NEUROSCIENCE FOR THE MENTAL HEALTH CLINICIAN

SECOND EDITION

Steven R. Pliszka

THE GUILFORD PRESS

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Also from Steven R. Pliszka

Treating ADHD and Comorbid Disorders: Psychosocial and Psychopharmacological Interventions

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About the Author

Steven R. Pliszka, MD, is Dielmann Distinguished Professor and Chair of the Department of Psychiatry at the University of Texas Health Science Center at San Antonio, where he served as Chief of the Division of Child and Adolescent Psychiatry from 1995 until 2015. Throughout his career, Dr. Pliszka has been involved in a wide range of administrative, research, clinical, and educational activities. His research focuses on attention-deficit/hyperactivity disorder (ADHD) and related disorders; he has been involved with numerous clinical trials of medications for ADHD and currently uses functional magnetic imaging to try to understand the mechanisms of action of ADHD treatments. Dr. Pliszka has also been involved in several projects to integrate mental health services into pediatric primary care. He maintains an active clinical practice and serves as the attending psychiatrist for two residential facilities for children with severe behavioral and emotional disorders.

Preface

The first edition of *Neuroscience for the Mental Health Clinician* was published in 2003, just after the close of the National Institute of Mental Health's "Decade of the Brain." The U.S. Congress declared that "to enhance public awareness of the benefits to be derived from brain research, the Congress, by House Joint Resolution 174, has designated the decade beginning January 1, 1990, as the *Decade of the Brain* and has authorized and requested the President to issue a proclamation in observance of this occasion." The 1990s saw the emergence of neuroimaging and genetics as tools for research into mental disorders, and the first edition hinted at what might be on the horizon. I discussed dopamine genes for attention-deficit/hyperactivity disorder (ADHD), which regions of the brain might be involved in ADHD or affective disorder, and how psychopharmacological agents might exert their therapeutic effects. I mapped out hypothetical pathways of disease which, I hoped, would prove to be representative of the major mental disorders studied.

With the second edition, it is astonishing to see how much has changed in a little over a decade. Indeed, one only has to look at the 1990s-style webpage of the Decade of the Brain (*www.loc.gov/loc/brain*) and compare it to the webpage of the Human Connectome Project (*www.humanconnectomeproject.org*) to see the new, incredible breadth of contemporary brain research. If you have not heard of the Human Connectome Project, then you should wonder whether you might be as outdated as an old Compaq PC. Of course, you might fairly retort, "What does it matter?" After all, did the Decade of the Brain really produce any clinically relevant information? Are we now just looking at fancier websites? Perhaps, in 10 years we will be saying that the Connectome Project has been a big

disappointment. Why not just wait to learn about these things until someone discovers their true clinical relevance?

Before answering this question, I would like to give my personal perspective. My career has been unusual in that I have always been a practicing psychiatrist in addition to my research activities. When I began my academic career in the mid-1980s, I was primarily interested in ADHD itself. I joined other researchers who focused on finding "deficits" in norepinephrine or dopamine brain systems. Why the focus on these two chemicals? Because stimulant medications, the principal treatment for ADHD, blocked their uptake into neurons. We sought the answer by measuring the metabolites of norepinephrine and dopamine in urine (a technique that seems quaint in retrospect), but no clear result emerged. As I entered the field, I was responsible for developing the clinical ADHD program in our Division of Child and Adolescent Psychiatry. I saw 10–15 children with ADHD a week, either on my own or as a supervisor for our psychiatry residents. Many of these children and their families would go on to participate in my first research studies. I began to notice that many of these children with ADHD had anxiety disorders as well. This presented a problem: It was believed by clinicians at the time that these disorders were opposites of one another and that stimulant treatment made anxiety worse. Moreover, norepinephrine was believed to be elevated in anxiety. So how could ADHD and anxiety coexist if ADHD was caused by norepinephrine being too low and anxiety was caused by increased norepinephrine? Trying to answer this question set me on the study of comorbidity of other disorders with ADHD. Today, it is well accepted that ADHD is frequently comorbid with a wide range of psychiatric conditions (Biederman, Newcorn, & Sprich, 1991; Pliszka, 2009). It was my inquiry into the role of norepinephrine in behavior that led me to appreciate that each diagnosis in the *Diagnostic and Statistical Manual of Mental Disorders* (DSM) was not a stand-alone entity. Thus, I was able to expand my view of the disorder and the reach of treatment. By becoming more up to date in one's understanding of where neurobiology currently stands, it is possible to gain greater insight into the needs of one's patients.

I do not shy away from the fact that two decades of neurobiology research have not yielded a biological test for psychiatric disorder or produced a revolutionary treatment. "It's coming; this time we really mean it," is hardly a clarion call. When I entered psychiatry residency in 1981, we treated ADHD with short-acting stimulants, depression with tricyclic antidepressants, mania with lithium, and psychosis or aggression with "first-generation" antipsychotics such as haloperidol. Today, we treat ADHD with long-acting stimulants and depression with selective serotonin reuptake inhibitors (SSRIs). We have added anticonvulsant medications to the regimen for mood stabilization while using newer "second-generation" antipsychotics for psychosis, mood stabilization, and aggression. Patient

outcomes (except for a possibly reduced side-effect burden) are unchanged. This state of affairs should not make us cynical about brain research; it should make us redouble our efforts. Cancer research took 60 years of both trial and error and focused effort to reach the cure rates we have today (Zeng et al., 2015). I put this question to all my clinical audiences: Would you go to an oncologist who said, "I don't keep up with the basic science of cancer; I just wait till someone tells me what is clinically relevant"? Obviously, you would not. No mental health professional should adopt the cavalier position that "brain function isn't 'clinically relevant'; therefore, I really don't need to know about it." All clinicians, at the very least, need to be able to explain to their patients what the current hypotheses are about the biological aspects of mental illness. We should no more call them "chemical imbalances" than we would cite the medieval theory of humors, which laid the basis for the use of leeches and bleeding treatments well into the 18th century.

A glance at the table of contents shows that this edition has retained the structure of the first edition, but there has been a significant change in the theme and depth of each chapter. In the 20th century, the study of mental illness was still very much influenced by the "lesion" model of neurology. We thought in terms of which "gene" or which "brain region" was defective in a given disorder; furthermore, there was an implicit idea that each disorder defined by the DSM would have a unique pattern of brain dysfunction. While chapters are still organized by disorder, the new edition focuses on the key idea that psychiatric disorders are not neatly cleaved off from one another but share etiological factors and certain types of brain differences. I speak less of deficits in a given brain region and more about brain *networks*; that is, how do different brain regions interact with each other to produce cognition, emotions, and behavior? How can disturbances in these regions lead to psychopathology? A quick comparison of the figures from the first edition to this one clearly illustrates this: I moved away from the "circuit board" or A-to-B-to-C pathway illustration to show multiple, interacting regions.

A new emphasis in this edition is the growing awareness of how environment shapes both the structure and function of the brain. We have known for decades that gene and environment interact; what is new is the science of *epigenetics*. Environment can shape gene expression, such that the gene activity of even identical twins differs sharply after many years. This in turn has important effects on brain anatomy and function. A recent study shows that children's brain growth is correlated with years of parental education and family income (Noble et al., 2015). This does not mean that poor people are born with small brains; rather, the limited environment of a child born into poverty may stunt the epigenetic mechanisms that lead to optimal brain development. This is particularly relevant to the

study of the effects of child abuse and neglect. Our genes are the hardware; epigenetics is the software that runs the brain development process. How we raise our children affects them in a more profound way than we could ever imagine. It implies that the responsibility of society for mental illness is also far greater. As Charles Darwin himself observed, "If the misery of our poor be not caused by nature, but by our social institutions . . . then great is our sin."

In addition to epigenetics and a brain network approach, this edition includes more detailed discussions of attention, memory, and higher cognitive function. It describes the deeper understanding of the role of neurotransmitters in behavior and emotion that has emerged in the last decade. The biological role of stress in affective and anxiety disorders is elucidated. A separate, more detailed chapter on autism spectrum disorders is included.

I would like to acknowledge many people who have assisted me with this edition. First and foremost, I would like to thank my wife, Alice Narvaez, PhD, for her enormous emotional support throughout this process and her invaluable editing and proofreading of each chapter. At each step of the process, she has provided critical feedback and has helped me to be clearer in what I have sought to convey to the reader. My son, Andrew, was taking his introductory chemistry and biology courses as a freshman in college as I wrote this book. His hard work mastering his own coursework filled me with pride and made me optimistic about how his generation will use the advances discussed here.

Many of my colleagues and friends have supported and encouraged me over the years. I would like to thank my fellow faculty members in the Division of Child and Adolescent Psychiatry for their hard work and support during my 20 years as Division Chief: Brigitte Bailey, MD, Joseph Blader, PhD, Margaret Farrell, MD, Louise O'Donnell, PhD, Rene Olvera, MD, Thomas Matthews, MD, Kenneth Matthews, MD, Donna Roybal, MD, Jessica Sandoval, MD, Tracy Schillerstrom, MD, and James Stedman, PhD. The psychiatry residents and medical students of the University of Texas Health Science Center at San Antonio (UTHSCSA) have been an inspiration to me; a neurobiology seminar for them became the seeds from which this book grew.

As the writing of this book came to a close, I was appointed Chair of the Department of Psychiatry at the UTHSCSA. The mental health field faces many challenges; I have become more aware of this now that I have responsibility for many Department entities that treat people with severe and persistent mental illnesses. It is my hope that greater understanding of the neurobiology of mental illness will lead not only to advances in biological treatments but also to a more humane perspective on how mentally ill people should be treated in society.

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PART I

BASIC PRINCIPLES

CHAPTER 1

Introduction

WHY ANOTHER BOOK ON NEUROSCIENCE?

There are literally thousands of books on the brain, so why should a mental health clinician read this one? What is different in this second edition? The first edition set out to integrate research on neurobiology for the practicing mental health clinician. Even psychiatrists find that despite being exposed to neuroscience and neuroanatomy in medical school, what they learned in neurology does not transfer very well to the treatment of mental disorders. Clinical neurology focuses on strokes, epilepsy, and degenerative diseases of the brain that can have psychiatric sequelae, but even most psychiatrists do not encounter these disorders in their daily practice. What continues to be of interest to psychiatrists and to the broader group of mental health practitioners is a book outlining the neurobiology of the disorders seen every day in the office: depression, mania, anxiety, personality disorder, and attention-deficit/hyperactivity disorder (ADHD). Moreover, since 2003, clinical trials of psychotropic medications, as well as advances in neurobiology, are beginning to change fundamentally the way we look at mental disorders.

For example, although antidepressants are effective in the treatment of depression and anxiety, only about one-third of adult patients experience complete remission after an initial course of treatment (Trivedi et al., 2006). These drugs are selective serotonin reuptake inhibitors (SSRIs) and, at least acutely, they increase the amount of serotonin available to the neurons. But embedded in this statement is a whole series of questions. Where exactly in the brain does serotonin reside? What role does it play in normal mood and behavior? What role, if any, does it play in the development of affective disorder? How does changing serotonin in the brain with medication

improve depression? Finally, if serotonin is a critical link in the treatment of depression, then why are other agents that have no effect on serotonin also effective treatments for affective disorder? These are the sorts of questions I seek to answer in this book about the many brain systems involved in mental disorders. Box 1.1 is a discussion of the conundrum regarding the clinical relevance of neuroscience to mental health diagnosis and treatment.

BOX 1.1. Is Neuroscience "Clinically Relevant" to Mental Health?

Psychotherapy can be done without assessing any currently available biomarker. Treatment with psychiatric medication remains based on the symptoms with which the patient presents (mania, depression, inattention). If a mental health professional is not involved in research, why should he or she be concerned with neuroscience? There are several reasons it is imperative.

- Health professionals have an ethical duty to remain current in the science of their profession. Imagine a cardiologist who said, "I don't really need to understand how the heart works, I just need to memorize the dose of antihypertension medication to give." So why would such an attitude be acceptable in a psychiatrist? Related to this is the responsibility to give up-to-date information to patients who request it, particularly in an era when patients can search the Internet themselves for information.
- Clinicians need to be armed with the facts to help their patients avoid being taken advantage of. For instance, an Internet search can yield a variety of companies that do genetic testing, often promising that the results will lead to optimal medication treatment of mental disorders. Many of these tests rely on single-candidate gene approaches that in fact have limited relevance and are being supplanted by newer, more powerful methods.
- Clinicians should able to participate actively in interpreting the neuroscience findings that will emerge rapidly in the next decade. If the clinician reads a headline in the morning paper that says, "Gene Linked to Autism," how seriously should it be taken? This book will give clinicians the ability to make up their own minds.
- Not only new medications but also dramatic procedures such as deep brain stimulation and brain implants may become standard treatments in the very near future. Mental health clinicians need help their patients decide whether these treatments are right for them. Psychiatrists do not want to be stranded outside the operating theater as passive bystanders.

Neuroscience is the great scientific frontier of the 21st century, much as were quantum physics and relativity at the beginning of the 20th century. I invite you to join me in this exciting intellectual challenge.

WHERE HAVE WE BEEN?

Table 1.1 shows pre-20th-century efforts at classification and treatment of mental disorders. It is illuminating to see how many of the debates regarding the nature of mental disorders have been played out over several centuries. As the 20th century progressed, three major thrusts emerged in the study of mental disorders (Table 1.2).

Classification of Disorders

The third edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-III; American Psychiatric Association, 1980) was extensively

TABLE 1.1. Early Developments in the Understanding of Mental Disorders

1247	Royal Bethlehem Hospital ("Bedlam") established in London.
1767	The Virginia House of Burgesses establishes Eastern State Hospital for the treatment of mental illness. Francis Fauquier, the Royal Governor, told the House, "It is expedient I should also recommend to your Consideration and Humanity a poor unhappy set of People who are deprived of their senses and wander about the Country, terrifying the Rest of their fellow creatures. A legal Confinement, and proper Provision, ought to be appointed for these miserable Objects, who cannot help themselves. Every civilized Country has an Hospital for these People, where they are confined, maintained and attended by able Physicians, to endeavor to restore to them their lost reason."[a]
1795	Philippe Pinel removes chains from the mentally ill at the Salpêtrière Hospital in Paris. In 1798, he publishes *Nosographie Philosophique ou Méthode de l'Analyse Appliquée à la Médecine*, dividing mental disorders into melancholia, mania with and without delirum, dementia and idiotism (cognitive impairment).
1841	The Association of Medical Officers of Hospitals for the Insane (now the Royal College of Psychiatrists) adopts a policy to limit restraint of mental patients (still a concern at inpatient facilities today).
1868	German psychiatrists William Griesinger and Heinrich Laehr debate whether mentally ill individuals should be treated in asylums or in the community.
1896	Sigmund Freud presents 18 cases to the Society for Psychiatry and Neurology in Vienna supporting his theory of seduction, that early sexual abuse leads to hysteria. He received "an icy reception from the donkeys" and abandons his sexual seduction theory.

[a]Nearly 250 years later, Terry McAuliffe, the Governor of Virginia at the time of this writing, stated, "Mental health services are a critical part of Virginia's healthcare and public safety services, and recent events in Newtown, Aurora, Oak Creek and Virginia Tech have all shown us that we need to take serious steps to continue to improve our mental health services. Beyond preventing violence, improvements in our mental health safety net can save us money and improve the quality of life for thousands of Virginians and their friends and family."

TABLE 1.2. Modern Evolution of the Study of Mental Disorders

1899	Emil Kraepelin divides psychosis into manic–depressive illness and dementia praecox (schizophrenia).
1900	Sigmund Freud publishes *The Interpretation of Dreams*—the beginning of psychoanalysis.
1913	John B. Watson publishes "Psychology as the Behaviorist Views It"—the beginning of the study of learning/conditioning in human behavior.
1934	Ladislas von Meduna, believing epilepsy and schizophrenia to be antagonistic disorders, introduces chemically induced convulsions as a treatment. In 1937, Italian psychiatrists Ugo Cerlitti and Lucio Bini develop electroconvulsive therapy (ECT). This is the first truly effective treatment for psychosis and affective disorder.
1937	Charles Bradley publishes "The Behavior of Children Receiving Benzedrine," showing dramatic improvements in the behavior of impulsive and overactive children treated with stimulants.
1938	B. F. Skinner publishes "The Behavior of Organisms: An Experimental Analysis." Introduces operant conditioning (effects of reinforcement and punishment on human behavior). Becomes the foundation of modern behavior therapies.
1949	John Cade reports that lithium salts can be used to treat "psychotic excitement" (mania).
1950	Paul Charpentier synthesizes chlorpromazine.
1952	At the urging of surgeon Henri Laborit, psychiatrists administer chlorpromazine to Jacques L. H., a 24-year-old manic patient, and observe dramatic improvement. Jean Delay and colleagues publish first clinical trial of chlorpromazine (Delay & Deniker, 1952).
1954	R. G. Bloch, A. S. Dooneif, and A. S. Buchberg report on the mood-enhancing effects of the anti-tuberculosis drugs iproniazid and isoniazid.
1958	Nathan Kline publishes his clinical experience of iproniazid and isoniazid as antidepressants. Roland Kuhn reports the effectiveness of the tricyclic drug imipramine in the treatment of depression. Both sets of drugs are noted to affect the monoamines serotonin and norepinephrine.
1967	J. J. Schildkraut and Seymour Kety publish "Biogenic Amines and Emotion," which summarizes the theory that deficits in norepinephrine and serotonin are related to affective disorder.
1974	David Wong and colleagues J. S. Horng, F. P. Bymaster, K. L. Hauser, and B. B. Molloy synthesize fluoxetine, the first clinically useful SSRI. SSRIs largely replace tricyclic antidepressants.
1992	J. W. Belliveau and colleagues publish first fMRI image of the human visual cortex, launching the use of this noninvasive technique for studying brain function.
1994	Risperidone, the first "atypical" antipsychotic thought to have fewer side effects and greater efficacy than "first-generation" antipsychotics, such as chlorpromazine, is approved by the U.S. Food and Drug Administration.
2003	Human genome is sequenced, raising the possibility of unlocking the genetic causes the mental disorders.

revised, based in large part on the Research Diagnostic Criteria (RDoC) developed at Washington University in St. Louis and the New York State Psychiatric Institute (Spitzer, Endicott, & Robins, 1978). These criteria were designed primarily to improve the reliability of psychiatric diagnosis for patients entering studies, and it was hoped that incorporating its principles into DSM would improve the reliability of clinicians' diagnoses. Emil Kraepelin's distinction between schizophrenia and affective disorder remains prominent in DSM. DSM is categorical, laying out the signs and symptoms of each disorder but allowing "comorbidity" (multiple disorders in a given individual) and including "unspecified" diagnostic conditions. There is enormous tension between such *categorical* approaches to disorders and a *dimensional* approach that attempts to just measure symptoms or impairment and apply a validated treatment. Box 1.2 describes a clinical case that indicates this is not an academic debate and has a real impact on patients.

BOX 1.2. Dimensional versus Categorical Approaches to Mental Disorders

Justin is a 7-year-old boy with a long history of multiple problems. He was a low-birthweight baby whose language was slow to develop. He was a difficult, fussy baby who was very hyperresponsive to the environment. As a toddler, he would he cover his ears and scream when there were loud sounds. He did not play well with others in preschool, staying by himself. He had constant temper tantrums and was noted to be very hyperactive in kindergarten. He has a number of minor physical anomalies of his face and ears but no other medical problems. He was evaluated by a psychologist due to his poor social skills. His Full Scale IQ was found to be 79, with reading and spelling skills consistent with his intellectual level. The psychologist diagnosed him with Asperger's syndrome due to his poor social relatedness and atypical anxieties around noises and preferences. The family began working with an applied behavioral analysis (ABA) certified therapist, and Justin was started on a stimulant for hyperactivity.

He continued to have serious difficulties with hyperactivity in first grade, not completing work, and having very poor relatedness to peers. He would sit in only one particular seat on the school bus and hit a child who had sat there before he could get to it. His parents took him to a special center for autistic disorders for an extensive 2-day work-up, which covered both medical and psychological factors. No genetic disorders were found. The center did *not* feel Justin met criteria for an autistic disorder but that he had three separate problems: ADHD, sensory-integration disorder (which accounted for the sensitivity to sounds), and a language disorder. The center attributed his social skills issues to ODD. How was the treatment plan changed? Not at all, except the insurance would no longer pay for ABA treatment, since Justin did not have autism!

The Elaboration of Psychological Theories to Explain Behavior and Emotion

In the first part of the 20th century, both psychoanalytic and behavioral theory expanded. Psychoanalysis was concerned initially with the treatment of "neurosis" (anxiety driven by unconscious conflict); later, "object relations theory" focused on how early attachment and separation experiences can drive more severe behaviors (borderline personality disorder). The work of Otto Rank and Carl Rogers (Kramer, 1995) led to "client-centered" therapy, which most therapists use today. The question "How does that make you feel?," which has now entered into common lay use, reflects the client-centered principle that cure is found by the awareness and experience of one's own emotions (and their nonjudgmental acceptance by the therapist). B. F. Skinner (1938) pioneered behaviorist theory, elaborating on how "operant conditioning" (reinforcement and punishment) shaped behaviors. Such work is now the basis of behavior therapy for a wide variety of conditions, from disruptive behavior to autism spectrum disorders. In the 1970s, Aaron Beck (1979) developed "cognitive-behavioral therapy" (CBT), which shifted the focus in the treatment of depression from unconscious conflict to changing the patient's recurrent negative thoughts, thus making the mind (rather than overt behavior) the focus of the treatment process.

Reasoning Backwards from the Known Chemical Mechanisms of Psychotropic Medication to Derive Biological Theories

As shown in Table 2.1, the original major psychotropic medications were discovered largely by chance. Modern psychotropics have a reduced side-effect burden (particularly antidepressants) but are not dramatically more effective. The 20th century saw the development of theories of mental illness based largely on the mechanisms of these treatments. These included the "biogenic amine" hypothesis of affective disorder, which implicated alterations in norepinephrine and serotonin as culprits in depression and mania (Schildkraut & Kety, 1967); the "excessive dopamine" hypothesis of schizophrenia (Madras, 2013); and the "dopamine deficiency" theory of ADHD (Wender, 1974). These theories put forward the idea that if a drug raised or attenuated a given neurotransmitter, then the disease must be due to lower–higher activity of that system in patients relative to controls. Given that psychotropic drugs affect a limited number of neurotransmitter systems and are effective in multiple disorders, these theories probably were doomed from the start. It is more likely that impacting these neurotransmitter systems attenuated the symptoms of the disorder without being related to the underlying cause of it—much the way that aspirin reduces fever regardless of the cause. Thus, the need for a new paradigm.

KRAEPELIN'S ERROR

In the first several decades of neuroimaging research, scientists would compare a group a patients with a disorder to a control group on both the neuroanatomy and the function of various brain regions using functional magnetic resonance imaging (fMRI). Often, statistically significant differences were found between the groups in terms of the size of brain regions (with the psychiatric group usually having smaller volume) and their function (either increased or decreased activity relative to control). To date, none of these findings have led to the holy grail of a "diagnostic test" for a mental disorder due to the high degree of overlap between the disease and control groups. More perturbing, when reading about different disorders, one notes that the *same* brain regions appear to be dysfunctional in widely different disorders. Advances in genetic research led to the search for specific genes for major mental disorders in hundreds of thousands of patients, with no results that have been clinically significant to date. Those genes that have been associated with mental disorder turn out to be related to multiple conditions (ADHD, autism, affective disorder, and schizophrenia; Cross-Disorder Group of the Psychiatric Genomics Consortium, 2013). Patients arrive at our offices seeking "the diagnosis," the "cause" ("Is it genetic?"; "Is it my fault?"); and, most importantly, a treatment that is based on an understanding of the cause. After all this time, why don't we have answers to these questions?

I explore the many reasons for this, but one reason is so obvious that we often miss it: Disorders *share* behaviors. People with mania and those with ADHD are impulsive; those with depression, ADHD, and dementia all have decreased concentration; and patients with depression and those with anxiety have strong emotional reactions to fearful stimuli. While Kraepelin, like those before and after him, sought a definitive divide (affective disorder vs. schizophrenia), such a divide simply may not exist as far as nature is concerned. This does not mean that diagnosis is unimportant, for it still helps us to select the right treatment. However, it does mean that to understand mental disorders, we must think beyond our diagnostic categories.

BEYOND DIAGNOSIS

The National Institute of Mental Health (NIMH) sought to break out of the box of diagnostic categories by creating the RDoC. The NIMH notes that genetics, physiology, and brain anatomy do not map one-to-one onto DSM disorders. Based on consensus among neuroscience researchers, the NIMH proposed various domains of functioning, shown in Table 1.3. These will

TABLE 1.3. RDoC of the NIMH

Negative valence systems
Acute threat ("fear")
Potential threat ("anxiety")
Sustained threat
Loss
Frustrative nonreward

Positive valence systems
Approach motivation
Reward valuation
Effort valuation/willingness to work
Expectancy/reward prediction error
Action selection/preference-based decision making
Initial responsiveness to reward
Sustained responsiveness to reward
Reward learning
Habit

Cognitive systems
Attention
Perception
Visual perception
Auditory perception
Olfactory/somatosensory
Multimodal perception
Declarative memory
Language behavior
Cognitive (effortful) control
Goal selection
Updating
Representation and maintenance
Response selection
Inhibition or suppression
Performance monitoring
Working memory[a]
Active maintenance
Flexible updating
Limited capacity
Interference control

Systems for social processes
Affiliation and attachment
Attachment formation and maintenance
Social communication
Reception of facial communication
Production of facial communication
Reception of nonfacial communication
Production of nonfacial communication
Perception and understanding of self
Agency
Self-knowledge
Perception and understanding of others
Animacy perception
Action perception
Understanding mental states

Arousal and regulatory systems
Arousal
Circadian rhythms
Sleep and wakefulness

[a]The Working Memory Workshop created a matrix with a different format. See the Working Memory Workshop Proceedings document to view the matrix for working memory and its subconstructs.

not be familiar to clinicians but I expand on them in future chapters and relate them, when possible, to current clinical conditions.

To help us orient ourselves, I briefly examine one of the domains, "Acute threat" (fear). When a person views aversive stimuli (traumatic scenes, fearful faces) or undergoes fear conditioning, a fear circuit is activated (Plate 1) (Hariri, Mattay, Tessitore, Fera, & Weinberger, 2003; LeDoux, 2000). The visual stimuli can reach the amygdala via a direct route through the thalamus or after more extensive processing through the visual cortex. Activation of the amygdala in turn can lead to increased output in the autonomic nervous system ("fight or flight"), as well as the hypothalamic–pituitary–adrenal (HPA) axis (stress hormones). This activation of the amygdala can be imaged with fMRI and often correlates with self-ratings of anxiety or fear. The NIMH listed roughly 15 genes and neurotransmitters found to be involved with this particular domain; experience also has a role in shaping it. Readers will be familiar with the term "genotype"—the DNA sequence of these various genes. The "phenotype" is the final state of the organism (round or wrinkled peas or, in clinical terms, the patient either has or does not have an "anxiety disorder"). These dimensions are related to the concept of an "endophenotype."

Plate 1 illustrates a typical fMRI study. A group of individuals undergo scanning while viewing both neutral and angry faces; for some, amygdala activation is strongly reactive; for others, it is less so. The high- and low-activation groups might be different endophenotypes, brought about by differences in their genes and experience. Not everyone with "high activity" in the circuit has an anxiety disorder, but anxiety disorders might come disproportionately from this group. The high-endophenotype group also might be at higher risk for affective disorder or impulsive aggression. After we understand the endophenotype, we can look for the factors that produce disease in those who have it. It is important to realize that the neither "high" nor "low" activity states measured on fMRI necessarily represent "abnormalities"; rather they average differences between the groups that may be associated with dysfunction when combined with a one set of circumstances and adaptation when exposed to alternative circumstances.

The example in Plate 1 represents an idealized state suggesting that fMRI results are interpretable at an individual level. fMRI has become clinically useful in epilepsy surgery to identify the precise language area in an individual patient presurgery, such that the neurosurgeon can work to spare these areas when removing an epileptic focus from the brain (Detre, 2004). fMRI of mental disorders has not yet reached that level. When contemplating the many fMRI studies that are reviewed here, bear in mind the fact that the "orange blob" one sees superimposed on the structural MRI represents the average brain activity in groups of people between several possible states: patients versus controls, control condition (i.e., rest) versus

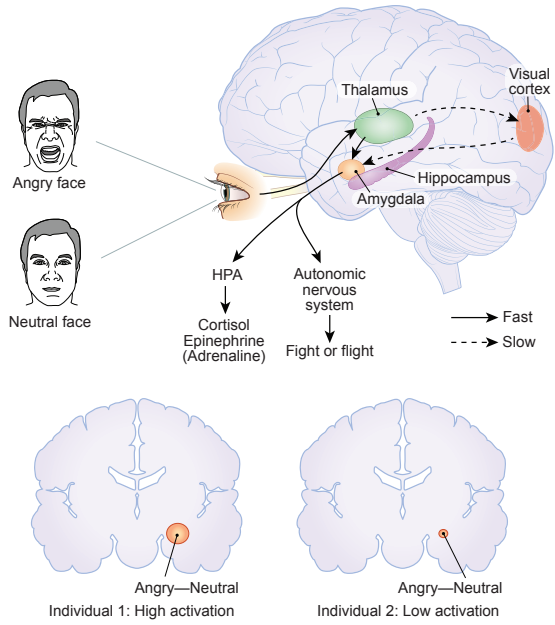


PLATE 1. Responsiveness of the amygdala circuit to threatening stimuli as an endophenotype.

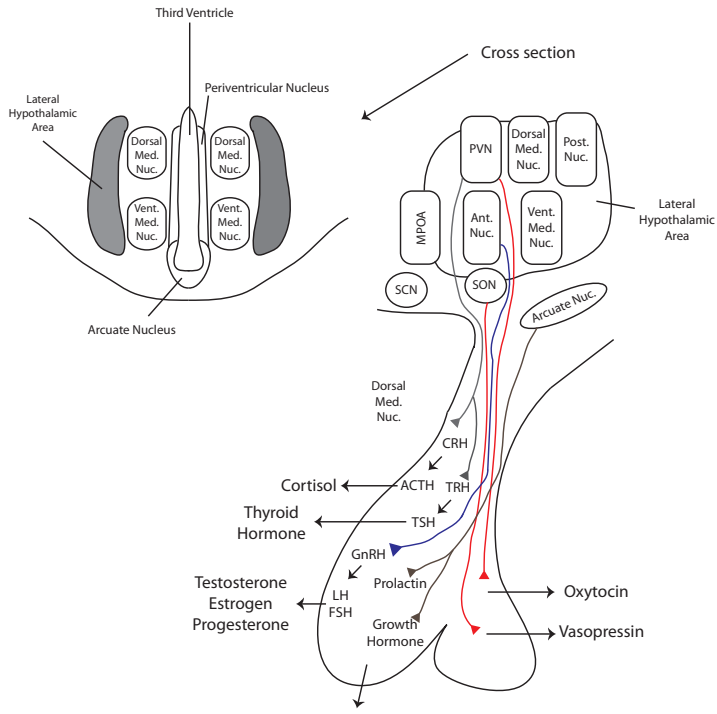


PLATE 2. The pituitary gland and its control of hormones.

activated condition (looking at faces), pretreatment versus posttreatment, or placebo versus active agent. Within any given group, the response might vary substantially. While the average response of activity in a brain region might rise in response to treatment in the group as a whole, some patients show no change in activity, others show an increase, and still others show a decrease. These individual differences may turn out to be important for selecting treatment or predicting treatment response. At present, however, many of the changes I review here are not perceptible on fMRI at the individual level.

BEYOND THE GENOME

Everyone is familiar with the double helix of DNA, which contains the genome (see the top of Figure 1.1). This is what everyone thinks of when we say "genetic"—the sequence of nucleotide bases (guanine, adenine,

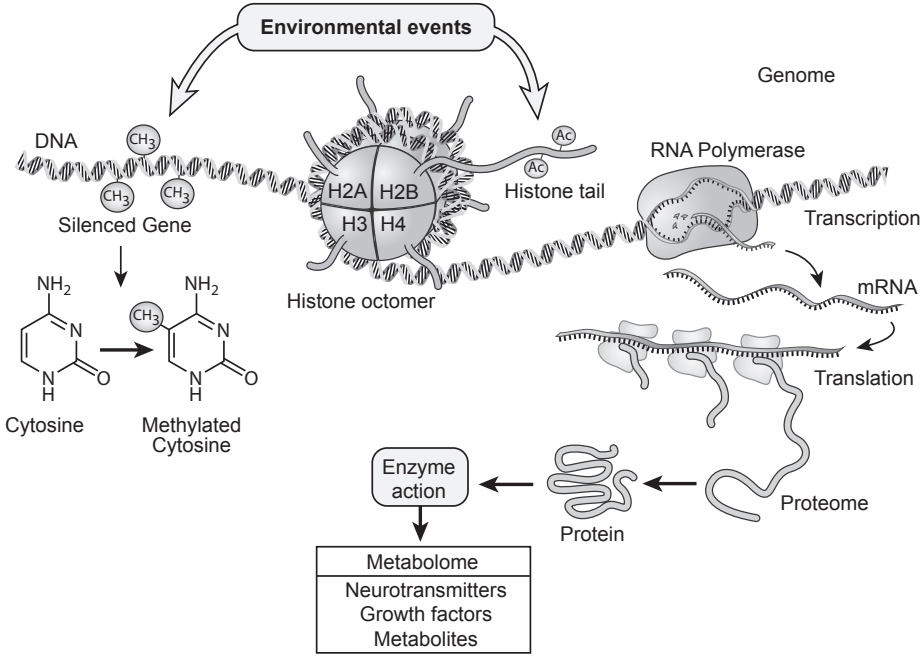


FIGURE 1.1. The genome (DNA sequence) is altered by mutation (permanent) but gene expression is variable and can be influenced by a wide array of environmental factors, which methylate DNA or affect histone proteins (epigenome).

thymine, cytosine). The Human Genome Project showed that human DNA contains about 21,000–30,000 genes (i.e., DNA sequences that code for a protein). The remainder is "noncoding" DNA that nonetheless may perform a regulatory function and should therefore no longer be viewed as "junk" or "nonsense" DNA. Mutations in the DNA may occur spontaneously or due to some toxic chemical or radiation. DNA is transcribed to messenger RNA (mRNA), and this process is highly regulated. Here, it is useful to introduce the concept of epigenetics ("above the genome"). Every cell in the human body has the same genome (46 chromosomes) but, obviously, some cells become skin or muscle cells, while others become neurons. Some process "above the genome" must determine each cell's destiny. Gene expression is controlled by two major processes (discussed in more detail in Chapter 5). In DNA methylation, a methyl group is attached to one of the carbons on the cytosine base; this generally will silence a gene. DNA strand are wound around histone proteins (see Figure 1.1); these proteins can be modified chemically by a number of enzymes either to enhance or to limit DNA transcription. More critically, these histone modifications can respond to a wide variety of complex environmental stimuli. In some cases, the changes in response to environment can be lifelong or even passed to the next generation. Strahl and Allis (2000) proposed the term "histone code" for this process. Each histone may allow 1,000 different regulatory states *per gene*, with perhaps 30,000,000 different histone states across the nucleus (Bridi & Abel, 2013). One can now see how so few genes in the human genome can produce the complexity of the brain, with multiple environmental inputs playing a key role.

The array of all RNAs that emerge from this symphony is termed the "transcriptome," while the final proteins produced are the "proteome." There is another set of regulatory processes that likely governs the production of the proteome. Many of these proteins are enzymes that participate in the creation and regulation of a variety of neurotransmitters, growth factors, and other elements critical to brain function; these are all termed the "metabolome." The role of each of these "omes" in mental disorders is likely to be substantial.

AN EVOLUTIONARY PERSPECTIVE

Mental illness exacts a terrible toll on the human population. The World Health Organization estimates that about 1 million people commit suicide every year, with suicide attempts about 20 times more common than completed suicides. Worldwide, 24 million people suffer from schizophrenia. In the United States, the annual cost of disability payments for the chronically

mentally ill is $3 billion and growing (*www.ssa.gov*). There appear to be very few real analogues of human mental illness, such as affective and autistic disorders, among our primate cousins. (*www.childhelp.org/pages/statistics*). Introducing an evolutionary perspective will be helpful because some of the changes in our genome and epigenome that made us human may also make us vulnerable to mental disorders.

Humans and chimpanzees shared a common ancestor 6–8 million years ago (Chimpanzee Sequencing and Analysis Consortium, 2005). During this time, there emerged an ape-like species, *Sahelanthropus tchadensis*, or "Toumai," which had a downwardly oriented foramen magnum (hole where the spinal cord exits the brain) that suggests bipedality. Table 1.4 shows other human ancestors, along with evidence of their changing genetics and cognitive skills that paralleled the growth in brain size (Somel, Liu, & Khaitovich, 2013). The genes noted in Table 1.4 may not be familiar at present, but they emerge in later chapters as risk genes for major mental disorders. We can understand some of the genome of our early human ancestors by extracting DNA from bones, but we cannot understand the epigenome because it is an active, living process of RNA transcription. For this, we must compare humans and our only living primate relative, the chimpanzee.

We share 95–99% of our genes with chimpanzees. The small amount that is not shared includes about 50,000 amino acid changes (in proteins that are transcribed); 30,000,000 point mutations (changing of one base in the DNA for another) in noncoding sequences; as well as other insertions, deletions, and arrangements of the DNA (Chimpanzee Sequencing and Analysis Consortium, 2005). King and Wilson (1975) first proposed that differences in *gene expression*, as opposed to changes in the genome itself, were more likely to underlay human evolution. Next-generation sequencing (NGS) technology looks not only at the DNA sequence but also the "transcriptome"—the array of RNA products that reflect gene expression (although these studies must be done on postmortem brains). Depending on the technique used, there are 200–450 genes differentially expressed in humans compared to chimpanzees (Konopka et al., 2012). These changes are particularly important in development. Liu and colleagues (2012) compared the mRNA expression of genes involved in neuronal communication across the lifespan in humans, chimpanzees, and macaques. The results are shown in Figure 1.2. Note, in the left panel, that the overall expression of these genes occurs later in life and remains high for an extended period. This delay or increased gene expression in turn correlates with a more gradual increase in the synaptic density (increase in neuronal connections) in humans, with a corresponding increase in cognitive capacity and flexibility. Understanding many of the genes that make us human also may give insights into the unique mental disorders of humans.

TABLE 1.4. Brief Summary of Human Ancestors

Ancestor	When lived	Bipedality	Brain size and growth rate	Cognitive skills	Genetics
Sahelanthropus tchadensis (Toumei)	8–6 million years ago	Very likely, foramen magnum downwardly oriented	360–370 cc (slightly smaller than adult chimpanzee)	Unknown	Unknown
Australopithines (Lucy—adult) (Selam—3-year-old)	4–2 million years ago	Definitely, but likely to be good climber, spent time in trees	460 cc (likely to have had slower brain growth than chimpanzees, leading to greater plasticity)	Unknown; some debate as to tool use	Unknown
Homo habilis ("handy man")	1.8–1.4 million years ago	Yes	510–687 cc (possible Broca's area in skull casts)	Stone tools, hairless, able to run during the day in order to hunt large animals	*HAR* mutations; *FOXP2* amino acid mutation; *SRGAP2* duplication; *GADD45G* enhancer deletion
Homo erectus	1.8 million–50,000 years ago	Yes	600–1,200 cc (Broca's area present)	Stone tools, control of fire, traveled out of Africa to Europe and Asia	
Homo heidelbergenis	500,000–100,000 years ago	Yes	1,274 cc	Primitive symbolic thought (ritual burial)	
Homo neanderthalensis	200,000–30,000 years ago	Yes	1,420 cc		
Homo sapiens	195,000 years ago–present	Yes	1,350 cc	Advanced cognitive abilities (art, language, sophisticated tools)	*FOXP2* regulatory mutation; *MEF2A* enhancer mutation

Note. FOXP2 is a transcription factor (the gene produces a protein that regulates expression of other genes involved in language and neuronal plasticity). Mutation in the gene leads to language disorder. There are two amino acid substitution differences between early humans and apes. In chimps, the *GADD45G* gene can suppress brain growth. A deletion in this gene in humans may have led to more cortical development. Duplication (higher gene dose) of *SRGAP2* leads to increased synapse formation in humans. *HAR* is part of a family of genes involved in cortical expansion. *HAR2* may be involved in the development of the human opposable thumb. The human version of *MEF2A* is related to a delay in synaptic formation. Adapted from Somel, Liu, and Khaitovich (2013) with permission from Macmillan Publishers Ltd. Copyright 2013.

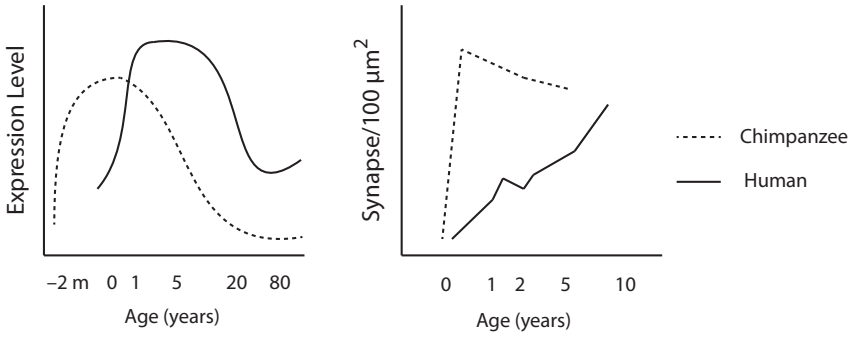


FIGURE 1.2. Left panel: Average expression of 184 genes involved in neuronal communication in chimpanzees versus humans. Note the higher expression later in life in humans. Right panel: Delay of expression of genes related to delay in increase of synaptic density, underlying greater plasticity in humans. Adapted from Somel, Liu, and Khaitovich (2013) with permission from Macmillan Publishers Ltd. Copyright 2013.

THE CLINICAL LANDSCAPE

To take in a more dimensional perspective, the mental disorders laid out by the fifth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5; American Psychiatric Association, 2013) are divided into the following categories: behavioral disorders, mood and anxiety disorders, tic/motor disorders, autism spectrum disorders, schizophreniform disorders, cognitive disorders, and alcohol/substance abuse disorders. These are listed in Table 1.5; Figure 1.3 shows their developmental course and high degree of overlap.

The best known of the behavioral disorders is ADHD, which affects up to 5–7% of schoolage children. Also included in this category are oppositional defiant disorder (ODD) and conduct disorder (CD). These three disorders are often viewed as falling along a spectrum, with ADHD consisting of maladaptive inattentiveness, impulsivity, and/or hyperactivity and ODD consisting of temper outbursts, excessive stubbornness, rule breaking, and socially offensive behavior toward others. CD, in contrast, consists of antisocial behavior, particularly aggressiveness toward people and property, stealing, lying, and sexual offenses. ADHD, ODD, and CD all must begin in childhood. Figure 1.3 shows that by adulthood, some children with ADHD no longer meet criteria for the disorder (i.e., their symptoms improve), so that the size of the ADHD circle is reduced. ODD and CD are not diagnosed in adults. Some of these youth desist in their maladaptive behavior; others evolve into the personality disorders, particularly those

TABLE 1.5. An Overview of DSM-5 Diagnoses

Behavioral disorders
- Attention-deficit/hyperactivity disorder
- Oppositional defiant/conduct disorders
- Cluster "B" personality disorders: antisocial, borderline, histrionic, and narcissistic personality disorder
- Disruptive mood dysregulation disorder

Mood and anxiety disorders
- Depression
  - Major depressive episode and dysthymia
  - Disruptive mood dysregulation disorder
- Bipolar disorder
  - Mania, cyclothymia, hypomania
- Panic attacks/panic disorder/agoraphobia
  - Phobias
- Posttraumatic stress disorder
- Generalized anxiety disorder

Tic disorders/obsessive–compulsive disorder

Autism spectrum disorders

Cognitive disorders
- Developmental cognitive disorders
  - Reading, mathematics, language, speech disorders
  - Cognitive disorders of senescence (dementia)
    - Alzheimer's disease
    - Dementia due to other medical conditions

Alcohol/substance abuse/dependence disorders

in the DSM-5 "Cluster B" category: antisocial, borderline, histrionic, or narcissistic disorders.

