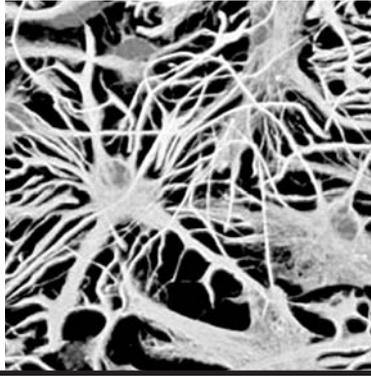


The diagrams above show the location of some key brain structures discussed in this report. The sagittal view shows a slice of the brain at about the midpoint as seen from the side. For instructional purposes, some structures are shown that are not technically visible at the mid point of the brain. The coronal diagram shows a slice through the forebrain viewed from the front. The diagrams show approximate locations only.

CHAPTER 3

A Primer on Brain Structure and Function



The brain is arguably the most complicated and least understood organ of the human body. Although much was accomplished in brain research during the 20th century, recent innovations in radiologic imaging, neurochemistry, neuroimmunology, genetics, and more have advanced our knowledge dramatically. We have learned, for instance, that adult brains are capable of creating new neurons, contrary to the conventional idea that humans are born with all the neurons they will ever have.¹ Modern imaging technology has allowed us to noninvasively observe patterns of neural activity during mental tasks, such as reading and adding numbers, so that we are beginning to get a much more dynamic view of structure and function.²

Modern imaging technology has allowed us to noninvasively observe patterns of neural activity during mental tasks.

Basic Neuroanatomy: Subsections of the Brain and Their Functions

The human brain can be anatomically divided into three broad regions: forebrain, midbrain, and hindbrain. The forebrain is the largest of these regions and contains the cerebral hemispheres, the areas most often associated with the unique cognitive abilities of humans. The cerebral hemispheres contain a number of deep-lying structures—including the basal ganglia, hippocampus, and amygdala—all enveloped in a wrinkled outer layer, the cerebral cortex.

The basal ganglia, clusters of cells that act as hubs for neural signals, are involved in a broad range of functions from motor control to emotion and learning. The hippocampus is highly involved in memory, particularly in the formation of new memories about experienced events (or episodic memory), and may be one of the first regions to undergo changes in Alzheimer's disease. The amygdala is involved in emotional processing, particularly in attaching emotional associations to memories. Another forebrain structure, the basal nucleus of Meynert, is a center for the production of the neurotransmitter acetylcholine.

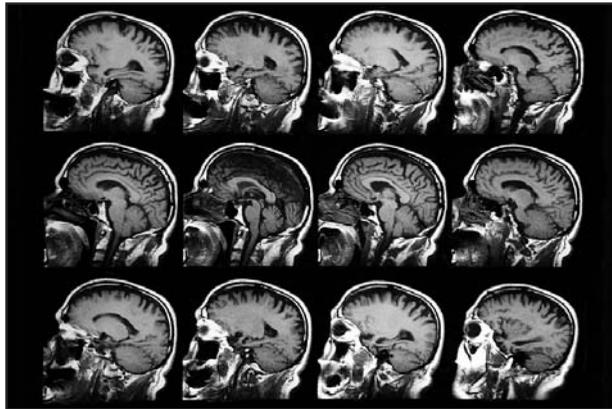


The first known written reference to the brain, this Ancient Egyptian hieroglyph was written around the 17th century BC.

Damage to either the gray matter of the cerebral cortex or the underlying white matter can produce specific cognitive deficits.

The tissue of the outer layer of the cerebral cortex consists mainly of neural cell bodies and is known as gray matter. Just beneath run neural projections that relay signals between cortical cells and virtually every other area of the brain. This tissue is known as white matter, owing to the myelin encasing the neural projections that makes it appear white to the naked eye. Damage to either the gray matter of the cerebral cortex or the underlying white matter can produce specific cognitive deficits. For example, lesions to Broca's or Wernicke's areas produce deficits in language expression and comprehension, respectively. Interruption of the white matter tracts connecting Broca's and Wernicke's areas produces more nuanced deficits in both language expression and comprehension.

