and secondary auditory association cortices (superior temporal gyrus and the planum temporale); primary visual cortex (calcarine cortex) projects to primary (occipital and posterior temporal lobes) and secondary visual association cortices (lateral and ventral temporal lobes and parietal lobes); and primary somatosensory cortex (postcentral gyrus) projects to primary and secondary somatosensory association areas (parietal lobes). Sensory association cortices project to polymodal/supramodal cortical regions (angular and supramarginal gyri, Brodmann’s
area 7 in the superior parietal lobes, the cingulate gyrus, the temporal poles, prefrontal cortex, and the hippocampal system. In the frontal lobes, premotor cortex can usefully be thought of as an association area for motor cortex. These association cortices serve simultaneously as data repositories (long-term memories – knowledge and skills) and data processors. While the idea of projection trajectories is a useful one, it must be borne in mind that within the cortex, connections are reciprocal (two-way). Thus, one cortical region does not send information to another cortical region – it elicits a pattern of neural activity in the connected region, and, through rapid back-and-forth exchange, the two regions (and other connected regions) settle into optimal or quasi-optimal patterns of activity corresponding to attractor states (a recurring theme in this book).

The concept of neural networks, first articulated by Wernicke, is implicit in connectivity principles. Modern imaging techniques seek evidence of anatomic connectivity by measuring functional connectivity – to which there are innumerable references in this book. This is a worthy enterprise provided that one bears in mind that functional connectivity may be state-dependent (e.g., motor cortex supports the representation of movements but also of a component of movement verbs), and that covariance in the activity of neurons in different regions of the brain may be produced not just by their connectivity but also by slowly recurring changes in the electrocortical rhythms in which they are simultaneously engaged.

Although the modularity of cortical function is defined by connectivity patterns, we have only incipient knowledge of the hows and whys of neuronal processing in any given region and essentially no knowledge of the basis for individual differences. Two questions may be asked: (1) What is the fundamental nature of the computational processing that takes place? and (2) How does the cytoarchitecture of a given cortical region endow it with certain, presumably optimal, processing capabilities given its particular functional specialty? Edmund Rolls (Chapter 14) provides some insight into the current state of the science bearing on question one. We have long had tantalizing clues on how to address question two but so far have not been able to make much sense of them.

At the beginning of the twentieth century, Brodmann discovered that the human cerebral cortex has six layers. He also found enormous variation in the thickness and cellular organization of different regions of the cortex. From analysis of microscopic and macroscopic features, Brodmann divided the cortex into a total of 52 areas [6]. Brodmann postulated that the structural differences between cortical regions had to do with differences in their functions. Undoubtedly this is true but, so far, the relationship between structure and function remains largely opaque with limited exceptions, e.g., the extraordinary thickness of layer 4 in calcarine cortex, reflecting the enormous afferent input from the lateral geniculate nuclei conveying visual input.

To perform their functions, neurons have to communicate – entraining each other in patterns of activity. The means of communication is primarily chemical and is achieved through the release of neurotransmitters. Some neurotransmitters provide the basis for data processing, e.g., glutamate (excitatory) and γ-aminobutyric acid (GABA, inhibitory). Others are best regarded as regulatory (acetylcholine, dopamine, norepinephrine, epinephrine, serotonin, and histamine) or modulatory (e.g., endorphins, somatostatin, neuropeptide-Y, and substance P). The brain also contains glia. These are cells that are not neurons but have many important functions in the brain, including providing physical support of neuronal structures, cleaning up after neurons through uptake of potentially toxic materials (e.g., glutamate), maintaining the blood-brain barrier, and forming myelin (the critical insulation around the axons of neurons).

With healthy aging, many changes take place in the brain. These may affect neurons, neural connectivity, neurotransmitter systems, and glia. They may affect some brain regions more than others. For example, the frontal lobes are heavily dependent on connectivity with posterior association areas, the medial dorsal thalamus, the basal ganglia, and limbic structures (e.g., the amygdala, lateral septal nuclei, the insula, the periaqueductal gray, and the nucleus solitarius). Thus, when there is degradation of white matter, frontal lobe functions may be differentially impaired.

This book begins with reviews of aging-related changes in anatomy and physiology. Chapter 4 reviews aging-related changes revealed by imaging studies and, thereby, starts the bridge linking anatomic alterations associated with aging to changes in cognitive functions. Subsequent chapters review aging-related alterations in cognitive functions, including memory, language, motor planning, attention, executive functions, emotions, and creativity. Chapter 5 includes some review of changes in vision
that may contribute to disorders of visual perception. Chapter 8 provides references to the large literature on aging-related changes in auditory function. Olfaction is reviewed in Chapter 6. There are certainly aging-related changes in somatosensory functions, but our limited knowledge of their relevance to cognitive functions did not seem to justify a separate chapter.

From the outset of this project, we encouraged authors to think strongly about potential mechanisms. Of course, because of the limitations of existing science, many of the mechanisms elucidated are at best tentative hypotheses. A startling number of mechanisms emerged, as well as a number of recurring mechanistic themes.

There are many means by which aging-related changes can be studied. The vast majority of the studies discussed are cross-sectional, which means that attribution of the differences they reveal to a process that extends across the life span requires an inference that the differences observed do not reflect an incipient degenerative process. Cross-sectional studies that involve more than two age groups can help to confirm such an inference. Longitudinal studies, in principle, can provide the most definitive evidence of changes associated with an aging process, as opposed to incipient dementia, but these studies also have problems, including duration, expense, practice effects, and population attrition. In this book, we encouraged use of the term “aging-related” when we believed that the preponderance of evidence suggested that the primary mechanism inducing a change was related to aging. Readers should be aware, however, that this is not necessarily a correct conclusion, particularly as it is a challenge to completely rule out the effects of an incipient disease process.

The final chapters discuss what can potentially be done to slow or reverse aging-related decline of cognitive functions, including the role of exercise, cognitive rehabilitation, and the use of pharmacological agents. We now have overwhelming evidence of the protective effect of cognitive reserve in delaying and even preventing dementia. The elucidation of specific mechanisms associated with aging-related cognitive decline, many potentially amenable to treatment (reviewed in Chapter 15), coupled with existing evidence of the value of some interventions (reviewed in Chapters 16–19), may provide pathways to increasing cognitive reserve. Hence, the last chapter of this book: “Preventing Cognitive Decline and Dementia.”

We hope that the knowledge gained from reading this book about brain aging may help to differentiate normal aging from brain diseases, reduce the adverse effects of brain aging, provide some assurance to those of us approaching late life that declining episodic memory and anomia are not necessarily symptoms of incipient dementia, and, optimistically, lead to further research on how the adverse effects of brain aging can be reversed, stopped, modified, or best managed.

References