Depressive and anxiety disorders can begin in childhood, with the latter being more common than the former. Figure 1.3 shows that by adulthood, the prevalence of these disorders increases substantially, such that the lifetime rates of affective and anxiety disorders (any subtype) each reach 10% of the adult population. There is considerable controversy regarding the diagnosis of bipolar disorder (BP) in childhood, but it is considerably rarer at this time than depressive or anxiety disorders. Note that during childhood, BP is highly *comorbid*, in that it almost always co-occurs with ADHD, other mood disorders, or ODD/CD. In DSM-5, a diagnosis of disruptive mood dysregulation disorder (DMDD) has been added to encompass children who show chronic aggression and mood lability but do not meet criteria for mania. Many of these children have been diagnosed as

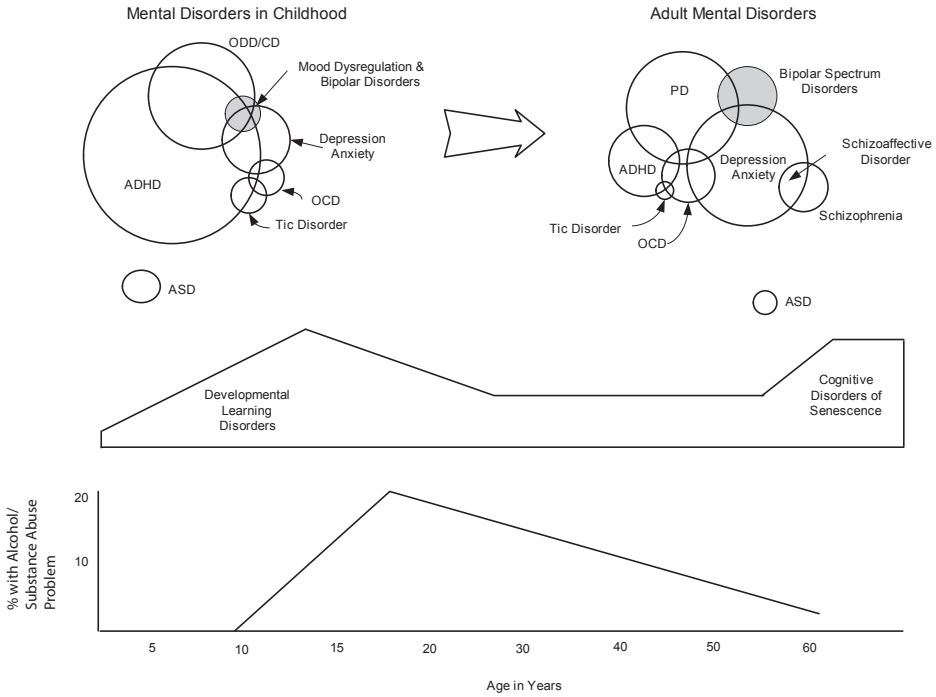


FIGURE 1.3. Life course of comorbidity of psychiatric disorders. ASD, autism spectrum disorders; OCD, obsessive–compulsive disorder; PD, personality disorders.

"bipolar disorder not otherwise specified" (NOS) under DSM-IV; in DSM-5, this disorder is grouped with the depressive disorders, although Table 1.5 includes it with the behavioral disorders.

By adulthood, BP becomes more common (at least 1% lifetime prevalence for the adult population); furthermore, BP is more often found in the absence of other disorders. Adult BP remains heterogeneous, however. The 1% figure applies to BP I disorder, which consists of a distinct episode of abnormal euphoric mood, increased energy, activity and sexual activity, grandiosity, and disturbances of thought. BP II consists of milder episodes of hypomania alternating with depressive episodes. Hagop Akiskal and his colleagues (2000) have described a spectrum of mood disturbances between classic BP I and BP II. When these "softer" BP cases are considered, the prevalence of the disorder may be as high as 5–8%. Furthermore, as shown in Figure 1.3, these BP spectrum disorders may overlap with the Cluster B personality disorders.

The schizophreniform disorders include schizophrenia itself and other psychotic disorders. These are quite rare in childhood and have an adult lifetime prevalence of about 1.5%. The line between schizophrenia and other disorders is not clear cut, however, and an undetermined number of patients fit into the overlapping condition of schizoaffective disorder, in which they have symptoms of both schizophrenia and affective disorder. The autism spectrum disorders begin in childhood and remain fairly consistent in their prevalence over the lifespan, although milder cases may remit. Finally, tic disorders also appear first in childhood but fall in prevalence with time. During childhood, obsessive–compulsive disorder (OCD) is rare (and frequently overlaps with tic disorders), but the prevalence of OCD rises during adulthood. OCD may have neurobiological correlates distinct from those of the other anxiety disorders.

The lower part of Figure 1.3 shows the life course of the cognitive and alcohol/substance abuse disorders. A patient with any of the mental disorders I have just discussed also may have one of these disorders. During childhood, there is a rise of the prevalence of reading disorder, mathematics disorder, and any of the disorders of language and speech. These frequently impair educational performance. Some of these individuals with learning disabilities improve (with maturity or treatment); thus, the prevalence of these disorders falls by young adulthood. In late adulthood, disorders such as Alzheimer's disease, as well as other medical disorders, begin to take their toll on a wide range of cognitive functions. However, it is important to understand that the majority of adults live out their lives without suffering dementia.

Alcohol and substance abuse begin to emerge in early adolescence and peak by young adulthood. They remain at a fairly consistent prevalence throughout the young adult years, then begin to decline in prevalence in late adulthood. This is because not only do many alcoholics or addicts achieve abstinence but also some patients die early due to the toxic side effects of excessive alcohol or illegal drugs. Almost every major mental disorder carries with it a risk of substance or alcohol abuse, and often it is difficult to tell whether the substance abuse disorder is secondary to the mental disorder or whether the abuse of substances led to the mental disorder. For instance, one patient who develops depression may abuse drugs to "self-medicate" the depression, while another patient may first develop a substance abuse disorder and later become depressed because of the effects of the substance (or its withdrawal) on mood. For still others, a single set of etiological factors may drive both the primary mental illness and the substance abuse disorder. Researchers in clinical neuroscience must carefully disentangle these multiple effects.

WHEN WILL WE FIND THE "CAUSE" OF PSYCHIATRIC DISORDERS?

This is a question patients are eager, often desperate, to answer. At any given time, a paper will present evidence of a gene, a gene product, volume of a brain region, or brain activity that is different in a patient group versus a control group. Lewis and González-Burgos (2008, p. 1), in a discussion of the pathophysiology of schizophrenia, laid out four "C's" that any given biomarker might represent:

- *Cause:* A true upstream factor that leads to the disorder and precedes it.
- *Consequence:* A deleterious effect of the cause on brain function. For instance, decreased brain size in Alzheimer's is the result of neuronal death, brought on by causative factors.
- *Compensation:* The brain's response to the causative factor, which may in fact be protective and reducing the negative effect of the cause.
- *Confound:* A product of factors frequently associated with, but not a part of, the disease process, or an artifact of the approach used to obtain the measure of interest.

To the degree possible, I try to identify the "C" to which a particular biomarker for a mental disorder belongs. The reader should bear in mind that an exciting finding today (a cause) may turn out to be a confound tomorrow. In that process of discovery, however, we grow closer to a greater understanding of not only mental disorders but also the nature of the human mind itself.

CHAPTER 2

Draw the Brain

Introduction to Clinical Neuroanatomy

Of all the topics to be presented in this book, it is neuroanatomy that the mental health clinician is most likely to find anxiety provoking. Mental health clinicians other than psychiatrists may not have had any neuroscience courses, either at the undergraduate or graduate level. Pick up a neuroanatomy textbook and it is easy to get lost after the first chapter. If one even had the time to learn the difference between the substantia nigra compacta and the substantia nigra reticulata, what relevance does it have to clinical work? Even psychiatrists find that they lose their grip on the neuroanatomy they learned in medical school because little of it seems to matter in the day-to-day care of patients. Yet, as the neuroscience of mental disorders advances, a basic understanding of neuroanatomy is critical in order to be a good consumer of the clinical neuroscience literature. More importantly, it is impossible to make any sense of information regarding neurotransmitters or brain imaging without this anatomical foundation.

Mental health clinicians without a strong science background need not shrink from the task; neuroanatomy can be made simple without being simplistic. This chapter has two major goals: to give the reader a grasp of the major structures involved in cognitive, motor, and emotional behaviors, and to provide a three-dimensional (3-D) grasp of how these structures relate to each other. This is most easily done by drawing the structures as you read. Indeed, it would be wise to draw them several times, so that you can reproduce them from memory. Once you have a grasp of the anatomy, it is easier to understand where the neurotransmitters (dopamine, norepinephrine, etc.) work in the brain (Chapters 3 and 4). You will then be prepared to take the step of understanding how the brain produces behaviors

and feelings (Chapter 5). These drawings are not intended to be exact anatomical replicas of the brain; they have been designed so that those without great artistic ability (like myself) can reproduce them.

STEP 1: THE BRAIN'S EXTERIOR

Get a stack of typing paper and some number 2 pencils. First, you must understand the terminology used to navigate around the brain. Draw a simple tube and a circle to represent a cross section. In development, the brain starts out as a tube (Figure 2.1, Step 1A). The part of the tube that will become the brain itself is the anterior or rostral ("beak" or "nose" in Latin) end; the opposite end is referred to as posterior or caudal ("tail"). Similar to a worm or salamander, the back side is referred as "dorsal," while the belly side is "ventral." On the right side of Step 1A, the neural tube is shown in cross section as though the anterior (rostral) end is toward you. (The tube's right and left are labeled so they appear reversed.) The center of the tube is the most medial part; as we move out along the radius of the tube, we are moving laterally. Step 1B in Figure 2.1 shows the progression of brain development. The tube is bending and the anterior end is expanding. In fact, imagine the cortex as a sphere or football; the dorsal portion represents the upper surface of the brain ("the northern hemisphere"), while the ventral portion represents the "southern hemisphere." The most ventral part of the cortex is close to the eyes and is therefore referred to as the orbital cortex. Note how the dorsal–ventral axis is maintained along the length of the brain and spinal cord.

In Step 1C of Figure 2.1, draw the cortex. Draw a vertical line in the middle of the cortex; this shows the central sulcus (Latin for "furrow" or "ditch"). It divides the frontal from the parietal lobe. The frontal lobes are involved in *action*. The very tips of the frontal lobes are involved in planning a motor movement. As you move toward the central gyrus, the areas of the frontal lobe become more involved in specific motor acts. Right in front of the central sulcus is the precentral gyrus, which contains neurons that send axons all the way to the spinal cord; each part of the precentral gyrus influences a particular group of muscles. Behind the central sulcus is the postcentral gyrus. This area receives information from the skin (after several relays); thus, it is termed the primary somatosensory cortex. The area behind the postcentral gyrus to the rear of the cortex is the parietal lobe. The posterior part of the cortex is the occipital lobe. The lateral sulcus (or Sylvian fissure) separates the parietal lobe from the temporal cortex. If the frontal lobes are involved in doing, then the parietal, occipital, and temporal lobes are involved in *perceiving* and *processing*. As noted, the postcentral gyrus receives somatosensory (touch) information. The occipital

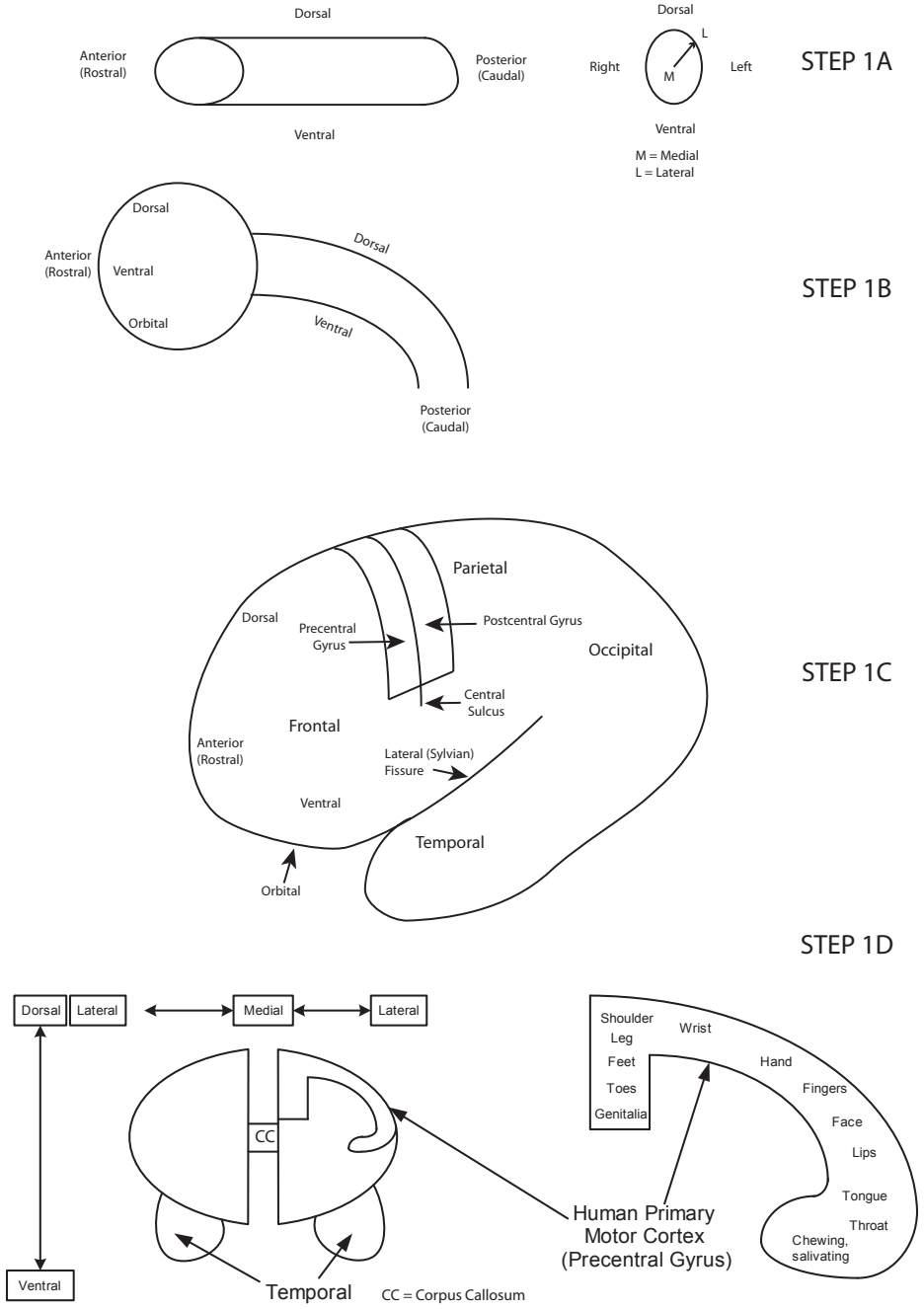


FIGURE 2.1. Navigating around the brain.

area receives visual information, and the superior temporal gyrus receives auditory information. Throughout the parietal and temporal lobes, information from these modalities is integrated and perception occurs. This is covered in more detail later (Chapter 7); for now, let's understand some differences in the way the parietal and temporal lobes process information. The parietal areas are concerned with "where" the objects we perceive are located in space, whereas the temporal lobe seems concerned with "what" they are (object identification). The parietal lobe also appears to be important in constructing our internal map of our own bodies, as well as our map of the external world. This is particularly true of the right parietal lobe, which also seems to be critical in maintaining alertness to what goes on around us.

In Step 1D of Figure 2.1, we are looking at the brain from the front. We can see more clearly the dorsal–ventral and medial–lateral orientation, as well as the corpus callosum, the band of white matter (axons) allowing the two hemispheres to communicate. This step also illustrates the homunculus in the primary motor cortex (precentral gyrus). Note how the motor strip devotes more space to the hands, fingers, lips, and tongue than to other muscle groups, indicating the importance of dexterity and speech in human life.

STEP 2: LOOKING INSIDE THE BRAIN

In the upper panel of Step 2 (Figure 2.2), we split off the left cortex. The eye in the upper panel shows the vantage point for the lower panel of Step 2. Draw the right cortex. On the medial side of the right cortex, draw the corpus callosum; note its U-shape. Around the corpus callosum is the "cingulate gyrus," a critical area involved in attention, impulse control, and regulation of emotion. It will be much discussed in later chapters. Label three of its divisions: the rostral anterior cingulate cortex (rACC), the dorsal anterior cingulate cortex (dACC), and the posterior cingulate cortex (PCC). Each of these divisions has a different role in the functions listed above.

STEP 3: ADDING THE HIPPOCAMPUS AND AMYGDALA

Below the cortex, draw a cylinder to represent the brain stem (see Figure 2.3). On the back (dorsal side) of the brain stem, draw two "bumps"; these are the superior colliculi (plural of *colliculus,* Latin for "mound"). Below the left superior colliculus, draw another bump; this is the left inferior colliculus. You cannot see the right inferior colliculus because it is behind the

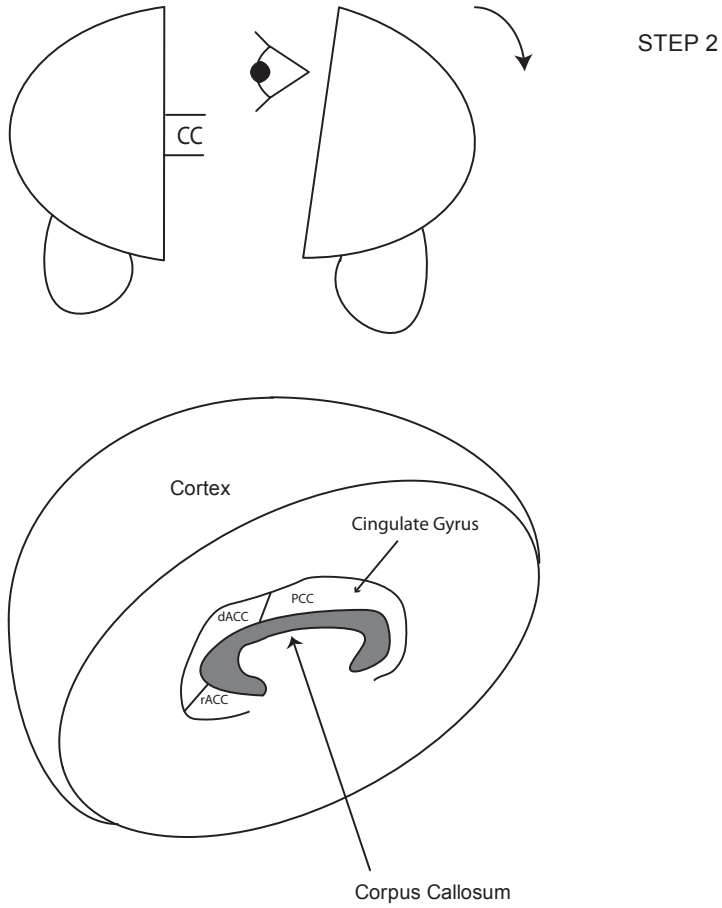


FIGURE 2.2. Medial view of the brain, showing the corpus callosum and cingulate gyrus.

brain stem. The four colliculi together are referred to as the tegmentum or tegmental plate (*tegmun* is Latin for "roof" or "covering"). The tegmentum forms the roof of the cerebral aqueduct of Sylvius, which you can also draw in. (This carries the cerebrospinal fluid [CSF] from the third ventricle to the fourth.) The superior colliculi help govern eye movements, while the inferior colliculi help orient us in response to auditory stimuli. In Step 2, we took off the left half of the cortex; now, we are going to put back a small piece of the left temporal lobe. Attached to it, draw the hippocampus, which looks like a horn. The hippocampus cannot be seen from outside the brain; it is on the medial side of the temporal lobe. The hippocampus

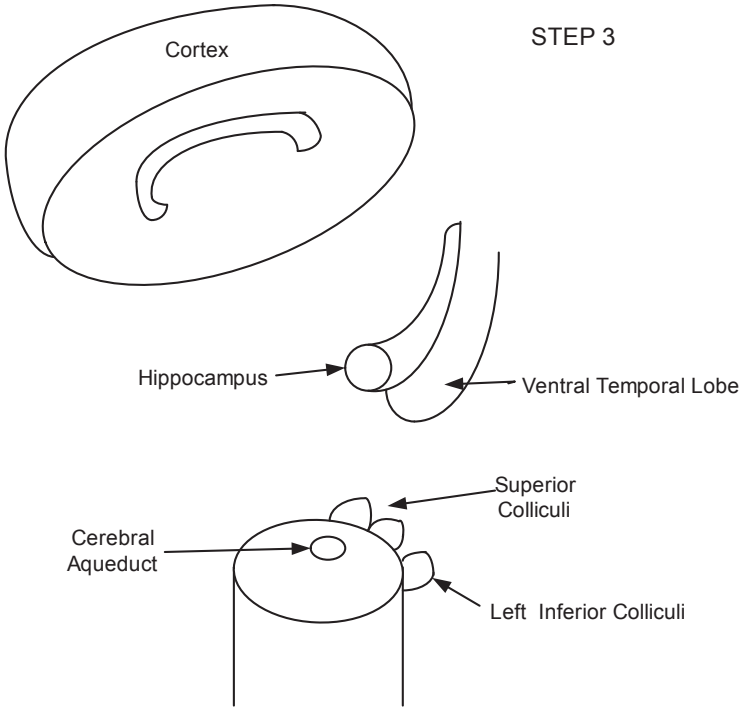


FIGURE 2.3. Relationship of the hippocampus and temporal lobe.

is much discussed in later chapters because it plays a role in both memory and anxiety. Its importance is best illustrated by the case of H. M., a man who had both of his hippocampi (there is one on each side) removed in the 1950s. This was necessary because H. M. had severe epileptic seizures that seemed to emanate from around his medial temporal lobes, where the hippocampus is located. After his surgery, H. M. appeared to recover completely. There was no neurological abnormality that would be apparent to the layman. However, H. M. lost all ability to form or access long-term memories. If he met a new person, H. M. would forget him or her within 5 minutes after he or she left the room. He would read the newspaper over and over again, with no memory of what he had read previously. The aide who cared for him at the nursing home had to introduce himself every morning, even after many years. When the aide died and H. M. was told of it, he asked, "Who's he?" Thus, the hippocampus is critical in shifting experience from short-term memory stores into long-term memory. Recent studies (which I review in Chapter 8) suggest that the hippocampus may

play a role in posttraumatic stress disorder (PTSD). Early physical or emotional abuse may cause changes in the hippocampus.

Just anterior to the hippocampus sits the amygdala; it also plays a role in memory. The amygdala is key in the formation (as opposed to the maintenance) of fear; it also is critical to our ability to recognize the biological significance of stimuli, such as identifying edible substances or interpreting sexual signals. It is strongly activated by perceptions of faces with emotional content (i.e., particularly angry affect). In primates, the amygdala plays a greater role in the management of affect and memory relative to the hippocampus than it does in lower mammals such as rats. The amygdala's role in processing affectively laden stimuli is discussed at length in Chapter 5.

STEP 4: THE FORNIX AND MAMMILLARY BODY

The next step is simple but does require some 3-D thinking (see Figure 2.4). Information is coming into the hippocampus through the ventral part of the temporal lobe. After processing, this information passes out of the hippocampus through the fornix. The fornix starts as a broad band of axons (white matter) that moves up and toward the middle of the brain (i.e., dorsally and medially). *Fornix* is Latin for "arch," and forming an arch is precisely what these axons do. As they approach the midline, the axons compress together, then turn vertically (ventrally) and form a column. This column terminates in the mammillary body (MB). There is an MB on each side of the midline of the brain, and these are visible on the underside of the brain. The hippocampus, fornix, and MBs form part of the Papez circuit, which will be completed in a later step.

STEP 5: TAKING ANOTHER VIEW; ADDING THE THALAMUS

In Figure 2.5, we are looking directly at the front (anterior view) of the brain. You can see the anterior (front end) of the hippocampus. Again, the fornix rises from the hippocampus and forms an arch, then funnels into a column and dives ventrally to reach the MB. In this anterior view, the "arch-like" nature of the fornix can be seen more clearly. Beneath the arch, we now draw an egg-like structure, the thalamus. The thalamus is a relay station consisting of multiple "nuclei," clusters of neurons that are named according to their location (anterior thalamic nucleus, ventral anterior nucleus, etc.). Information from the sensory organs is processed here before being relayed to the cortex. Also here are "motor nuclei," where

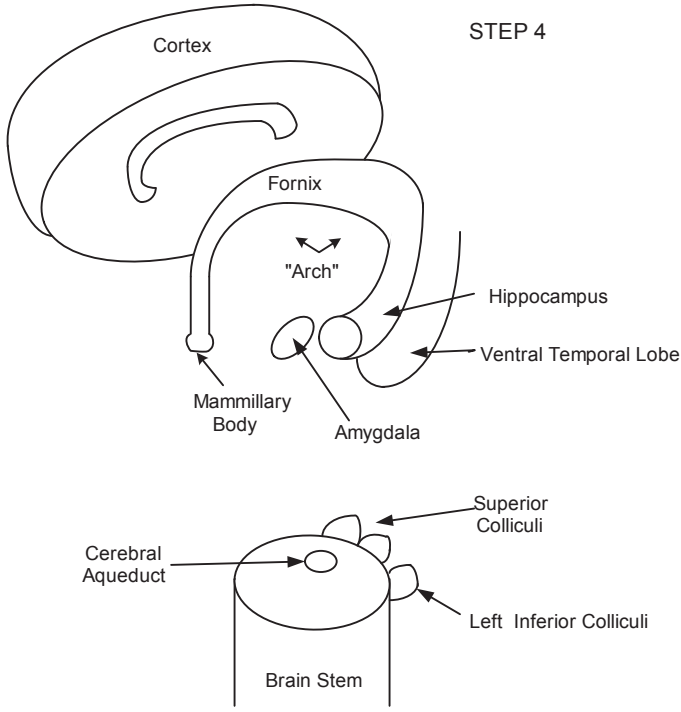


FIGURE 2.4. The fornix and the mammillary body.

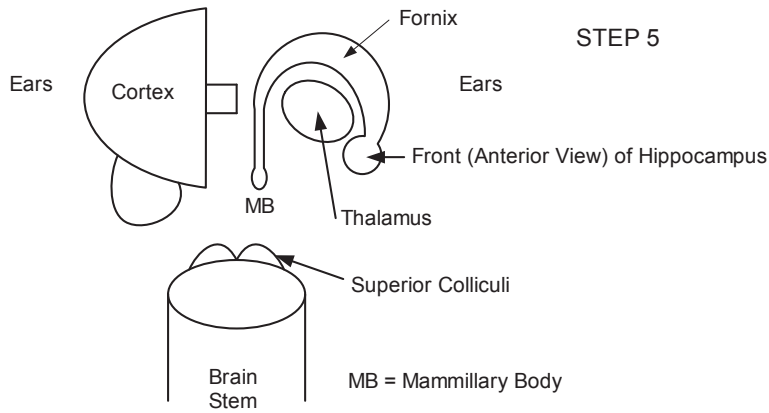


FIGURE 2.5. Looking at the fornix and thalamus from the front (anterior view).

motor commands from the frontal cortex and the basal ganglia (to be discussed in Chapter 5) are processed. Note how the egg-shaped thalamus fits in the bend of the hippocampus and fornix. Draw a much smaller egg-like structure below the thalamus, this is the "subthalamic nucleus." It is appropriately named, since it is below the thalamus. It also is involved in motor behavior.

STEP 6: THE BASAL GANGLIA

The basal ganglia, a set of structures involved in selecting and initiating actions, play a major role in voluntary motor movements and habits. While traditionally involved in motor activity, the basal ganglia are also involved in cognition and emotion. The basal ganglia consist of the striatum (caudate and putamen), the globus pallidus, the subthalamic nucleus, and the subtantia nigra (compacta and reticulata sections). In Step 6 (Figure 2.6), we first draw the striatum; in Step 7 (Figure 2.7), we will see where it fits in the brain. The important thing to bear in mind is that the caudate and putamen are one structure—the striatum. (The dorsal part of the striatum is often called the "neostriatum," because it is a later evolutionary development in higher animals; the ventral striatum is more primitive.) The caudate and putamen resemble a tadpole, with the putamen appearing as a

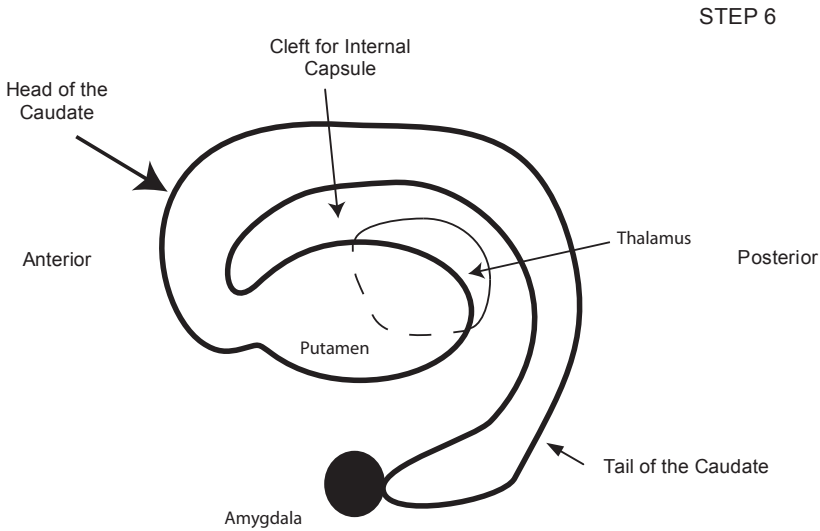


FIGURE 2.6. The caudate and putamen (neostriatum).

large head. At the anterior part of the putamen, the structure bends around 180 degrees and bulges out slightly. This forms the head of the caudate. The caudate runs posterior and tapers into the body, then bends downward (ventrally) to form the tail of the caudate. There is a space between the putamen and the caudate; through this cleft runs the "internal capsule," which carries axons from the frontal lobe neurons, which are making their way to the caudate and putamen, the brain stem, and ultimately to the spinal cord.

STEP 7: VISUALIZING THE GLOBUS PALLIDUS

In Step 7A of Figure 2.7, we are first looking at the caudate and putamen from the lateral view. To see the globus pallidus, first cut off the tail of the caudate. Next imagine that you are turning the putamen and the head of the caudate around, so that you are now looking at it from behind. Now you can see the globus pallidus clinging to the medial side of the putamen in Step 7B. *Pallidus* is Latin for "pale"; it is named for the color of the tissue in the fresh brain. The globus pallidus is divided into two parts: the interna, which is closer to the midline of the brain (at the top of the hill), and the externa, which lies next to the putamen. Notice also two areas on the most ventral part of the striatum and globus pallidus externa. These structures are the ventral striatum and ventral pallidal area, respectively. The ventral striatum is a more primitive structure. Whereas the neo (dorsal) striatum is involved in more complex motor acts and plays a role in linking cognition to motor behavior, the ventral striatum is more concerned with those behaviors related to survival, particularly aggression, sexuality, and eating. The neostriatum converses with the frontal lobes; the ventral striatum converses with the limbic parts of the cortex (i.e., those related to emotion). Rats self-stimulate parts of the ventral striatum via an implanted electrode; they also press a button to inject drugs of abuse directly into this area. It is thought that the circuitry of the ventral striatum is critical to the experience of reward.

STEP 8: WHERE DO THE BASAL GANGLIA FIT?

Step 8 (Figure 2.8) recreates Step 4. Next insert the thalamus under the "arch" of the fornix. Insert the smaller subthalamic nucleus beneath it. Insert the neostriatum (i.e., the caudate and putamen, in gray) just lateral to the fornix. Note that I have used dotted lines on the column of the fornix to indicate that the caudate is passing anteriorly (in front of) this structure. The tail of the caudate bends around to reach the amygdala. We are now

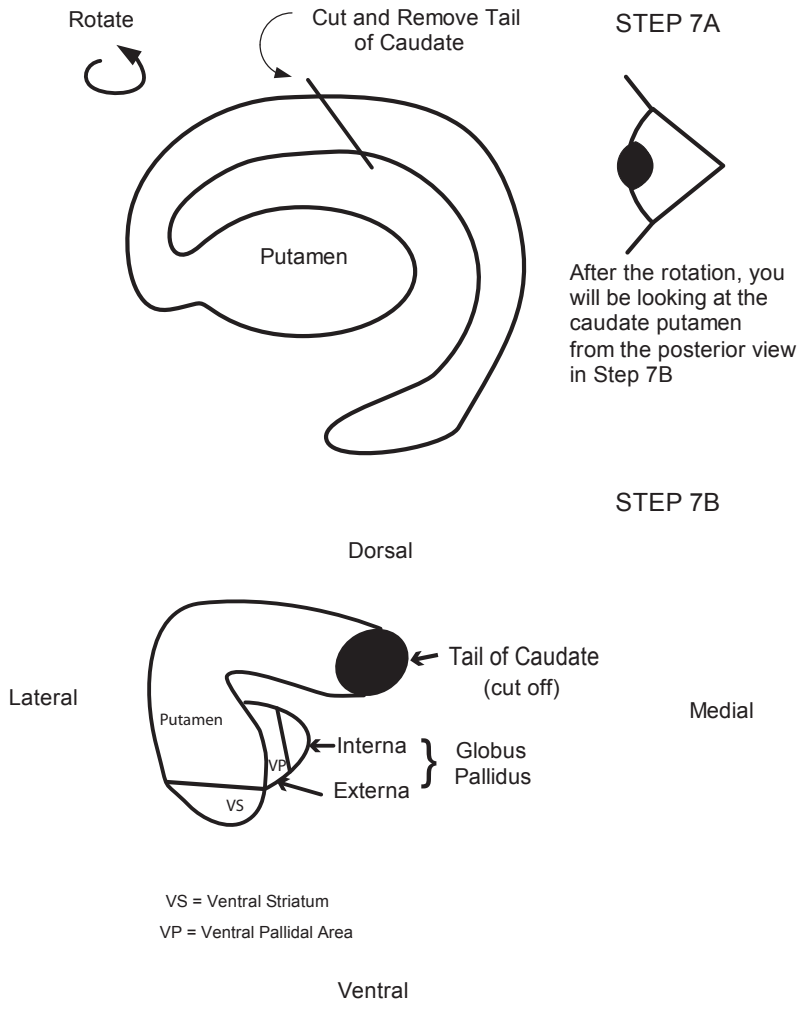


FIGURE 2.7. The striatum and the globus pallidus.

also in a position to see the internal capsule between the putamen and the caudate. Axons from neurons in the frontal cortex (those concerned with motor behavior) come together and pass through this cleft. Some neurons branch off to reach the caudate and putamen, others proceed to the thalamus, while still others continue ventrally to the spinal cord. This forms the ventral corticospinal tracts. One neuron in the precentral gyrus can send an axon through the "internal capsule" down to the spinal cord.

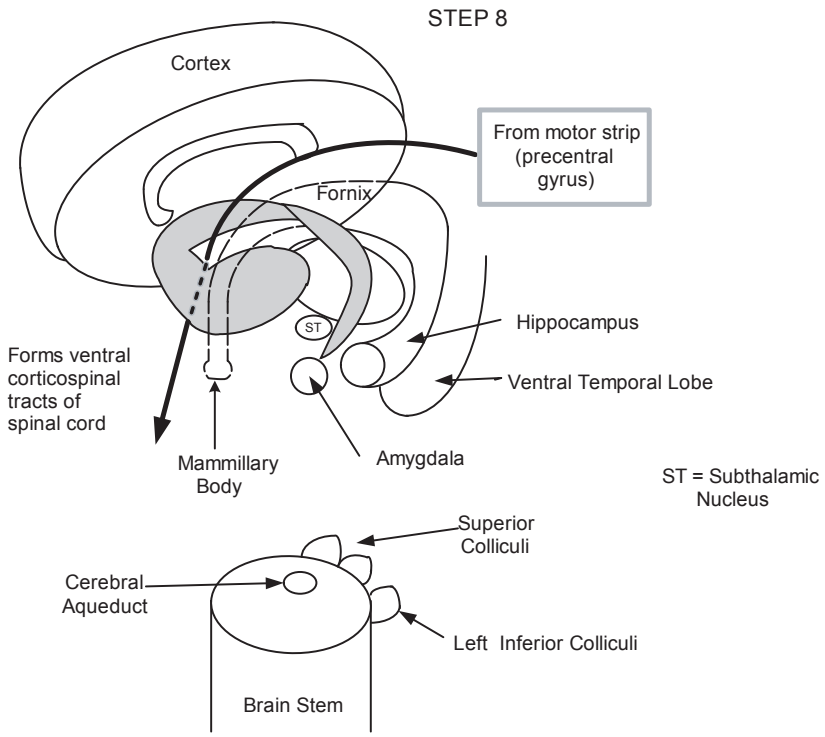


FIGURE 2.8. Putting it all together.

STEP 9: A FIRST ATTEMPT AT FUNCTIONAL NEUROANATOMY; UNDERSTANDING THE PAPEZ CIRCUIT

In Step 9 (Figure 2.9), you should redraw Step 4, then add the egg-shaped thalamus. Leave out the striatum for the time being. Label the corpus callosum (white matter), connecting the two hemispheres. Next draw the cingulate gyrus wrapping around the corpus callosum. Below the thalamus, sketch in the hypothalamus (*hypo* = below). The hypothalamus is involved in many bodily functions, but for now let's note that it is the "head ganglion of the sympathetic nervous system," in that it influences the "fight-or-flight" reaction. Information about the *current* state of the world enters the temporal lobe (1) and is then transferred to the hippocampus (2). After processing in the hippocampus (covered in more detail in Chapter 5), the information is transferred via the fornix to the MB (3), then from the MB

to the anterior thalamus (4). The anterior thalamus sends the information to the cingulate gyrus, where it interacts with older information in long-term memory stores (5), then returns to the hippocampus (6). Thus, the hippocampus is in a position to compare information about the current state of the world with information from the past and to determine whether what we are currently experiencing is familiar or not. Furthermore, the hippocampus can project to the hypothalamus (7) to activate the sympathetic nervous system. This may cause our "adrenaline to flow," particularly if the hippocampus matches the current state of the world to a painful memory, producing anxiety. Thus, you can see how dysfunction in the hippocampus might lead to inappropriate levels of anxiety when there is no danger around (as in panic attacks or PTSD). The physiology of anxiety is more complicated than this (involving the amygdala as well), but this example illustrates how neuroanatomy is relevant to behavior.

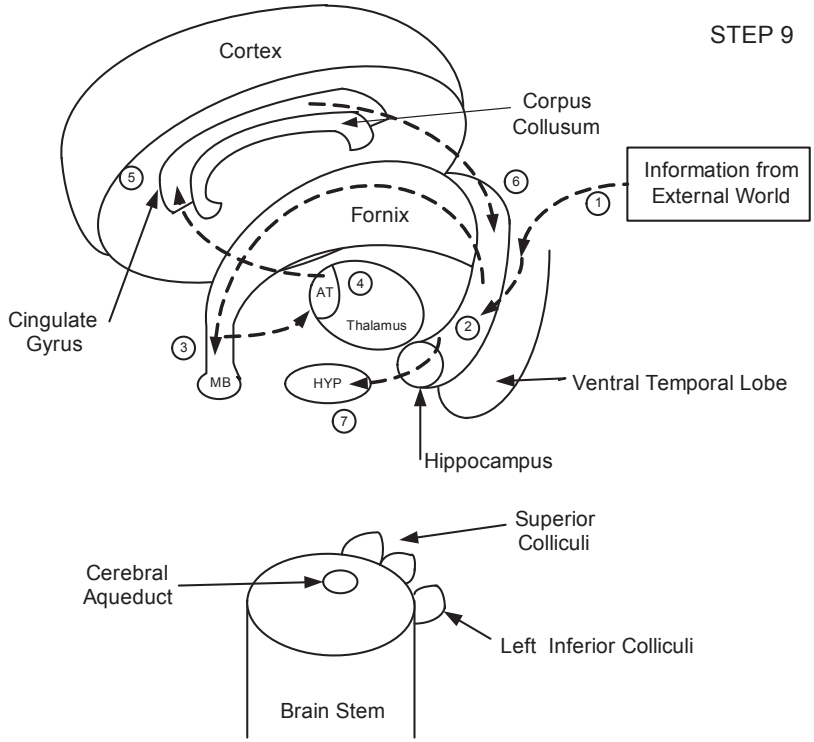


FIGURE 2.9. Functional neuroanatomy.

STEP 10: THE BASAL GANGLIA AND THEIR CONNECTIONS—WHAT ARE THEY FOR?

In Step 10 (Figure 2.10), two circuits are illustrated: the "limbic" circuit on the left side and the "sensorimotor" striatum circuit on the right. For now, we do not take up the functional aspects of the circuit; rather, we focus on how these circuits are put together. In the limbic circuit, note that information flows back and forth between the cingulate gyrus (limbic cortex) and the dorsomedial nucleus of the thalamus (1). The limbic cortex sends information in a one-way direction to the ventral striatum (2). Within the ventral striatum there is a key structure, the *nucleus accumbens*. This is the part of the ventral striatum most involved in the reward processes discussed earlier. From the ventral striatum, the information flows to the ventral pallidum (3), then back to the medial–dorsal thalamus (4). Note the box labeled "Ventral Tegmental Area (Dopamine)." Anatomically, this area lies ventral to the tegmentum, the structure formed by the superior and inferior colliculi (see Step 4). The cell bodies of these neurons produce the neurotransmitter dopamine that is released at synapses in the prefrontal cortex and ventral striatum (nucleus accumbens). The pathway from the ventral tegmental area (VTA) to the nucleus accumbens (5) is quite interesting. If an electrode is inserted into this pathway in a mouse, the animal will press a button to stimulate the pathway with electricity, causing the neuron to release dopamine into the accumbens. If a very small tube is surgically placed in the accumbens, an animal will inject cocaine into the area, which causes a very sudden release of dopamine. In later chapters I explore how this mechanism is relevant to substance abuse disorders. A final part of this circuit involves the projection of dopamine neurons from the VTA to the neocortex (6). This pathway, the "mesocortical" dopamine pathway, may play a critical role in the pathophysiology of attention-deficit/hyperactivity disorder (ADHD) and psychotic disorders. It also may play an important role in "working memory"—the ability of the brain to hold information "online" while plans for an appropriate response to the current environment are made.

The sensory–motor striatum, shown on the right side of Step 10, is more complicated but has a structure similar to the limbic striatum. Again, there is an interchange of information between the frontal lobes and the thalamic nuclei, this time with the ventral anterior and ventral lateral nuclei (1). The frontal lobes also send information to the neostriatum (2). There are three pathways out of the neostriatum. Two of these pathways project to the globus pallidius, but to different parts of it. The direct pathway goes immediately to the globus pallidus interna (3a). The indirect pathway projects to the globus pallidus externa (3b). Information is then transferred

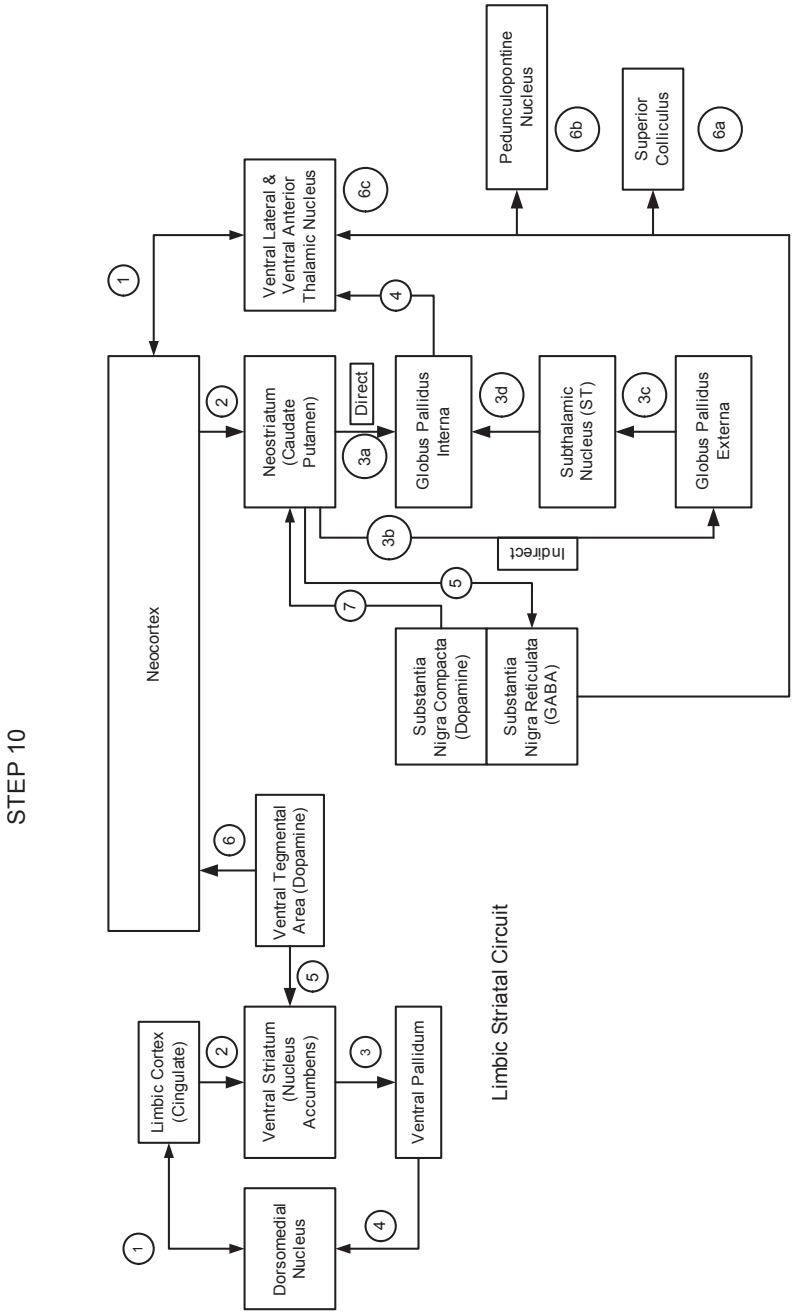


FIGURE 2.10. The basal ganglia and their connections.

to the subthalamic nucleus (3c); from there, it is passed on to the globus pallidus interna (3d). From the interna, the information flows back to the ventral lateral and ventral anterior thalamic nucleus (4). The third pathway from the neostriatum flows to the substantia nigra reticulata (5). The reticulata differs from the compacta in that it uses gamma-aminobutyric acid (GABA) as a neurotransmitter, whereas the compacta, like the VTA, uses dopamine. GABA, as I discuss later, is an inhibitory transmitter; it turns off neuronal impulses. The reticulata then projects to and releases GABA into three structures: the superior colliculi (6a) (which play a role in eye movements), the pedunculopontine nucleus (PPN) (6b) (which is found in the brain stem and governs major muscles of the trunk involved in balance, standing, and walking), and the ventral lateral and ventral anterior thalamic nucleus (6c). I explore motor behavior in depth in Chapter 5, but for now, it is important to understand the role of the two parts of the substantia nigra. The reticulata uses the inhibitory neurotransmitter GABA. When GABA is released into the colliculi, the thalamus, and PPN, their activity is inhibited. Furthermore, the substantia nigra reticulata is tonically active (i.e., the neurons are nearly always firing) and motor movement is prevented. For the person to move, this inhibitory influence must be withdrawn. The substantia nigra compacta, through the influence of dopamine on the neostriatum (7), plays a major role in removing this inhibitory influence and allowing the initiation of new behaviors. This is why persons with Parkinson's disease (in which dopamine is depleted in the compacta) lose the ability to initiate new motor action; the movements they can produce are slow and jerky.