The midbrain and hindbrain are both smaller than the forebrain but regulate essential involuntary functions, such as heart rate and breathing. One hindbrain structure, the cerebellum, is also involved in movement and the learning of motor skills. Clusters of cells (nuclei) located in the midbrain and hindbrain produce essential neurotransmitters and interconnect with higher areas of the



brain. These include the substantia nigra and raphe nuclei, which produce dopamine and serotonin, respectively. Both dopamine and serotonin have a wide range of effects on cognition, and dopamine in particular is involved in motor function. Since the nuclei of the midbrain and hindbrain are the centers of neurotransmitter production and interact with virtually every other part of the central nervous system, damage to any one of them can dramatically affect a host of neurological functions.

The Brain at the Cellular Level

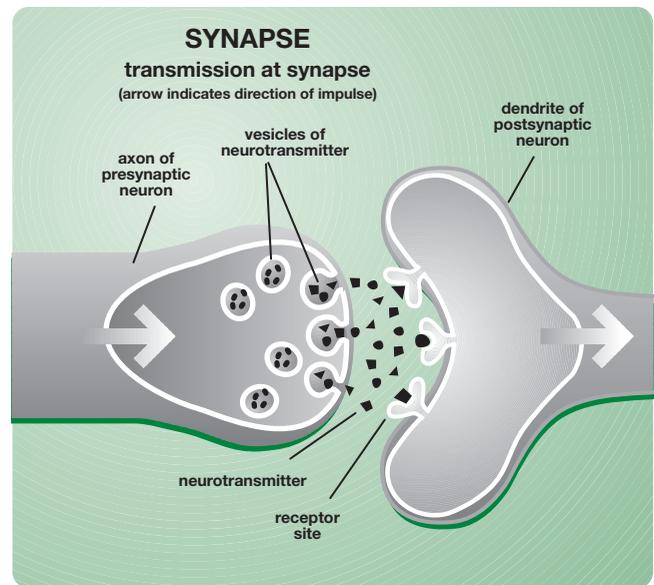
The brain consists of roughly 100 billion neurons and an additional 1–5 trillion support cells known as glia. Estimating the exact number of cells in the brain has been difficult due in part to their sheer density. Neurons connect to one another at microscopic points of contact, known as synapses, where signals are transmitted through the release of neurotransmitters. Each individual neuron can have anywhere from a handful to several thousand synapses with other

neurons, putting the potential number of synapses in the brain in the hundreds of trillions.³ Furthermore, synaptic connections are not static but can change depending on how frequently they are activated or in response to chemical signals in their environment, such as hormones or growth factors. It is this web of dynamic interconnections that is thought to underlie the brain's ability to orchestrate everything from unconscious activities, such as heart rate and breathing, to higher functions such as language, emotion, memory, and the ability to make conscious physical movements. Formation of new memories, in particular, is believed to be mediated by the modulation of synaptic connections.^{4 5}

Neurotransmitters released into the synapse bind to receptor proteins embedded in the post-synaptic cell wall much like a key fitting into a lock. Once bound to the receptor, the neurotransmitter-receptor complex can change the cell's electrochemical state, making it more excited. If a neural cell becomes sufficiently stimulated, it will initiate a new neural impulse, which will then trigger the release of neurotransmitters at another synapse, where the process repeats.

Repeated activation can increase the strength of the synaptic connection between two neurons in a phenomenon known as long-term potentiation, so that an incoming neural impulse of the same strength will trigger a stronger response in the post-synaptic cell once the connection is potentiated. A similar phenomenon in which synaptic connections are weakened, known as long-term depression, can also occur. Long-term potentiation has been closely associated with performance in animal models of learning and memory, and presence of soluble amyloid-beta, a protein thought to be of importance in the development of Alzheimer's disease, has been shown to interfere with potentiation.⁶

The strengthening and weakening of synaptic connections is thought to be the most basic element of information processing in the brain, similar to the storage of 0s and 1s in a computer system. If we view the activation of a single synapse as analogous to the processing of one operation by a computer, and assume the brain has 100 billion neurons with an average of 10,000 synapses each that become activated