SUMMARY

The focus of this chapter has been to present the brain in three dimensions and familiarize you as to how these structures fit together. In the following chapters, I focus on specific neurotransmitters. There are specific pathways in the brain for each neurotransmitter, and we will be drawing in these pathways in the next chapters. It would be cumbersome to draw a 3-D picture each time we wish to consider a different neurotransmitter. Therefore, once you have mastered the 3-D structure of the brain in Steps 1–9, you should draw the general brain figure shown in Figure 2.11. You are looking at a lateral view (from the side of the brain), but one-half of the brain has been removed to allow you to visualize the hippocampus, the fornix, and the caudate putamen. At this point, the globus pallidus cannot be seen, but remember that it is medial to the striatum. The fornix is represented as a simple tube. I have added one more structure to those we have already

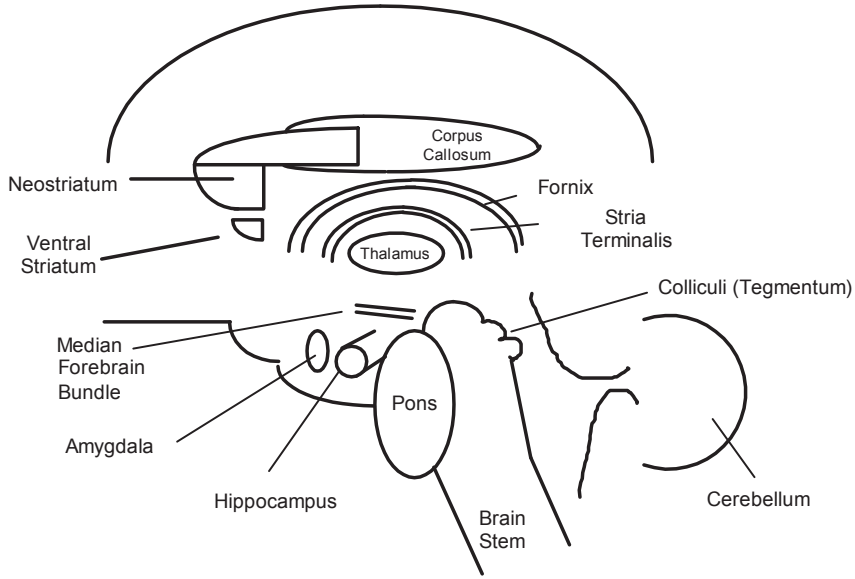


FIGURE 2.11. A simplified view of the brain.

discussed—the stria terminalis. Like the fornix, it carries the axons of neurons and connects the amygdala to the hypothalamus. It also is a means by which neurotransmitters reach the amygdala from the brain stem.

The first step, understanding the neuroanatomy of the brain, is complete. The next step is to understand how neurons communicate internally and with each other. You will then be able to look at how the different parts of the brain work together to generate behaviors, cognition, and emotions.

CHAPTER 3

Neuronal Communication

The neuron is the microprocessor of the brain (Figure 3.1). Hundreds of dendrites project from the cell body; these in turn are covered with thousands of synapses that receive input from the axons of multiple other neurons. The axons release neurotransmitters onto receptors in these synapses. A particular neuron may receive input anywhere from one to 100,000 different axons on its dendrites. Thus, the neuron is not a simple relay; instead, this complex input is integrated so that the neuron may formulate a response. A single axon may signal one neuron, or the axon may branch to send signals to thousands of neurons. Since there are 100 billion neurons in the brain, with each having hundreds or thousands of connections to each other, the complexity of the brain circuitry is self-evident. As shown in the upper panel of Figure 3.1, most neurons have a prominent nucleus. Within the nucleus is the nucleolus, where ribosomes (small black circles) are produced. Ribosomes are transported into the nucleus, then out into the cytoplasm, where they may become attached to the rough endoplasmic reticulum (ER). Messenger ribonucleic acid (mRNA) that is *transcribed* from DNA in the nucleus is *translated* into proteins at these sites. Note the heterochromatin in the nucleus; this is DNA that cannot yet be transcribed. Various epigenetic events (introduced previously in Plate 2) may cause the histone proteins in the chromatin to be altered and make these genes available for transcription.

In the postsynaptic neuron, the multitude of receptors produce many different types of signals. Among the most significant is whether the neuron produces an electrical transmission (the "action potential"). This electrical signal travels down the axon and upon reaching the synaptic bouton (end of the axon), the neuron releases its own neurotransmitter onto the

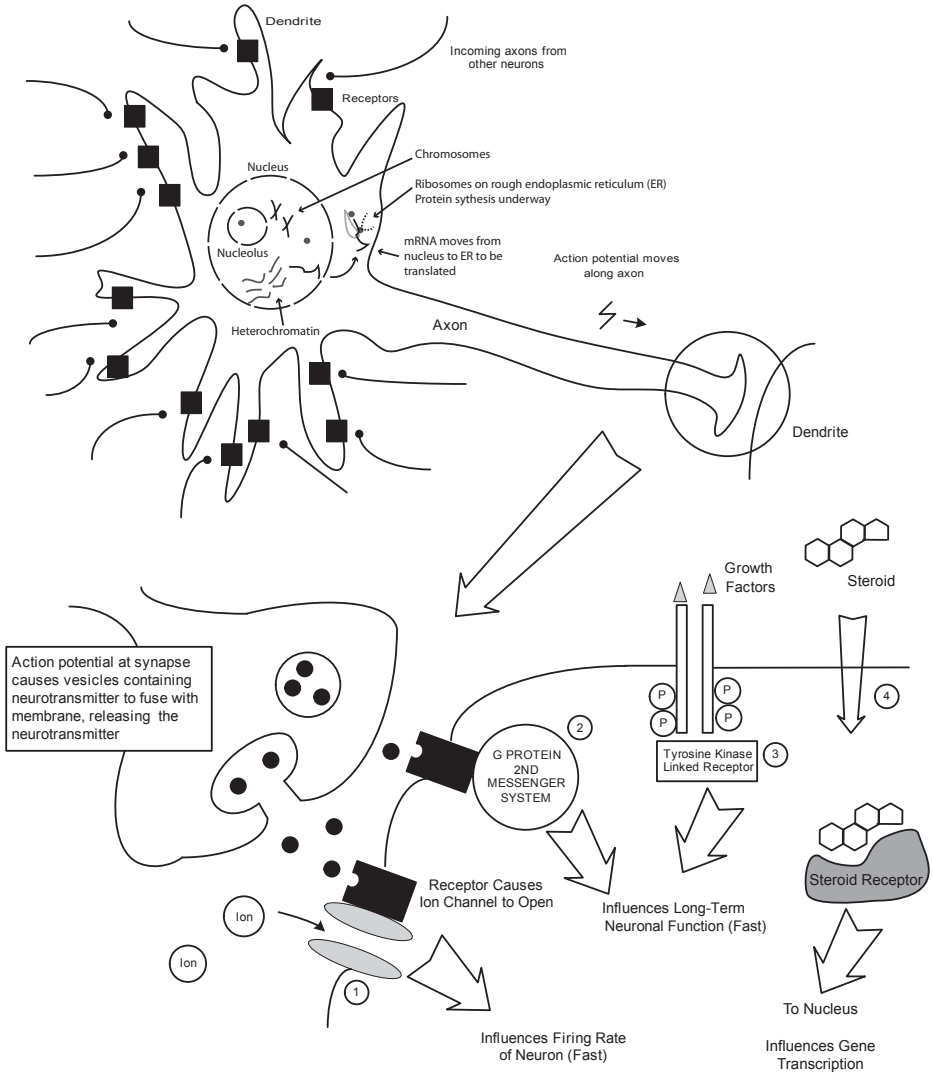


FIGURE 3.1. Fundamentals of neurotransmission.

neighboring dendrites. When a neurotransmitter binds to a receptor, the neuron can be affected in a variety of ways, as shown in the lower part of Figure 3.1.

Four types of receptors in neurons are discussed in this chapter. The first is the "ligand-gated ionotropic" receptor (1). When a neurotransmitter binds to this receptor, it causes a channel to open in the neuronal membrane and ions flow through it. Ions are positive or negative electrically charged particles. The ions involved in neuronal functioning are sodium (Na^+), potassium (K^+), chloride (Cl^-), and calcium (Ca^{2+}). The flow of these ions in or out of the neuron is the critical factor in stimulating or inhibiting the neuron's firing (action potential). The three other receptor systems have more subtle effects on the neuron. Receptor (2) is linked to the "G protein second messenger system." The neurotransmitter is the first message, in that when the G protein is activated, it turns an enzyme in the cytoplasm on or off. This has long-term effects on neuronal function. While the effects of the ionotropic receptor turn on and off within milliseconds, the processes set in motion by the G protein may last anywhere from milliseconds to hours. Receptors linked to G protein are often referred to as "metabotropic" receptors because they affect long-term cellular processes.

The receptor tyrosine kinase (RTK) system is stimulated by growth factors (3). While neurotransmitters are generally small molecules, growth factors are generally proteins of intermediate size; for example, brain-derived neurotropic factor (BDNF) has 119 amino acids. Growth factors such as BDNF work in the general region where they are released. When a growth factor binds to the part of RTK outside the membrane, phosphate groups bind to inner portions of RTK. This activates a complex series of enzymes that play a major role in nurturing neurons. High levels of stress that reduce release of growth factors can result in neuronal atrophy. Thus, the processes governed by the RTKs may be highly relevant to stress-induced psychiatric disorders. Finally, the body produces a number of well-known steroid hormones (4) such as cortisol, estrogen, and testosterone, among others. Steroid hormones consist of a number of carbon rings fused together. As a result, they can pass directly through the neuron membrane into the cytoplasm. Here, they attach to a receptor that then travels to the neuron nucleus, altering gene activity.

GLIA

Surprisingly, neurons constitute only about 10% of the cells in the brain. The remaining are glial cells: microglia, oligodendrocytes, and astrocytes (Figure 3.2). "Microglia" are the immune cells of the nervous system; they also remove dead cells and debris. They play a role in degrading

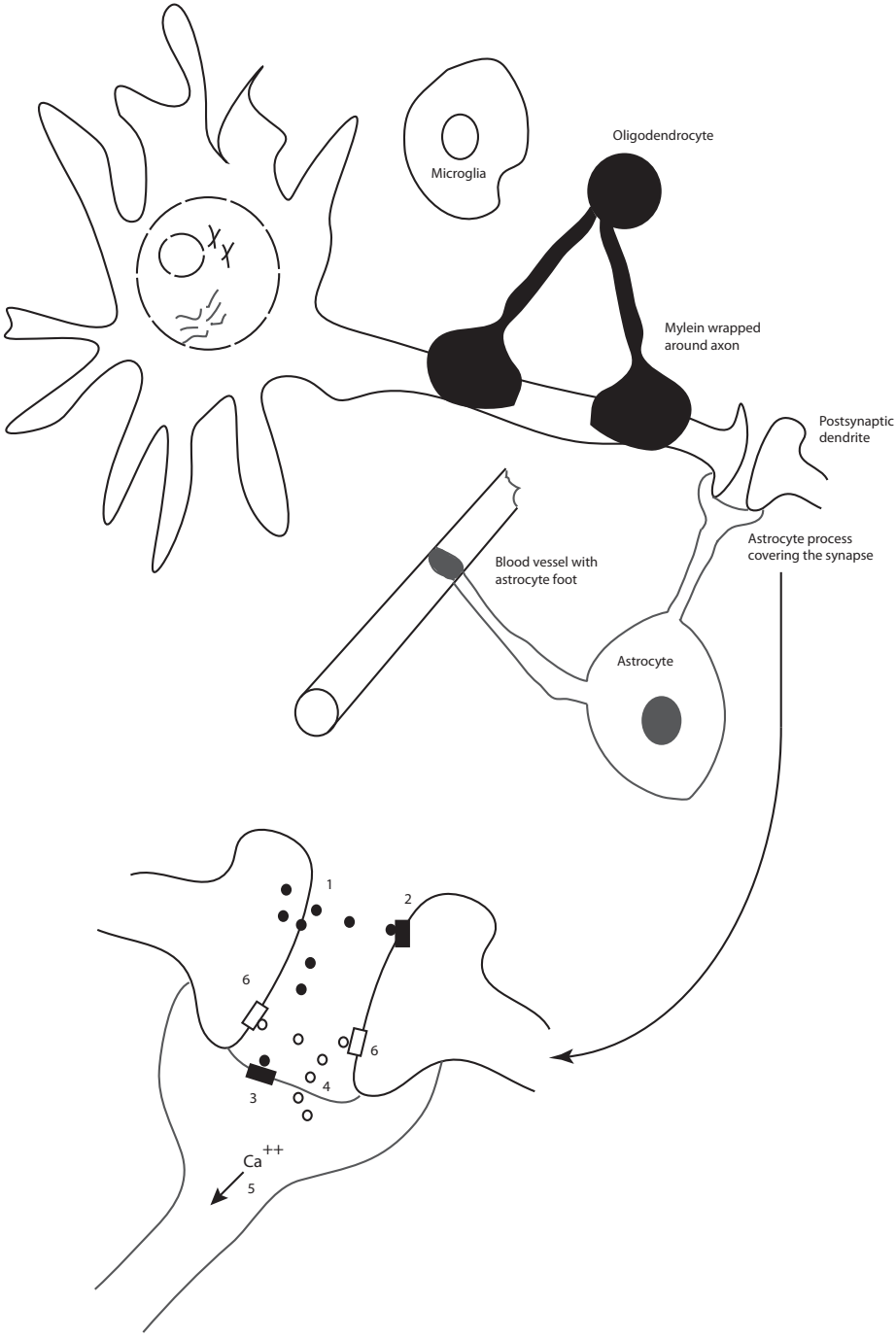


FIGURE 3.2. Glial cells and their functions.

synaptic connections and are active in neurodegenerative disease, but it is not known whether they are inappropriately active in such disorders or whether their activity is a result of the destructive process. "Oligodendrocytes" are involved in the production of myelin, which surrounds axons and increases conduction of the action potential. "Astrocytes" were once viewed as merely support cells for neurons, but it is now clear they have a complex role in neuronal communication. Astrocytes have foot processes that surround blood vessels, where they form part of the blood–brain barrier. They carry nutrients to the neuron, as well as control the blood flow to the neuron. Astrocytes form processes across the synapse, linking the pre- and postsynaptic neuron (see lower inset of Figure 3.2). When the presynaptic neuron releases a neurotransmitter (1), it binds to receptors both on the postsynaptic neuron (2) and on the astrocyte (3). When the receptor on the astrocyte is activated, a calcium wave is created within the astrocyte (5); these waves can signal other astrocytes within their neighborhood. The astrocyte releases substances that attach to receptors on *both* the pre- and postsynaptic neuron (6); this can either increase or decrease the activity across the synapse (Allen & Barres, 2009). Astrocyte–neuron interactions are key in a number of brain process and diseases.

HOW DO NEURONS FIRE?

Neurons maintain an electrical charge, like tiny batteries. We first see how this voltage is produced, then it will be clear how the neuron generates the action potential that ultimately causes the release of neurotransmitters. Figure 3.3 illustrates how the "membrane potential" is produced.

Figure 3.3A shows a neuron with K^+, Cl^-, and Na^+ ion channels. Each channel can admit only one type of ion, with Na^+ channels being much less permeable than K^+ and Cl^- channels; that is, Na^+ has more difficulty flowing in or out of the neuron than the other two ions. In Figure 3.3A, we first add potassium chloride (KCl) to the solution. The K^+ and Cl^- distribute themselves on each side of the membrane. In Figure 3.3B, 120 mM of K^+ ions are injected inside the neuron, but these K+ ions are associated with 120 mM of negatively charged proteins (A–). These large proteins *cannot* pass through the ion channels or the membrane. Since there is now an excess of K^+ inside the neuron, K^+ begins to flow out of the neuron, down its *concentration* gradient. Since the proteins cannot follow the K^+ ions, a separation of charge is created. The positively charged K^+ ions move out, leaving the negatively charged proteins behind. With more K^+ on the outside than inside, the inside is negative relative to the outside. After only a small amount of K^+ has flowed out, enough of a charge separation has built up so that K^+ can no longer flow out against the *electrical* gradient. Figure

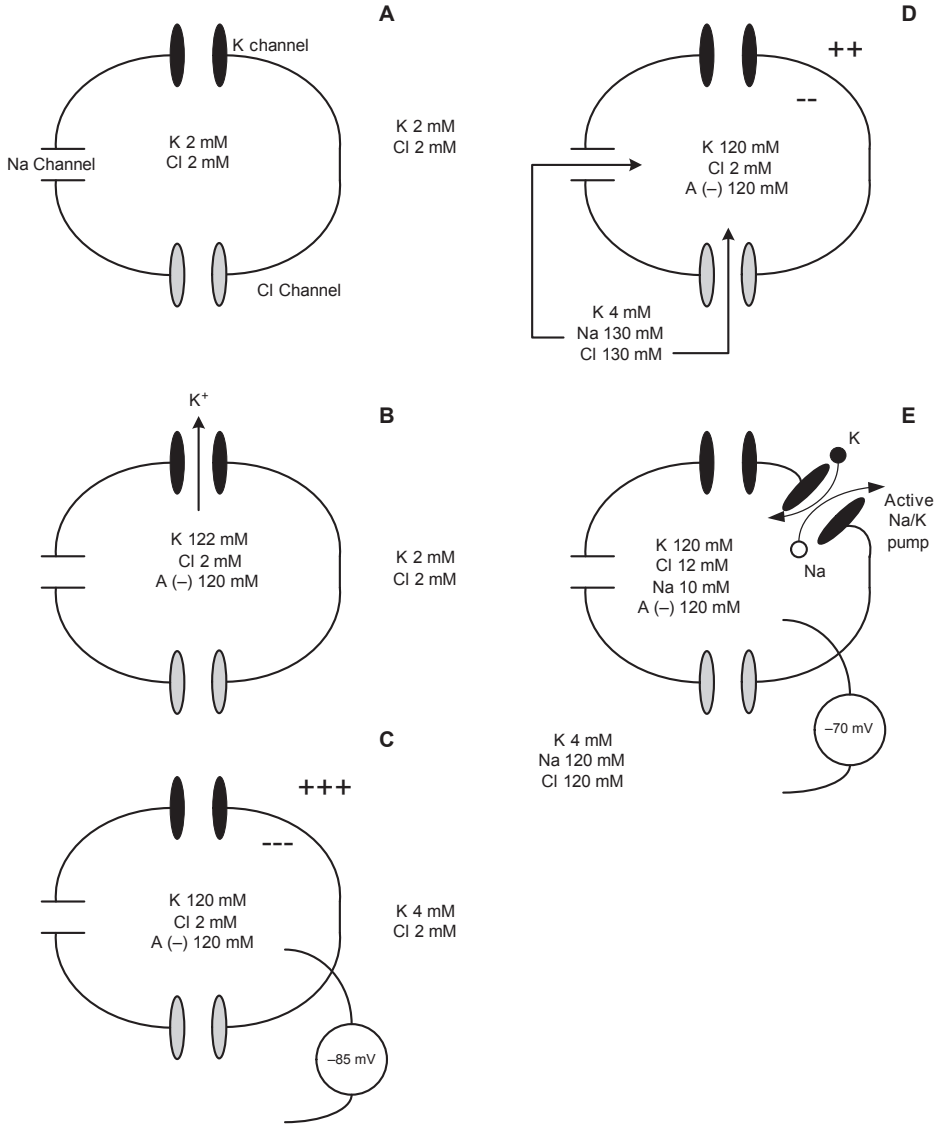


FIGURE 3.3. Understanding the neuron membrane potential.

3.3C shows the neuron after the K^+ has reached equilibrium, and the electrical and concentration gradients are balanced. Since there is an unequal distribution of charge, a potential (i.e., a voltage difference) is set up. The inside and outside of the neuron are analogous to the positive and negative terminals of a battery. The membrane potential, if it were based only on K^+, would be about –85 mV.

The cell is no longer at osmotic equilibrium because of the large concentration of negative proteins inside the cell. Water would flow into the cell and cause it to burst. This does not happen, however, because of the large concentration of NaCl in the extracellular fluid. As shown in Figure 3.3D, when NaCl is added, Na^+ begins to flow down its concentration gradient, as well as down its electrical gradient. Cl^- follows Na^+ as the negative ion. However, Na^+ and Cl^- channels are significantly less permeable relative to K^+ channels. Subsequently, equilibrium is established as the flow of K+ out of the cell balances the flow of Na^+ and Cl^- into the cell. The combined equilibrium of the three ions leads to the final membrane potential of –70 mV (Figure 3.3E). Like any battery, the neuron would "run down" and lose its charge if there were not an active process that maintains the membrane potential. Left to itself, Na^+ ions would leak into the neuron and K^+ ions would leak out to the point that no charge was left. Thus, the neuron must actively pump K^+ and Na^+ ions in and out of the cell, respectively (see upper right segment of Figure 3.3E). The action of this pump requires considerable energy. Neurons require a steady supply of oxygen and glucose, making them highly sensitive to damage when deprived of their blood supply, as in a stroke.

THE ACTION POTENTIAL

Figures 3.4 and 3.5 take us through the mechanism that leads to an action potential being generated. Figure 3.4A shows the neuron at rest. Two ligand-gated channels are closed and two passive open channels (one for Na^+ and one for K^+) are open. On either side of the passive channels are the "voltage-gated" ion channels, which are closed at rest. In Figure 3.4B, a neurotransmitter binds to the receptor, which causes the ion channels to open. Na^+ flows into the cell and K^+ flows out. *This localized flow of ions, by itself, does not trigger the action potential.* Rather, it produces voltage changes around the area of the receptors. As a result, the membrane in that particular area becomes more positive relative to areas around it. The key to triggering the action potential is whether enough neurotransmitter has been released to open sufficient ligand-gated channels to produce the electrical change needed to open the voltage-gated Na^+ channels.

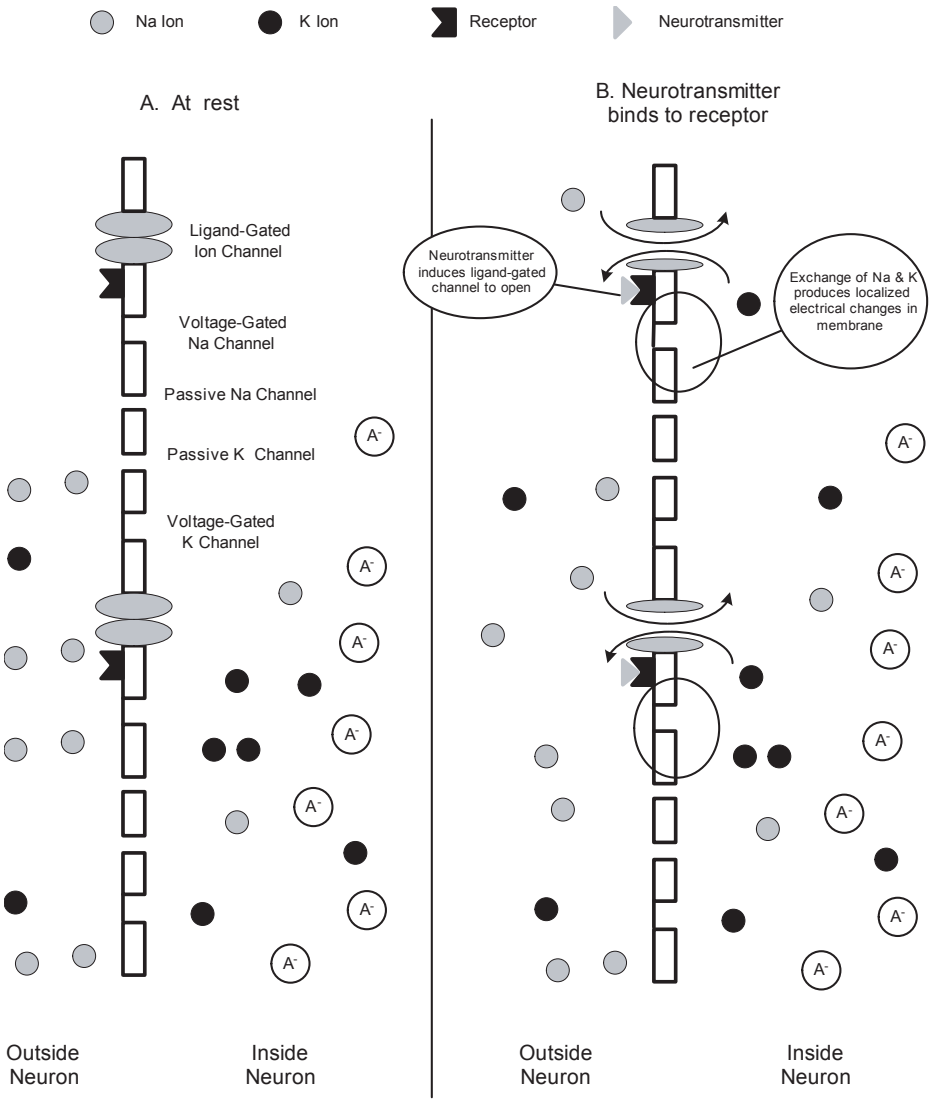


FIGURE 3.4. Understanding the action potential: (A) The neuron at rest. (B) A neurotransmitter binds to an ionotrophic receptor.

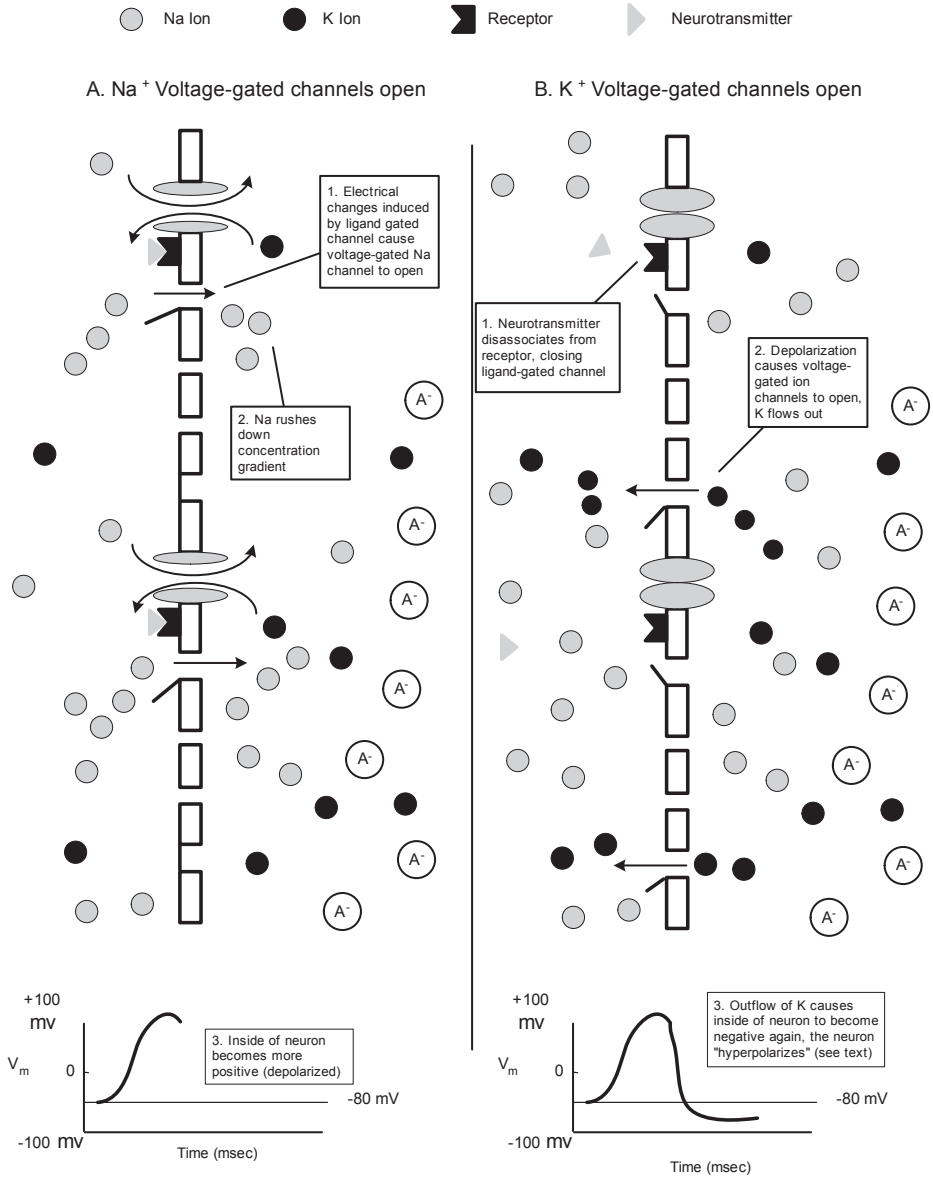


FIGURE 3.5. Understanding the action potential: (A) Entry of Na^+ causes membrane potential to become positive. (B) Outflow of K^+ restores negative membrane potential and induced hyperpolarization.

Figure 3.5A shows that when the voltage-gated channels open, Na^+ rushes into the cell, down its concentration gradient. This causes the inside of the cell to become more positive relative to the outside, as noted in the graph at the bottom of Figure 3.5. The neuron has become "depolarized." In Figure 3.5B, the neurotransmitter has disengaged from the receptor, closing the ligand-gated channel. The depolarization has now caused the voltage-gated K^+ channels to open and K^+ rushes out of the cell down its concentration gradient. As shown in the graph in the lower part of Figure 3.5B, the membrane potential returns to being negatively charged (inside compared to outside). Notice that the neuron "overshoots"; that is, the membrane is more negatively charged than it was before the action potential was triggered because so much K^+ has flowed out of the neuron through its voltage-gated channels. This process is referred to as "hyperpolarization." The neuron enters a refractory period in which it is more difficult for it to generate another action potential. Since the membrane is so negative on the inside relative to the outside, much more neurotransmitter will be required to induce the opening of enough voltage-gated Na^+ channels to fire another action potential. After several minutes, the membrane will drift back up to –70 mV and the neuron may fire again. *The neuron can regulate its firing rate by adjusting the size of the postaction potential hyperpolarization.* If the neuron leaves the voltage-gated K^+ channel open for a longer time, the membrane is more hyperpolarized and the refractory period is longer. If the neuron shuts off the K^+ voltage-gated channel earlier, then the membrane is not so hyperpolarized (because less K^+ flowed out) and the neuron can fire again sooner. Second messenger systems play a central role in this process by regulating how long the voltage gate remains open.

Figure 3.6A shows how the action potential propagates down the axon. When the ligand-gated channel is opened by the neurotransmitter, Na^+ flows in (1). The voltage changes due to this inflow of Na+ cause the voltage-gated channels to open (2), further increasing the flow of Na^+ into the neuron (3). Now, the voltage changes induced in Step 3 flow further down the axon, inducing the next group of voltage-gated channels to open (4). Once again, more Na^+ flows in (5), and these voltage changes are transmitted to the next set of voltage-gated channels. The process continues until the action potential reaches the end of the axon.

When the action potential reaches the synapse, it leads to the release of neurotransmitter (Figure 3.6B). Previously, an organelle within the neuron, the endosome, pinched off a small sphere called a vesicle (1). The vesicle fills with the neurotransmitter (2), then moves to the edge of the membrane, a process referred to as "docking" (3). When the action potential reaches the end of the axon (4), it causes the opening of voltage-gated calcium channels (5). When the calcium enters the synapse, enzymes are activated that fuse the vesicle to the membrane, disgorging the neurotransmitter into the

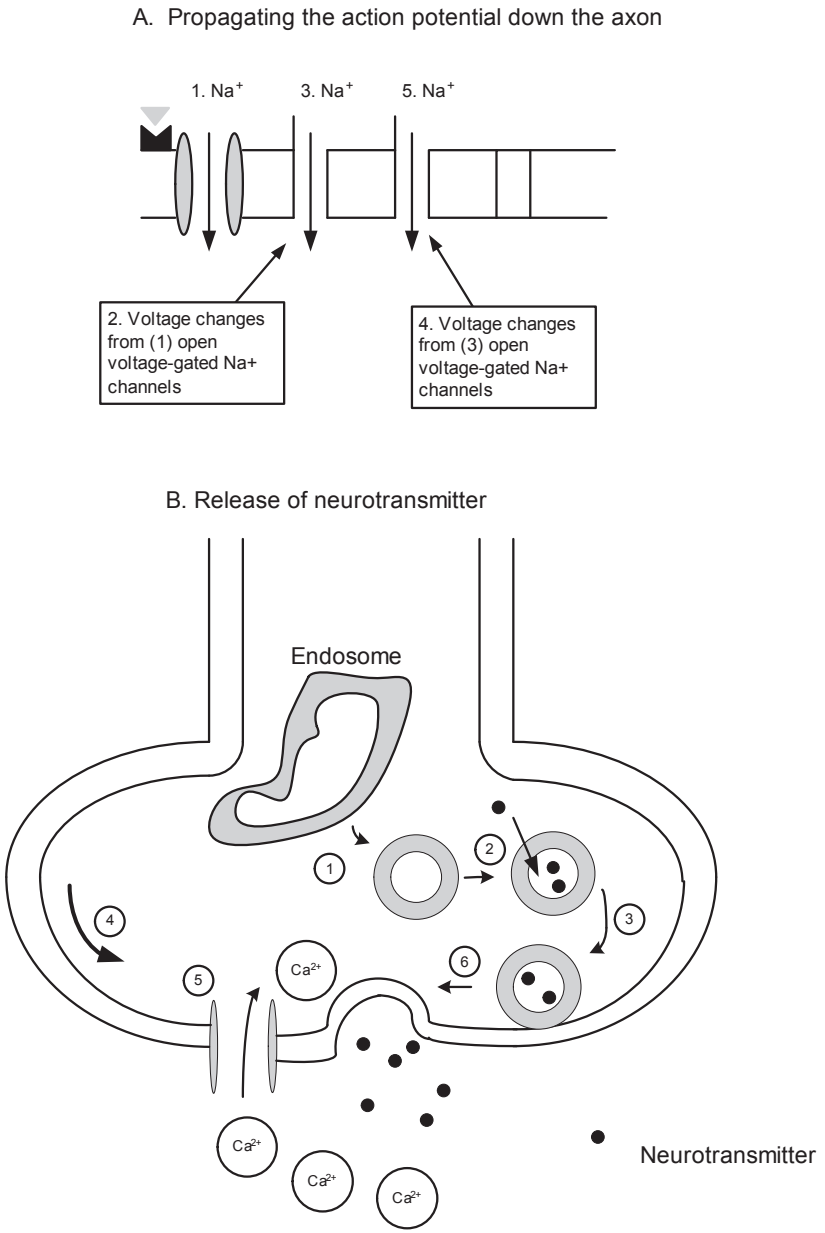


FIGURE 3.6. Propagation of the action potential and release of neurotransmitter.

synaptic cleft (6). Alterations in these calcium channels may be part of the pathophysiology of diverse psychiatric disorders including bipolar disorder and schizophrenia.

THE G PROTEIN SYSTEM

Figure 3.7 shows this key second messenger system. At rest, the G protein is attached to the inside of the neuron membrane, extending into the cytoplasm of the cell. It is only very loosely associated with its receptor. When the neurotransmitter stimulates the receptor, it changes shape such that the G protein can bind to it. A G protein consists of alpha (α), beta (β), and gamma (γ) subunits. The amino acid structures of these subunits vary between G proteins, conveying different functions (Zackartow, Darman, & Nestler, 2012). The human genome codes for over 600 G

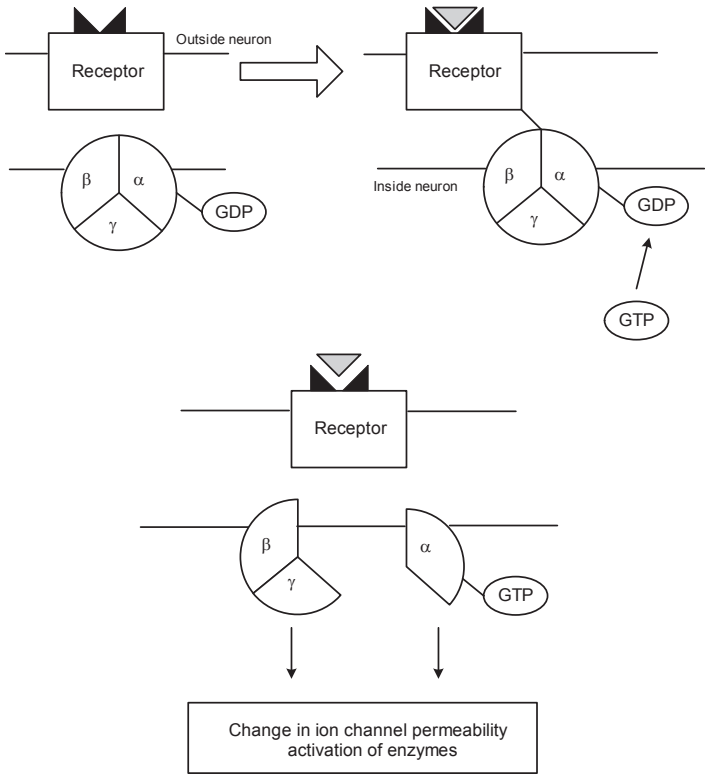


FIGURE 3.7. The action of G proteins associated with the metabotropic receptor.

protein-coupled receptors (Baltoumas, Theodoropoulou, & Hamodrakas, 2013). The alpha subunit, during the resting state, is bound to a molecule of guanosine diphosphate (GDP). When the G protein associates with the receptor, another shape change occurs, such that guanosine triphosphate (GTP) replaces the GDP. When this occurs, the G protein splits into an alpha-GTP and a beta–gamma subunit. These two parts of the G protein become active, activating enzymes in the neuronal cytoplasm (alpha-GTP) and changing ion channel permeability beta–gamma. Two critical enzymes activated by alpha-GTP are adenylyl cyclase and phospholipase C.

ADENYLYL CYCLASE

Adenosine triphospate (ATP) is a molecule of adenosine (one of the bases in DNA) with a chain of three phosphate groups attached to it. The enzyme adenylyl cyclase transforms ATP into cyclic adenosine monophosphate (cAMP) by cleaving off two of its phosphates and making a circular bond with the final phosphate left on the adenosine molecule (Figure 3.8).

Two different receptors are shown at the top of Figure 3.8. The receptor on the left is linked to a G protein with an $alpha_s$ subunit that *stimulates* adenylyl cyclase. In contrast, the receptor on the right is linked to a G protein with a different subunit ($alpha_i$); its effect is to *inhibit* the activity of adenylyl cyclase. This stimulation and inhibition of adenylyl cyclase is *not* the same as the stimulation or inhibition of an action potential. When adenylyl cyclase is stimulated via G-$alpha_s$, ATP is transformed into cAMP. Cyclic AMP can then activate a number of cytoplasmic enzymes, an example of which is protein kinase A (PKA). A "kinase" is an enzyme that puts two molecules together; a principal function of kinases in the neuron is to attach phosphate groups to proteins and regulate their function. The PKA is composed of four parts: two catalytic units, which actually add the phosphates, and two regulatory subunits, which bind cAMP. When two cAMP molecules bind to PKA, it breaks apart and the catalytic units then can enter the nucleus of the neuron. Here, they add a phosphate group to CRE-binding protein (CREB). CRE stands for "cAMP-responsive element." CRE is a segment of the DNA to which CREB can bind, facilitating the transcription of the nearby gene. New proteins can be synthesized, which is critical in the long-term life of the neuron.

THE PHOSPHOINOSITIDE SYSTEM

The phosphoinositide (PI) system helps regulate the level of calcium in the neuron. In the discussion of the action potential, it was noted that the

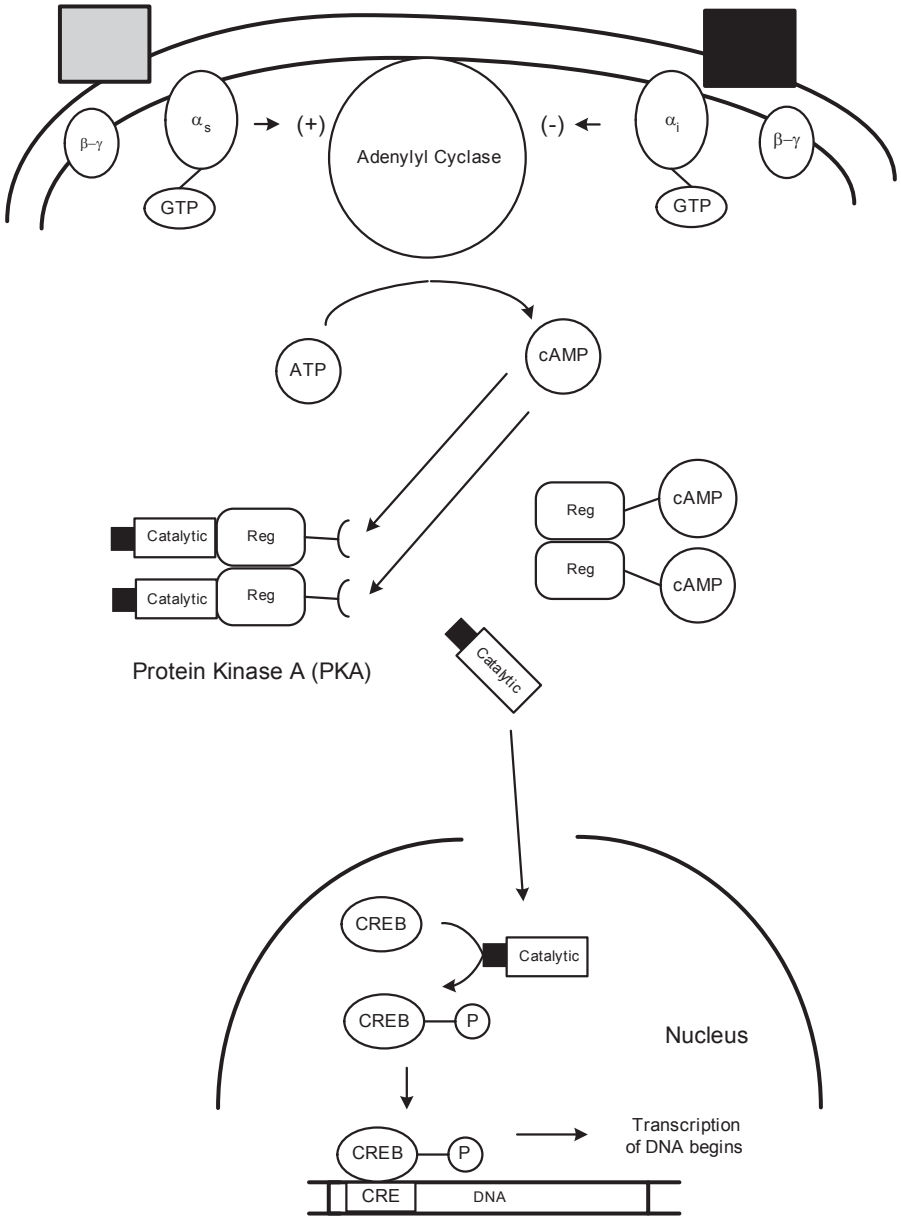


FIGURE 3.8. Actions of cyclic AMP (cAMP).

neuron had a low level of Na^+ inside, while the Na^+ level in the bloodstream (i.e., the extracellular fluid) was very high, very much like seawater. Thus, when cells first evolved, they developed mechanisms to pump Na^+ out of them so that the chemical milieu inside of the cell was very different from the seawater around them. When animals emerged on land, they had to develop a mechanism to bring the ocean with them. The plasma of blood has a similar concentration of ions as seawater; the kidneys and a variety of hormones work to maintain this balance of salts. Calcium is present in high concentrations in seawater and in our bloodstream, yet it is maintained at very low levels inside cells. The concentration of Ca inside neurons is 1/10,000th of that found outside the cell. In the neuron, the endoplasmic reticulum contains very high levels of calcium, similar to that found outside the cells. Why all this trouble to regulate calcium? In Figure 3.8, cAMP activated PKA, which in turn activated CREB by placing a phosphate group on it. Nature found phosphorylation to be a very efficient way to regulate cell activities, but high levels of calcium make the chemical reaction needed to add or cleave off the phosphate group very difficult. Hence, cells evolved ways to keep their intracellular calcium very low. A bonus of this system is that by subtly adjusting intracellular calcium levels, neurons can regulate the activity of a wide variety of enzymes and actions.

The top part of Figure 3.9 illustrates the molecule phosphatidylinositol 4,5-biphosphate (PIP_2), which has three parts. Inositol is a six-carbon ring with hydroxyl (oxygen–hydrogen, –OH) attached to each carbon. Because oxygen carries an electrical charge (i.e., it is polar), it likes being in water (hydrophilic). This part of the molecule resides in the cytoplasm of the neuron. The inositol molecule is linked to a molecule of glycerol, which is a three-carbon chain with a hydroxyl group on each carbon. Inositol binds to one of the carbons, but very long fatty acids bind to the other two carbons. These fatty acids are "oily," and water and oil don't mix. They are hydrophobic and remain inserted into the membrane. At rest, the PIP_2 molecule is all in one piece.