10 times per second, then the brain can perform a staggering 10 quadrillion (10^{16}) operations per second. By comparison, current high-end home computers perform around 20 billion operations per second, and the fastest supercomputer in the world as of June 2007 performed around 600 trillion (6×10^{14}) operations per second. In terms of this analogy, it would take about 17 supercomputers or half a million high-end personal computers to match the processing speed of a single healthy human brain. Thus, although it would be grossly inaccurate to state that brains and computers function in the same way, the human brain can nonetheless be viewed as a truly prolific information processor, owing in large part to its extensive web of interconnections. Loss of synapses—decreases in the brain's connections—occurs in many neurodegenerative conditions such as Alzheimer's disease.⁷

Glial Cells

When first discovered, these cells were thought simply to provide structural support for neurons by holding them in place and so were called “glia,” Greek for “glue.” Glial cells are now understood to play numerous vital roles in the brain. There are three main types of glial cells in the central nervous system, each with specific functions:

- Astrocytes help to regulate the neuronal environment by absorbing and releasing chemicals. They have been implicated in diverse roles ranging from participation in signal transmission to regulation of neuronal activity and synaptic network formation.
- Oligodendrocytes wrap neural extensions in myelin, a fatty insulating substance that greatly increases the speed at which neural impulses travel.
- Microglia perform immune functions in the brain and are extremely sensitive to signals in their surroundings that indicate distress.

Although the brain is normally protected from most pathogens by the blood-brain barrier, when infectious agents do enter the brain microglia react quickly in order to minimize damage to sensitive neuronal tissue. The microglial response to cellular distress signals is twofold, propagating distress signals to other microglia

through the release of chemical messengers and releasing cytotoxic chemicals that can lead to neural cell death. Cytotoxic chemicals include those that trigger apoptosis (programmed cell death), as well as other highly reactive chemicals such as hydrogen peroxide and nitric oxide that can directly damage cells. In other words, while microglia provide a quick reaction to infectious agents, the price of their rapid immune response can be the destruction of many healthy nerve cells.

Under normal circumstances, microglia facilitate brain reorganization, assisting in such tasks as synapse remodeling, controlled cell death, and the clearing of cellular debris. They are also important in regulating brain development and can exert neuroprotective effects through the release of anti-inflammatory chemicals and growth factors. However, microglia have many known pathological roles as well, most of which are thought to result from their chronic overactivation. One role that has gained significant notoriety is the selective destruction of dopamine-producing neurons through chronic and progressive inflammation in Parkinson's disease (see chapter 6).⁸ In some cases, destruction of neurons can lead to further release of microglia-activating compounds, resulting in a vicious cycle of microglial activation and cell death. Chronic microglial activity has been implicated in the causation and development of Alzheimer's disease as well, and may also be involved in other forms of neurodegeneration including multiple sclerosis, amyotrophic lateral sclerosis, and Huntington's disease.⁹

HOW *it* WORKS



The Blood Brain Barrier

Cells lining the walls of blood vessels in the brain, as well as associated glial cells, participate in regulating the passage of chemicals into and out of the central nervous system, forming what is known as the blood-brain barrier. Astrocytes (a type of glial cell) physically contact blood vessels and can influence their activity and gene expression patterns through the release of chemical messengers. Although microglia are usually not considered part of the blood-brain barrier, they are both physically and functionally associated with it. Microglia do not perform any actual barrier function themselves but rather influence barrier properties through release of chemicals such as nitric oxide, interleukin 1-beta and tumor necrosis factor-alpha (see chapter 6).^{11 12 13}

The selectivity with which the blood-brain barrier regulates the passage of substances into and out of the brain changes under different conditions. For instance, permeability increases markedly under conditions of oxygen and glucose deprivation, as well as in response to proinflammatory biochemical signals. During development, higher permeability can allow toxicants into the developing brain. Dysfunction of the blood-brain barrier also commonly occurs at the other end of the lifespan, and higher levels of permeability have been correlated with more rapid progression of dementia. However, while changes in blood-brain barrier permeability are associated with dementia, their significance in the disease process is still unclear.

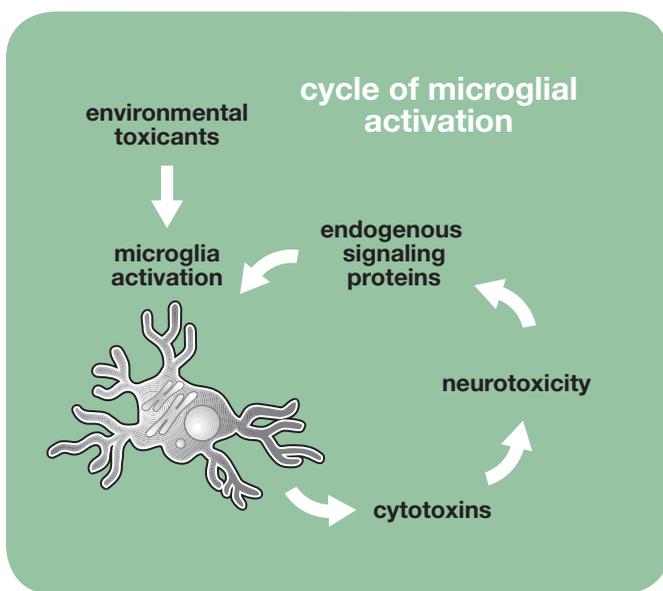
Neurologic Changes in Alzheimer's and Parkinson's Diseases

Typically, dementia first affects the forebrain structures involved in memory and judgment and then progresses to hindbrain structures that regulate balance and coordination. While virtually every region of the brain may sustain some form of damage in neurodegenerative disease, certain areas appear to undergo pathological changes more frequently than others. As the structure most commonly associated with memory, damage to the hippocampus is generally considered to result in some of the first clinical symptoms of Alzheimer's disease. Studies of human patients as well as controlled studies in animals have demonstrated that hippocampal damage produces profound deficits in spatial navigation and episodic memory.¹⁴

The basal nucleus of Meynert is another brain structure that is commonly affected in neurodegenerative disease. Damage to this area has classically been associated with Alzheimer's disease¹⁵ but is common in other forms of neurodegeneration as well.¹⁶

Since the basal nucleus of Meynert is a central part of the brain's acetylcholine system, the loss of neurons in this area deprives

higher brain regions of acetylcholinergic input. The neurotransmitter acetylcholine has known roles in learning and memory and has been shown to play a role in long-term potentiation.¹⁷ Animal studies show that damaging acetylcholine-producing neurons in the basal nucleus of Meynert and damaging the higher cortical areas to which they connect yield similar behavioral impairments.¹⁸ Pharmacologically blocking acetylcholine activity has negative effects on measures of



Certain substances from the nutritional and chemical environment are able to cross the blood-brain barrier and trigger microglial activation. When activated, microglia attempt to eliminate the perceived threat by releasing cytotoxic chemicals that may also damage neurons, which in turn can lead to the release of more microglia-activating compounds.

cognitive performance,¹⁹ and most medications that have been shown to temporarily improve cognitive function in Alzheimer's disease work by increasing brain levels of acetylcholine. Thus, it is not surprising that the loss of a neurotransmitter so intimately involved in learning, memory, and cognition would be a common finding in dementia.

Loss of dopamine-producing neurons in the substantia nigra is a cardinal feature of Parkinson's disease. As cells in this region normally project to parts of the basal ganglia which in turn project to several other higher brain regions, their loss also has widespread effects on brain function. Among the most notable of these effects is loss of the ability to execute voluntary movements, the primary symptom of Parkinson's disease. Among other cognitive processes, dopamine signaling is involved in attention, memory, and motivation. It has also been extensively studied for its roles in the brain's pleasure systems and addiction. Abnormal dopaminergic signaling is thought to explain the compulsive risk-seeking behaviors (such as compulsive gambling) that occur in a subset of medicated Parkinson's patients.²⁰ While dopaminergic dysfunction is of central importance in movement disorders, it may be a factor in cognitive impairment as well.²¹

Other neurotransmitter systems such as serotonin, glutamate, and norepinephrine also show some evidence of involvement in neurodegenerative disease. Although discussing the roles of each system in these disorders is beyond the scope of this chapter, it is worth noting that deficits in multiple neurotransmitter systems may interact synergistically to affect cognition. Furthermore, changes in the expression of neurotransmitter receptors and other factors that affect neural communication may also be important in age-associated cognitive impairment.