When a neurotransmitter attaches to a receptor linked to the PI system, the alpha-GTP subunit activates the enzyme phospholipase C. This enzyme, which is attached to the membrane, splits the PIP_2 molecule into two parts (bottom half of Figure 3.9). The inositol part of the molecule is set free in the cytoplasm as inositol triphosphate (IP_3). IP_3 attaches to a receptor on the endoplasmic reticulum; this opens a calcium channel, and calcium flows out of the reticulum into the cytoplasm. This rise in calcium activates another enzyme, calmodulin. Back at the membrane, the piece of the PIP_2 molecule left behind is called diacylglycerol (DAG). DAG, in turn, activates protein kinase C (PKC), which also phosphorylates cytoplasmic enzymes. IP_3 is then recycled to produce more PIP_2. The enzymes activated by the PI system play critical roles in the neuron's life. Excessive activation

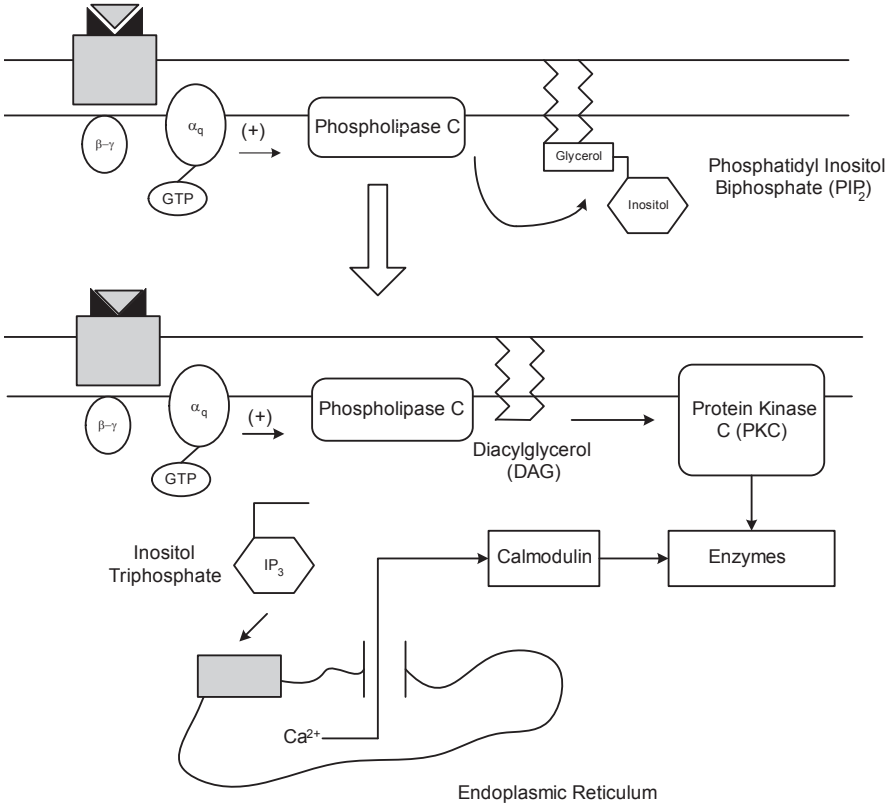


FIGURE 3.9. The phosphatidylinositol 4,5-biphosphate (PIP2) second messenger system.

of PKC can lead to tumors. Calcium-activated enzymes are crucial in the formation of synaptic vesicles and efficient neurotransmitter release.

HOW SECOND MESSENGER SYSTEMS WORK TOGETHER

Figure 3.10 shows how the second messenger systems regulate one major facet of neuron function—how frequently the neuron can fire an action potential (Nicoll, 1988). In the top left graph of the figure, a neuron is stimulated with the neurotransmitter glutamate; the glutamate has stimulated sufficient ligand-gated ion channels to trigger action potentials. In the top right graph, the neuron is first exposed to the neurotransmitter's norepinephrine (NE) or acetylcholine (Ach) *prior to* glutamate stimulation.

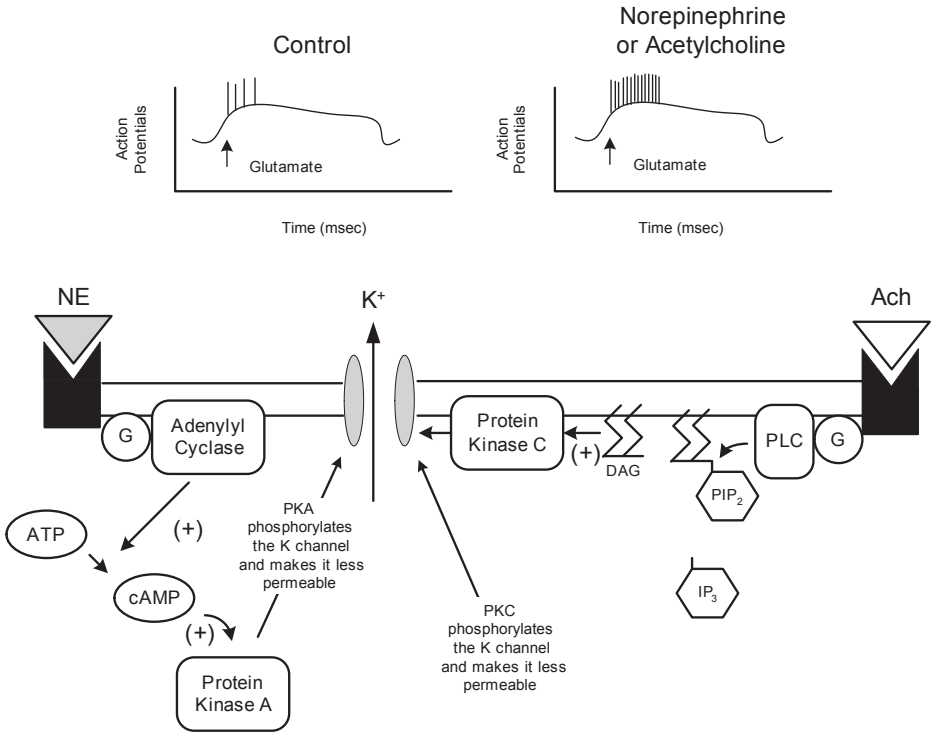


FIGURE 3.10. Interaction of second messenger systems to modify neuronal excitability. Abstracted from Nicoll (1988) with permission from the American Association for the Advancement of Science.

Notice that even though the same amount of glutamate is used, the neuron responds more vigorously in the presence of NE or Ach. The bottom half of the figure illustrates this. Remember that the ability of the neuron to fire again is governed by the degree of hyperpolarization; the more K^+ that leaves the cell, the more negative the membrane becomes and the more difficult it is to fire another action potential. By decreasing the K^+ outflow, the hyperpolarization is decreased and the neuron can fire sooner. When NE binds to its receptor, adenylyl cyclase is activated by the G protein system. cAMP is formed, which activates PKA. PKA phosphorylates the K^+ channel, making it less permeable to K^+, and reducing the outflow of K^+. Ach, by binding to one of its receptors, activates a G protein that turns on phospholipase C (PLC), achieving the same result. PIP_2 is cleaved, and DAG activates PKC. PKC, like PKA, phosphorylates the K^+ channel, reducing the hyperpolarization and allowing more rapid firing.

GROWTH FACTORS AND THE RTK SYSTEM

Growth factors play a crucial role in neuron proliferation and survival (Brady & Lau, 2012; Friedman, 2012). Specific growth factors such as BDNF, Nerve growth factor (NGF), and the neurotropics are discussed in detail in later chapters. Most neurotransmitters are unidirectional, in that they are released by the presynaptic neuron and bind to a receptor on the postsynaptic neuron. Growth factors, on other hand, also can reach a target neuron by two additional ways. Other cells in the brain besides neurons can produce growth factors and release them onto a neuron. The postsynaptic neuron can release a growth factor that travels back to the presynaptic neuron to bind to a receptor there, thus becoming a retrograde messenger. The RTKs are proteins that span the neuron's membrane, occurring in pairs (see Figure 3.11, panel 1). These proteins have many tyrosine amino acids as part of their structure, which can bind phosphate. The enzyme Ras is bound nearby to the inside of the neuronal membrane. Like the G protein, it binds a molecule of GDP in the inactive state. When growth factors bind to RTK (2), their shape alters, such that they cling together, becoming "dimers." Once "dimerized," the tyrosines bind four phosphate molecules, enabling the RTK to replace GDP on Ras with GTP (3). The next step involves an array of "adaptor proteins" (4) that build a bridge from the RTK to the active Ras (3). This can trigger a number of complex steps. First, Ras can now activate Raf (5), an enzyme that is free in the cytoplasm. Raf in turn phosphorylates (mitogen-activated protein kinase [MEK]). Note that this is a cascade of steps, each step amplifying the signal it received. Now MEK can phosphorylate (extracellular signal-regulated kinase [ERK]), which enters the nucleus and induces transcription of genes just as CREB did in Figure 3.8.

The array of adapter proteins also can activate the enzyme phosphatidylinositol 3-kinase (PI3K) (6). Described in Figure 3.9, PIP_2 was split into two different molecules. In the RTK system, PI3K performs a very different function; it adds another phosphate to PIP_2 to make PIP_3. PIP_3 then switches on *Akt*, another enzyme that travels to the nucleus to activate gene transcription. Notice that the active RTK also can activate phospholipase C (7), just like the G_q in the PIP_2 second messenger system. This splits PIP_2 and releases IP_3 to go to the endoplasmic reticulum and raise the level of intracellular calcium, leading to further enzyme activation.

PI3K/*Akt* and MEK/ERK converge on the enzyme *mTOR*, which has recently been implicated in autism (Tang et al., 2014). As complex as this description is, PI3K/*Akt* and MEK/ERK are just some of the pathways involved in the RTK system. All of these RTK pathways have complex effects during neural development, as well as throughout the lifespan. They help determine neuron growth and stimulation of neurons by growth

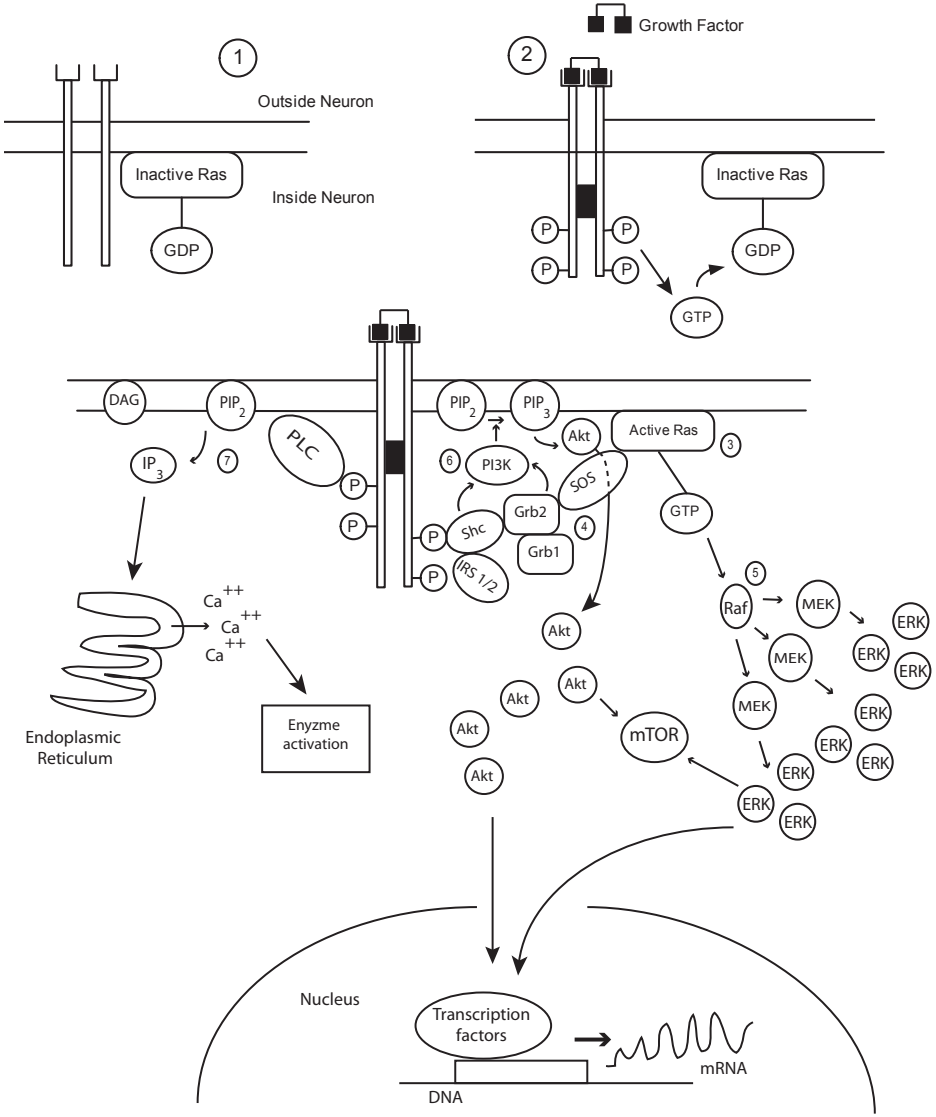


FIGURE 3.11. The RTK system.

factors to avoid cell death. They help regulate the rate of neuronal firing, as well as the formation and dismantling of synapse between neurons. Proteins in the system are highly likely to be the targets of future psychotropic drugs. In Chapter 11, I discuss the role of ketamine as a treatment for affective disorder; ketamine may exert its therapeutic effect through this system.

SUMMARY

We have examined the mechanisms by which neurotransmitters invoke responses in neurons. They may open ion channels and trigger the firing of the neuron. They also may open ion channels that further hyperpolarize and thus inhibit firing. Through G proteins, they activate enzymes that control calcium levels or initiate the transcription of DNA. Finally, growth factors set in motion a series of complex events that are critical to neuronal survival. It is important to note that it is not the neurotransmitter that conveys which of these mechanisms is used but rather the nature of the receptor. Some neurotransmitters only open ion channels, others only act through G proteins, while still others bind to an array of receptors, each of which uses a different mechanism. In the next chapter I examine the anatomy and function of each of the major neurotransmitters and growth factors thought to be involved in mental disorders.

CHAPTER 4

Neurotransmitters

We examined in Chapter 3 the neuroanatomy of the brain and the mechanisms by which chemical neurotransmitters convey their messages to the interior of the neuron. The next step is to examine the major neurotransmitter systems involved in the communication between neurons. For each of these neurotransmitter systems, several questions need to be answered:

- Where in the brain is the neurotransmitter system located? What is its origin (where the cell bodies of the neurons are found) and to where do these axons project (Nieuwenhuys, 1985)?
- To how many different types of receptors does the neurotransmitter bind? Are these receptors ionotropic (directly influencing ion flow and affecting the probability of an action potential) or metabotropic (using second messengers to influence the long-term function of the neuron)?
- What are the behavioral effects of neurotransmitter system activity in the brain? This last question is the most complex to answer. To do so, we need to go beyond an isolated view of a system to examine how neurotransmitter systems interact. In animals, a new technique called optogenetics (see Box 4.1) is increasingly used to understand these interactions.

GLUTAMATE

The amino acid glutamine is found in dietary protein; after entering the brain, it is transformed into glutamic acid, or glutamate. Glutamate itself does not cross the blood–brain barrier, and its level is tightly regulated by

BOX 4.1. Optogenetics: An Improved Way to Study the Functioning of Neurons?

Brain function is a symphony of thousands of neurotransmitters and growth factors working together. When we perform an fMRI, the activity we see is the sum of all these neurotransmitters working together, even when we measure an area known to be rich in a given neurotransmitter. If we image the ventral striatum, we know that dopamine is influencing it, but so are glutamate and GABA, as well as others. Even in a small area of the brain, we are seeing the sum of the activity of hundreds or thousands of neurons. Optogenetics, currently done only in animals, allows scientists to turn individual groups of neurons on and off, allowing us to examine the behavior of the rodent (Deisseroth, 2015; Tye & Deisseroth, 2012). Figure 4.1 illustrates the basic process. Microscopic algae need to swim toward the light to perform photosynthesis. To achieve this (Figure 4.1A), the neurons that activate their flagella have special ion channels that activate in response to light. These "opsins" include channelrhodopsin (blue light causes sodium ions to enter, depolarizing the neurons) and halorhodopsin (green/yellow light causes chloride ion to enter, hyperpolarizing the neuron). The particular opsin gene is removed from the algae nucleus and spliced to a promotor gene that is specific for a neuron type (Figure 4.1B). The vector is inserted into a virus, and the virus injected into a region of the brain. In the example in Figure 4.1C, the virus only inserts the ion channel gene into the pyramidal neurons of the cortex. An optic fiber probe can then be inserted through the skull to the area where the channels were inserted. If blue or yellow/green light is pulsed into the area, the pyramidal cells will fire or be inhibited, depending on the type of ion channel that is inserted. The surrounding basket cells will be unaffected. In this way, it is possible to study individual circuits in brain diseases. As we see in later chapters, this may become a therapeutic technique for humans in the future.

the brain regardless of the amount of glutamine in the diet. Glutamate is the principal excitatory neurotransmitter in the brain; it also is the most abundant, constituting 60% of all the neurotransmitters (Hassel, 2012). Figure 4.2 shows the glutamate pathways in the brain.

Pathway (1) represents the *cortico–cortico* connections that are present throughout the neocortex. They are symbolized here by a single pair of neurons that represents the millions of connections both within each hemisphere and that cross the hemisphere. Pathway (2) is one of the longest in the brain. The cell bodies originate in the precentral gyrus of the frontal cortex, and their axons descend through the internal capsule. Two pathways branch off to the pons and to the red nucleus in the brain stem, where they excite motor neurons that govern a wide variety of muscles. In the brain stem, a third part of this pathway crosses to the other side of the body (decussation), then proceeds down the spinal cord, where it excites motor

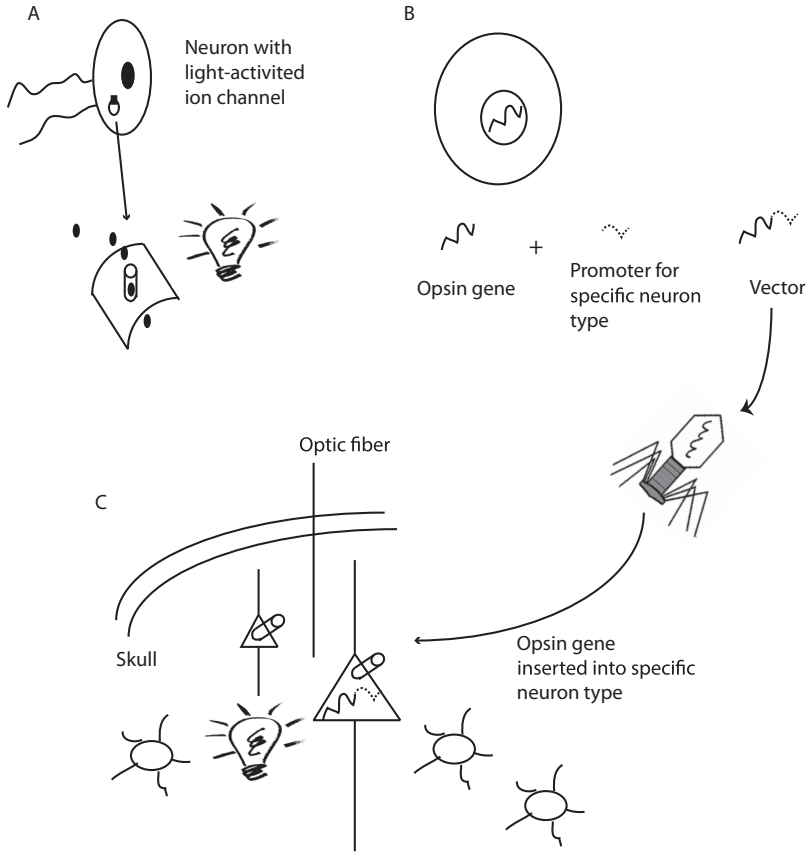


FIGURE 4.1. Optogenetics.

neurons that actually cause muscles to contract. Due to the decussation, a stroke on one side of the cortex will cause weakness on the opposite side of the body. Pathway (3) is equally important in governing motor behavior. These cell bodies also originate in the cortex and project to the neostriatum (caudate and putamen). Pathway (4) projects from the prefrontal cortex to the ventral striatum. Pathways (3) and (4) together are called the *corticostriatal* pathways. Pathway (5) shows an excitatory "motor loop" between the cortex and the thalamus, referred to at the *corticothalamo–thalamo* cortical pathway. Pathway (6) shows how information from the hippocampus uses a glutamate pathway; these axons project though the fornix to reach the mammillary body. This pathway is part of the Papez circuit discussed in Chapter 2. The amygdala sends a glutamate projection to the

ventral striatum (7). Make note of the fact that the ventral striatum has glutamate input from the prefrontal cortex (4), the hippocampus (6), and the amygdala (7); these are all critical components of the reward circuitry to be discussed in Chapter 6. A large number of glutamate neurons have cell bodies in the inferior olive of the brain stem (7), which project to the cerebellum. These neurons are involved in motor coordination.

Figure 4.3 shows the wide variety of receptors to which glutamate can bind. Receptors are often named for the chemical that binds to the receptor in the laboratory, even when these substances are not found in the brain. There are three types of ionotropic glutamate receptors: alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA), kainate, and *N*-methyl-D-aspartate (NMDA). The first two are very similar and are considered as one. As shown in Figure 4.3, when glutamate binds to the AMPA/kainate receptor, it opens a ligand-gated ion channel; Na^+ and K^+ are exchanged. This leads to the opening of voltage-gated Na^+ channels, triggering an action potential. The NMDA receptor, when activated, allows calcium to flow into the neuron, where it can activate a series of neuronal enzymes. Glutamate and the amino acid glycine both must bind to receptor sites to achieve this. The metal zinc (Zn) can enhance the opening of the channel but

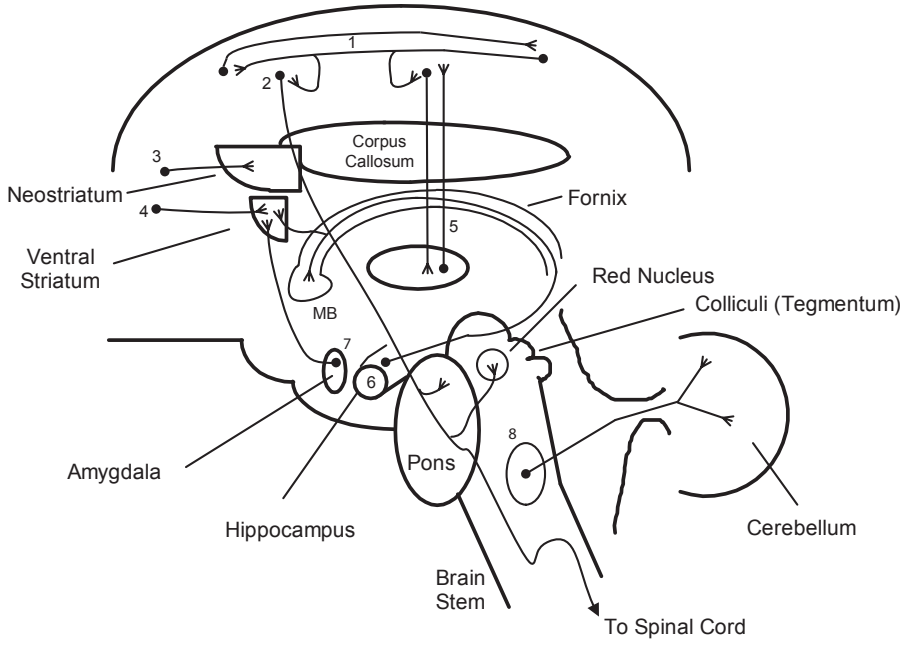


FIGURE 4.2. The glutamate pathways.

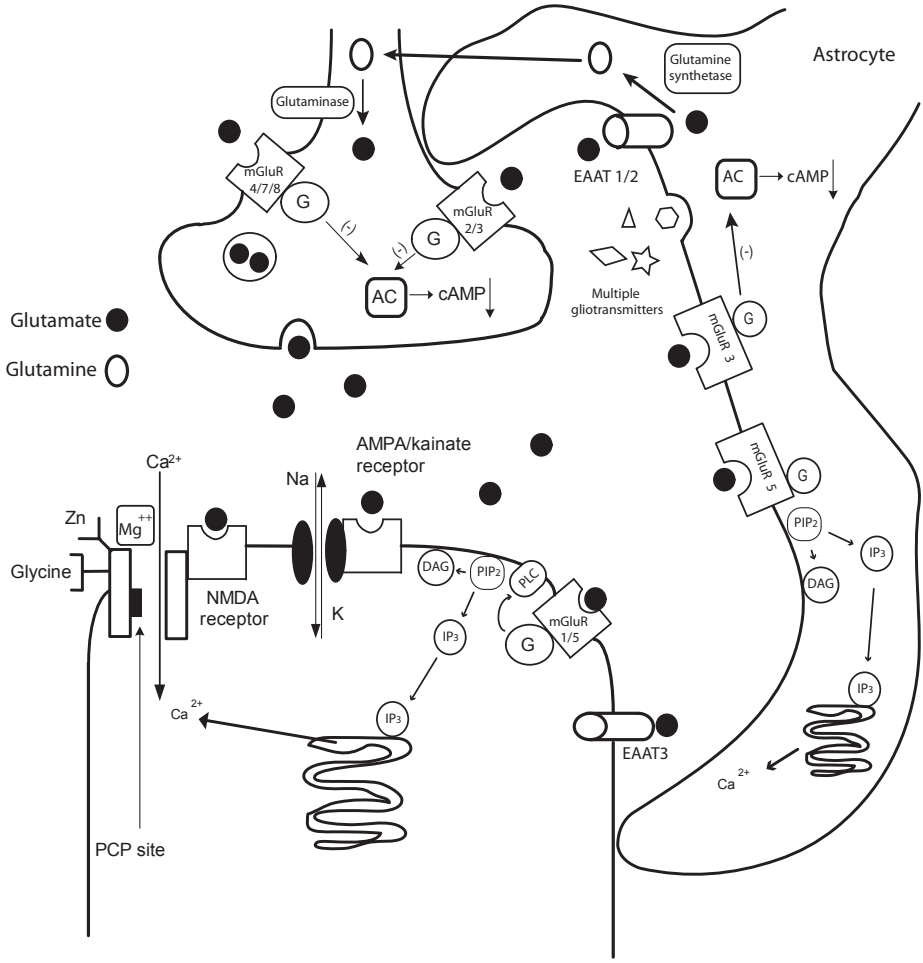


FIGURE 4.3. The tripartite glutamate synapse and glutamate receptors.

is not required. Once the channel is opened, the calcium still cannot enter because a magnesium (Mg) ion blocks the channel when the neuron is at rest. It is only when the neuron has been depolarized by the action of sufficient AMPA/kainate receptors that the Mg ion "moves out of the way" and the calcium enters. This process turns out to be critical in learning and memory (Chapter 7). Also of interest to the study of schizophrenia and drug abuse, the drug phencyclidine (PCP) blocks the calcium from entering the neuron. PCP is a powerful hallucinogen; thus, the NMDA receptor may play a role in the pathophysiology of psychosis (Poels et al., 2014).

Glutamate also binds to receptors that are metabotropic in nature, making the glutamate synapse very complex (Hassel, 2012; Herman, Busber, Conn, & Jones, 2012). These receptors are involved in learning and synaptic plasticity generally and may be implicated in a wide range of psychiatric disorders. There are eight different types of glutamate metabotropic receptors, grouped into three classes, summarized in Table 4.1. These metabotropic receptors are found throughout the brain. Class I (mGluR 1 and 5) metabotropic receptors can enhance the excitatory effect of glutamate in neurons and are found postsynaptically both on neurons and astrocytes. MgluR5 receptors on astrocytes can trigger calcium signaling, which allows communication between different neurons; they also can cause the release of a wide variety of "gliotransmitters" (odd shapes in Figure 4.3). These gliotransmitters include glutamate itself as well as D-serine (now an experimental drug for anxiety), adenosine triphosphate (ATP), and neuropeptides. The actions of these gliotransmitters and astrocyte calcium signals have been shown to play a role in animal models of schizophrenia and Alzheimer's disease. Disturbances in gliotransmitters may lead to glutamate overactivity and neuronal damage (Halassa, Fellin, & Haydon, 2007). Finally, Class II and III metabotropic receptors are found mainly presynaptically, where they act as autoreceptors, decreasing glutamate release and preventing glutamate overstimulation (feedback inhibition).

Figure 4.3 also shows the excitatory amino acid transporters (EAATs), which are involved in the reuptake of glutamate. In most neurotransmitter systems, this is done by a transporter on the presynaptic neuron, but in the glutamate system, EAATs are either on the postsynaptic neuron or on the astrocytes. Glutamate is metabolized back into glutamine in the astrocyte; it can then reenter the neuron to be transformed back into glutamate.

TABLE 4.1. Glutamate Metabotropic Receptors

Family	Receptors	Second messenger	Function	Location
Class I	mGluR1 mGluR5	G_q—PIP_2 system	Increased NMDA and AMPA/kainite action, increased excitability	Postsynaptic on neurons, also on astrocytes
Class II	mGluR2 mGluR3	$G_{i/o}$—adenylyl cyclase system	Feedback inhibition	Mainly presynaptic, also on astrocytes
Class III	mGluR4 mGluR6 mGluR7 mGluR8	$G_{i/o}$—adenylyl cyclase system	Feedback inhibition	Mainly presynaptic, mGluR6 found only in retina

GAMMA-AMINOBUTYRIC ACID

Gamma-aminobutyric acid (GABA) is the principal inhibitory neurotransmitter in the central nervous system and represents about 25% of the neurotransmitters in the brain (Olsen & Li, 2012). GABA pathways are shown in Figure 4.4. Notice the large number of small neurons spread throughout the cortex (1). Examining the inset at the top of the figure illustrates how these interneurons make up the "circuit board" of the cortex. The neurons of the cortex are arrayed in six layers, with large "pyramidal" neurons in layer 3. The dendrites of these pyramidal neurons run parallel to the surface of the brain in layer 1, and their axons project downward. These neurons receive excitation by many glutamate neurons and are surrounded by a variety of GABA interneurons. Basket, Martinotti, and wide-arbor interneurons all synapse on the dendrites of the pyramidal cells, thus influencing their *input*. In contrast, chandelier and neurogliaform cells synapse on the cell body or axon, influencing the cell's *output* (Huang, Di Cristo, & Ango, 2007; Kubota, 2014; Mendez & Bacci, 2011). This balance of input and output is critical for the maintenance of the pyramidal cell's rhythmic firing, which is picked up by the electroencephalograph (EEG). Dysfunction in this circuit is likely related to diverse neuropsychiatric disorders, which are addressed in later chapters. The cognitive deficits in schizophrenia may be related to GABA–glutamate frontal circuit dysfunction (Lewis & González-Burgos, 2008), which I discuss in Chapter 12.

The "long" GABA pathways are complex. Pathway (2) originates in the neostriatum and terminates in the globus pallidus interna (GPI). These axons synapse on other GABA cell bodies in the GPI, which in turn project to the thalamus (3). Another set of GABA neurons leaves the neostriatum (4) and projects to the globus pallidus externa (GPE). The GPE neurons also use GABA and project to the subthalamic nucleus (STN) (5). Another GABA pathway (6) starts in the neostriatum and ends in the substantia nigra reticulata (SNR). From the SNR, GABA pathways (7) spread out to three locations: the thalamus, the superior colliculi, and the pedunculopontine nuclei (PPN). Parts of the thalamus, as we saw with the glutamate pathways, are involved in the motor circuitry. The superior colliculi are important for eye movements. The PPN helps govern the muscles of the trunk. The SNR is "tonically active," releasing GABA onto these structures, inhibiting their neurons. If the motor circuits of the thalamus, the colliculi, and the PPN are turned off, there is no movement. When a new movement is desired, the cortex and basal ganglia work together to shut off the SNR, thus making the movement possible. Finally, there is a long projection of GABA neurons from the caudal hypothalamus to the entire cortex; the role of this pathway remains unclear.

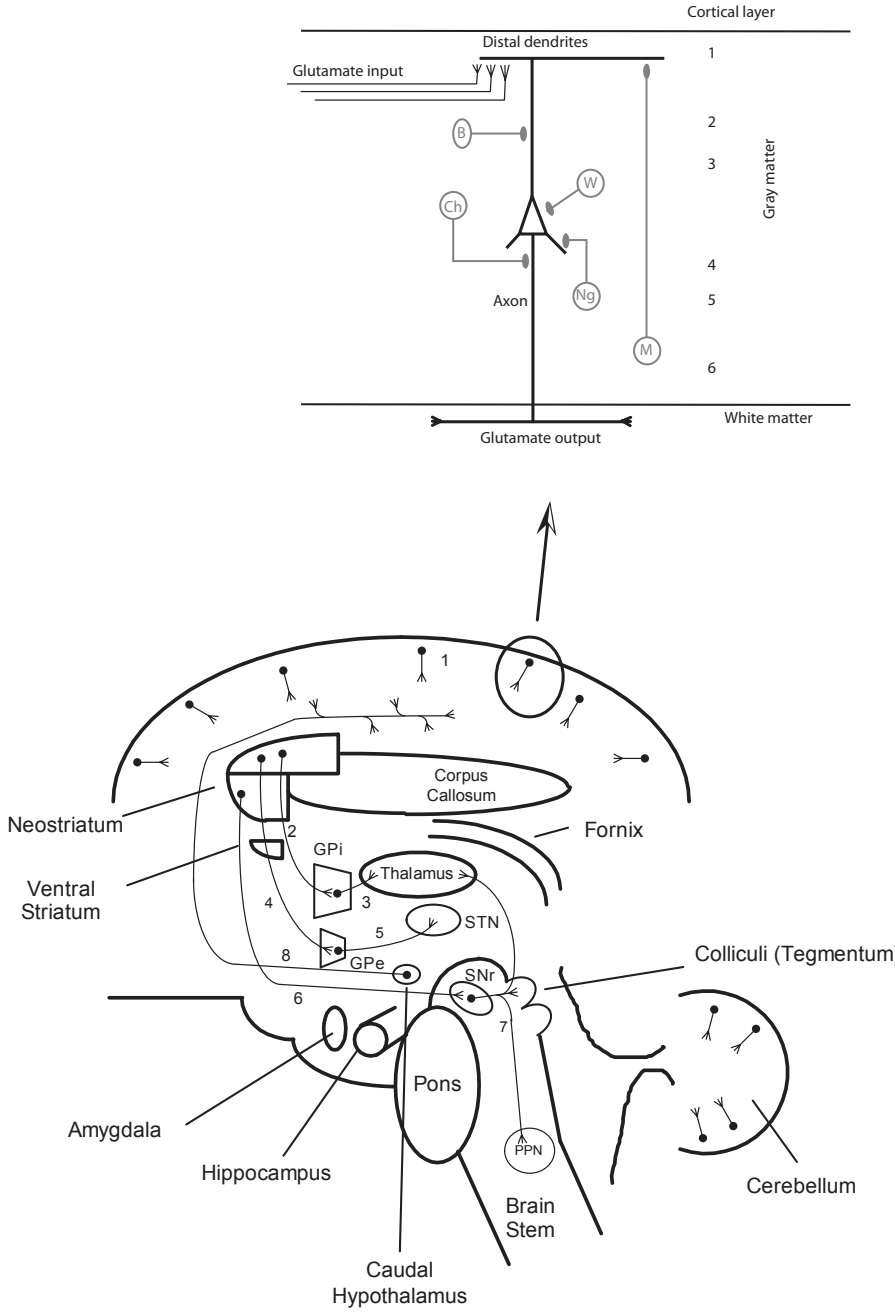


FIGURE 4.4. The GABA pathways and GABA interneurons in the cortex.

A GABA synapse is shown in Figure 4.5. Like the glutamate synapse, it is surrounded by an astrocyte, which plays a role in the synthesis and degradation of GABA. When GABA is taken into the astrocytes, it is metabolized into glutamate and then glutamine, which can travel back to the GABA neuron, where the process is reversed. GABA has two receptors, $GABA_A$ and $GABA_B$. The $GABA_A$ receptor is ionotropic and is linked to a chloride channel. When GABA binds to the receptor, the channel is opened and chloride can flow into the neuron. This increases the negative charge inside the neuron, hyperpolarizing it and making the neuron less likely to fire. The lower left portion of Figure 4.5 shows the $GABA_A$ receptor in more detail. It is composed of five protein subunits that form the channel. There are two GABA binding sites, found between the alpha and beta subunits. Between the alpha and beta subunits is the benzodiazepine site, where drugs such as diazepam (Valium) bind. When a benzodiazepine such as a diazepam binds to this site, GABA is more potent at opening the channel, enhancing inhibition of the neuron. If neurons are firing inappropriately during a seizure, benzodiazepines enhance GABA's inhibitory effect, terminating the seizure. Inside the channel, there is a site at which barbiturate drugs such as phenobarbital bind, also increasing the flow of chloride into the neuron. Ethanol acts at a site on the gamma subunit, also enhancing GABA's effect. $GABA_A$ receptors are very heterogeneous because there are multiple subtypes of all the subunits. The alpha unit has six subtypes, the beta unit has four, and the gamma unit has three. $GABA_A$ receptors with different subunits vary in their response to GABA and therapeutic drugs (Olsen & Li, 2012).

$GABA_B$ receptors are metabotropic and inhibit adenylyl cyclase. As shown in Figure 3.8 in Chapter 3, this would lead to reductions in cAMP, and with less phosphorylation of the potassium channels (due to less activity of PKA), there would be greater outflow of K^+. This, too, would hyperpolarize the neuron and decrease the firing rate, though on a longer time scale. $GABA_B$ receptors are found both pre- and postsynaptically.

ACETYLCHOLINE

Acetylcholine (Ach) is the neurotransmitter used by peripheral neurons that innervate the muscles; stimulation of Ach receptors on muscles results in their contraction. Botulinum toxin produced by bacteria prevents the release of Ach and paralyzes muscles. Commercially, minute amounts of the toxin (BoTox) can prevent facial muscles from contracting, thus reducing wrinkles. Within the brain, Ach plays critical roles in learning and alertness (Newman, Gupta, Climer, Monaghan, & Hasselmo, 2012). Drugs that block Ach can produce deficits in cognition; in toxic doses, they

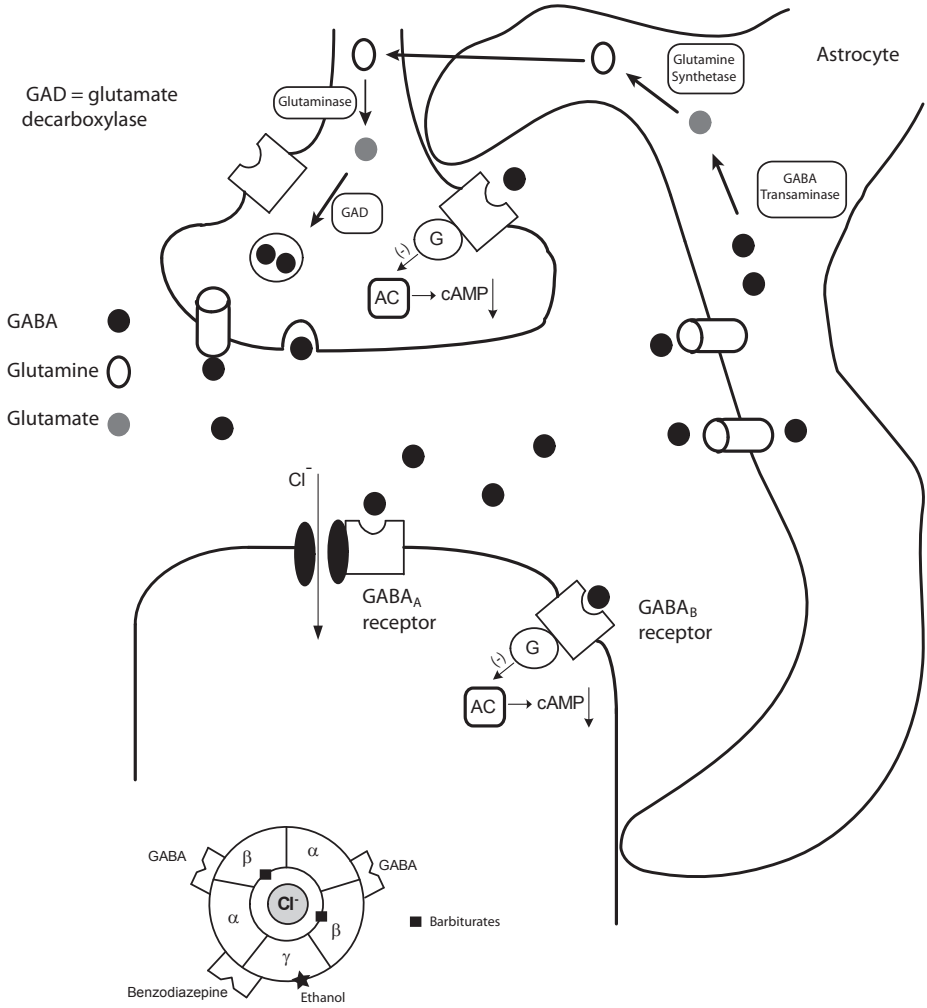


FIGURE 4.5. The GABA synapse, GABA receptors, and the $GABA_A$ receptor chloride channel.

produce delirium. Dementia is often treated with Ach agonists, although with mixed results. The diverse Ach pathways are shown in the lower part of Figure 4.6. A major pathway (1) originates in the PPT nucleus and laterodorsal pontine tegmentum (LDT), and projects to the thalamus. This pathway is part of the "reticular activating system"—the array of inputs from the brain stem to the thalamus and cortex that govern the level of arousal and alertness. This pathway also projects to the ventral tegmental

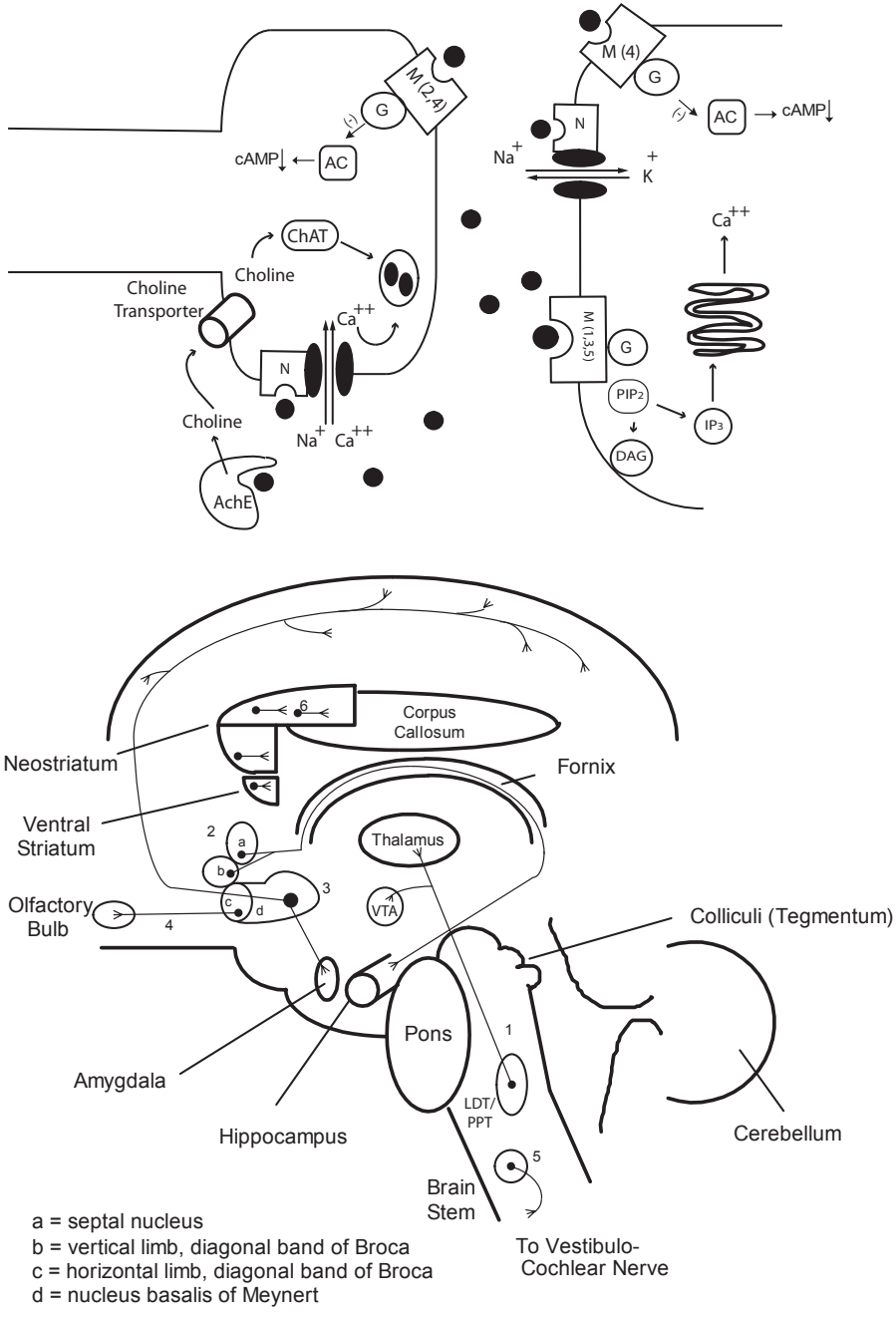


FIGURE 4.6. The acetylcholine pathways and receptors.

area (VTA), where Ach modulates the release of dopamine. Another Ach pathway (2) begins in the septal nucleus (a) and sends its axons through the fornix to reach the hippocampus. These Ach inputs are critical in regulating the firing rhythm of the hippocampus (a key aspect of the memory circuit; see Chapter 7). Just ventral to the septal nucleus is a group of Ach neurons that together form the Ach forebrain complex (3). These are the vertical limb of the diagonal band of Broca (b), the horizontal limb of the diagonal band of Broca (c), and, the largest of the three, the nucleus basalis of Meynert (d). These neurons send their axons through the cortex and also to the amygdala. Ach neurons project to the olfactory bulb (4), while brain stem Ach neurons (5) project to the vestibular–cochlear nerve, which is important in balance. This is the reason anticholinergic drugs are helpful in motion sickness. Importantly, there are small Ach interneurons throughout both the neo- and ventral striatum. In the neostriatum, they are a critical aspect of the brain's motor circuitry. In the ventral striatum, Ach is released onto the ends of dopamine neurons, further enhancing dopamine release. These Ach interneurons play a role in both motor behavior and addiction.

When Ach is released from its neurons, it can bind to one of two major types of receptors, nicotinic and muscarinic (upper part of Figure 4.6). Nicotinic receptors are ionotropic; when Ach binds to them, an ion channel is opened that leads to the firing of an action potential as Na^+ and K^+ are exchanged. Nicotinic receptors are on the muscles peripherally, as well as in the cortex and autonomic nervous system (but not in the midbrain). In the striatum, only nicotinic receptors are found. Unusual for ionotropic receptors, Ach nicotinic receptors are found both pre- and postsynaptically. Stimulation of these presynaptic receptors allows Ca^{++} to enter, further enhancing Ach release. As with the $GABA_A$ receptor, the channel of the nicotinic receptor is made of multiple proteins arranged in a tube (alpha, beta, gamma, delta, epsilon); each of these proteins has multiple versions leading to 17 different subtypes of nicotinic receptors.

Ach also binds to muscarinic receptors that are metabotropic and act through G proteins (Bubser, Byun, Wood, & Jones, 2012; Jones, Byun, & Bubser, 2012). Muscarinic receptors have five subtypes. Subtypes 2 and 4 inhibit adenylyl cyclase. Presynaptically, this acts as an autoreceptor, reducing Ach release. Postsynaptically this reduces the permeability of voltage-gated K+ and enhances the responsiveness of the neuron to other inputs (see Figure 3.10). Subtypes 1, 3, and 5 all act through the PIP_2 second messenger system—the increase in intracellular Ca^{++} activates a variety of enzymes and transcription of genes. Muscarinic receptors are found throughout the cortex and brain stem but not in the striatum.

To understand the action of Ach in the body, it is necessary to review the functions of the autonomic nervous system, as shown in Figure 4.7. The autonomic nervous system governs many of the body's basic functions:

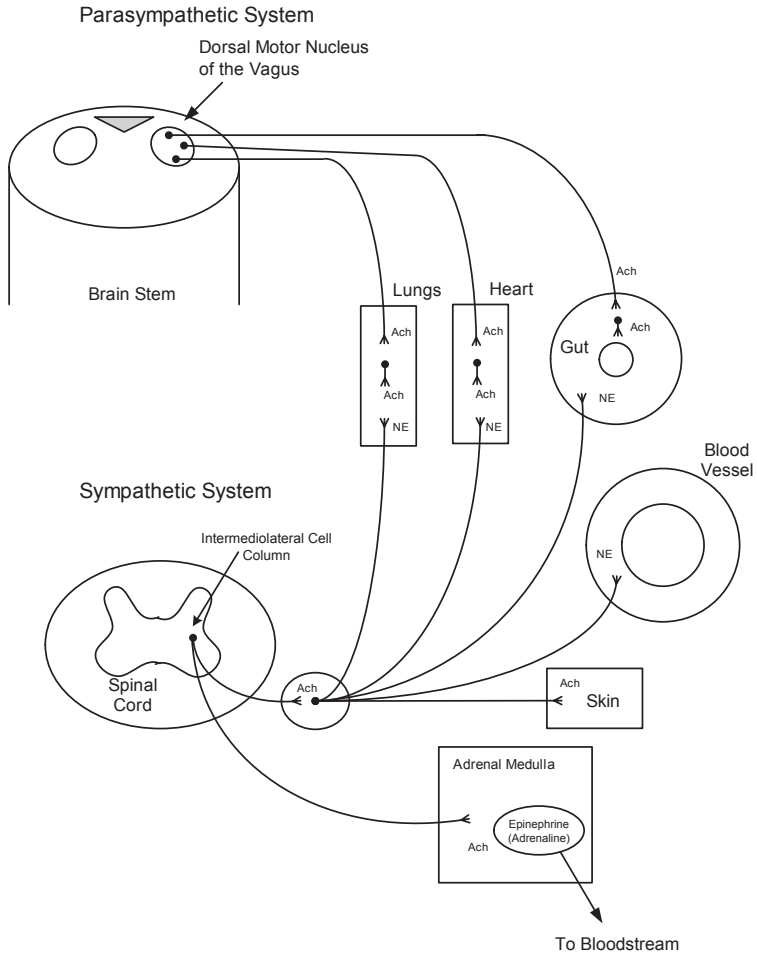


FIGURE 4.7. Overview of the parasympathetic and sympathetic nervous systems.

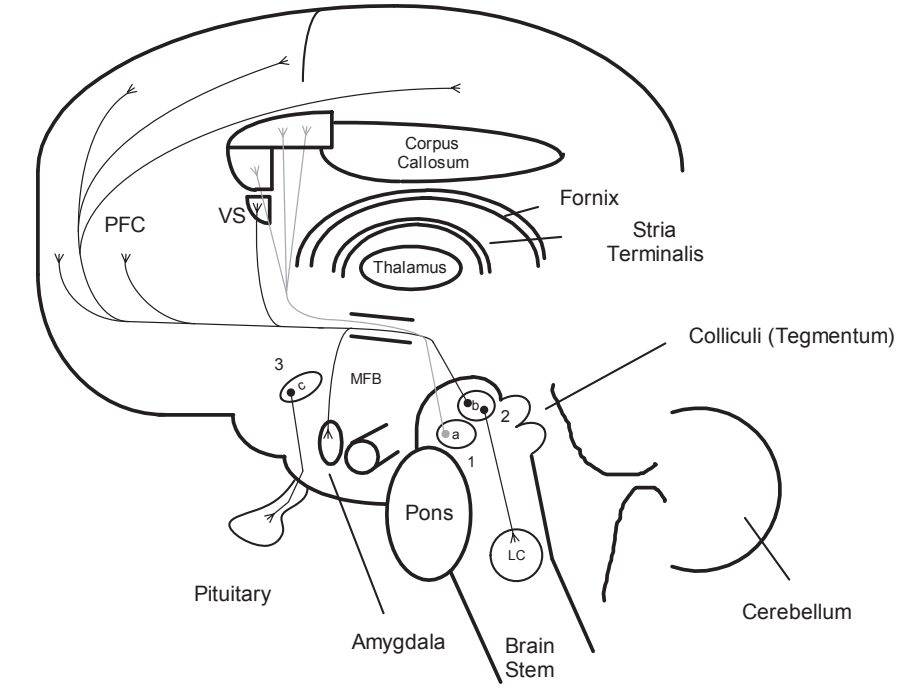
heart rate, respiratory rate and volume, digestion, and sexual function, among others. It is subdivided into the parasympathetic and sympathetic systems. The parasympathetic system slows heart rate, enhances digestion and defecation, and, with sexual arousal, causes erection of the penis. It helps the body meet its physical needs. In contrast, the sympathetic nervous system increases heart rate, shifts blood flow away from the periphery and into the muscles, and inhibits digestion. Part of the sympathetic response involves the release of epinephrine (adrenaline) into the bloodstream. This is the "fight-or-flight" reaction. Sympathetic activation leads to high

arousal and the experience of agitation, anger, and/or anxiety. The top part of Figure 4.7 shows the parasympathetic nervous system. It is a two-neuron chain. Neurons in the dorsal motor nucleus of the brain stem send axons out into the vagus nerve, which travel to the heart, lungs, and gut via different branches. These are termed the "preganglionic" neurons, and they release Ach onto smaller "postganglionic" parasympathetic neurons. Ach binds to muscarinic receptors on these neurons, causing them in turn to release Ach onto muscarinic receptors on the heart, lungs, and gut. When this happens, heart rate is slowed, gut motility increases, and the bronchi are restricted. There are also preganglionic parasympathetic neurons in the sacral (lowest) area of the spinal cord; these project to the bladder, rectum, and sexual organs. These connections are not shown in Figure 4.7.

The lower part of Figure 4.7 shows the sympathetic nervous system (SNS). The preganglionic nerves have their origins in the middle part of the spinal cord, in a column of cells that runs from just below the neck to above the sacrum. This is the intermediolateral (IML) cell column. From here, the axons project to a line of ganglia along the outside of the spinal column, where they release Ach onto the second neuron in the sympathetic connection. The postganglionic neurons release the neurotransmitter norepinephrine onto muscles in the heart and blood vessels. This release causes heart rate to rise and blood vessels to constrict, and blood flows more readily to muscles. Norepinephrine is released onto the bronchi of the lungs, causing them to open up so the person can breathe more deeply and get more oxygen to the blood. (Asthma inhalers mimic the effect of norepinephrine in the lungs.) The IML also sends Ach neurons to the adrenal medulla (the adrenal glands sit atop the kidneys), and here Ach causes the release of epinephrine (EPI; adrenaline) into the bloodstream. EPI, too, increases heart rate and causes constriction of blood vessels.

DOPAMINE

Dopamine cell bodies are located primarily in two major groupings, shown in Figure 4.8. The first is the substantia nigra compacta (SNC). The axons of these neurons project to the striatum (1); this route is termed the "nigrostriatal pathway" (light gray in figure). The second major grouping is the ventral tegmental area (VTA). The axons of these neurons travel forward through the median forebrain bundle, then spread out to innervate two regions: the prefrontal cortex and the ventral striatum (2). These two routes are the mesocortical and mesolimbic dopamine pathways (black in figure), respectively. As shown in Figure 4.8, the densest dopamine projections are to the primary motor cortex, although the other frontal areas are strongly innervated as well. Virtually no dopamine is found in the primary



a = substantia nigra compacta
b = ventral tegmental area (VTA)
c = nucleus infundibularis
LC = locus coeruleus

FIGURE 4.8. The dopamine pathways.

somatosensory cortex, and very little is found in the occipital cortex. In contrast, there are substantial dopamine projections to the parietal and temporal lobes.

The projections from the VTA to the ventral striatum have particularly interesting properties. In rodents, a very thin electrode can be inserted into the brain, so that its end is placed in the VTA. Once the animal recovers from the surgery, it roams its cage. The electrode is connected to a lever; when the animal presses the lever, the electrode stimulates the VTA–ventral striatum pathway. This causes action potentials to be fired in the axons, and dopamine is released into the nucleus accumbens (a subset of neurons within the ventral striatum). The rat finds this rewarding and will continue to press the bar to receive the stimulation. In another type of experiment, a very thin glass tube can be inserted directly into the nucleus accumbens.

These rats will then press levers that directly release cocaine into the accumbens. The cocaine blocks the reuptake of dopamine, increasing the amount of dopamine in the accumbens. The smallest of the dopamine pathways is the tuberoinfundibular (3). The axons of these neurons release dopamine into the pituitary, where the dopamine inhibits the release of the hormone prolactin. In females, prolactin promotes breast development; males do not appear to utilize prolactin. Antipsychotic drugs block dopamine receptors. When this occurs in the pituitary, there is an increase in prolactin, which can lead to unwanted production of milk (galactorrhea).

There are five subtypes of dopamine receptors, as shown in Table 4.2 (Gnegy, 2012). The "D_1 family" consists of the D_1 and D_5 receptors. Both of these receptors are linked to G proteins that stimulate adenylyl cyclase. In contrast, the D_2, D_3, and D_4 receptors are linked to G proteins that inhibit adenylyl cyclase and are referred to as the "D_2 family." The dopamine receptors have very different distributions in the brain. D_1 and D_2 are found almost predominantly in the neostriatum, whereas D_3 receptors are found in the nucleus accumbens and may play a significant role in the pleasure circuit described previously. D_3 receptors are the most sensitive, requiring less dopamine to trigger them than the others. The D_1 and D_4 receptors are found in the cortex; D_5 receptors are found in the hypothalamus and the hippocampus.

Dopamine's role in the brain appears related to motor behavior and action. If dopamine is depleted from the SNC and dorsal striatrum, there is a loss of ability to initiate movement, leading to parkinsonism. Dopmine's function in the ventral striatum is clearly related to reward and motivation.

TABLE 4.2. Dopamine Receptors

	D_1	D_2	D_3	D_4	D_5
Second messenger system	Activate adenylyl cyclase	Inhibit adenylyl cyclase			Activate adenylyl cyclase
Location in brain	Neo- and ventral striatum, cortex	Neo- and ventral striatum	Ventral striatum, hypothalamus	Frontal cortex, medulla, midbrain	Hippocampus, hypothalamus
Pre/postsynaptic	Postsynaptic	Both pre- and postsynaptic	Postsynaptic	Postsynaptic	Postsynaptic
Affinity for dopamine[a]	2,000	2,000	30	450	250

[a]Smaller number means dopamine binds more readily to the receptor.

These two properties clearly imply that dopamine is a "go" neurotransmitter; its release makes motor behavior *more* likely. In a seminal paper, Schultz, Dayan, and Montague (1997) noted that dopamine neurons fire *more* in response to an unpredicted reward but *less* when a predicted reward does *not* appear. As Talia Learner summarized, "This finding led Schultz et al. to propose that dopamine neurons encode 'reward prediction error.' That is, they tell you whether or not things are as good, better, or worse than you expected" (*http://neuroblog.stanford.edu/?p=4765*). This relates to risk taking, a critical component in personality and addiction disorders (see Chapter 10). More broadly, dopamine neurons in this circuit encode "salience," which helps the animal to recognize all kinds of important signals necessary for survival (Winton-Brown, Fusar-Poli, Ungless, & Howes, 2014). When we say something is salient, we are saying *that is related to or predicts* reward, threat, novelty, or emotional significance. Dysfunction in assessed salience may be involved in psychosis (see Chapter 12). Dopamine, through its cortical projections, plays a key role in processing information. In order to understand this, we must first examine the norepinephrine system.

NOREPINEPHRINE

The first thing to bear in mind regarding norepinephrine is that it is found peripherally within both the sympathetic nervous system (SNS) and the brain. Figure 4.9 (top) shows the complex projections of the central norepinephrine system. The cell bodies of most norepinephrine neurons in the brain are found in the LC in the brain stem. From here, the axons of norepinephrine neurons project to many different areas of the brain. Some travel down to the spinal cord, where they synapse on neurons that are receiving sensory information from the skin and internal organs. LC neurons do not communicate directly with the IML cell column. Norepinephrine neurons project to the pons and cerebellum, but their most important projections are to the cortex. These projections are very widespread. In Figure 4.9, the number of branches of the neuron represents the densities of the cortical norepinephrine projections. LC neurons branch off to enter the fornix and stria terminalis that lead to the hippocampus and amygdala, respectively. These structures also receive norepinephrine input via smaller, direct branches. Finally, norepinephrine neurons from the LC project to the dorsal raphe, where serotonin cell bodies are found. Thus, norepinephrine plays a role in governing the output of the serotonin system.

The LC is not the only source of norepinephrine within the brain. A second set of norepinephrine-containing neurons is found just below (caudally to) the LC. These norepinephrine neurons project to the spinal cord,

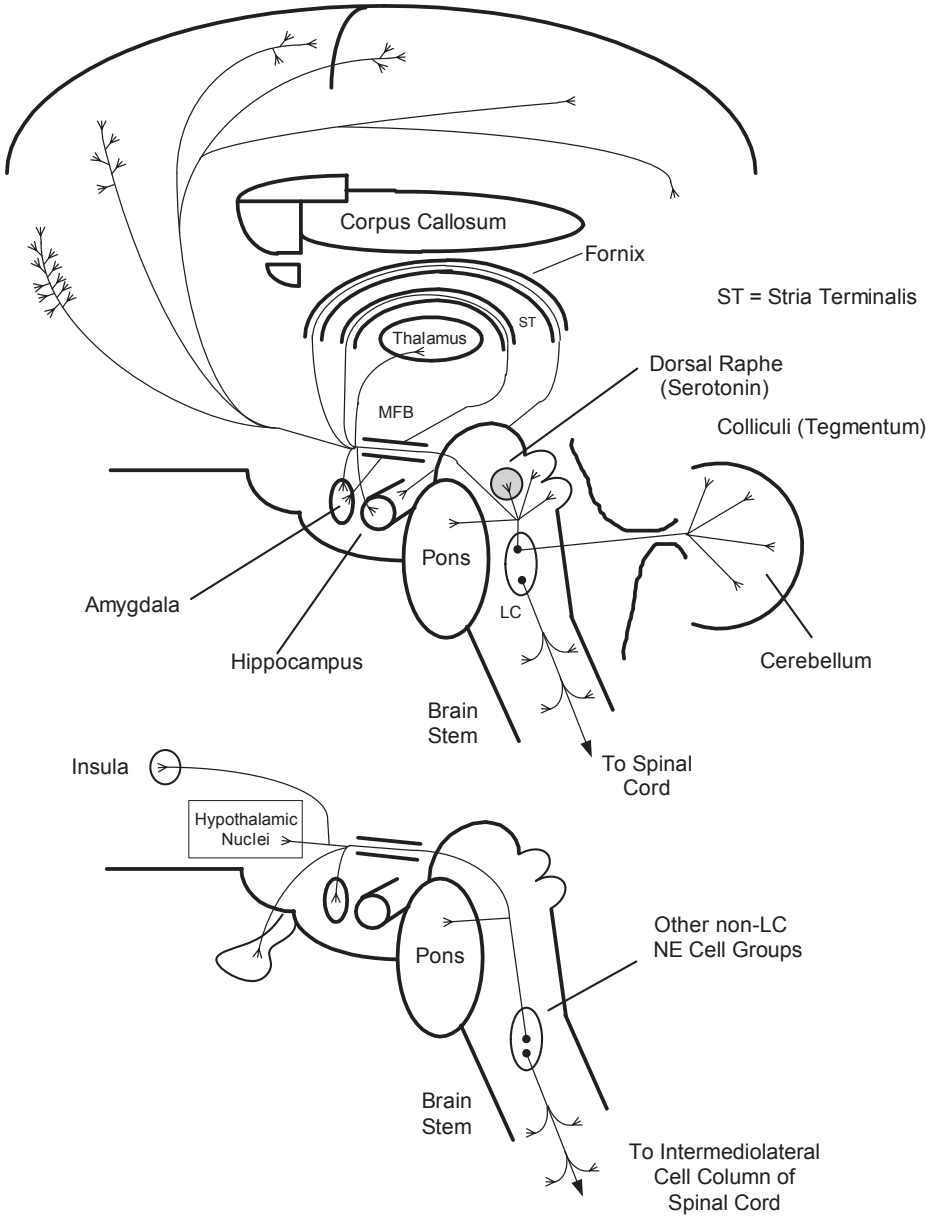


FIGURE 4.9. The norepinephrine pathways.

where they synapse on the IML, influencing the SNS directly (lower part of Figure 4.9). These neurons also project to the hypothalamus, where they help regulate "releasing factors," molecules that travel to the pituitary and regulate a wide variety of hormones. The non-LC norepinephrine neurons also project to the insula, a structure critical in emotional regulation.

Norepinephrine has a variety of receptors to which it can bind. These receptors are divided broadly into alpha and beta categories, which are further divided into subtypes, as shown in Table 4.3 (Gnegy, 2012). The table shows their different second messenger systems. None of the norepinephrine

TABLE 4.3. Norepinephrine Receptors

	Alpha receptors					
	$Alpha_{1A}$	$Alpha_{1B}$	$Alpha_{1D}$	$Alpha_{2A}$	$Alpha_{2B}$	$Alpha_{2C}$
Second messenger system	PIP_2 to IP_3/DAG			Inhibit adenylyl cyclase		
Location in brain	Cortex	None	Cortex	Frontal cortex	Thalamus	Hippocampus
Location in body (PNS)	Blood vessels; leads to contraction			Platelets; enhances clotting	Liver	Heart, lung, aorta
Pre/postsynaptic	Postsynaptic			Both pre- and postsynaptic; presynaptic receptors decrease norepinephrine release		

	Beta receptors		
	$Beta_1$	$Beta_2$	$Beta_3$
Second messenger system	Activate adenylyl cyclase		
Location in brain	Cortex, hypothalamus	Cortex, hypothalamus	?
Location in body (PNS)	Heart[a]	Liver[b], lungs[c]	Fat tissue[d]
Pre/postsynaptic	Post	Pre/post	Post

[a]NE in bloodstream increases heart rate.
[b]NE leads to increase in blood sugar (glucose).
[c]NE opens bronchi in lungs, increasing oxygenation of blood.
[d]NE leads to breakdown of fat.

receptors are ionotropic; all are metabotropic. Alpha$_1$ receptors are found only on the postsynaptic neuron, whereas alpha$_2$ receptors are found both pre- and postsynatically. Alpha$_2$ receptors have much greater affinity for norepinephrine than do alpha$_1$ or beta receptors. Presynaptically, alpha$_2$ receptors reduce norepinephrine release and LC firing when stimulated by norepinephrine.

Why is there such a wide projection of norepinephrine neurons? In classic studies, Barry Jacobs (1990) summarized studies of the functioning of LC in cats. In these experiments, an electrode is inserted (under anesthesia) into the brain stem of a cat in order to record the firing of the LC neurons. The cat awakes and behaves normally. (Because the tissue of the brain itself feels no pain, the procedure bothers the cat very little.) During sleep, the LC is essentially turned off. When an animal is awake, the LC fires at a very slow rate. However, if a novel stimulus appears in the environment, it fires a volley of action potentials. If the stimuli are repeated and have no significance for the animal, the LC stops firing after several repetitions of the stimulus. When the animal is grooming or eating, the LC also decreases its firing rate. If a predator appears, the LC fires vigorously, and plasma norepinephrine level rises. It may not be threat per se but rather any signal that is part of a learned scenario that triggers the LC; the stimulus signals that something is about to happen based on past experience.

Marius Usher and colleagues (Usher, Cohen, Servan-Schreiber, Rajkowski, & Aston-Jones, 1999) studied the activity of LC neurons in awake primates, applying a technology similar to that used in the cat studies just described. Monkeys learned to press a switch when a target appeared and were rewarded with a drink of juice. Nontargets also appeared on the screen, and the monkey had to learn not to press the switch. (This task is similar to the continuous performance test, a measure on which individuals with attention-deficit/hyperactivity disorder [ADHD] often do poorly.) The results showed that as the monkeys learned the task, the LC fired in response to the target, but it ceased to fire when the distractors appeared. The LC also responded when the reward appeared. These quick bursts of the LC in response to stimuli are referred to as the "phasic activity." Usher and colleagues (1999) also measured the ongoing activity of the LC in between the appearance of the stimuli. They found the baseline activity of the LC varied. The monkeys' best performance was obtained when the LC baseline activity was low *and* phasic bursts were associated with the targets. In contrast, if the LC baseline activity was high, the monkeys made many more false alarms. The authors suggested that LC activity showed a U-shaped relationship to attention. At very low levels of tonic LC activity, the animal is sedated, inattentive, and unresponsive to the environment. At moderate levels of norepinephrine activity, the animal is alert, and the LC responds crisply to stimuli in the environment that are novel or have

meaning. At high levels of LC activity, the animal becomes very aroused and responds to multiple (and perhaps irrelevant) events in the environment. *In contrast to dopamine, however, the LC does not fire in response to a reward* (Rajkowski, Majczynski, Clayton, & Aston-Jones, 2004).

What does norepinephrine do to its target neurons? Figure 3.10 indicated that norepinephrine can enhance the "signal-to-noise" ratio for neurons. That is, the baseline activity of the targeted neuron declines, and it becomes more responsive to input. Thus, part of norepinephrine activity may help "tune" the neurons to help them process and prioritize incoming information about the current state of the world. This is not the whole story, however. LC projections to the amygdala and hippocampus are involved in fear and anxiety modulation, whereas norepinephrine input to the cortex plays a major role in working memory and executive function.

Over the last several decades, Amy Arnsten and colleagues (Arnsten, 2009; Arnsten, Wang, & Paspalas, 2012; Ramos & Arnsten, 2007) have studied the role of both dopamine and norepinephrine relative to prefrontal cortex neuronal information; this is summarized in Figure 4.10 (review Figure 3.10 before tackling this figure). A hypothetical cortical pyramidal neuron is shown receiving excitatory input from the two glutamate neurons. The neuron on the left side is carrying a key signal, while the neuron on the right is carrying a noise signal. Note the voltage-gated K^+ channel labeled "HCN" on the left dendrite of the pyramidal neuron in Figure 4.10. In Figure 3.10, we encountered a voltage-gated channel that was *shut down* by being phosphorylated by protein kinase A (PKA). This HCN K^+ channel is a different type: PKA has the opposite effect on it, *opening* the channel and allowing more K^+ to flow out (thus hyperpolarizing the neuron and inhibiting it). When norepinephrine is released, it binds preferentially to an $alpha_2$ receptor on the dendrite (given the higher affinity of norepinephrine for this receptor subtype). This closes the HCN channel as shown in the sequence of events below (numbers refer to Figure 4.10):

norepinephrine (1) → $alpha_2$ (2) → ↓cAMP (3) → ↓PKA (4) →
close HCN K channel (5) → ↓hyperpolarization→ ↑neuron firing

Thus, stimulation by low amount of norepinephrine will *increase the signal*. What is dopamine's role? Examine the right side of Figure 4.10, where dopamine is released (6) and binds to a D_1 receptor (7). Note how the D_1 receptors trigger the opposite effects of the $alpha_2$ receptors:

dopamine (6) → D_1 (7)→ ↑cAMP (8) → ↑PKA (9) →
open HCN K channel (10) → ↑hyperpolarization→ ↓neuron firing

Dopamine, acting through D_1 receptors, *decreases the noise*. The combined effects of moderate amounts of dopamine and norepinephrine therefore

improve the critical information flow (see arrow flowing from left into pyramidal neuron). Stress can increase the amount of norepinephrine and dopamine release. Increasing amounts of norepinephrine markedly changes the circuitry by now stimulating alpha$_1$ and beta receptors. When alpha$_1$ receptors are activated on the neuronal body (11), the PIP2 system is activated, leading to the following events involving yet another voltage-gated K^+ channel, the SK channel:

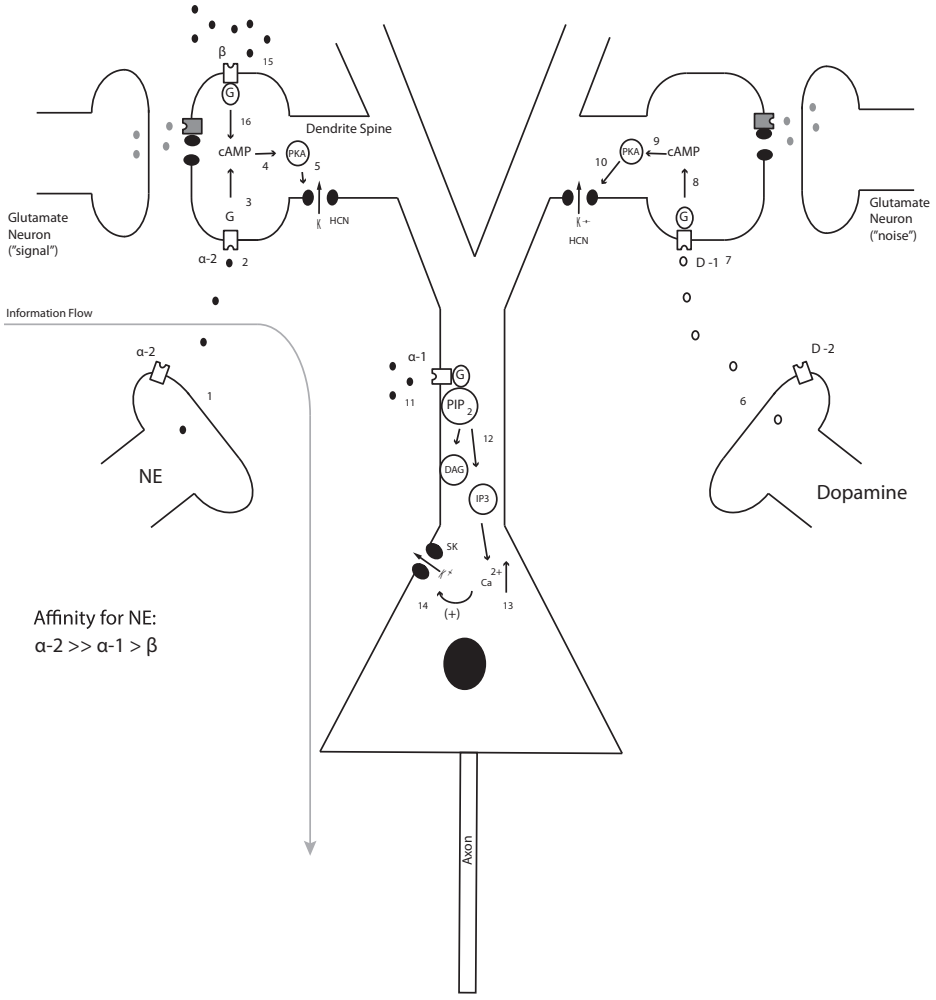


FIGURE 4.10. The role of dopamine and norepinephrine in prefrontal cortex function.

↑norepinephrine → alpha$_1$ (11) → ↑DAG/IP$_3$ (12) → ↑Ca^{2+}(13) → open SK channel (14) → ↑hyperpolarization→ ↓neuron firing

Now the signal is *degraded*. In high-stress situations, focusing on specific input may not in fact be beneficial. Arnsten and colleagues (2012) suggest that this elevation of norepinephrine disconnects the prefrontal cortex neurons from external stimuli, thus allowing the brain to be guided by subcortical, instinctual impulses. At very high levels of stress, even higher levels of norepinephrine activate beta receptors, further degrading the signal (note the opposite effects of stimulating alpha$_2$):

↑↑norepinephrine (1) → beta (15)→ ↑cAMP (16) → ↑PKA (4) → open HCN K channel (5) → ↑hyperpolarization→ ↓neuron firing

How do norepinephrine and dopamine "know" what information is "signal" or "noise"? Of course, they do not "know" intrinsically. Each of these systems has been programmed by previous experience in terms of what each individual has found to be critical to his or her functioning. Disturbances in these circuits are relevant to executive function problems in a wide range of mental disorders, including ADHD and schizophrenia.

To comprehend fully how the norepinephrine system is involved in the brain's reaction to stimuli in the environment, we must understand how the central norepinephrine system and the SNS work together, even though there are no direct anatomical links between them. Figure 4.11 shows this relationship. Information about external stimuli in the environment reaches the brain through vision, hearing, and touch (somatosensory function). This information is integrated in the cortex to form our perception of the world. When stimuli are being sent to the cortex, the brain stem is alerted as well; neurons within the paragigantocellularis (PGi) are activated (1). The PGi has projections both to the LC (2) and the spinal cord, where it activates the IML (3). The SNS is activated. The LC projects throughout the cortex, as seen in Figure 4.9. As described previously, the stimuli might be associated with some experience. For instance, an animal might recognize a predator. The animal will be ready because the SNS has been activated already by the PGi. On the other hand, the stimulus might be meaningless, so the IML should be turned off. How would this happen?

Note the position of the hypothalamus in this circuit. It is receiving information from the prefrontal cortex and the cingulate gyrus (4). The prefrontal cortex may be responding to the stimuli in light of long-term plans as opposed to immediate needs. The cingulate, along with the amygdala and hippocampus, accesses past memories about the stimulus, as well as the relevance of the stimulus to current biological needs. The hypothalamus also is receiving information from the nucleus tractus solitarius (NTS), which is

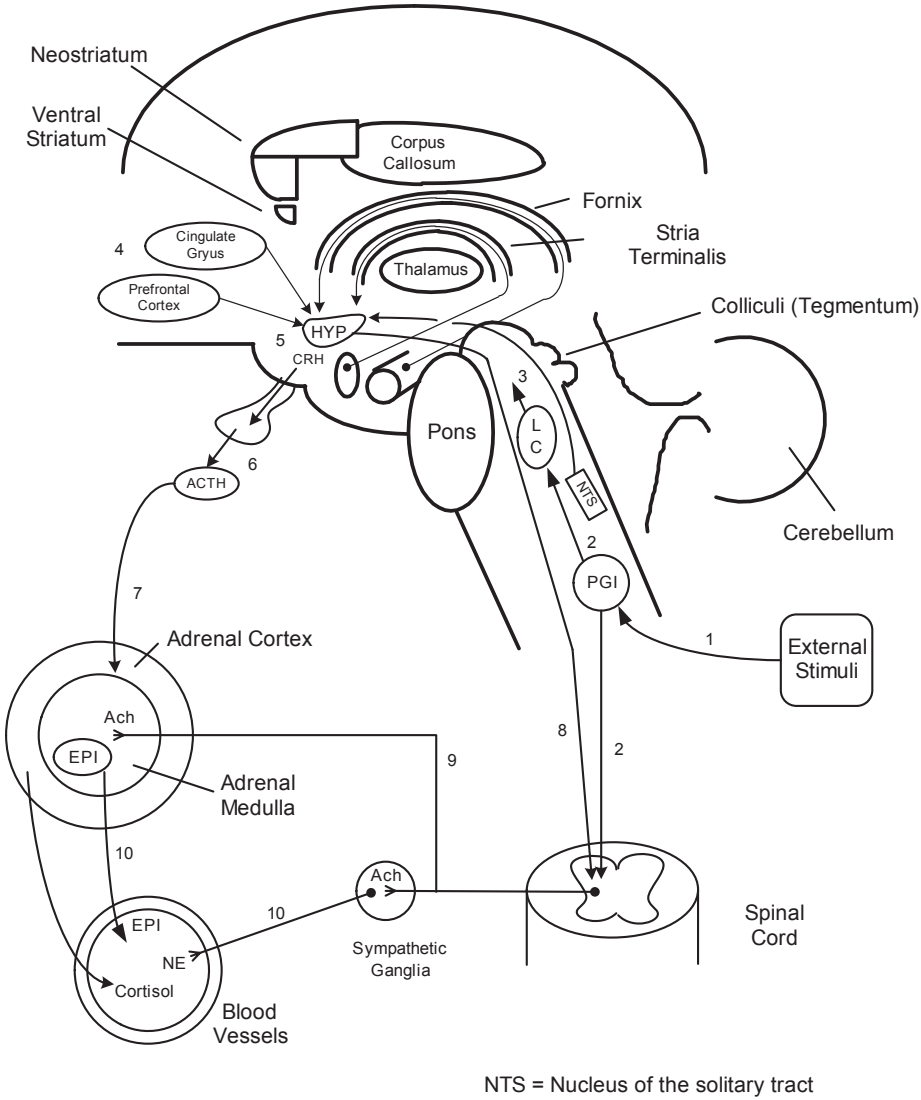


FIGURE 4.11. The norepinephrine system and the stress response.

in touch with the biological state of the body (fluid balance, glucose level, etc.). All of this information is weighted at the hypothalamus (5), which can send two major outputs that govern the stress response. First, it releases corticotropin-releasing hormone (CRH) to the pituitary, and the pituitary responds by releasing adrenocorticotropic hormone (ACTH) (6). ACTH travels through the bloodstream to the adrenal medulla, where it causes the medulla to release cortisol. The hypothalamus also projects directly to the IML (7), where the SNS can be activated directly. EPI (adrenaline) is released into the bloodstream. The fight-or-flight reaction can begin.

SEROTONIN

Figure 4.12 shows the diverse pathways of the serotonin (5-hydroxytryptamine, or 5-HT) system. Serotonin, as a neurotransmitter, appeared very early in evolution. It is found in the nervous system of the sea slug (*Aplysia*), where it plays a role in the animal's memory. Serotonin facilitates the withdrawal of the creature's gill in response to an event that previously had been associated with a noxious stimuli. In the leech, another primitive creature, serotonin neurons influence its ability to swim through the water and latch onto a warm body. These examples illustrate the fact that serotonin must play some crucial role in the nervous system if it appeared so early in evolution and has been conserved in higher animals, including humans. Serotonin is widely distributed in the brain stem. Figure 4.12 focuses on three major nuclei termed "raphe." The dorsal (a) and median (b) raphe project to a wide variety of areas in the brain. The dorsal raphe (dotted line) proceeds through the median forebrain bundle. Before doing so, it innervates the dopamine-containing neurons of the SNC and the VTA, thus influencing the output of the dopamine system. It projects to the striatum (indicating a strong role in motor behavior) and the entire cortex. The median raphe also sends its projections through the median forebrain bundle but has *no* projections to the striatum. Separate projections then proceed through the stria terminalis and the fornix to reach the amygdala and hippocampus, respectively. The median raphe also projects to the cortex, as well as to the superior colliculi and cerebellum. There are serotonin inputs to the hypothalamus, particularly to a subset of this area, the nucleus suprachiasmaticus. This nucleus is critical in regulating circadian rhythm, such as the sleep–wake cycle.

The raphe magnus/pallidus (c) projects downward (caudally) to the spinal cord, where it modulates sensory input. It may play a role here in "gating" pain stimuli; therefore, drugs that affect serotonin often play a role in pain management. These serotonin neurons also synapse on motor neurons, so serotonin clearly plays a role in movement and particularly in

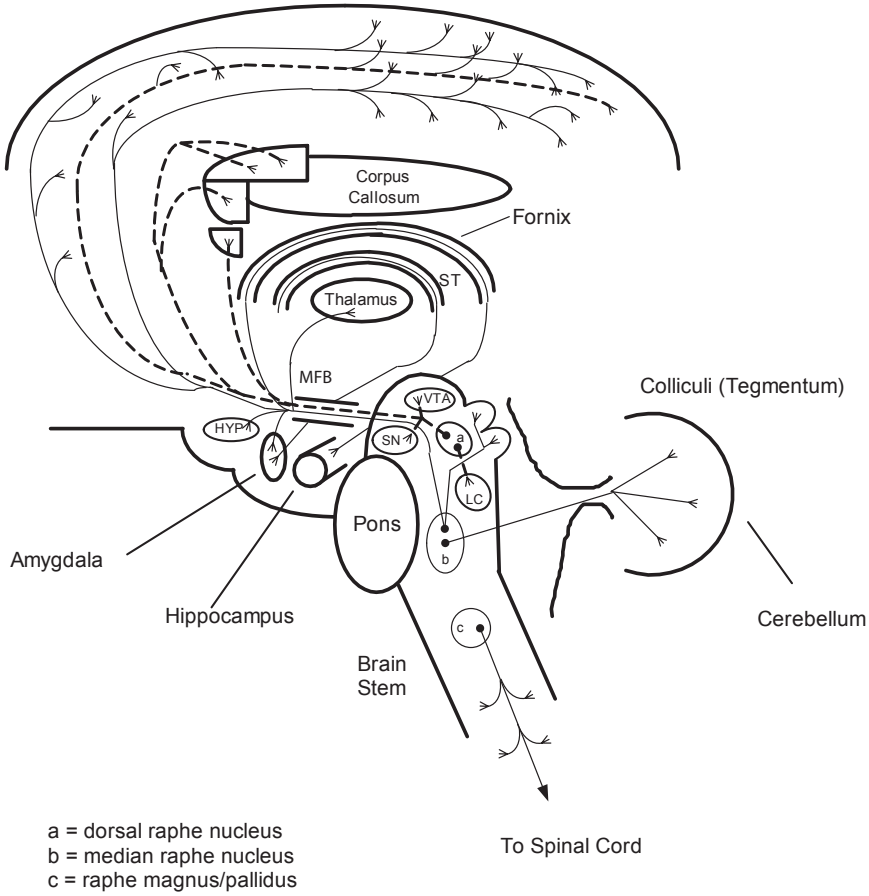


FIGURE 4.12. The serotonin pathways.

setting the strength of reflexes. Finally, these serotonin neurons also synapse on the IML, thus playing a role in the output of the SNS.

Figure 4.13 shows a simplified serotonin synapse. Dietary tryptophan is taken up by the neuron and converted to serotonin; serotonin's action is then terminated by reuptake into the neuron. Serotonin either may be repackaged in vesicles or metabolized by the enzyme monoamine oxidase (MAO) into 5-hyroxyindoleacetic acid (5-HIAA), a metabolite that can be assessed in spinal fluid. The serotonin transporter, MAO, and 5-HIAA figure prominently in the later discussion of both mood and aggression. There are 14 different subtypes of serotonin receptors, divided into seven families (Hensler, 2012). The 5-HT_1 family is known to be both pre- and

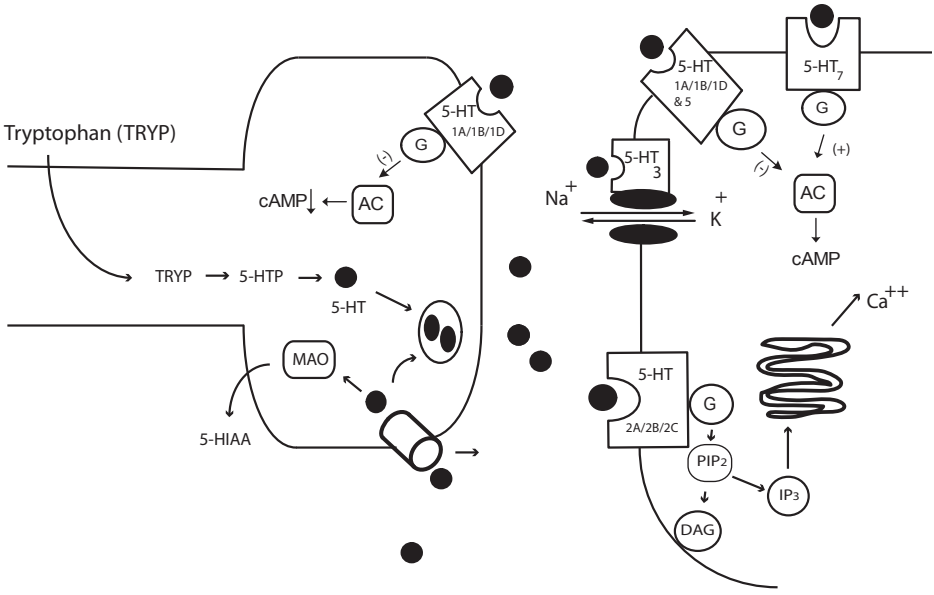


FIGURE 4.13. The serotonin synapse and receptors.

postsynaptic (with the 5-HT_{1B} receptor being the primary autoreceptor), while the others are predominately postsynaptic. 5-HT_1 and 5-HT_5 receptor activation reduces neuronal firing, while activation of the other subtypes increases firing. Since the 5-HT receptor subtypes have varying degrees of affinity for serotonin, the ultimate effect of serotonin stimulation on neuronal firing cannot be easily predicted. Figure 4.14 shows how different types of serotonin receptors are arranged in different parts of the brain in a very intricate pattern. They are found postsynaptically on both the cortex pyramidal neurons and the GABA inhibitory neurons that surround the pyramidal neurons (Lesch & Waider, 2012). Serotonin receptors also serve as "heteroreceptors" on both the GABA interneurons and pyramidal neurons. The left lower part of Figure 4.14 illustrates the concept of the hetereoreceptor. The open neuron has a presynaptic autoreceptor at the end of its axon, where its *own* neurotransmitter attaches, most often reducing neurotransmitter release. In contrast, the filled neuron is releasing a neurotransmitter that binds to a presynaptic hetereoreceptor on the end of an axon on a *different* neuron. Activation of the hetereoreceptor may either increase or decrease neurotransmitter release.