Pathological Markers of Neurodegenerative Disease

Post-mortem studies of the brains of patients with neurodegenerative diseases often show characteristic abnormalities, known as pathological markers. While they do not show the whole picture of what has gone wrong in a cognitively impaired brain, these abnormalities are considered to be the microscopic physical manifestations of the disease process.

Conventional definitions of neurodegenerative diseases often suggest that each one has a circumscribed set of pathological features. For example, Alzheimer's disease is said to be characterized by amyloid plaques and neurofibrillary tangles, and Parkinson's disease

by Lewy bodies. In reality, however, pathology is often spread across a spectrum, with significant overlap in pathological markers and cognitive symptoms across many supposedly distinct disease states. The notion of a continuum of pathological and cognitive features in neurodegenerative disease is further addressed in chapter 5.

Amyloid plaques, the principle pathological marker of Alzheimer's disease, consist of aggregates of a small protein known as amyloid-beta. While normally produced throughout the body and potentially playing some important physiological roles at low concentrations, increased amyloid-beta levels in Alzheimer's disease lead to the formation of insoluble aggregates in the brain. These aggregates, also known as senile plaques, in turn seem to be associated with damage to nearby brain cells and microglial activation.

Neurofibrillary tangles are the second pathological hallmark of Alzheimer's disease and consist of a modified structural protein known as tau. Neurofibrillary tangles and other abnormal tau aggregates also occur across a spectrum of other neurodegenerative conditions, such as frontotemporal dementia and multiple system atrophy. Under normal circumstances tau proteins assist in stabilizing the structure of the neuron, but in disease states they may stick to one another inappropriately, leading to cellular dysfunction. Although the links between neurofibrillary tangles and amyloid plaques are unclear, they tend to appear together in Alzheimer's disease and may both be necessary for cognitive impairment to occur.

Lewy bodies are a third type of pathological marker comprised of intracellular aggregates of the protein alpha-synuclein as well as an assortment of other proteins. While the physiological function of alpha-synuclein has yet to be explained, it tends to be concentrated around synapses and may be involved in cell structure arrangement.²² Although best known for their appearance in the substantia nigra in most cases of Parkinson's disease, Lewy bodies have also been found in several other forms of neurodegeneration, and distinct cortical and subcortical types have been recognized. While it is still not clear what causes the formation of Lewy bodies, they may result from the buildup of waste products when cellular protein recycling mechanisms stop functioning properly.²³

Even though pathological markers are often associated with cellular dysfunction in the brain, they should not necessarily be thought of as the drivers of the disease process. Pathological markers



Even though pathological markers are often associated with cellular dysfunction in the brain, they should not necessarily be thought of as the drivers of the disease process.

usually appear as parts of feedback loops in which their formation contributes to cellular dysfunction, which in turn contributes to their formation. However, they may not be the initiators of these vicious cycles. Instead, systemic conditions and environmental influences may well create the conditions for these processes to occur and, perhaps in the setting of susceptibility genes, provide the impetus to set them into motion. We discuss the conditions of oxidative stress and inflammation as key factors in these processes in chapter 6.

Normally, the brain maintains its function well into the late years of life even though structural changes associated with normal aging may be present. Neuroscientists have described considerable plasticity in the aging brain that permits recruitment of new pathways to accomplish neurological functions when older, well established pathways no longer work as well as they once did because of the normal aging process.

The next chapter summarizes general physiologic changes associated with normal aging and considers the aging brain in the context of total life history. Distinguishing changes associated with normal aging from those that are the manifestations of neurodegenerative disease is often difficult and subject to considerable debate.