So what does serotonin do? It is not surprising that such an ancient and widespread neurotransmitter influences many behaviors. Nakamura (2013) studied monkeys while continuously monitoring the activity of

both VTA dopamine neurons and dorsal raphe neurons via implanted electrodes. The monkeys preformed tasks for rewards that at times were either larger or smaller than the monkeys had been trained to expect. As described earlier in the section of this chapter on dopamine, the VTA neurons responded in a phasic manner (which means that the neurons turned on and off quickly during the trial) to reward, being active when the reward was larger than expected and turning off when the reward was smaller than expected (Schultz et al., 1997). In contrast, the dorsal raphe neurons showed a "tonic" level of activity during the trial (which means that they continued to fire over the trial). However, there were different *sets*

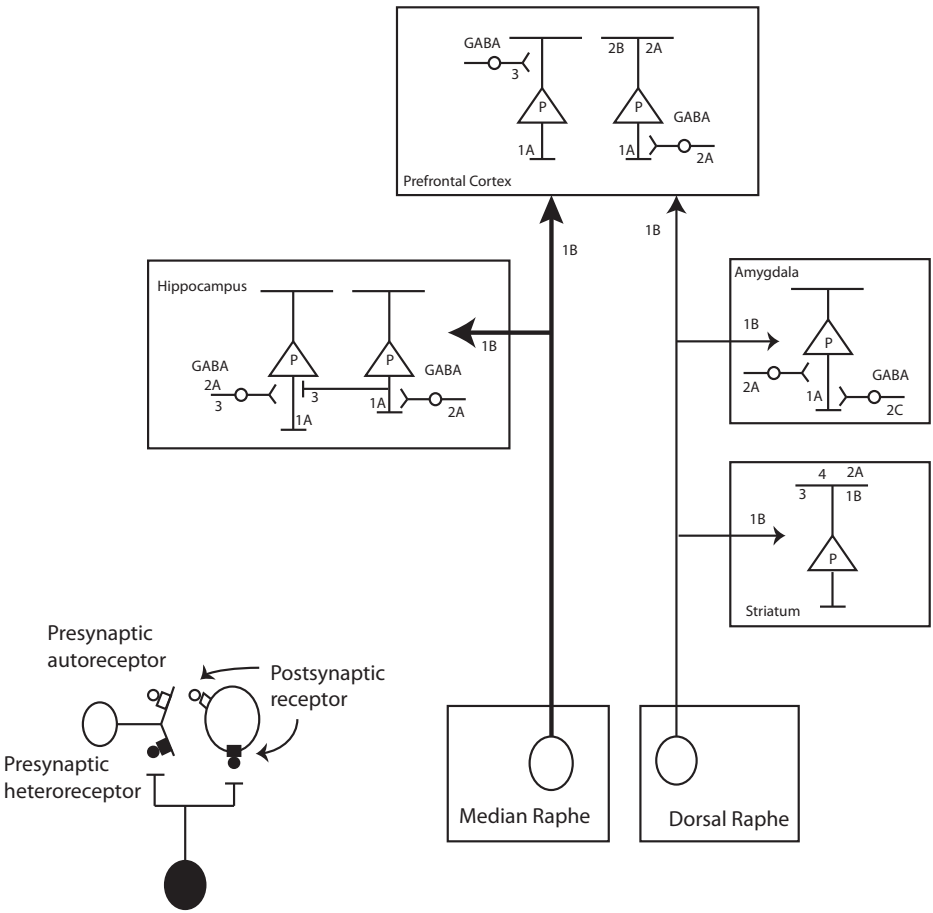


FIGURE 4.14. The distribution of serotonin receptor subtypes in the brain. Illustration of heteroreceptors (lower left).

of serotonin neurons in play: Some responded to small rewards, whereas others responded to large rewards. Put differently, serotonin "set the expectations" (large or small reward) for the task, while dopamine responded immediately (increased in response to an unexpected reward, decreased in response to no reward). (For completeness, the LC norepinephrine neurons are included. Note that they respond only to the target, not the reward.) Because of the projections of the serotonin system to the hypothalamus and spinal cord, this system also is well placed to mobilize physical resources in response to stress. Thus, serotonin plays a role in mood, aggression, pain, sexual behavior, and attachment. If norepinephrine is the "stop, look, and listen" system (also responding phasically to events other than reward) and dopamine is the "let's go or not, depending on what's in it for me" system, then serotonin plays a more subtle modulatory role. In Nakamura's (2012) words, it helps to "provide a reward context"; that is, serotonin helps adjust behavior for changing environments (reward or no reward). Just as a serotonin neuron helps the sea slug extend or retract its gill in response to a positive or negative environment, so it helps us adjust our more complex behaviors in response to our highly variable environment.

NEUROPEPTIDES

The most well known of the over 100 neuropeptides are listed in Table 4.4. Rather than small molecules like the neurotransmitters, peptides are chains of amino acids. The neurotransmitters studied so far are released and act only within the synaptic cleft of the neuron; they do not diffuse throughout the brain. They are rapidly broken down or taken back up into the neuron quickly to terminate their action. In contrast, peptides can diffuse and act at sites in the brain away from their release site. Similar to classical neurotransmitters, peptides have receptors that are highly localized. Sometimes, the peptide is released along with a conventional neurotransmitter. Whereas the small chemical neurotransmitter acts rapidly, as described previously, the effects of the peptide are more prolonged.

The pain-reducing and addictive potentials of morphine, heroin, and other opiate drugs are well known. The brain produces three natural, or endogenous opiates of its own: beta-endorphin, enkephalin, and dynorphin (Bodnar, 2013). Small neurons that release these substances are found throughout the brain and spinal cord. In the spinal cord, they are concentrated in the pain-receiving area. Enkephalin and dynorphin neurons are found in the caudate putamen, from which they project to the globus pallidus; the peptides are co-released with GABA in these neurons. The endogenous opiates bind to three types of receptors, first named with Greek letters but now often given English acronyms in the literature: delta (DOR), kappa (KOR), and mu (MOR). Beta-endorphin and morphine bind most

TABLE 4.4. A Partial List of Neuropeptides

Class	Peptide	Function
Opioid peptides	Beta-endorphin	Activates mu receptor with exercise and injury; morphine and naloxone/naltrexone bind to mu receptor
	Enkephalin	Activates delta receptor; massive projection from striatum to globus pallidus
	Dynorphin	Activates kappa receptor; more widely distributed in brain, less dense in striatum, heavy concentration in brain stem; naltrexone binds to kappa
Pituitary peptides	Oxytocin	Uterine contraction, breast feeding (bloodstream), social bonding, sexuality (central)
	Vasopressin (AVP or ADH)	Induces kidneys to retain water (principal role) but some released to brain; may play a role in social behavior
	Prolactin	Milk production (bloodstream), social bonding (central)
	Growth hormone	Growth of bones and muscles, but has effects on brain development
	Adenocorticotropic hormone (ACTH)	Induces adrenal medulla to release cortisol in response to stress; also has extensive projects to LC, raphe, and VTA
	Gonadotropic hormones (LH, FSH)	Sexuality, reproduction, secondary sexual characteristics, appetite regulation
Gut–brain peptides	Substance P	Uses neurokinin-1 (NK-1) receptor; coexists with glutamate; enhances inflammation; also involved in mood, separation anxiety
	Cholescystokinin (CCK)	Release in gut stimulated by PNS and presence of fatty acids; aids digestion, increases satiety; widespread distribution in cortex, VTA (released with dopamine), amygdala, and hippocampus; stimulation of CCK receptor-4 induces anxiety
	Neuropeptide Y (NPY)	Increases food intake, increases growth of fat; release induced by stress; also widely distributed in hypothalamus, cortex, and limbic system; five receptor subtypes (Y_1–Y_5)
	Leptin	Produced by liver and fat tissue; enters the hypothalamus; induces satiety and reduces food intake

(continued)

TABLE 4.4. *(continued)*

Class	Peptide	Function
Gut–brain peptides *(continued)*	Galanin	Widely expressed in brain, gut, and spinal cord; may have extensive neuroprotective effects
	Orexin	Only 10K to 20K neurons in hypothalamus; stimulates appetite and wakefulness
	Ghrelin	Secreted when stomach is empty; enters hypothalamus and stimulates appetite
Hypothalamic releasing peptides	Corticotropin-releasing factor (CRF)	Induces release of ACTH from pituitary, but found throughout cortex and brain stem; stimulation of CRF-1 receptor induces anxiety
	Gonadotropin-releasing hormone (GnRH)	Induces release of LH and FSH; may influence social behavior and appetite

tightly to the mu receptor, whereas dynorphin binds strongly to the kappa receptor. The enkephalins have greater affinity for the delta receptors. All of the endogenous opiate receptors inhibit adenylyl cyclase.

Jon-Kar Zubieta and colleagues (2001) used [11C]carfentanil, a positron-emitting substance that binds to mu receptors in the brain so that the receptors can be visualized on a positron emission tomographic (PET) scan. PET scans were obtained on 20 human volunteers while they were exposed to painful stimuli; the participants also rated the amount of pain they experienced. Opiate receptor activation during painful stimuli was found in many regions, including the anterior cingulate, prefrontal cortex, thalamus, and hypothalamus. The amount of opiate receptor activation correlated negatively with how intensely the participants experienced pain. The greater the opiate receptor activation in the nucleus accumbens, amygdala, anterior cingulate, and thalamus, the less intense the participants rated the pain. This raises the interesting question of whether people with lower levels of opiate receptor activation would have a lower tolerance for pain. In 2014, Zubieta and colleagues posted a 3-D PET scan of a patient scanned during a migraine and again when pain free (*www.jove.com/video/50682/3d-neuronavigation-vivo-through-patient-s-brain-during-spontaneous*). This scan clearly shows how the patient, during her migraine, has more of her mu opiate receptors occupied and how her brain released endorphins to combat the pain. Endogenous opiates also regulate other neurotransmitters, such as dopamine, serotonin, and norepinephrine (see Figure 4.15), thus playing a role in mood regulation (Lutz & Kieffer, 2013).

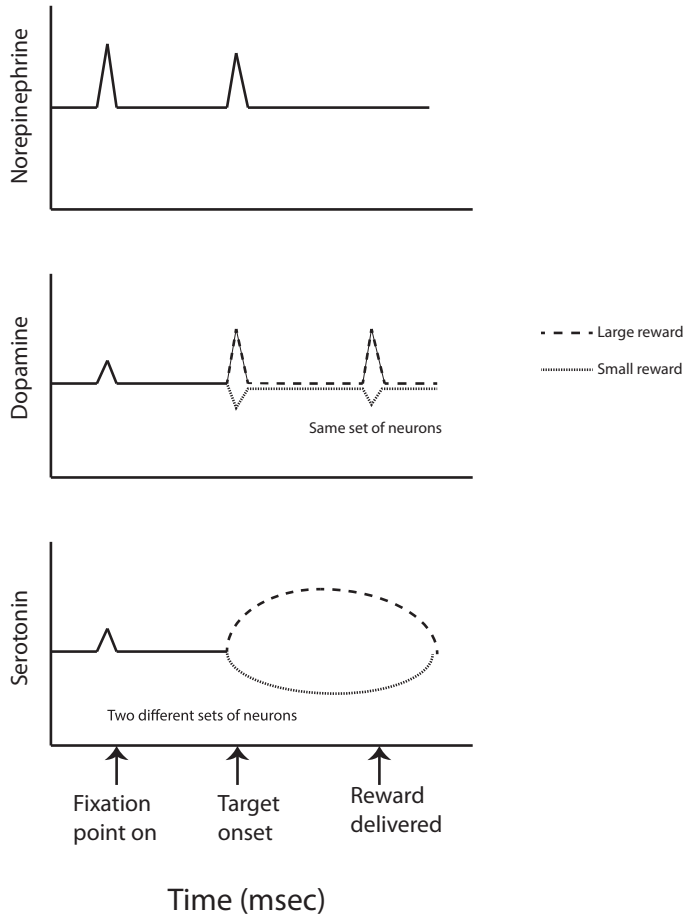


FIGURE 4.15. Different roles of norepinephrine, dopamine, and serotonin in response to events in the environment.

Oxytocin neurons were first found in the hypothalamus, from which they project to the posterior pituitary. When oxytocin is released in pregnant females, it initiates uterine contractions. It also triggers milk ejection in nursing mothers. The sound of a crying infant causes hypothalamic neurons to release oxytocin. Oxytocin neurons in the hypothalamus project to other areas of the limbic system, including the nucleus accumbens, amygdala, VTA, medial preoptic area, and hippocampus (Lieberwirth & Wang, 2014). The latter two areas form part of the maternal circuitry (Rutherford, Williams, Moy, Mayes, & Johns, 2011) and are illustrated in Figure 4.16.

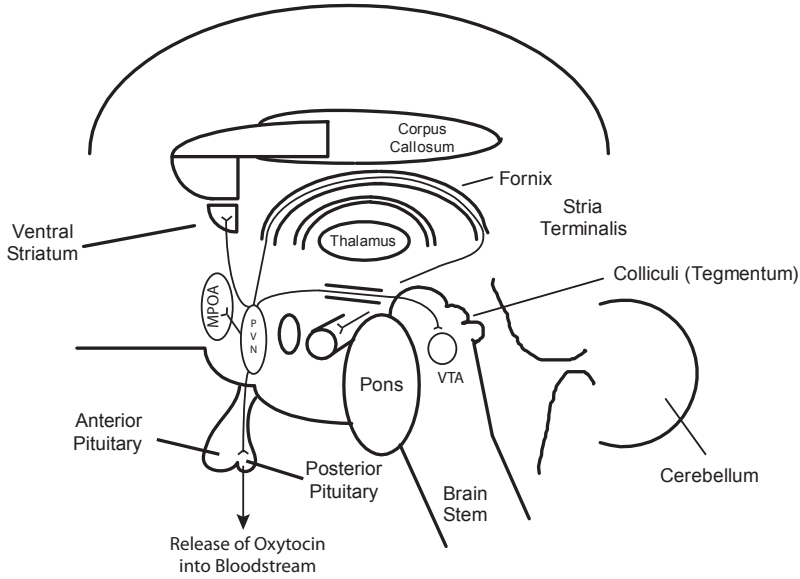


FIGURE 4.16. The oxytocin pathways.

Oxytocin is found in males as well, and it has been shown to play a role in bonding and sexual behavior. Prairie voles (a type of rodent), which are monogamous and engage in high levels of maternal behavior with their offspring, have much higher oxytocin receptor density than species of voles that are polygamous (Cho, DeVries, Williams, & Carter, 1999). Whereas injecting oxytocin into the brains of female mice increases their maternal behavior, injecting an oxytocin antagonist reduces it (Lieberwirth & Wang, 2014). Carmichael, Warburton, Dixen, and Davidson (1994) had human participants engage in sexual intercourse while their blood oxytocin levels were assessed. There was a positive correlation between the number and intensity of orgasms and plasma oxytocin levels in both males and females. When humans are administered intranasal oxytocin during laboratory studies, they show increased levels of interpersonal trust (van IJzendoorn & Bakermans-Kranenburg, 2012). There are multiple variations of the oxytocin gene in humans, which may relate to variations in social bonding (Lieberwirth & Wang, 2014). Disturbances in oxytocin also may be related to autistic spectrum disorders.

In the discussion of norepinephrine and the stress response, we have already discussed CRH, ACTH, and cortisol. Plate 2 shows the neuroanatomy of the other hypothalamic hormones. The periventricular nucleus (PVN) releases CRH and thyrotropin-releasing hormone (TRH)

to stimulate the release of ACTH and thyroid-stimulating hormone (TSH; gray neurons). The red neurons show the pathways from the PVN and supraoptic nucleus (SON) to the posterior pituitary to release oxytocin and vasopressin, respectively. The anterior nucleus (blue) contains neurons that release gonadotropin-releasing hormone (GnRH) to the anterior pituitary, which in turn releases follicle-stimulating hormone (FSH) and luteinizing hormone (LH). These govern the release of the sex hormones estrogen, progesterone, and testosterone. Neurons from the arcuate nucleus (drawn in brown), govern the release of prolactin (involved in milk production, as well as social bonding) and growth hormone. These hormones all may have roles in mental disorder well beyond their traditionally defined physiological functions.

GROWTH FACTORS

The final group of neurotransmitters to consider are the growth factors. Growth factors are also peptides; they transmit their signals to the neuron via the receptor tyrosine kinase (RTK) system that was reviewed in Chapter 3. Growth factors can be produced by support cells (glia) of the nervous system, as well as by neurons themselves. As their name implies, they are critical in early development for neuronal division and growth, but they continue to be important throughout the life of the animal in preventing neuronal death. Of particular importance are a subgroup of the growth factors, the neurotropins, which support the differentiation and survival of specific subsets of neurons. These neurotropins are nerve growth factor (NGF), brain-derived neurotropic factor (BDNF), and neurotropins 3 (NT 3) and 4/5 (NT 4/5). Neurotropins may be released from anywhere in the brain. Often, the postsynaptic neuron releases a neurotropin back onto its presynaptic neuron. NGF is needed for sympathetic neurons to develop in the fetal period and to be maintained throughout life. NGF also is found in the cortex and hippocampus, as well as in the forebrain cholinergic neurons. BDNF supports outgrowth of axons from both neurons; higher levels of neuronal activity stimulate release of BDNF, which in turn promotes neuron growth (Deinhardt & Chao, 2014) and connectivity (Ninan, 2014; Zagrebelsky & Korte, 2014). A single mutation in the BDNF gene (*rs6265*) results in a methionine amino acid replacing a valine amino acid. Having this mutation may interact with a childhood history of abuse to produce both depression and changes in hippocampus volume (Frodl et al., 2014; Ninan, 2014). I therefore return to the neurotropins in great detail in Chapter 11, on affective and anxiety disorders.

CHAPTER 5

Genetics and Epigenetics

Humans have 23 pairs of chromosomes (one pair of sex chromosomes and 22 pairs of autosomes). Since the Human Genome Project was completed in 2003, it has been known that less than 2% of the DNA in the human genome codes for proteins, and that humans have only about 20,000 to 25,000 "genes" (International Human Genome Sequencing Consortium, 2004). The 98% of the genome that does not code for proteins was once viewed as "junk" or "nonsense" DNA; today, it is known that such a term is inappropriate. While we do not know the role of this "non-protein coding DNA," much of it does serve a critical regulatory process for gene/protein expression. Box 5.1 and Figure 5.1 give an overview of how DNA is transcribed first into messenger RNA (mRNA), then translated into proteins. How this process is regulated is termed "epigenetics." If the DNA sequence is the genetic "hardware," then epigenetics is the "software" actually running the genetic computer. Environment has major impact on epigenetics. As organisms become more complex, the amount of their nonregulatory DNA (and capacity for epigenetic control) increases from a mere 20% in bacteria to the 98% in humans (Taft, Pheasant, & Mattick, 2007).

Disorders such as cystic fibrosis or Huntington's disease are caused by single genes, and the pattern of inheritance follows Mendel's laws. In disorders such as cystic fibrosis, the gene by itself is sufficient to cause the disorder (although there may scores or hundreds of different defects in the particular gene). In other cases there is a gene × environment interaction. In phenylketonuria (PKU), a child inherits two copies of a gene that result in the child producing an inactive form of the enzyme that breaks down the amino acid phenylalanine. Untreated, the phenylalanine builds

up in the body and produces serious neurological dysfunction, including intellectual disability. However, if the environment is altered by restricting phenylalanine from the diet immediately after birth, then neurological and psychological development is generally normal. The change in diet does *not* impact the expression of the enzyme protein, however. In contrast, with epigenetics, environmental factors modify the processes described in Box 5.1 to change gene *expression*, but never cause mutations (change in the DNA structure itself). Thus, identical twins who have identical DNA at conception may begin to show difference in gene expression as a result of different

BOX 5.1. An Overview of Epigenetic Process Governing Transcription of DNA to RNA and of Translation of RNA to Protein (Figure 5.1)

a. The double helix of the DNA is packed into the chromosomes in the form of chromatin, which consists *histone* proteins. Histones are grouped together in eight spheres (an octomer) around which the DNA is wound like thread on a spool (upper left). These octomers repeat throughout the chomatin. The chromatin exists in two forms: a dense, packed form in which the genes on the DNA cannot be transcribed, and an open form in which the spools of histones unwind to expose the DNA for transcription. A process called "acetylation" governs the shift from packed to open. When enzymes called "histone acetyltransferases" (HATs) place acetyl groups on the "tail" of the histones, the chromatin opens up to expose the DNA. A protein-coding area of DNA (a gene) has a promoter region, as well as exons and introns. Proteins called "transcription factors" bind to the promotor site, allowing the RNA polymerase to attach. The polymerase converts one strand of the DNA to messenger RNA (mRNA), then the introns are cut out and the exons are spliced together to form the completed mRNA. The mRNA leaves the nucleus and attaches to a ribosome, where transfer RNA (tRNA) carrying amino acids can bind to it; as the proteins are linked to each other the protein is formed.

b. A gene can be silenced by the removal of acetyl groups from the histones by histone deacetylases (HDATs). The chromatin then reverts to its packed, dense state, and transcription is no longer possible.

c. There is another form of gene silencing, independent of histone modification that can operate even when the chromatin is in the open state. Methyl ($-CH_3$) groups can be attached to the DNA itself. When these groups are heavily concentrated in the promotor region, the RNA polymerase cannot bind to the promotor.

d. Micro RNAs (miRNAs) are small nucleic acids that not translated into proteins. When they leave the nucleus, they play a further role in regulating protein expression, often inhibiting translation of the mRNA by attaching themselves to it.

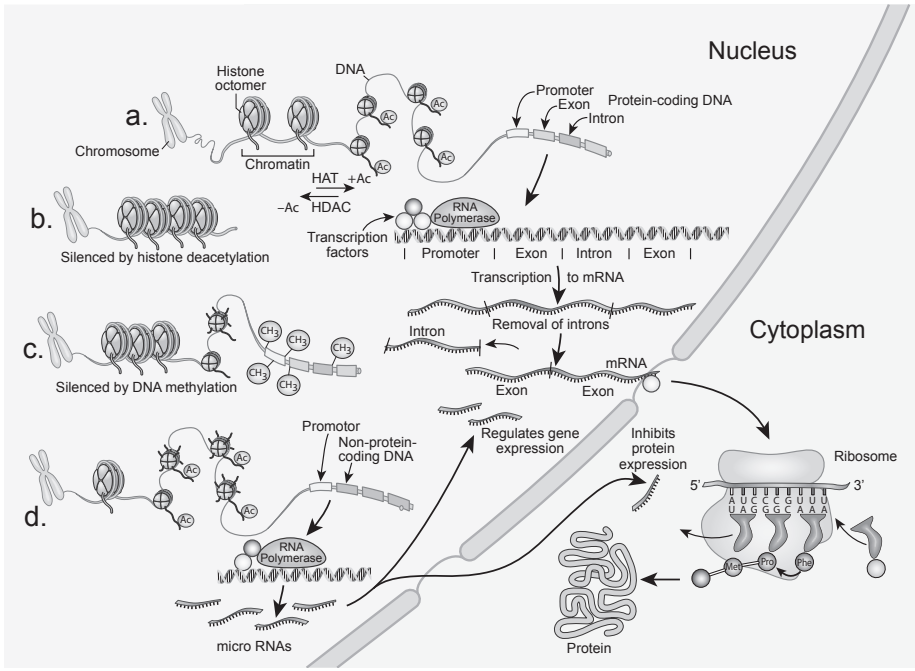


FIGURE 5.1. Overview of regulation of gene expression.

environmental exposures. Here, I define environment very broadly, from chemical insults *in utero* to both diet and stress in early life. Whereas some epigenetic changes can be reversed, others may be permanent and, in some cases, passed on to the next generation.

WHAT IS HERITABILITY?

Heritability (h^2) has been used in many studies of mental disorders (Plomin, DeFries, McClearn, & McGuffin, 2008). It is a measure of how much of the *variance* of a trait can be attributed to genetics. Take the example of human height. Imagine a village in a developing country in which nutrition is quite poor. We go to the village and measure the height of every adult person, and we find a typical bell curve; but the mean height of the population is lower than that in the Western World, as shown in Figure 5.2. A generation later, we go back and measure the adult heights of the children of the first generation and find that the mean height of the population has not changed. We find that the relatively shorter people in generation 1 have

had the relatively shorter children in generation 2. Thus, the offspring of individuals A1, B1, and C1 occupy the same relative positions in the second generation as their parents did (A2, B2, and C2).

Now suppose that agricultural improvements are introduced for the next generation. When we measure the height of the grandchildren, we find that the mean height of the population has risen. When we look at the heights of the individuals, however, we find that the relative position within the population of the offspring is similar to that of the previous generation. Although all the offspring are taller than their parents, the relatively

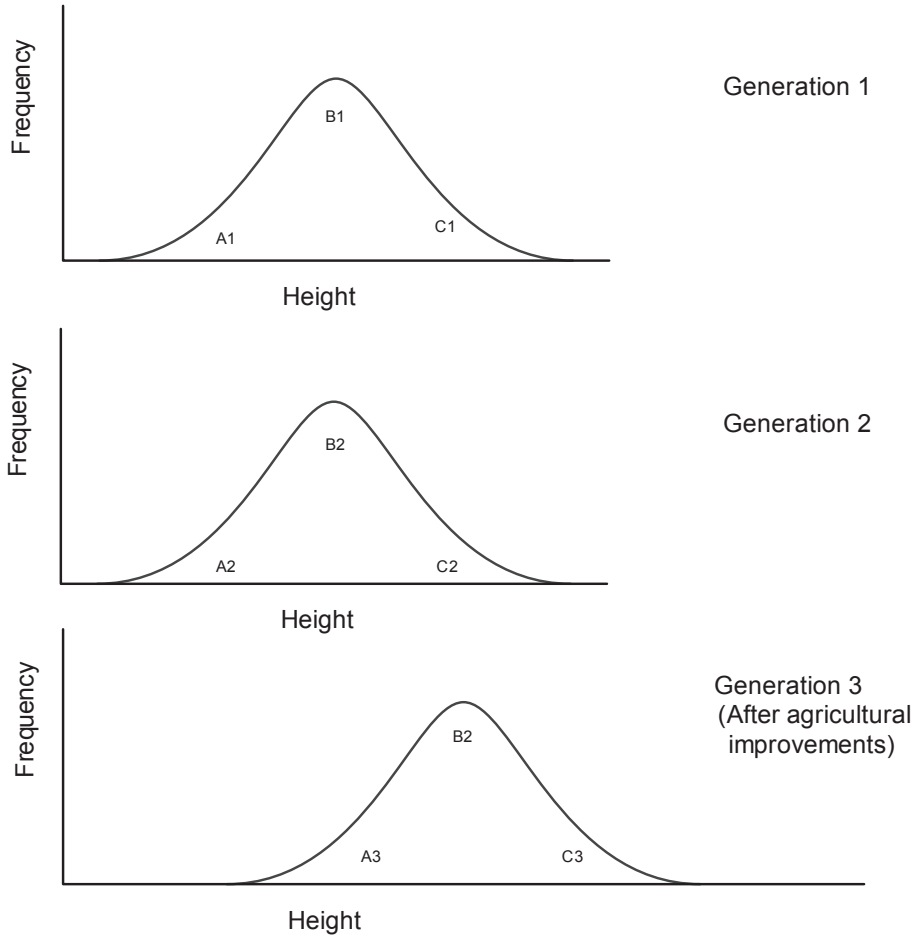


FIGURE 5.2. Effects of gene and environment on human height.

shorter parent (A2) still has the relatively shorter children (A3); similarly, the tallest parents (C2) still have the taller children (C3). When heritability for a trait is high, the amount of variance in the trait (i.e., the point within the population at which the individual falls) is determined by genetics. Heritability does not say anything about the point at which the *mean* of the population will fall, nor does high heritability preclude the effects of environment, as is seen after the introduction of agricultural improvements. In humans, heritability is calculated from twin studies and ranges from 0 (no effect of genetics on variance) to 1.0 (genetics governs all the variance). What kind of trait has a heritability of 0? Consider the width of men's ties. If we measured tie width in the 1950s, we would find a very small mean, but there still would be variance in the widths. Some men might like ties one-half inch wide, others would wear ties 1½ inches wide. If we examined the tie widths of their sons in the 1970s, mean tie width would have expanded. Some men, again, would like the widest 5-inch tie, whereas others would prefer a mere 2 inches. But unlike height, there would be no correlation between the width of tie worn by fathers and sons because there is no gene governing choice of tie width. Because heritability is zero, the environment can determine all the variance: We may decree that everyone will wear exactly the same width tie. With height, no matter how we adjust the environment, even to the point of making everyone eat the same thing every day, we cannot make everyone the same height. Heights will always fall along a bell curve, and genes will govern an individual's relative position within the bell curve.

Traditionally, heritability has been assessed by comparing fraternal (dizygotic [DZ]) and identical (monozygotic [MZ]) twins on a trait and determining how similar or different the two types of twins are. For instance, the heights of a large set of DZ and MZ twins are measured. We then calculate the correlation between the heights of the pairs of twins. If each MZ twin was the exact height of his or her twin, then the correlation would be a perfect 1.0. In fact, the correlation of their heights comes to .95. The DZ twins are not so similar in height; the correlation is .50. The (simplified) formula for heritability is $2(MZ_{correlation} - DZ_{correlation}) = 2$ (.95 – .50) = .9. That is, 90% of the variance in height is related to genetics. This process can be repeated with a wide variety of measures, including intelligence, psychiatric disorder, personality traits, and even musical ability. Thomas Brouchard (2004) summarized this data; selected results from this paper are shown in Table 5.1. Here I introduce two more key concepts. Shared environment means those things the twins shared (grew up in the same neighborhood, had the same parents). Nonshared environment is what *differed* between the twins (one had a head injury, only one twin got the really good math teacher in high school). In general, shared environment has less effect on the variance in personality that one might expect, and very little effect on psychiatric disorder.

TABLE 5.1. Estimates of Broad Heritability and Shared Environmental Influences of Nonadditive Genetic Effects for Selected Psychological Traits

Trait	Heritability	Nonadditive genetic effect	Shared environmental effect
Extraversion	0.54	Yes	No
Neuroticism	0.48	Yes	No
Positive emotionality	0.50	Yes	No
Religiosity	0.30–0.45	No	0.20–0.40
Specific religion	0	N/A	N/A
Intelligence			
Age 5	0.22	No	0.54
Age 7	0.40	No	0.29
Age 10	0.54	No	0.26
Age 18	0.82	No	No
Age 50	0.85	No	No
Psychiatric illness			
ADHD	0.75	?	No
Schizophrenia	0.80	No	No
Major depression	0.37	No	No
Anxiety disorder	0.30–0.40	No	In females
Alcohol dependence	0.50–0.60	No	Yes
Antisocial behavior	0.41–0.46	No	0.09–0.20

Note. Data from Bouchard (2004).

"Nonadditive genetic effect" means that "genes for personality, in addition to simply adding or subtracting from the expression of a trait, work in a more complex manner, the expression of a relevant gene depending to some extent on the gene with which it is paired on a chromosome or on genes located on other chromosomes" (Brouchard, 2004, p. 149). Suppose there are three genes (A, B, and C) that have *additive* effects for a disorder. A person has a 10% chance of developing the disorder if they inherit any of the genes individually (A, B, or C). If you have two of the genes, you have a 20% risk, and if you have all three, you have a 30% risk. In *nonadditive* effects, things get complicated. For example, if you have A alone, you have no risk for the disorder. If you have A + B, you have a 10% chance of getting the disorder, and if you have A + C, you have an 80% chance of the getting the disorder, yet if you have A + B + C, you have only a 15% chance.

In Table 5.1, note the high heritability of intelligence and most psychiatric disorders. So why haven't we found the genes?[1] This is the problem of hidden (or missing) heritability. These nonadditive genetic effects may raise

[1]It might be that twin studies are fatally flawed, and while this is not my view, the reader can see the argument online at *www.independentsciencenews.org/health/still-chasing-ghosts-a-new-genetic-methodology-will-not-find-the-missing-heritability*.

the heritability rate but make the genes much more difficult to find. In the previous example, we would not find gene A, B, or C alone to be related to the disorder in a genetic study, since only particular combinations raise the risk. On the other hand, the epigenetic mechanisms (not fully appreciated in 2004) may supply the answer. Before going here, we need to review further the basic principles of molecular genetics.

MOLECULAR GENETICS

Chromosomes consist of long strands of DNA, made up of the four bases in two complementary chains: thymine (T), guanine (G), adenine (A), and cytosine (C). Since DNA occurs in pairs, each person has two alleles at each location; thus an individual can be a homozygote (AA or BB) or a heterozygote (AB) for a given locus. Two concepts are key to understanding mutations in the DNA: single-nucleotide polymorphisms (SNPs, pronounced "snips") and copy number variants (CNVs) (see Figure 5.3). An SNP occurs when one nucleotide in the DNA sequence is changed (i.e., from an adenosine to a guanine, as shown). If an SNP occurs in a protein-coding

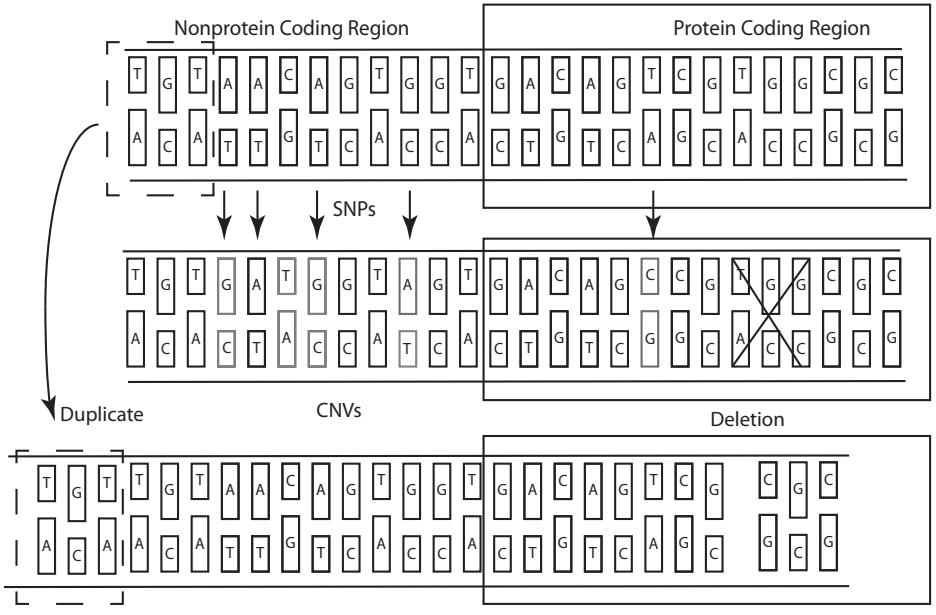


FIGURE 5.3. SNPs and CNVs.

region, the protein may no longer function and the mutation could be fatal. Thus, SNPs do not tend to accumulate in the protein-coding area (these areas are "conserved"). In the non-protein-coding area (formally known as junk DNA), SNPs are more common. Thus, each person's DNA sequence is unique, and the human genome contains about 3.3 million SNPs (with about only 10,000 of these occurring in protein-coding regions). CNVs, on the other hand, are "chunks" of DNA that are either copied or deleted. Again, if this occurs in a protein-coding area of DNA, function of the brain can be disrupted; CNVs are often related to developmental disabilities.

SNPs and CNVs can be detected by using SNP array (Plomin et al., 2008). Briefly, a sample of the individual's DNA from a cheek swab or blood is digested with enzymes. The enzymes cut the DNA at different positions, depending on the pattern of that person's SNPs. This results in a giant jigsaw puzzle of DNA fragments for each chromosome. Fluorescent probes are attached to these fragments, and the DNA is placed on the array to which the patient's fragments will attach. If a patient is "AA" at a given DNA location, there will be more fluorescence at the "A" spot on the allele. If an SNP occurred and that person is now "AB," there will be less fluorescence there, and none at all if a CNV deletion cut out the "AA." If a CNV duplicated the area (AAAA), the fluorescence will be even higher than normal.

When genetic testing is done for clinical reasons, the mere detection of a duplication–deletion might diagnose a condition (see Chapter 13). In the early days of genetic research on psychiatric disorders, "candidate gene" approaches predominated. Investigators looked for a mutation in a gene one might think is logically connected to the disorder. For instance, in attention-deficit/hyperactivity disorder (ADHD) research, stimulants act as dopamine agonists, so looking for mutations in dopamine genes made sense. Alterations in the genes for both the dopamine transporter and the D_4 receptor were found in the last decade of the 20th century (Swanson et al., 2000). Even at the time, however, it was known that these polymorphisms only accounted for a small amount of the variance in the expression of symptoms of ADHD. In contemporary psychiatric research, many SNPs are referred to as "markers" or "polymorphisms," and they are not necessarily deleterious. In g*enome-wide association studies* (GWAS), tens of thousands of patients and controls have their DNA collected and subjected to an SNP array analysis. It then can be determined which SNPs or CNVs are associated with the disease. The region of the chromosome around the marker can be searched for genes that might be relevant to the disorder. *Interestingly, these large studies have not validated the candidate genes implicated by the early work*. Only a handful of genes have been found to be associated with the major mental disorders, and these genes raise the risk of all the disorders and are not unique to any one disorder

(Cross-Disorder Group of the Psychiatric Genomics Consortium, 2013). In subsequent chapters, I discuss some of the seminal candidate gene studies in disorders such as ADHD and depression, but the failure to replicate early candidate gene studies must always be borne in mind.

McCarroll and Hyman (2013) reviewed some critical points regarding modern psychiatric genetic research and pointed out that our genome is not a "perfectly composed Shakespearean sonnet, with a place for everything, and everything in its place" (p. 579). Every fertilized human zygote will have about 100 potentially gene-disrupting variants, yet most of the time, these do not cause disease. The DNA we inherit from our parents contains thousands of variants from our ancestors that affect the genes themselves or the expression of genes. McCarroll and Hyman went on to say, "The human genome . . . is less a Shakespearean sonnet than a collection of seven billon drafts" (p. 579). Yet identifying a gene with little effect by itself in a disorder is not a trivial thing. The *HMGCR* gene regulates levels of low-density lipoprotein (LDL) in the blood. Mutations in this gene account for less 1% of the heritability of LDL levels (Keebler et al., 2009). Yet the understanding of the role of LDL in cardiovascular disease has obviously led to the development of statins that impact millions of people who do not have any mutation of the LDL gene itself. As a preview, the cross-disorder study mentioned earlier has found a variation in the *CACNA1C* gene for the voltage-gated calcium channel that is related to schizophrenia, autism, ADHD, and bipolar disorder. This suggests that medications directed at calcium dynamics might have wide relevance for treatment of psychiatric disorders.

EPIGENETICS

We now expand on the mechanisms of DNA methylation and histone modification introduced in Box 5.1 (Figure 5.1). For all mammals, including humans, maternal care is critical to survival and future development. Over the last decade, Michael Meaney and his colleagues (Bagot & Meaney, 2010; Belay et al., 2011; Francis, 2009; Kaffman & Meaney, 2007; Weaver et al., 2004; Zhang, Labonte, Wen, Turecki, & Meaney, 2013) have studied the epigenetics of rat maternal behavior. Mother rats engage in a variety of nurturing behaviors, including arching their backs to allow pups access to their nipples, as well as repetitive licking and grooming (LG) of the pups. Mother rats are highly variable in this behavior: Some engage extensively in LG, while others very rarely do it, appearing (in human terms) to "neglect" their pups. Pups of high-LG mothers show *decreased* fearfulness in adulthood, while pups of low-LG mothers grow up to have intense stress responses (including increased release of stress hormones). Female offspring

of low-LG mothers show decreased LG behaviors when they become mothers. If the offspring of low LG mothers are removed from her and given to a high-LG mother, the pups grow up to be less fearful, just like as the biological offspring of the high-LG mother. The next series (Figure 5.4) illustrates how this process is mediated epigenetically.

The pup's sensory experience of being licked and groomed is transmitted by the skin to the sensory association areas of the pup's cortex and brain stem, as well as to limbic system structures such as the amygdala. These structures project to the median raphe nucleus containing serotonin. The serotoninergic neurons of the median raphe project to the hippocampus (review Figure 4.13). Figure 5.4 shows a hippocampal neuron of the pup of a high-LG mother. Serotonin activities a 5-HT_7 receptor, which in turn stimulates adenylyl cyclase. The resultant increased production of cyclic adenosine monophosphate (cAMP) leads to activation of protein kinase A (PKA), which phosphorylates the cAMP-responsive element-binding protein (CREB). CREB-phosphorylated (P) triggers the transcription of nerve growth factor (NGF) inducible protein A (NGFIA); once the mRNA is translated into the NGFIA protein, it returns to the nucleus. NGFIA, now in combination with CREB-P, can remove methyl groups from the promoter of the glucocorticoid receptor (GR) gene allowing the transcription of GR. This is the receptor that will bind the stress hormone cortisol. Cortisol does not need a receptor on the outside of the cell; it diffuses through the membrane of the neuron to bind to the GR. When this happens, it triggers a variety of events in the neuron (not shown) that result in an alteration of the hippocampal output to the hypothalamus. This results in decreased output of corticotropin-releasing hormone (CRH) from the hypothalamus, which in turn reduces ACTH output from the pituitary. As a result, less cortisol is released from the adrenal glands, for a more modest stress response.

What happens in the case of the low LG mothers and their pups? Figure 5.5 shows that the lack of serotonin input to the 5-HT_7 receptor results in less activation of adenylyl cyclase (AC), with reduced cAMP levels. There is inadequate PKA activation to create CREB-P. NGFIA is not produced at adequate levels and without CREB-P; the promoter of the GR gene remains methylated the GR gene is silenced. This in turns means fewer GRs in the cytoplasm. Now the output to the hippocampus is the opposite of that in the case of the high-LG mothers: Release of CRH is increased, leading to more ACTH being released from the pituitary, with a subsequent increase in cortisol. A much stronger stress response is mounted. More importantly, the adult offspring of low-LG mothers are more fearful than are offspring of the high-LG mother.

Why do female offspring of low-LG mothers continue their "neglectful" behavior into the next generation? To understand this we need also to look at the hypothalamus. The medial preoptic area (MPOA) is one of

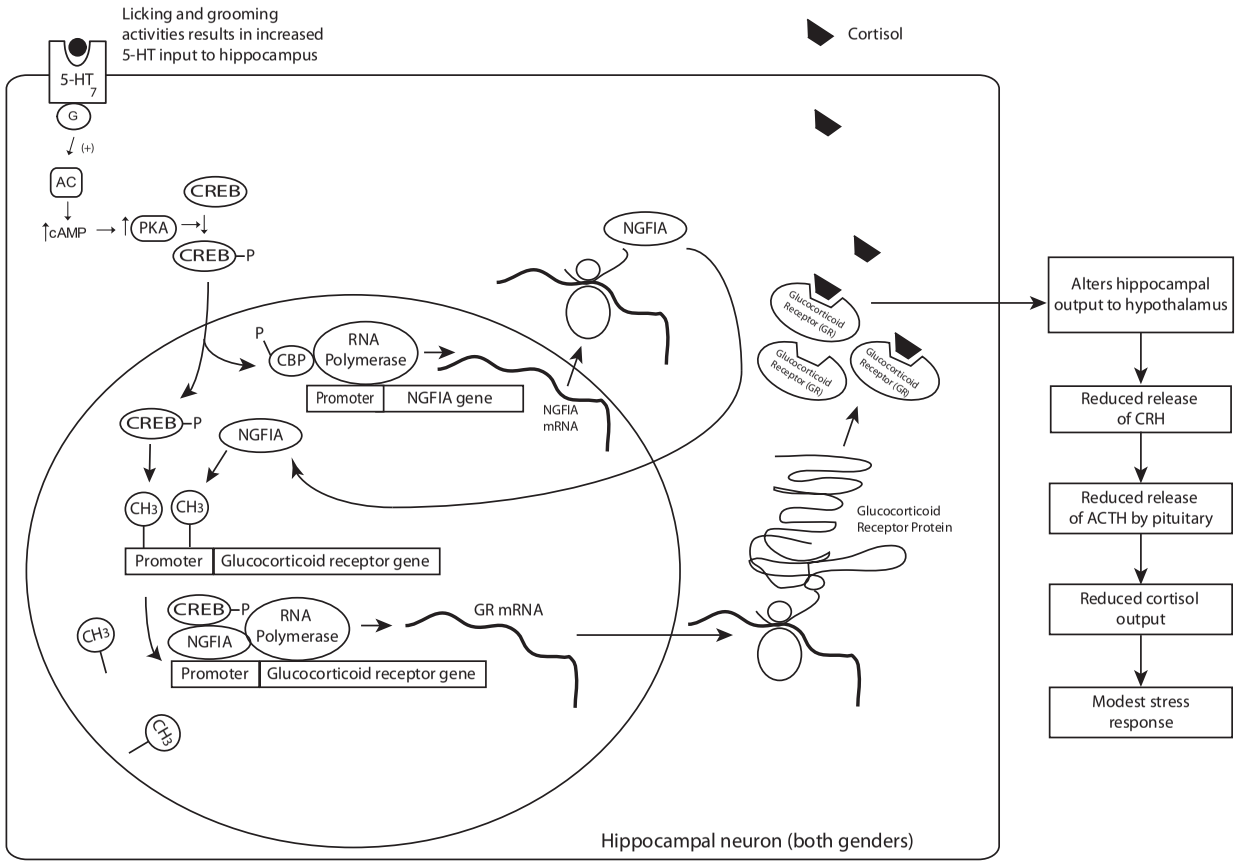


FIGURE 5.4. Effects of adequate maternal care on stress response in rats.

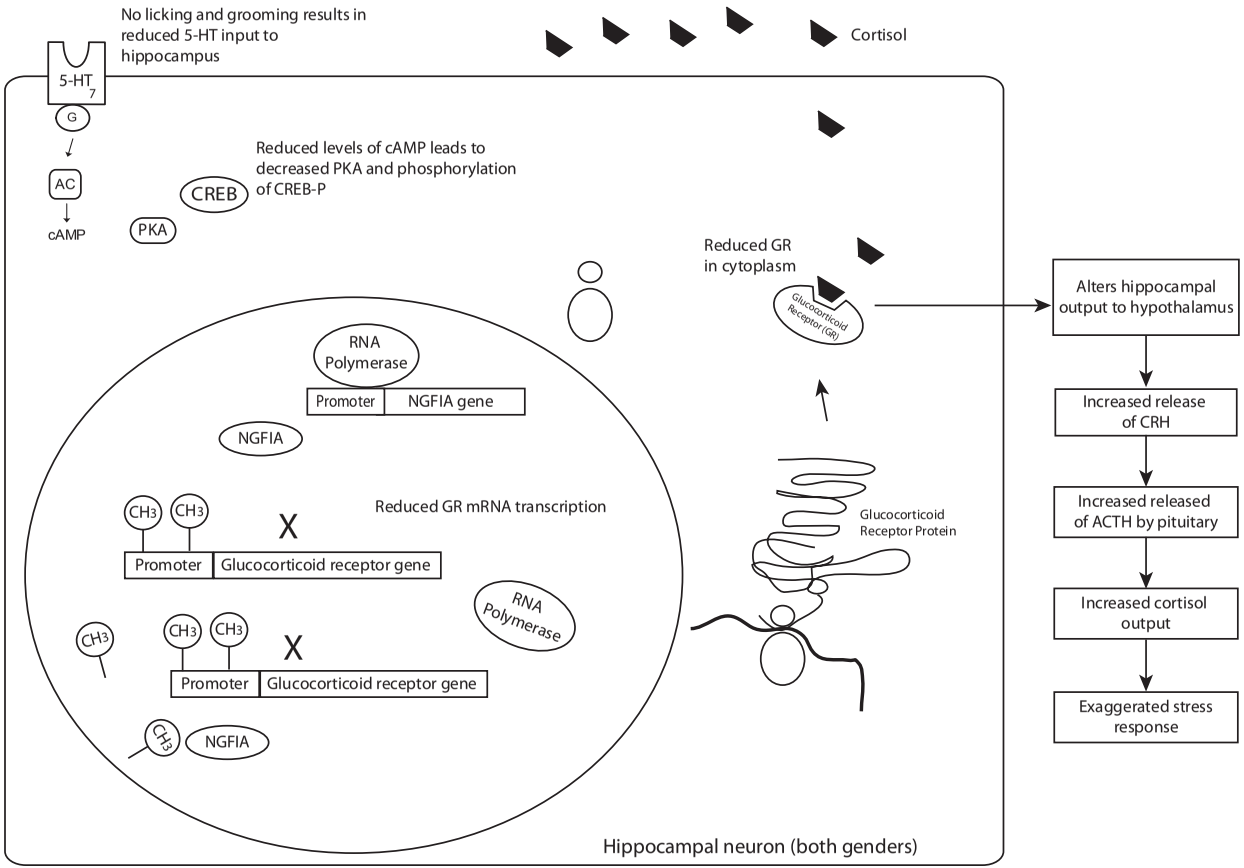


FIGURE 5.5. Effects of deficient maternal care on stress response in rats.

the hypothalamic nuclei, and it is highly involved in maternal behavior. It receives oxytocin input from the periventricular nucleus (PVN) of the hypothalamus. Figure 5.6A shows an MPOA neuron in the offspring of a high-LG mother. Maternal behavior directed toward the pup leads to increased prolactin and other ligands of the receptor tyrosine kinase (RTK) (1). As a result, a protein called Stat5 has two phosphate groups added to it, and it moves into the nucleus (2). The high levels of LG have led to demethylation of the promoter of the estrogen receptor, allowing Stat5 to activate transcription of the gene for the estrogen receptor (*ER*) alpha gene (3). The mRNA is translated, and the *ER* is assembled (4). The *ER* remains in the cytoplasm. Like cortisol, estrogen diffuses through the membrane of the neuron; when it attaches to the *ER* (5), it enters the nucleus, where it activates the transcription of the oxytocin receptor (*OTR*) gene (6). The *OTR* mRNA is translated (7), and the *OTR* reaches the cell membrane. When the female pups reach adulthood and become mothers themselves, oxytocin released by the birthing process and the presence of the pups can activate the *OTR* and the phosphatidylinositol 4,5-biphosphate (PIP_2) second messenger system associated with it. The MPOA neuron itself will release oxytocin to its targets, leading to increased maternal behavior.

Figure 5.6B shows the MPOA neuron of the offspring of a low-LG mother. There will be reduced activation of RTK due to the low level of maternal behavior (1). Even if phosphorylated Stat5 is produced, the lack of maternal behavior means that the promoter of the *ER* gene remains methylated and the gene is silenced (2). There is reduced production of *ER* (3) such that there are inadequate *ER*–estrogen complexes available to activate the *OTR* gene (4). With reduced *OTR,* the neuron is less responsive to oxytocin, leading to decreased maternal behavior in the grown up offspring once they become mothers. The fate of these pups can be changed if they are fostered by a high-LG mother; then the sequence of events in Figure 5.6A can proceed and the pup grows up to be high-LG mothers!

It is clear that the mechanisms in Figures 5.4, 5.5, and 5.6 are highly relevant to a wide range of mental disorders in which anxiety and attachment problems occur. Methylation of the *GR* promoter and other genes in humans in being studied in posttraumatic stress disorders in both children and adults, and will figure prominently in our study of these disorders (see Chapter 11). The rat pups can be cross-fostered to avoid the ill effects of low LG, but this must occur in the first week of the rat's life. Wait too long, and the epigenetic changes become fixed for life. Human parent–infant bonding is clearly more complex than that in the rat. Nonetheless, it is sobering to reflect on the fact that when the human infant is born, the mother's brain releases oxytocin and estrogen. As the mother holds, caresses, and talks to her infant, these same genes for GR, ER, and OTR (and no doubt many others) are being demethylated and these genes are activated, possibly

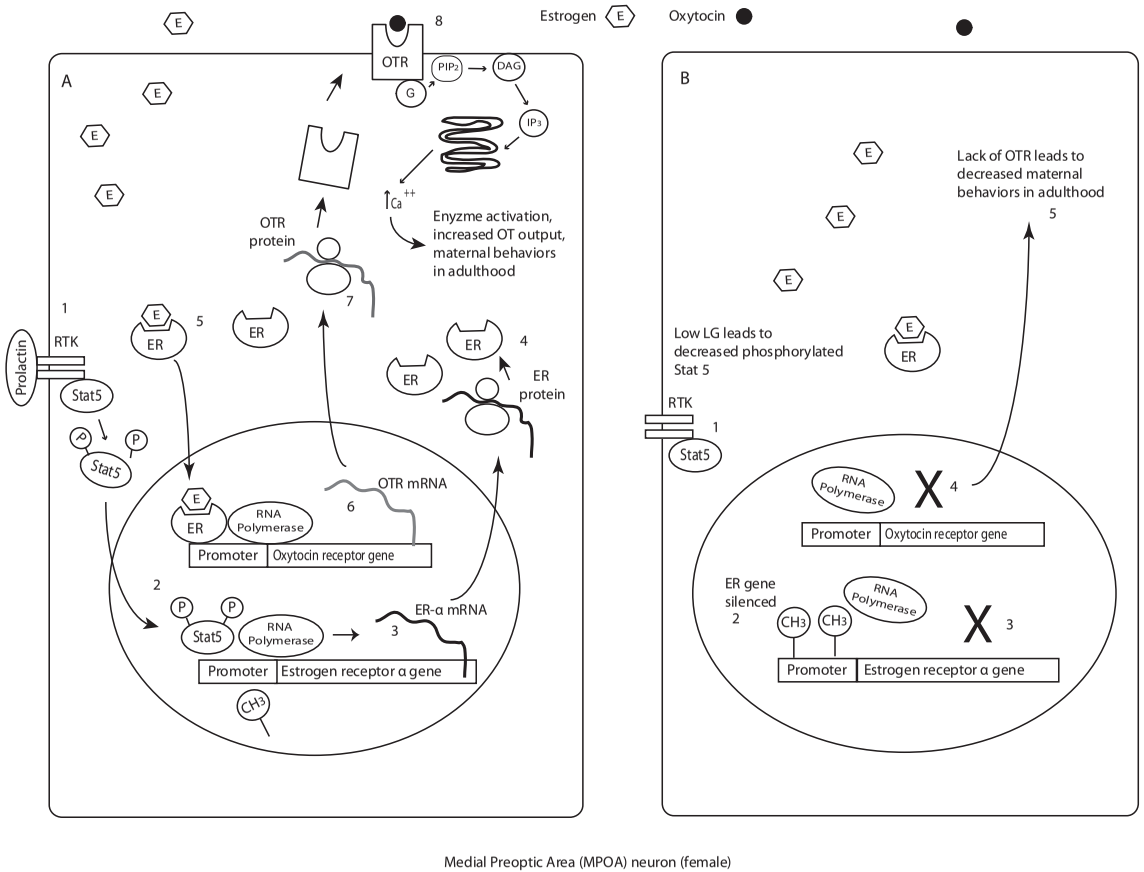


FIGURE 5.6. Epigenetic effects of maternal care on maternal behavior in offspring.

leading to lifelong changes. Thus, while epigenetics leads away from genetic determinism, it should not lead us to environmental naiveté. We should not say, "Well the environment can just erase the effect on the genes of early neglect." Rather, we should reflect on the sobering thought that our behavior affects not only our own genes but also the genes of our children. These epigenetic changes, in some cases, can be inherited themselves. Lars Bygren and his colleagues (Bygren, 2013; Bygren et al., 2014; Pembrey, Saffery, & Bygren, 2014) studied birth, death, and harvest records covering hundreds of years in a small village in Sweden. They were able to correlate death records with those of the harvests. In a good year, food would be plentiful, but in some years the crops failed and food supply was very short. Children who were between ages 9 and 12 years when food was in short supply grew up to have children who lived *longer* than the offspring of children who were well fed when they were ages 9–12. Children of less-well-fed individuals had less cardiovascular disease. This effect persisted into the grandparent's generation! What happens between ages 9 and 12 years? For boys, this is the period when sperm are developing, and many epigenetic changes influence what genes will be expressed in the next generation. This is very worrisome in view of the current childhood obesity epidemic. The larger point is that public policy may need to come to terms with the fact that early trauma may not always be easily erased, that it marks our genes and the genes of our children.

CHAPTER 6

Fear, Reward, and Action

We move about our environment to obtain or produce the things we need, principally food, clothing, shelter, and sex. We also move to avoid discomfort and danger; humans can be both prey and predator. Out of these primitive needs evolved a complex system for governing motor behavior. We have the drives of thirst, hunger, and sex, and when we satisfy these needs, we experience pleasure. If we are to avoid that which is dangerous, we must recognize it and be motivated to flee from or attack it. Thus, brain systems evolved to produce both fear and pleasure; disturbances in these systems may be related to a wide variety of mental disorders. These fear and pleasure systems are built on the circuits that produce motor behavior. Mental health clinicians may feel that the study of motor behavior is of more interest to the neurologist or physical therapist, but in this chapter, you will learn that how we *move* is tied to how we *feel*. The two are integrally related.

Suppose you wish to drink a cup of coffee while reading this chapter. The full cup sits on your desk. The frontal cortex issues a command to take a sip of the coffee. The ongoing behavior (holding the book or electronic reader) must be interrupted, and your dominant hand must grasp the cup. The brain has a generic, habitual program ("Drink from a cup") that you learned when you were around a year old and that, by the time you were in elementary school, became so refined that you could do it with one hand. Almost without thinking, your hand grasps the cup and lifts it to your mouth. Once the generic program is activated ("Grasp, lift, and drink"), the behavior must be executed according to the specific situation. On this particular day, the coffee cup is a unique shape, weight, and distance from

your hand. The brain must calculate all of these parameters "on the fly" and adjust the strength of your grip, the speed at which it comes to your mouth, and so on. How is this done?

UNDERSTANDING MOTOR BEHAVIOR

Motor behavior involves interactions of the cortex, the basal ganglia, and the cerebellum (Brodal, 2004; Nieuwenhuys, 2008a). The cortex, particularly the premotor and prefrontal areas, is involved in conceptualizing the motor acts that are to be performed. The precentral gyrus, discussed in Chapter 2, has neurons that project all the way to the spinal cord. These neurons are probably involved in fine adjustments to motor movements. Virtually every area of the cortex except the primary visual and auditory cortices projects to the caudate and putamen of the basal ganglia. The caudate receives input from multimodality association cortices. The putamen receives relatively more input from primary somatosensory areas, as well as secondary auditory and visual areas (Brodal, 2004). This division of input suggests that the caudate deals more with the cognitive information involved in initiating motor action, whereas the putamen processes information about the sensory context in which that movement occurs. Two points are key:

1. The circuitry between the cortex and the basal ganglia is involved in the *planning, initiation,* and *termination* of motor movements. This circuit is silent during the actual performance of the movement.
2. Accurate *performance* of a movement involves the circuitry between the cortex and the cerebellum.

How do the cortex and basal ganglia initiate and terminate movements (Gazzaniga, Ivry, & Mangun, 2014)? Briefly review Step 10 (Figure 2.10) in Chapter 2. In Figures 6.1–6.3, inhibitory gamma-aminobutyric acid (GABA) neurons are in gray, excitatory glutamate neurons are in black, and modulating dopamine neurons are gray or black depending on their action at different GABA neurons. Figure 6.1A shows the basal ganglia "at baseline," which means that there is ongoing motor activity and no command that the cortex has been received to change the activity. Notice that the globus pallidus interna (GPI) and the substantia nigra reticulata (SNR) are active. The GABA neurons of these structures are inhibiting the thalamus; hence, there is no information flow between the thalamus and the cortex. Once the cortex has determined that a new motor behavior is needed, the glutamate neurons of the cortex activate the GABA neurons of the striatum

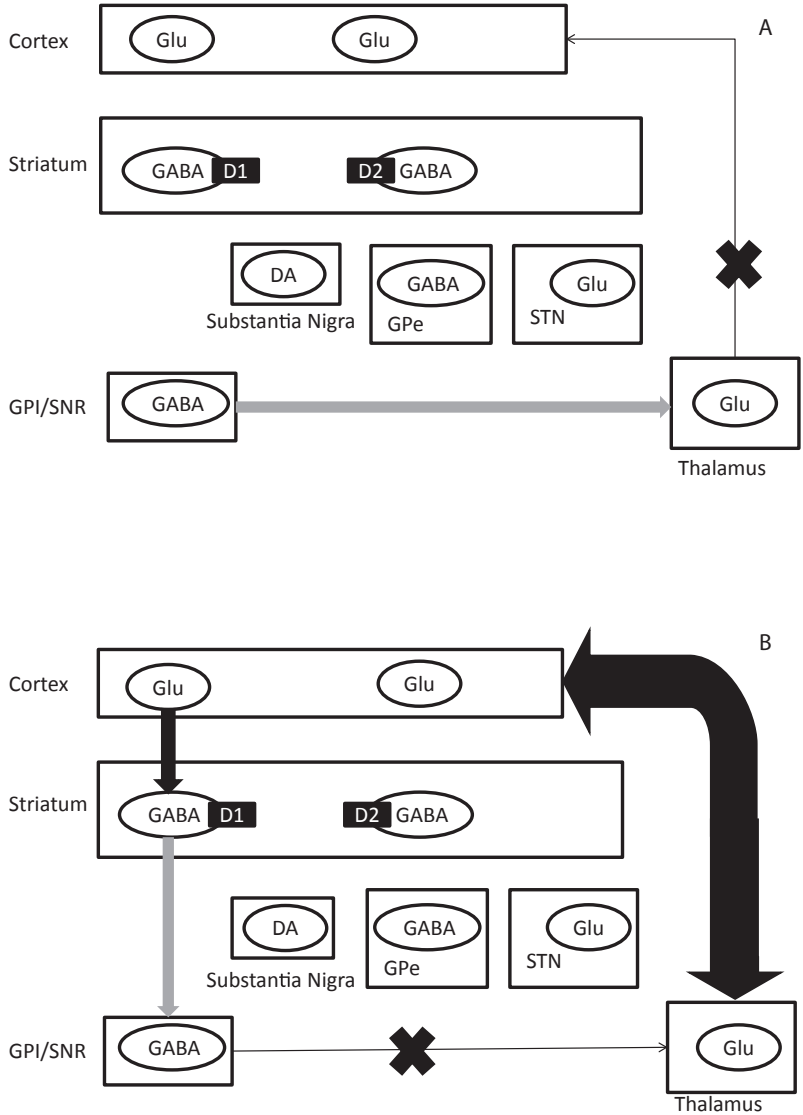


FIGURE 6.1. (A) The basal ganglia prior to initiation of new motor program. The SNR/GPI actively inhibits the thalamocortical loop. (B) The direct pathway allows activation of the thalamocortical loop and an initiation of new motor program. DA, dopamine.

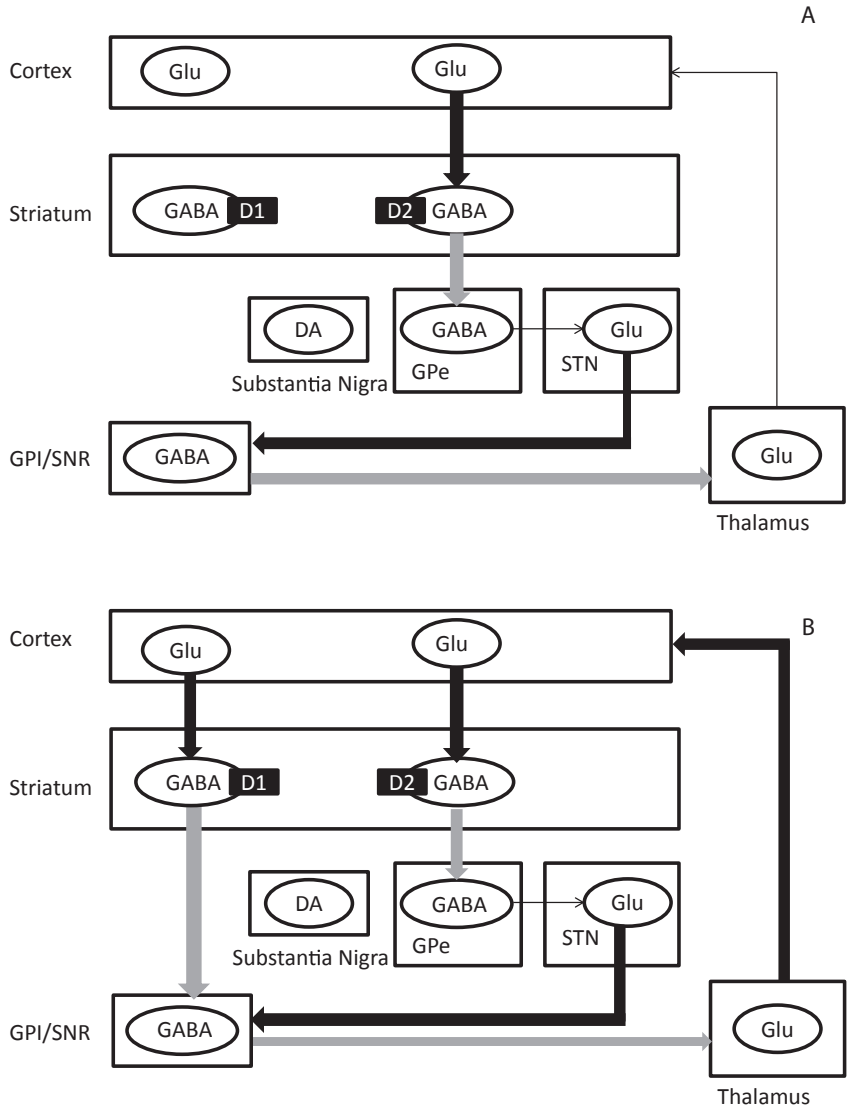


FIGURE 6.2. (A) The indirect pathway opposes the effect of the direct pathway, providing a brake on initiation of the motor program. (B) The direct and indirect pathways work together to provide smooth initiation of the motor program. DA, dopamine.

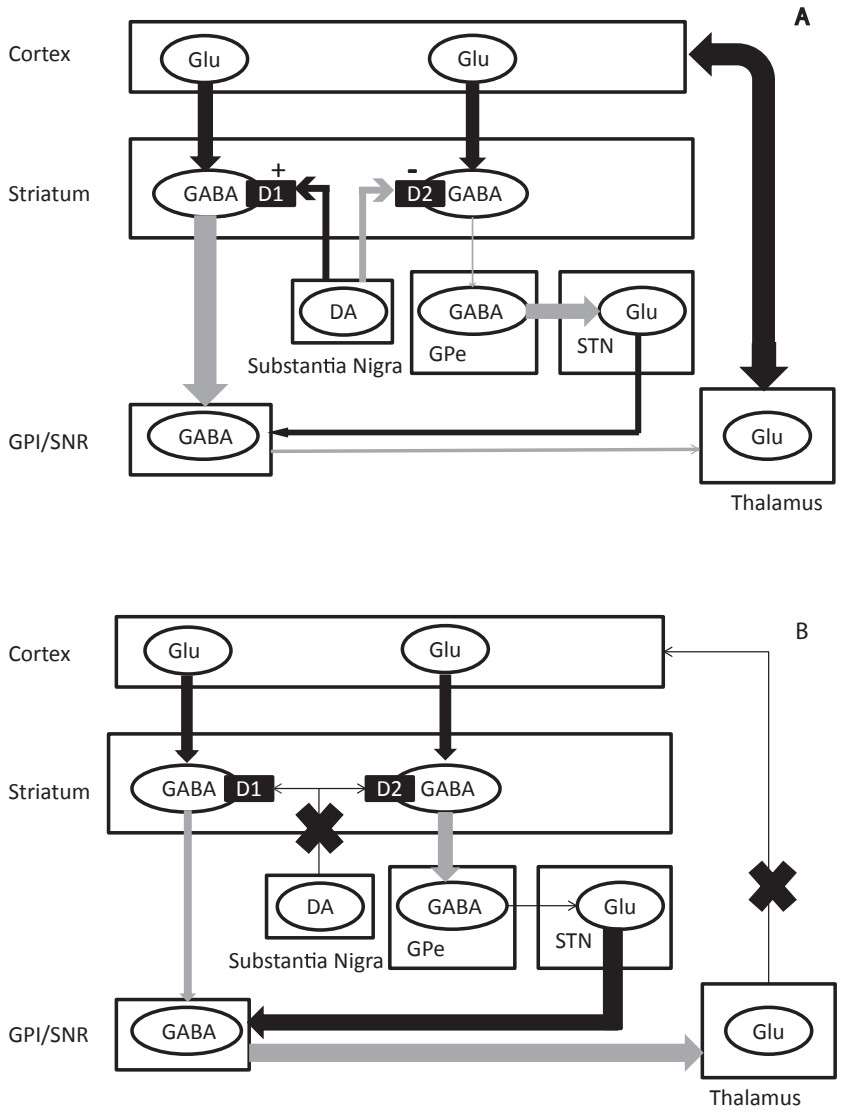


FIGURE 6.3. (A) Dopamine (DA) stimulates the direct pathway and inhibits the indirect pathway, and facilitates the initiation of movement. (B) Lack of dopamine in Parkinson's disease or when its receptors are blocked by antipsychotics leads to inability to initiate movement (bradykinesia).

(Figure 6.1B). The striatal neurons release more GABA into the GPI/SNR, inhibiting it. The thalamus is released from inhibition and the thalamic–cortical connection springs to life. The route from striatum to GPI/SNR to the thalamus is termed the "direct pathway." By itself, it would lead to an overactivation of motor activity. Figure 6.2A shows the operation of the parallel "indirect pathway." Cortical neurons project to a separate set of GABA neurons in the striatum; these striatal neurons travel to the globus pallidus externa (GPE). The striatal GABA neurons inhibit the GABA neurons in the GPE; therefore, less GABA is released into the subthalamic nucleus. The subthalamic nucleus contains glutamate neurons that project to and stimulate the GPI/SNR, the *opposite* effect of the direct pathway. Thus, the indirect pathway serves as a brake on the direct pathway. In real life, of course, the direct and indirect pathways work together, as shown in Figure 6.2B. Imagine that the direct pathway is like the gas pedal and that the indirect pathway is like a brake in a car, and you are driving with a foot on each, balancing them to speed up or slow down; this gives a sense of how the two pathways collaborate. Humans can have a stroke that specifically affects the subthalamic nucleus, disabling the indirect pathway. Such persons have a basal ganglia function more similar to that in Figure 6.1B, in which there is excessive activation of the direct pathway. Such patients develop "hemiballism"; when they try to initiate a movement, they may make wild, exaggerated movements on the side of the body opposite that with the damaged subthalamic nucleus. (This very disabling condition can be seen at *www.youtube.com/watch?v=V6cxZa6gy6g*.)

Our view of the basal ganglia is not complete, however, without assessing the critical role of dopamine in the circuit. Note in Figure 6.3A that the substantia nigra compacta (SNC) contains dopamine neurons that project and synapse on the GABA neurons of the striatum (the nigrostriatal dopamine pathway). Recall from Chapter 3 that when stimulated, the dopamine receptor (D_1) activates the adenylyl cyclase, while stimulation of D_2 receptors inhibits adenylyl cyclase. Thus, dopamine has *opposite* effects on the GABA neurons of the direct and indirect pathways:

- In the direct pathway, dopamine leads to increased firing of the GABA striatal neurons and greater inhibition of the GPI/SNR. Dopamine facilitates the direct pathway, *enhancing* initiation of movement.
- In the indirect pathway, dopamine lead to decreased firing of the GABA striatal neurons, which means greater activation the GABA neurons in the GPE. This inhibits the subthalamic nuleus, reducing glutamate excitation of the GPI/SNR. Notice that this *decreases* the braking effect of the indirect pathway, thus also enhancing initiation of movement.

The overall effect of dopamine in both pathways is to facilitate the imitation of movement. Figure 6.3B show how in Parkinson's disease (or when D_2 receptors are blocked by antipsychotic medication), dopamine cannot play this role, such that patients cannot smoothly initiate motor behavior. This leads to the "bradykinesia" (slow movement), tremor, and gait problems seen in the disorder.

THE CEREBELLUM AND CONTROL OF ONGOING BEHAVIOR

Figure 6.4 illustrates the role of the cerebellum in monitoring ongoing motor performance. The motor association areas of the frontal lobe and the sensory association areas of the parietal lobe send information about the motor movements to the cerebellum (1). This input is arranged in such a way that the body surface is mapped onto the cerebellum. Information from the visual association cortex that is involved in processing motion is particularly important. These data are first relayed to the brain stem on

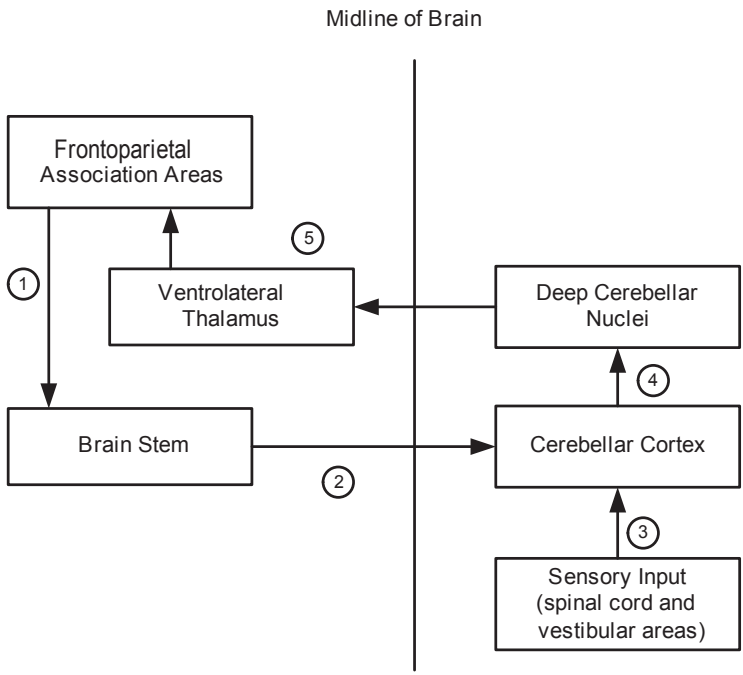


FIGURE 6.4. Cortical–cerebellar circuits monitor and adjust ongoing motor behavior.

the same side of the brain; they then cross over to the cerebellar cortex on the other side (2). The cerebellum also receives direct sensory input from the spinal cord, particularly data about the position of various body parts in space (3). The cerebellar cortex integrates information from the neocortex about the intent, context, and nature of the motor movement with the sensory data about how well the motor movement is being performed. A "corrective" signal is generated, and the deep cerebellar nuclei transfer these data back to the opposite side of the brain (4). The thalamus receives this information, and it is relayed back to the motor cortex. Here, new motor programs can be initiated to adjust the action according to environmental circumstances. Figure 6.5 illustrates how the cortex, basal ganglia, and cerebellum alternate their activity as a motor behavior progresses. The cortex conceptualizes, the basal ganglia activate the needed generic motor program for the task, and the cerebellum adjusts this program based on sensory input about the current situation and the cortex's overall plan. This sequence is repeated billions of times for every movement sequence, whether it is walking to the mailbox or performing a Rachmaninoff piano concerto.

CORTICOSTRIATAL LOOPS

There are five major circuits among the cortex, thalamus, and basal ganglia, each playing a specific role, as shown in Figure 6.6 (Alexander, DeLong, & Strick, 1986). Figures 6.1–6.3 demonstrated the function of the motor

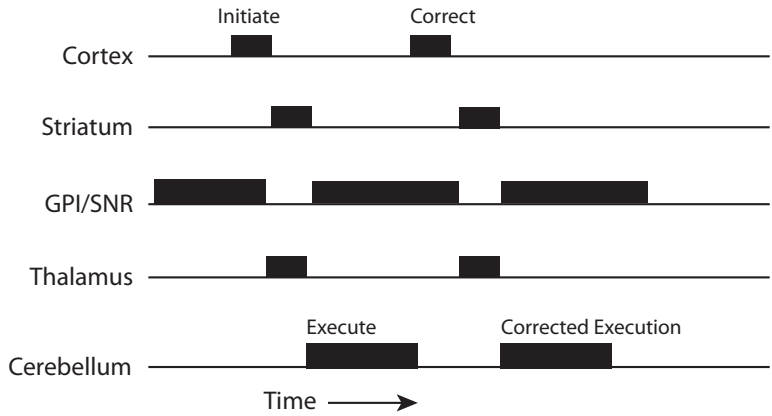


FIGURE 6.5. Changing activity of basal ganglia and cerebellar circuits as motor behavior is initiated, executed, and terminated.

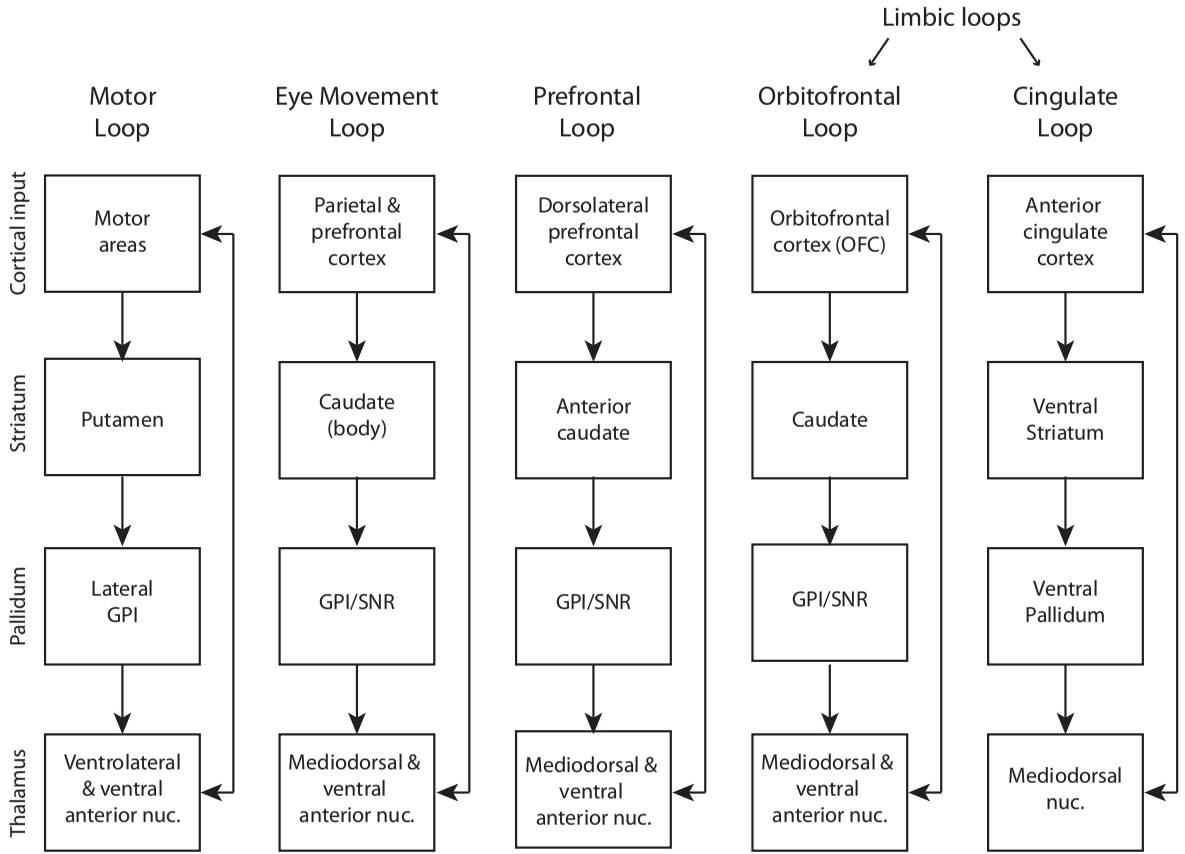


FIGURE 6.6. The five cortical–striatal loops.

loop shown on the far left in Figure 6.6. Primates depend on vision for navigating the environment, so it is perhaps not surprising that a separate loop is dedicated to eye movements. The remaining three loops are referred to as "nonmotor" loops. The prefrontal loop is involved in certain types of learning (Schroll & Hamker, 2013). These include "working memory," which is the ability to hold objects/concepts in mind and actively manipulate them. When performing such tasks, the cortex and caudate nuclei of this loop are active, even if no motor behavior is initiated. Patients with diseases of the basal ganglia, such as Parkinson's or Huntington's, invariably develop dementia, in addition to their motor problems, in the final stages of the disease. Next, the two limbic loops are considered in detail.

THE LIMBIC STRIATUM

Imagine that the motor loops are engaged in some routine motor action. Parallel to this action, the limbic loop (limbic striatum) is operating (see Figure 6.7). As with the motor loop, new behavior can be initiated with the help of dopamine inputs, but the inputs come from the ventral tegmental area (VTA) rather than the SNC. As in the motor loop, dopamine facilitates the direct pathway by increasing firing of the "nucleus accumbens," a key part of the "ventral striatum" (these terms are often used interchangeably). When the GABA neurons of the ventral striatum increase their firing, the tonic output of the ventral pallidum (analogous to the GPI/SNR) is inhibited, and the dorsomedial thalamus is released from inhibition, leading to initiation of a new motor program.

How is this different from what the motor loop does? Notice that the amygdala and the hippocampus have input to the VTA and ventral striatum. Whereas the previously described motor loop plays a role in initiating routine motor behaviors, the limbic loop plays a role in initiating actions related to the survival of the organism. The limbic striatal loop, together with the amygdala and hippocampus, helps to determine responsiveness to stimuli in the environment, particularly when the stimuli evoke fear or are related to reward. It governs responses to signals showing the presence of food when we are hungry, to signs of threat, and to sexual stimuli. It creates the drive to pursue desirable stimuli and to flee from or fight dangerous stimuli.

In the last several decades, many imaging studies have been performed in which humans are exposed to a wide variety of rewarding stimuli (Daniel & Pollmann, 2014; Schultz, 2007). These stimuli may be intrinsically rewarding, such as food, juice or sexual stimuli, or they may be stimuli that we have learned are rewarding such as money. These things, along with complex stimuli such as music or art, can activate the nucleus accumbens/

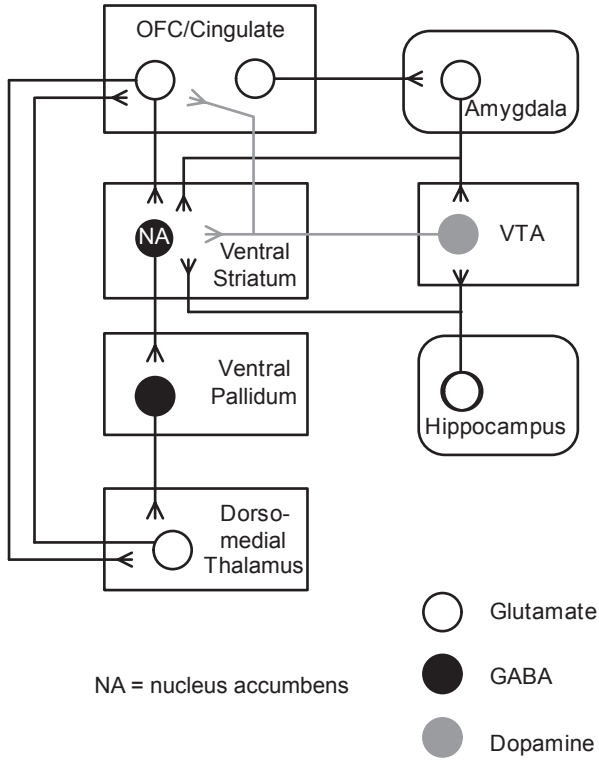


FIGURE 6.7. Detailed circuitry of the limbic–striatal loop.

ventral striatum. Recall from Chapters 2 and 4 that rodents will press a lever to stimulate the VTA to ventral striatum dopamine pathway via an implanted electrode. When humans are exposed to rewarding stimuli, dopamine release to the ventral striatum results in an increased blood flow which can be assessed on functional magnetic imaging (fMRI). See how the ventral striatum receives excitatory glutamate inputs from the anterior cingulate cortex and orbitofrontal cortex, as well as the amygdala and hippocampus (Plate 3). The increased activity in the ventral striatum during reward is clearly shown in the functional magnetic resonance imaging (fMRI) results in Plate 4. Winning money in a video game (Thut et al., 1997), looking at beautiful faces (Aharon et al., 2001) or sports cars (Erk, Spitzer, Wunderlich, Galley, & Walter, 2002), listening to music (Blood & Zatorre, 2001), and exposure to comedy (Mobbs, Greicius, Abdel-Azim, Menon, & Reiss, 2003) all activate the striatum. When an anxious subject is given a placebo and has a reduction in anxiety (placebo response),

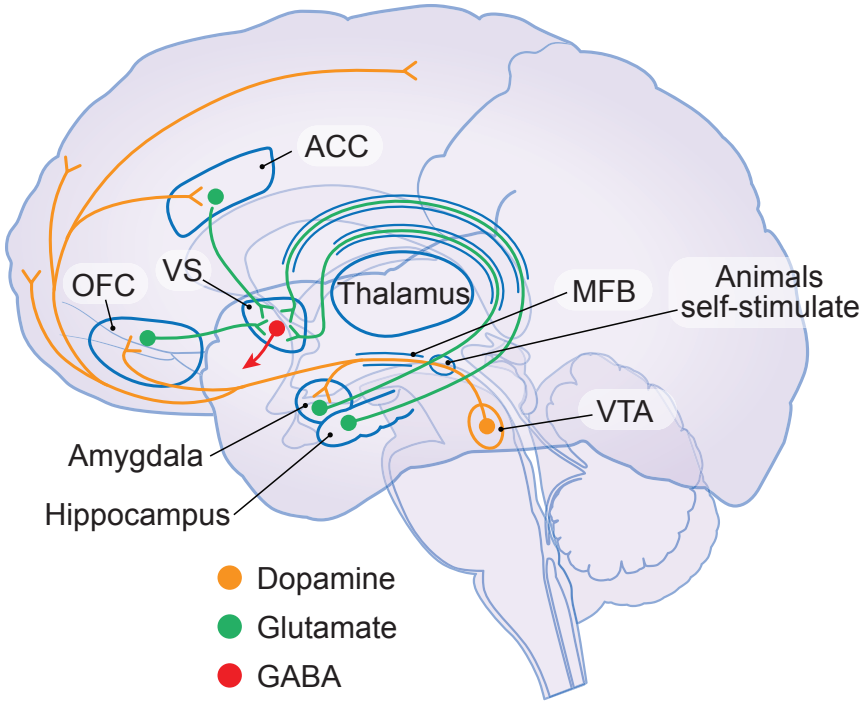


PLATE 3. Input to the ventral striatum.

the ventral striatum is also activated (Petrovic et al., 2005). The ventral striatum decreases its activity when an expected reward does *not* appear (O'Doherty, Critchley, Deichmann, & Dolan, 2003). de Quervain and colleagues (2004) demonstrated that when subjects in a game get to punish another player who has cheated or harmed them, revenge is indeed sweet because the ventral striatum is activated just as if the subject had eaten sugar. fMRI studies strongly suggest that dopamine released into the nucleus accumbens/ventral striatum induces this increase in the fMRI signal (Knutson, Adams, Fong, & Hommer, 2001; Knutson, Gibbs, Knutson, & Gibbs, 2007).

THE AMYGDALA

The amygdala is a critical structure in formulating an emotional response. Classical conditioning, by which an individual reacts with fear to a harmless stimuli that has been repeatedly paired with a noxious stimuli, does not occur if the amygdala is damaged. The role of the amygdala involves much more than fear, however. Monkeys whose amygdalae have been removed bilaterally develop Klüver–Bucy syndrome, in which they lose all sense of fear. The monkeys also become hypersexual in a strange way; male monkeys no longer can recognize when a female is receptive, and they engage in sexual behavior with inanimate objects. They lose the ability to recognize food and put inedible objects into their mouths. This phenomenon has been termed "psychic blindness," because it is not due to any sensory deficit per se; rather, the animal loses the ability to recognize the biological significance of stimuli. A similar syndrome can be seen in humans who experience damage to both amygdalae.

The function of the amygdala can be better understood by examining its complex inputs and outputs in Figure 6.8. The amygdala has inputs from three principal regions, as indicated in the boxes on the left of Figure 6.8 (Nieuwenhuys, 2008b). First, it receives information from both the olfactory bulb and structures that inform the amygdala about the physical state of the body. The hypothalamus and the nucleus tractus solitarius (NTS) report data on blood volume, sugar level in the bloodstream, concentration of the plasma, and other physical parameters. The amygdala, therefore, has information about the body's physical needs. It contains receptors for sex hormones. Second, the amygdala is regulated by dopamine, norepinephrine, and serotonin via projections from the midbrain. It has input from the limbic cortex, particularly the orbitofrontal cortex, anterior cingulate cortex, insula, and temporal lobe. The fusiform face area lies within the temporal lobe. This region recognizes facial expressions (particularly angry faces) and provides direct input to the amygdala. The oribitofrontal cortex

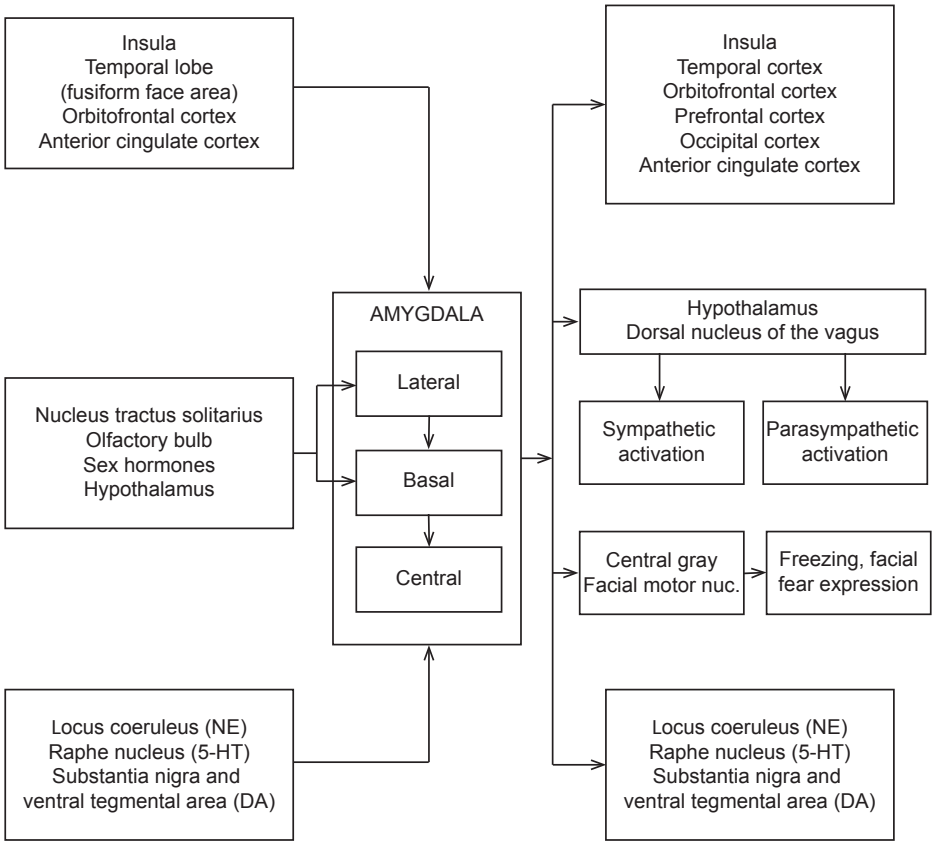


FIGURE 6.8. The connections of the amygdala.

and amygdala interact with each other; the orbitofrontal area provides a long-term representation of expected rewards, while the amygdala updates the value of these reward based on the current environment and the state of the body (Murray, 2007). The orbitofrontal cortex may inhibit the amygdala at times ("Not now!"), while the amygdala may drive the orbitofrontal cortex when rewards are rising or danger is acute ("Do it now!").

As a result of these connections, the amygdala is the place in which the perception of stimuli is matched to information about its biological significance. The temporal lobe, for instance, is important in visual perception. An assembly of neurons in the temporal lobe may recognize that an object is round, red, and has a stem on the top, but the basolateral amygdala integrates the smell of the object with memories of it being eaten, and we recognize it as an apple. Furthermore, if we are hungry and signals of

food deprivation are reaching the amygdala via the corticomedial area, the amygdala will set up a drive to eat. The motor programs needed to obtain the apple and consume it are more likely to be set in motion. The output of the amygdala is shown in Figure 6.8 as well. The central nucleus of the amygdala is the interface with various output systems. The amygdala issues commands to the hypothalamus to activate the parasympathetic or sympathetic nervous system, depending on the demands of the situation. It projects to the locus coerulus and VTA to control the release of norepinephrine and dopamine. It also can directly produce facial expression (baring the teeth, etc.) and freezing of posture. The startle reflex is greatly increased. Thus, the amygdala helps us to recognize the things we need for survival (food, sexual partners), alerts us to things that may harm us (predators), and helps provide the motivation for behaviors to gratify our needs or escape harm (flight or fight). The amygdala also sends input back to the cortex, but to a much wider range of cortical areas compared to those from which it gets input. As a result, higher-level thinking can be brought to bear on behavior triggered by more instinctual impulses.