Endnotes

1. Gage F. Neurogenesis in the adult brain. *J Neurosci*. 2002;22(3):612-613.
2. Ogawa S, Tank DW, Menon R, et al. Intrinsic signal changes accompanying sensory stimulation: functional brain mapping with magnetic resonance imaging. *Proc Natl Acad Sci USA*. 1992;89(13):5951-5955.
3. Drachman, DA. Do we have brain to spare? *Neurology*. 2005;64:2004-2005.
4. Bliss T, Collingridge G, Laroche S. ZAP and ZIP, a story to forget. *Science*. 2006;313:1058-1059.
5. Whitlock J, Heynen AJ, Shuler MG, et al. Learning induces long-term potentiation in the hippocampus. *Science*. 2006;313:1093-1097.
6. Chen QS, Kagan BL, Hirakura Y, et al. Impairment of hippocampal long-term potentiation by Alzheimer amyloid beta-peptides. *J Neurosci Res*. 2000;60(1):65-72.
7. Terry RD, Masliah E, Salmon DP, et al. Physical basis of cognitive alterations in Alzheimer's disease: synapse loss is the major correlate of cognitive impairment. *Ann Neurol*. 1991;30:572-580.
8. Gao H, Jiang J, Wilson B, et al. Microglial activation-mediated delayed and progressive degeneration of rat nigral dopaminergic neurons: relevance to Parkinson's disease. *J Neurochem*. 2002;81:1285-1297.
9. Block ML, Zecca L, Hong JS. Microglia-mediated neurotoxicity: uncovering the molecular mechanisms. *Nat Rev Neurosci*. 2007;8:57-69.
10. Bowman GL, Kaye JA, Moore M, et al. Blood-brain barrier impairment in Alzheimer disease: stability and functional significance. *Neurology*. 2007;68:1809-1814.
11. Block ML, Zecca L, Hong JS. Microglia-mediated neurotoxicity: uncovering the molecular mechanisms. *Nat Rev Neurosci*. 2007;8:57-69.
12. Yamagata K, Tagami M, Takenaga F, et al. Hypoxia-induced changes in tight junction permeability of brain capillary endothelial cells are associated with IL-1beta and nitric oxide. *Neurobiol Dis*. 2004;17:491-499.
13. Mark KS, Miller DW. Increased permeability of primary cultured brain microvessel endothelial cell monolayers following TNF-alpha exposure. *Life Sci*. 1999;64:1941-53.
14. Verhaeghen P, Marcoen A, Goossens L. Facts and fiction about memory aging: A quantitative integration of research findings. *J Gerontol*. 1993;48:157-171.
15. Whitehouse PJ, Price DL, Struble RG, et al. Alzheimer's disease and senile dementia: loss of neurons in the basal forebrain. *Science*. 1982;215(4537):1237-1239.
16. Samuel W, Alford M, Hofstetter CR, et al. Dementia with Lewy bodies versus pure Alzheimer disease: differences in cognition, neuropathology, cholinergic dysfunction, and synapse density. *J Neuropathol Exp Neurol*. 1997;56(5):499-508.
17. McKay BE, Placzek AN, Dani JA. Regulation of synaptic transmission and plasticity by neuronal nicotinic acetylcholine receptors. *Biochem Pharmacol*. 2007;74(8):1120-1133.
18. Muir JL. Acetylcholine, Aging, and Alzheimer's Disease. *Pharmacol Biochem Behav*. 1997;56(4):687-696.
19. Muir JL. Acetylcholine, Aging, and Alzheimer's Disease. *Pharmacol Biochem Behav*. 1997;56(4):687-696.
20. Imamura A, Uitti RJ, Wszolek ZK. Dopamine agonist therapy for Parkinson disease and pathological gambling. *Parkinsonism Relat Disord*. 2006;12(8):506-508.
21. Kaasinen V and Rinne JO. Functional imaging studies of dopamine system and cognition in normal aging and Parkinson's disease. *Neurosci Biobehav Rev*. 2002;26:785-793.
22. Alim MA, Ma QL, Takeda K, et al. Demonstration of a role for alpha-synuclein as a functional microtubule-associated protein. *J Alzheimers Dis*. 2004;6(4):435-442.
23. Olanow CW, Perl DL, DeMartino GN, et al. Lewy-body formation is an aggresome-related process: a hypothesis. *Lancet Neurol*. 2004;3(8):496-503.