Ono and Nishijo (2000) reviewed studies that examined activity of amygdala neurons in awake monkeys. Electrodes were inserted into these neurons, and the animals were trained to perform various tasks. Amygdala neurons fired strongly when the animals saw a preferred food (an orange) but not when they saw a more mundane food. The amygdala was active when the monkeys saw a model of a spider but not a roll of tape. The activity of amygdala neurons varied according to the need state of the animal. When the monkeys were thirsty, the sight of their water bottles elicited strong amygdaloid activity but not after the monkeys drank their fill. On the other hand, the juice bottles always elicited amygdala activity, even when the monkeys were not thirsty. The reason is most likely that the juice was so tasty that the amygdala signaled its desirability even when the animals' thirst was quenched. This is consistent with human experience. When we are full, we may ignore unappealing food, but still we may consume a favorite dish.

In an early study, Whalen and colleagues (1998) showed pictures of faces to volunteers undergoing fMRI. This study used a "backward masking" technique. Participants looked at neutral, happy, or fearful faces. The happy and fearful faces were presented so quickly (33 milliseconds [msec]) that participants were not consciously aware of the face having been presented. The emotional face was followed by a neutral face that was on the screen for 167 msec. When asked afterward, the participants had no awareness of having seen angry or happy faces, yet the right amygdala was more strongly activated by the fearful faces relative to the happy faces. Thus, the amygdala not only processes the emotional content of faces, it does so at an unconscious level. Simply seeing the expanded whites of another's

eyes (without seeing the face) also is sufficient to activate the amygdala (Whalen et al., 2004). LaBar, Gatenby, Gore, LeDoux, and Phelps (1998) performed a similar experiment in which subjects underwent an fMRI scan while they were shown two different visual stimuli. After one stimulus, they received a mild electric shock, whereas after the other stimulus, they did not. The scan measured brain activity in response to both stimuli, and the activity during the nonshock scans was subtracted from that during the shock scans to see what areas of the brain were activated by fear. The right amygdala was specifically activated by the visual cue linked to shock; interestingly, it was also linked to extinction. As the shock was omitted, the amygdala appeared to play a role in recognizing that a painful experience was no longer coming. The investigators also measured changes in skin sweating (a measure of autonomic activation and a common fear response). The amount of sweating correlated very strongly with amygdala activation.

Amygdala neurons do not process information related only to fear, however. They recognize stimuli that are pleasurable or reinforcing as well. In a review of studies measuring the activity of individual amygdala neurons in monkeys, Murray (2007) found that amygdala neurons recognized both negative and positive stimuli, and would stop firing quickly if the stimulus no longer was linked to a particular outcome (extinction).

COMPLETING THE CIRCUIT

The amygdala and hippocampus both provide input to the VTA, thus influencing dopamine released in the ventral striatum. O'Donnell and Grace (1995, 1996; Grace, 1991, 1995, 2000) have studied the relative effects of the amygdala and hippocampus inputs on the ventral striatum. Grace proposed that the hippocampus increases the ability of the organism to stay "on task," that is, to execute the behavior according to a long-term plan. The amygdala also facilitates the flow of information from cortex to ventral striatum, but in a very different fashion. The amygdala can facilitate information flow only 30–40 msec after it has been stimulated from elsewhere in the brain. Grace uses a "bear and butterflies" paradigm to describe the relative contributions of the hippocampus and amygdala to motor action. He gives an example of a man in the forest searching for butterflies. As the man walks, he scans the area for butterflies; if he sees one he wishes to add to his collection, he sweeps it up with his net. The hippocampus is critical in driving this type of "context-dependent" behavior. The man must keep in mind the type of butterfly he wants, scan intently for it, remember where he is likely to find it, and so on. The hippocampus facilitates activity in the limbic loop conducive to this behavior and increases resistance to distracting stimuli. The motor striatal loop initiates and maintains the specific

motor behaviors (looking, reaching, swinging the net, etc.). Now imagine that a bear suddenly emerges from the forest. It is not in the man's interest to ignore the bear. As the bear is perceived, the amygdala is informed and recognizes it as a predator. The amygdala activates the fear response and initiates an "affective override of current task focus"; that is, the man drops his net and runs.

To expand Grace's analogy, suppose that a bear does not appear, and that the man works hard all morning collecting his butterflies. Around noon, he becomes hungry. The amygdala begins to respond. Suddenly the man notices apples hanging from the trees to which he had not paid attention all morning. Again, the amygdala may interrupt the current task to initiate behaviors such as climbing the tree to pick an apple. VTA dopamine input to the ventral striatum has a pronounced effect on which type of influence, amygdaloid or hippocampal, predominates in this structure. The greater the dopamine input, the more the affect-laden inputs of the amygdala will take control. The study of this limbic circuit comprising amygdala, hippocampus, VTA, cortex, and ventral striatum is critical to the study of affective, impulse control, and addictive disorders.

SUMMARY

We have focused on the amygdala, the ventral striatum, and their many connections to understand their role in the processing of fear and reward. We have seen how the amygdala reacts to the facial expression of emotion. Chapters 11 and 13 on mood and autism spectrum disorders, respectively, expand on this concept, examining how the amygdala is a "hub in brain networks that support social life" (Bickart, Dickerson, & Barrett, 2014). The connections of the amygdala with multiple cortical regions underlie higher-level social behaviors.

CHAPTER 7

Attention and Memory

In Chapters 2–4, we were concerned with neurotransmitters and their pathways. In Chapter 6, we examined the circuits involved in fear, reward, and action. As we explore attention and memory, we become more concerned with the connectivity *between* brain regions. This theme continues as we explore other higher-cognitive functions. Increasingly, perturbations in these connections are thought to play a major role in mental health disorders.

ATTENTION

To *remember* something we must first *attend* to it. The psychologist William James (1890, pp. 403–404) wrote, "Everyone knows what attention is. It is the taking possession by the mind, in clear and vivid form, of one out of what seem several simultaneously possible objects or trains of thought." In English, we say "Pay attention," while the French say "Faites [make] attention," and the Spanish say "Pon [put] atención." Note that in these three languages, the words imply a cost or effort. "Paying" attention is something we can do intensely only for limited periods.

The study of attention is closely related to that of inhibition. In the example of a student taking a multiple-choice examination, she must take in all of the relevant parts of the problem as she reads the question. She must ignore the hum of the air conditioner in the room, the faint sound of students playing Frisbee outside the examination hall, and her own internal distractors (e.g., plans for a weekend party). As she scans the possible answers, the correct answer appears to crystallize at some point; she then selects and acts on a response. The student must not select too quickly

(impulsively) before considering all the responses or wait too long and run out of time (obsess). Thus, attention is divided into "top-down" and "bottom-up" components. The former searches the environment for relevant information and suppresses distractors; the latter detects the relevant target (the correct answer, in the previous example) and allows the triggering of action. The bottom-up system also detects novel events that, while not relevant to the task, may be critical for survival. If the student taking the examination smells smoke, it might be time to flee the room rather than continue with the examination.

Maurizio Corbetta and Gordon Shulman (2011; Corbetta, Patel, & Shulman, 2008) have developed an influential model suggesting how the top-down and bottom-up attention systems are mapped onto the brain. The control of attention is widely distributed throughout the brain, as shown in Figure 7.1. Imagine a simple task in which a subject must press a button when a certain stimulus, such as a letter or shape, appears on the screen. The screen contains many distractors, such that detecting the target requires an effortful search. The subject must hold the task in mind (what the target looks like and what the rule is for pressing the button). This requires use of the top-down system (open boxes in Figure 7.1), which is distributed bilaterally in the frontal eye fields (FEFs) and the intraparietal sulcus (IPS). The FEF–IPS also exerts control over the visual areas in the occipital lobe, actually making the visual cortex more sensitive to target stimuli (top-down biases in Figure 7.1). While the FEF–IPS network is bilateral, stimuli that are only in the right or left visual field more strongly activate the FEF–IPS network in the opposite hemisphere.

The bottom-up system (gray boxes in Figure 7.1) is more right lateralized, consisting of the temporoparietal junction (TPJ), ventral frontal cortex and anterior insula (VFC/AI), and medial frontal gyrus (MFG). When the target is detected, a "sensory salience" signal is sent to the TPJ. This will feed forward to the VFC/AI, triggering a response (pressing the button). If the subject presses the button in response to a distractor (failure of top-down), an error of commission is made. If the subject waits too long, then the target is missed (failure of bottom-up), and an error of omission is made. These two systems must be balanced; thus, top-down and bottom-up overlap, as shown by those regions with both gray and white boxes. The right MFG is strongly connected to both networks. The MFG receives "filtering" signals (what is relevant, what is not) from the top-down system and uses this information to allow the bottom-up system to adjust. See how MFG feeds forward to the VFC/AI and TPJ. It also sends a reorienting signal back to the top-down system in the event the bottom-up activation suggests that adjustments need to be made to its biases.

The cingulate cortex is illustrated between the two brains. Review Step 2 of the "Draw the Brain" (Chapter 2) to refresh your sense of its medial

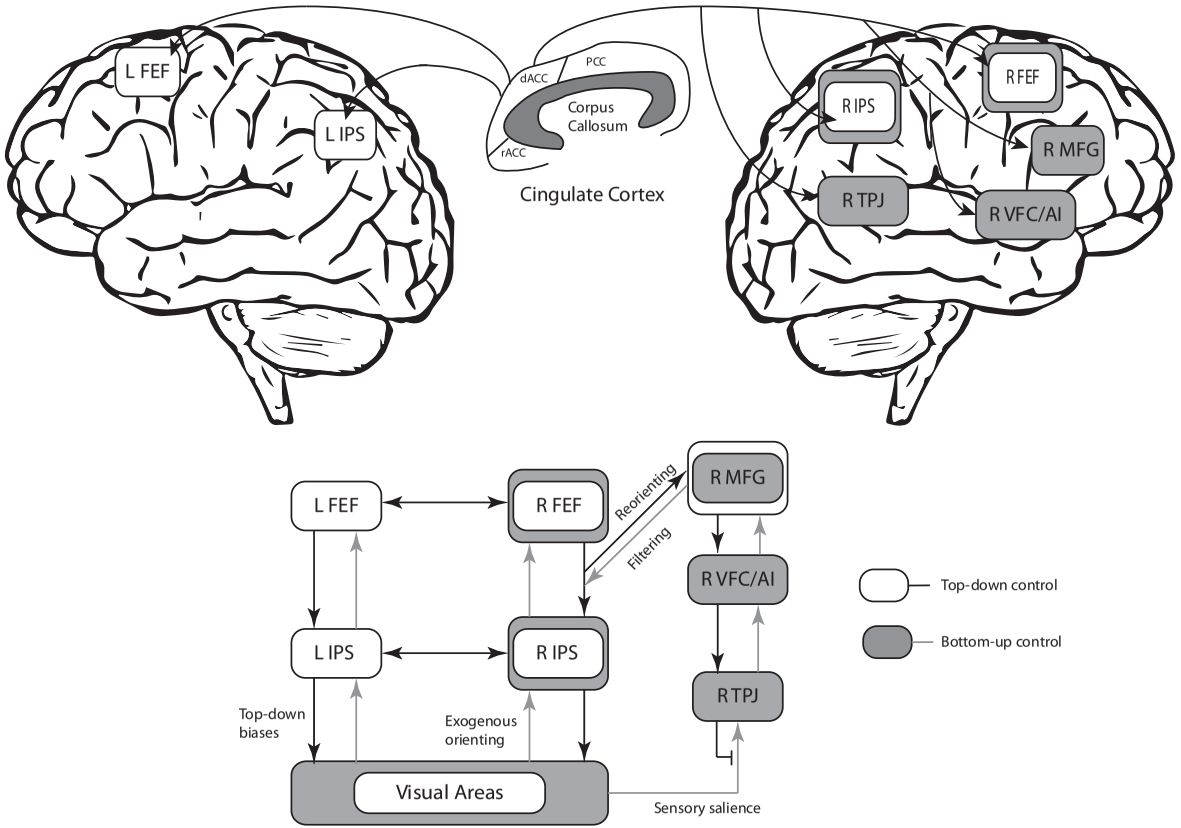


FIGURE 7.1. Model of dorsal (top-down) and ventral (bottom-up) attention. Adapted from Corbetta, Patel, and Shulman (2008) with permission from Elsevier. Copyright 2008.

location between the two hemispheres. Recall that the cingulate is part of the Papez circuit. The cingulate cortex is involved in attention, memory, emotion, reward, and pain. Here, I focus on the dorsal anterior cingulate cortex (dACC), which plays a major role in attention and cognitive control. The dACC receives input from the frontal lobe and projects back to the areas involved in both top-down and bottom-up systems (arrows in upper part of Figure 7.2). The activity of the dACC is illustrated by the Stroop task (Golden, 1990), in which a subject is shown color words printed in ink of different colors and asked to *read* the word rather than say the color of the ink. For most of the words, the ink color is congruent with the written word (e.g., the word "red" is written in red ink). On some of the trials, the ink color is incongruent (e.g., the word "green" is printed in blue ink). In this case, the subject must inhibit the natural response to say "blue," read the word, and say "green." His or her reaction time will be just a little slower on these incongruent trials. During functional magnetic resonance imaging (fMRI), the dACC is much more active during the incongruent trials relative to the congruent trials (Bush et al., 1999). This suggests that the dACC monitors for conflict and may also monitor for errors (Botvinick, Braver, Barch, Carter, & Cohen, 2001; Carter, Botvinick, & Cohen, 1999; Carter et al., 1998). When subjects commit an error on a task while undergoing fMRI, the dACC is more strongly activated relative to correct responses; strong activation of the dACC on error trials predicts better performance on subsequent trials. More broadly, the dACC monitors and detects situations in which there is a discrepancy between expected and actual outcomes. The dACC can enhance locus coeruleus activity (increasing norepinephrine levels and improving executive function; see Chapter 4) as well as give feedback to the dorsal (top-down) and ventral (bottom-up) systems regarding success or failure on the task. This entire network must be well-connected and running smoothly for optimal attention and inhibitory control.

ACTIVE ATTENTION VERSUS THE "DEFAULT MODE"

The previous circuitry operates in a conscious, active mode. We recruit it when there is a task at hand. It is mentally intensive, in that we tire after a limited deployment of the system. There is a great deal of individual variability as to the degree with which we can "pay attention." Much of the time, we do not actively engage this active attention network. We spend time daydreaming, distracted by random thoughts or events in the environment. This "default mode" is not always a waste of time, however. When an artist or inventor waits for "inspiration," or when we engage in creative, free-floating thought processes, a specific network of regions distinct from active attention is deployed. Figure 7.2 shows this default mode (Buckner,

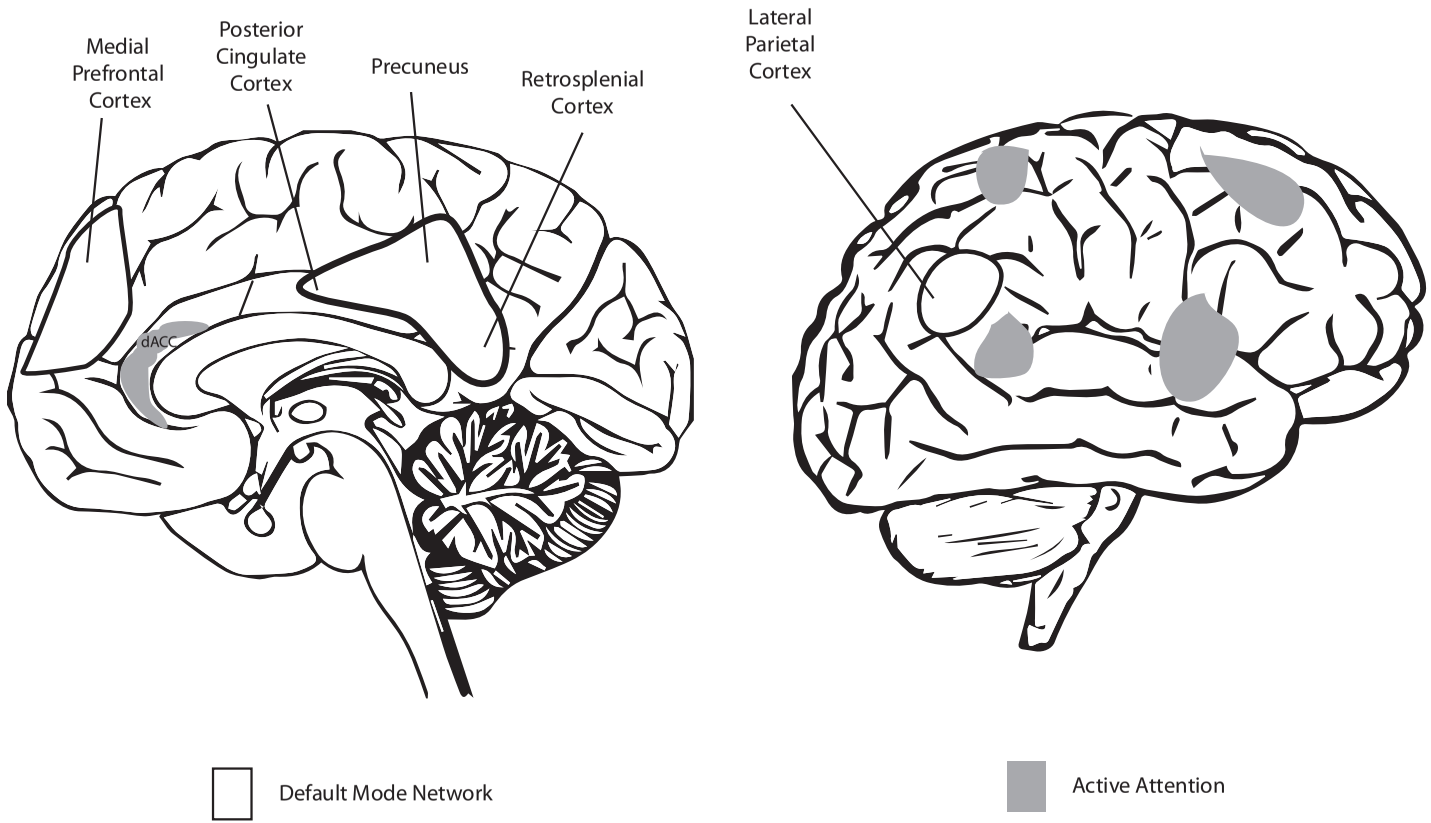


FIGURE 7.2. Active and default mode networks in the cortex.

Andrews-Hanna, & Schacter, 2008). It consists of the precuneus, posterior cingulate cortex (PCC), lateral parietal cortex, medial prefrontal cortex, and the retrosplenial cortex (RSC). (The "splenium" refers to the band of white matter [axons] crossing from one hemisphere to another.) The default mode system plays a major role in our sense of consciousness. It is active even in the absence of external stimuli (indeed, it is not even connected to sensory systems) and when we are self-reflective.

One of the striking aspects of the default mode system is that is "anti-correlated" with the active system (Castellanos et al., 2008). When the top-down and bottom-up systems are engaged in a task, the default mode system is actively inhibited. This can be seen in fMRI "resting state" studies in which subjects are simply asked to lie in the fMRI (usually with eyes open) and "not think about anything in particular." In resting state fMRI, one area of the brain is selected as a "seed"; when the seed is active, it determines which other areas either rise or fall in activity. In Figure 7.2, gray (active mode) and white (default) regions have high connectivity, which means that when one is active, the other is inhibited, and vice versa. Efficient attention requires this anti-correlation; patients with attentional problems (e.g., those with attention-deficit/hyperactivity disorder [ADHD] or dementia) often fail to suppress the default mode when performing an attention task. The default mode is also important in memory.

MEMORY

Table 7.1 lists the various forms of memory. Short-term memory is notable for its limited capacity. Working memory, part of executive function, involves the active, online mental manipulation of information; it is considered in the Chapter 8. Short-term memories are more easily transformed into long-term memories if they have some context. This is illustrated by the problem people have remembering passwords for multiple websites and electronic devices, and the need to use some meaningful link, such as a birthday, spouse name, or child's name. Years ago, I was in New York for a meeting and went out for a stroll. While walking down Fifth Avenue in Manhattan, I happened on the main branch of the New York City Public Library, with its well-known statues of lions. Almost immediately, the film *Ghostbusters* came to mind. With the memory of the film, the soundtrack, unbidden, began to run through my head. Next came thoughts of Dan Aykroyd and Bill Murray, and memories of watching *Saturday Night Live* in the late 1970s with friends from medical school, some of whom I had not seen or thought of in over a decade. This vignette illustrates the *contextual* nature of human memory. It is not organized like an encyclopedia. There is not one place in the brain in which memories, say, of fourth grade are

TABLE 7.1. Types of Memory

- *Sensory memory:* Register of events in the environment, often unconscious, for up to 10 seconds, is forgotten if not moved to short-term memory.
- *Short-term memory:* Information lasts seconds to minutes (remembering an unfamiliar phone number), has a limited capacity.
- *Working memory:* Actively holding information in memory and manipulating it (solving a word problem in your mind) is considered part of executive function.
- *Long-term memory:* Memories stored for days to years, can be lifelong.
  - *Declarative memory:* Memory for events and facts.
    - *Episodic memory:* Memories of personal experiences about one's own life (what, where, when, and with whom they occurred).
    - *Semantic memory:* Memory for facts, concepts ("What is the capital of Texas?")
  - *Nondeclarative memory:* Involuntary or unconscious long-term memory.
    - *Conditioning memory:* Reacting to a sound that has been associated with pain.
    - *Procedural memory:* Memory for a motor act (tying shoes, walking the same route to work), can be performed "without thinking about it."

stored right next to those of fifth grade. Human memory is quite different from that of the hard drive of a computer. On a computer, each piece of information is stored at a specific location on the drive; each document has an address that the computer uses to locate the file when instructed to do so. When we open a file, the computer searches the hard drive until it finds the file. The immense speed of the processing unit of the computer allows this task to be executed quickly. Neuronal transmission is far too slow to use such a method. Imagine if, whenever you had to recall your phone number, your brain had to go through all of our memories to locate the information. The brain would never finish the task in time to make a phone call. The method of storing and retrieving memories in the brain uses a completely different paradigm.

LONG-TERM POTENTIATION

Donald Hebb (1949) first proposed that neurons could learn by changing the strength of their synaptic connections. Figure 7.3 illustrates the phenomena of kindling and long-term potentiation (LTP). The upper part of the figure demonstrates kindling. If neuron A fires only sporadically, then neuron B is never sufficiently depolarized to fire. This corresponds to example 1 in the upper part of Figure 7.3. If, on the other hand, neuron

A fires a train of action potentials, then neuron B does fire (example 2). If neuron A repeatedly depolarizes neuron B, neuron B will become sensitized. Changes will occur postsynaptically in neuron B, such that it now requires only a modest input from neuron A to fire (example 3).

LTP itself is shown in the lower part of Figure 7.3. Neurons A and B both stimulate neuron C. Neuron A fires sporadically, which is insufficient to depolarize neuron C and generate an action potential (example 1 in lower part of the figure). Neuron B strongly stimulates neuron C, producing an action potential. Now, consider the situation in which the firing of A and B are temporally linked (example 2). A modest input from neuron A is always followed by a strong train of impulses from neuron B. The impulses from neuron B cause a depolarization. If this association (if A, then B) is repeated consistently enough, then neuron C learns this relationship. From this point forward, it now fires in response only to the input from A (example 3). Although LTP can occur in many places in the brain, its action in the hippocampus is what is relevant to memory (Lee, 2014; Morris, 2013).

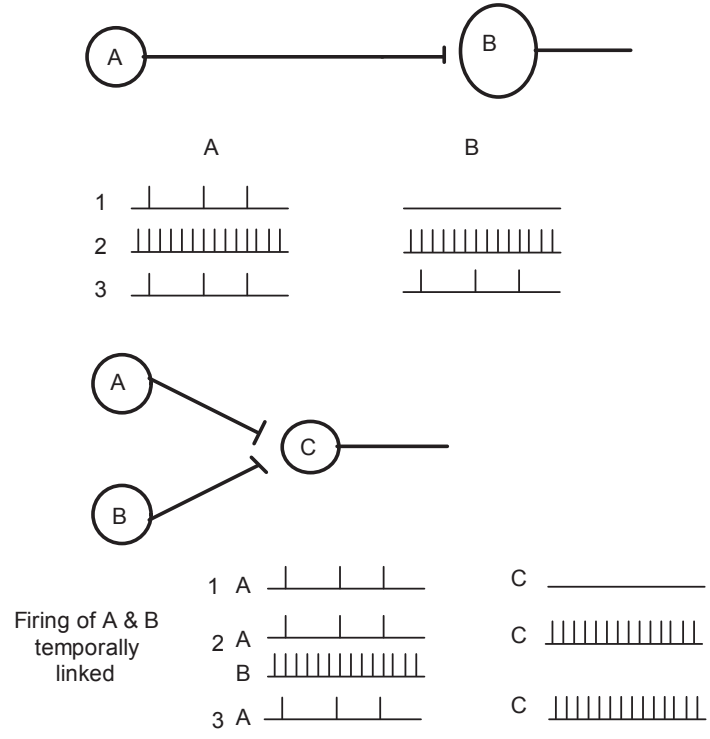


FIGURE 7.3. Neuronal activity is modified by experience.

THE HIPPOCAMPUS

Figure 7.4A shows the outward anatomy of the hippocampus (also review Step 2 in Chapter 2, "Draw the Brain"). The hippocampus receives input from the RSC (discussed as part of the default mode network), the parahippocampal cortex (PHC), the perirhinal cortex (PRC), and the entorhinal cortex. These four input regions send processed information to the hippocampus from multiple areas of the cortex (Nieuwenhuys, 2008c). In Figure 7.4B, the hippocampus has been flattened to illustrate its two sheets of neurons: the dentate gyrus and the cornu ammonis (CA). They are interdigitated like a jelly roll. Figure 7.4C shows a cross-section of Figure 7.4B, illustrating how the dentate gyrus and CA are positioned with respect to each other.

Figure 7.5 is a schematic that shows the internal circuitry of the hippocampus. Information flows from the four input areas to synapse on the neurons of the dentate gyrus. Axons from the dentate project to the CA3, one of the subdivisions of the CA, are referred to as mossy fibers due to their appearance under the microscope. Glutamate is released onto the CA3 neurons, which in turn fire and stimulate the CA1 neurons. The pathway from CA1 to CA3 is referred to as the "Schaffer collaterals." Finally, the neurons of CA3 project to the subiculum; from there, information leaves the hippocampus.

Figure 7.6 illustrates the critical concept of how the hippocampal circuit just described fits into the Papez circuit. Let's imagine a simple act of remembering. Suppose a person you don't know makes a remark of no particular consequence to you. You perceive both the person and the remarks at the time they occur. This perception is represented by the two boxes at the top of Figure 7.6. Your visual association cortex assembles the attributes of the person's face, while your auditory cortex and language processing areas decode the person's speech. If, in fact, what the person says is truly of no consequence, you soon move on, and the experience will fade from your short-term memory. Now, suppose the person says something of great relevance to you, for example, that you've just won the lottery and are a multimillionaire. You may well remember this individual for the rest of your life. What processes in the brain underlie this phenomenon?

Both the auditory (what the person said) and the visual (the person's face) inputs are transmitted to the entorhinal cortex and other input areas of the hippocampus (1). From here, the information is transferred to the dentate gyrus (2), then onto CA3 (3) and CA1 (4). Processing in CA1, involving LTP, is critical to memory information, as is more fully described in Figure 7.7. After processing in CA1, information moves on to the subiculum (5), from which it is sent in diverse directions. Note that from the subiculum, the hippocampus can influence the output of the ventral tegmental area

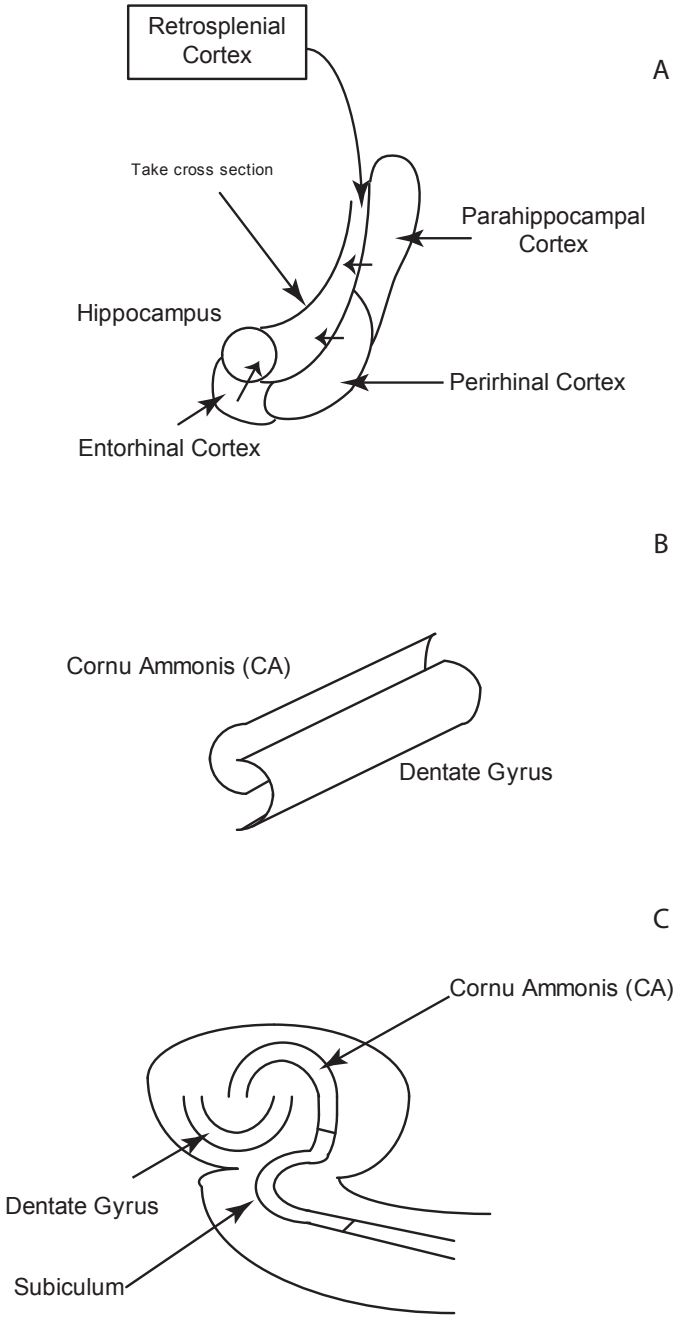


FIGURE 7.4. The inputs and anatomy of the hippocampus.

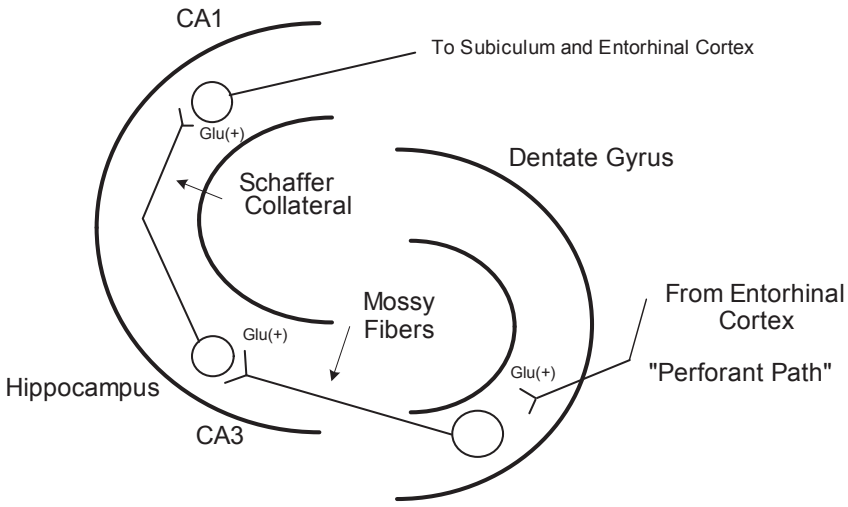


FIGURE 7.5. The circuitry of the hippocampus.

(VTA) and locus coeruleus, adjusting dopaminergic and noradrenergic tone, respectively. The hippocampus is connected to the hypothalamus, which in turn governs the output of the autonomic nervous system (ANS; emotional reaction). The inset in Figure 7.6 is enlarged in Figure 7.7.

Figure 7.7A shows a dendrite of a CA3 neuron. Note that it is receiving input from neurons carrying information about the person's face and what the person is saying. Figure 7.7A represents the situation in which what is said is of no consequence. Neuronal firing is at a low level, releasing some glutamate onto the CA3. This glutamate binds to alpha-amino-3-hydroxy-5-methylisoxazole-4-proprionic acid (AMPA)/kainate receptors, but not enough to depolarize the neuron. Recall from Chapter 4 that if the neuron does not become depolarized, magnesium continues to block the calcium channel associated with the *N*-methyl-D-aspartate (NMDA) receptor. Thus, even if glutamate managed to stimulate an NMDA receptor, the magnesium block would prevent any calcium from passing through the channel.

Figure 7.7B represents the situation is which you have just been awarded several million dollars. Such an announcement would be highly arousing; the neurons carrying the auditory information would be firing vigorously, releasing large amounts of glutamate onto the CA3 neuron. The AMPA/kainate receptors are stimulated, and their Na/K channels open, depolarizing the neuron. This depolarization removes the magnesium blockade. Now, the rather modest release of glutamate induced by

the visual (facial) input binds to NMDA receptors and opens the channel. The main event of LTP begins. Calcium flows into the neuron, activating a number of enzymes. These include calmodulin, which in turn activates calmodulin kinase II (CaMKII). The influx of calcium also activates various protein kinases, which phosphorylate and therefore activates a number of cellular proteins.

Figure 7.7C shows how the influx of calcium activates nitric oxide synthase (NOS). NOS produces the gas nitric oxide (NO). NO becomes

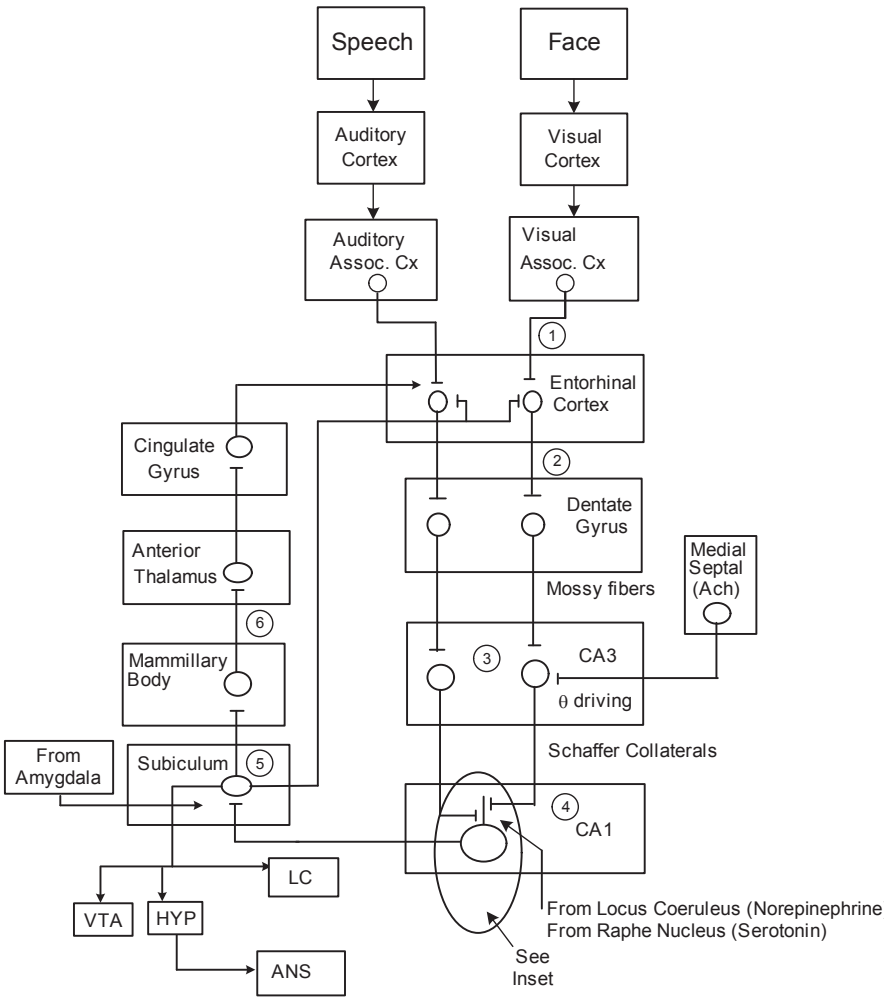


FIGURE 7.6. The role of the Papez circuit in memory.

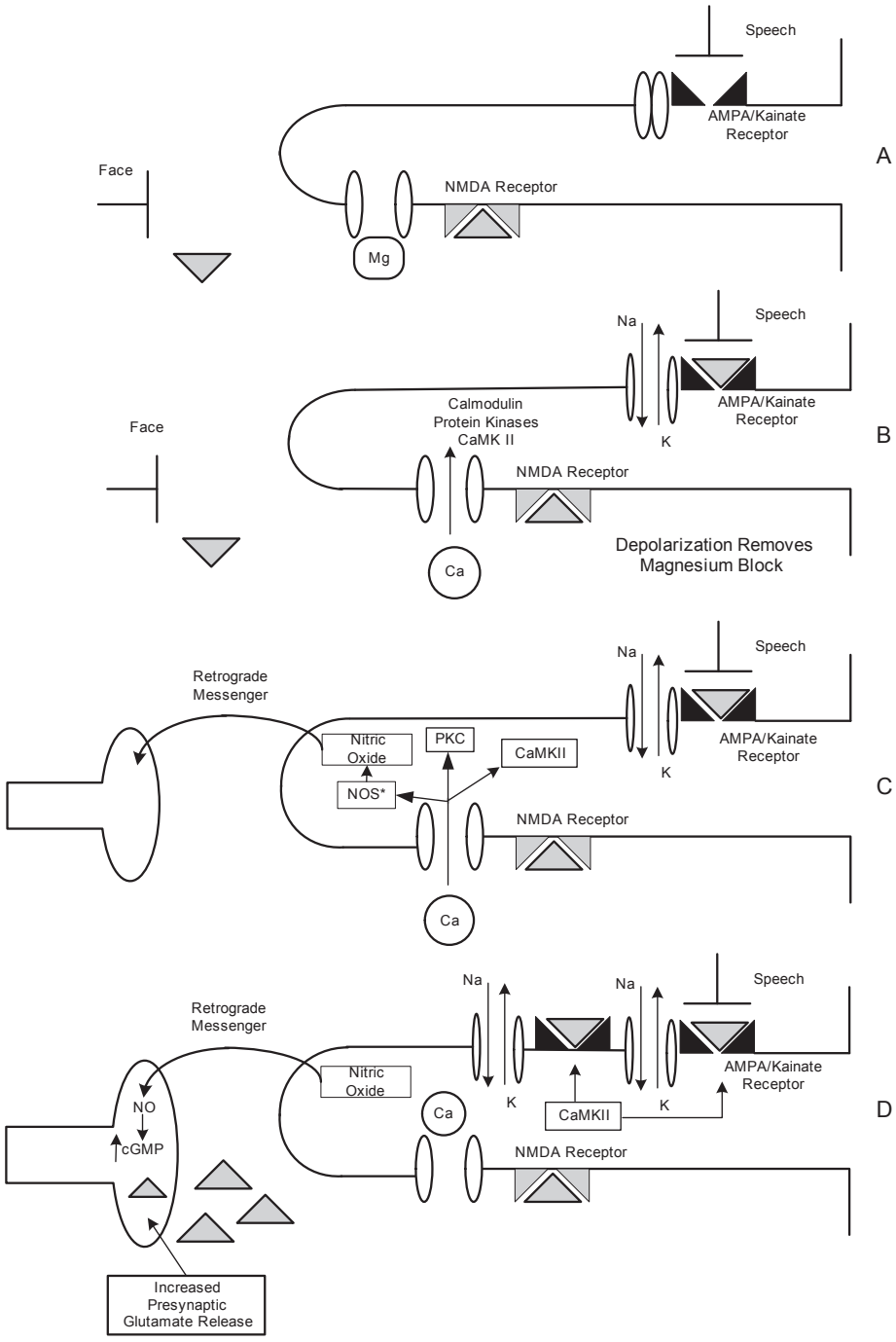


FIGURE 7.7. The mechanism of long-term potentiation.

a retrograde messenger; it diffuses back to the presynaptic neuron. The final stage of LTP is shown in Figure 7.7D. When NO enters the presynaptic neuron, it stimulates enzymes that increase the production of cyclic guanylyl monophosphate (cGMP). cGMP, in turn, stimulates enzymes that ultimately cause increased presynaptic release of glutamate. CaMKII activates processes that increase the number of postsynaptic AMPA/kainate receptors, enhancing postsynaptic sensitivity.

Now, any reminder of the person's face will trigger an increased release of glutamate presynaptically. The postsynaptic membrane has been made more sensitive, so that any appearance (or thought) of the person's face will trigger the same perceptions as the announcement that you just won a million dollars. The hippocampus has paired the association of the major event (winning a million dollars) with the appearance of the person who announced it to you. A critical point here is that the hippocampus stores not store the memory of winning a million dollars or the appearance of your benefactor, but accesses the *association* between the two.

Now, return to Figure 7.6. Suppose, many years later, you are walking through an airport and you notice the face of the person who announced that you had become a millionaire. When you see this person, the visual input enters the hippocampal circuits. Because the CA3 connections have been strengthened as described, CA3 neurons fire more easily. This information moves on to the subiculum and then into the Papez circuit (6). The information moves through the mammillary bodies and the anterior thalamus, on to the cingulate gyrus, and back to the entorhinal cortex. What is happening here? The information about the current state of the world (seeing the face in an airport) is being shunted quickly through the cingulate gyrus, which can access past memories (particularly those that carry heavy emotional baggage). Quickly the association is recognized: This is the person who told you that you were a millionaire, and all the happiness of that moment is also triggered. Because the subiculum has access to the locus coeruleus, the VTA, and the ANS, an emotional reaction is triggered. You again feel elated; you rush up to the person and tell him or her how happy you are to see him or her.

Some things we remember for only a few hours, whereas other memories last a lifetime. The effect of LTP, mediated through the NMDA receptors, lasts only hours to weeks. Other processes are important in maintaining a memory for months or years. Returning to Figure 7.6 momentarily, notice that acetylcholine neurons from the septal nucleus project to the hippocampus. The cholinergic neurons help set a particular firing rate of the hippocampus neurons, referred to as the "theta rhythm." Winson (1990) found that theta rhythm appears at different times in different species of animals. In the cat, it occurs during hunting; in the rabbit, it arises during

apprehension (freezing); and in the rat, it is seen during active exploration. The consistent feature of theta rhythm is that it appears when the animal is engaged in specific behaviors that are critical to survival. During such times, LTP is much more easily induced in the hippocampus at each peak of the theta rhythm (Pavlides, Greenstein, Grudman, & Winson, 1988).

Figure 7.8 shows that to maintain LTP over the long term, other factors involving the nucleus must be brought into play. Processes inducing LTP via the NMDA receptor are again shown in the dendrite. Notice the norepinephrine and serotonin receptors at the top of the neuron; this noradrenergic input comes from the locus coeruleus, whereas the serotonergic input is from the raphe. When norepinephrine stimulates the $alpha_1$ receptor, G proteins are activated, which lead to the production of cyclic adenosine monophosphate (cAMP), which in turn stimulates protein kinase A (PKA). The serotonin $5\text{-}HT_{1A}$ receptors on the hippocampus also activate PKA; CaMKII, which was activated in the induction phase of LTP, can further stimulate PKA. PKA will phosphorylate the K channels, which, as you recall from Chapter 2, will decrease the outflow of K during the hyperpolarization stage. This will make the neuron less refractory to firing again. The more often the neuron is depolarized, the longer the magnesium block of the NMDA receptor calcium channel remains relieved. This means a greater influx of calcium and even more LTP. PKA also can translocate to the nucleus, and this is where the processes most critical to LTP maintenance are involved. PKA activates the cAMP-responsive binding element (CRE) CREB protein. In Figure 7.8, two types of CREB are shown. CREB-1 binds to the CRE and enhances the transcription of DNA into messenger RNA. Messenger RNA then guides the expression of multiple proteins, leading to neuronal growth, the sprouting of new dendrites, and strengthening of the synapses. These processes lead to physical changes in the neuron that hardwire the association between events into the brain. In addition to norepinephrine, other factors can affect the maintenance of LTP. CREB-2 actually inhibits the development of the processes previously described. PKA will inhibit the binding (via the microtubule-associated protein [MAP] kinases) of CREB-2 to CRE, enhancing the effects of CREB-1. These MAP kinases also are influenced by the growth factors, such as brain-derived neurotropic factor (BDNF), which activate them via the tyrosine kinase receptor system. Finally, cortisol, released in response to stress, binds to its receptor in the cytoplasm; it enters the nucleus and influences DNA transcription as well.

The locus coeruleus activates in response to new stimuli. Stress influences the release of cortisol and growth factors, so it is easy to see how stress has an effect on memory. Painful and stressful events are particularly well remembered. Many people still can recall exactly where they were

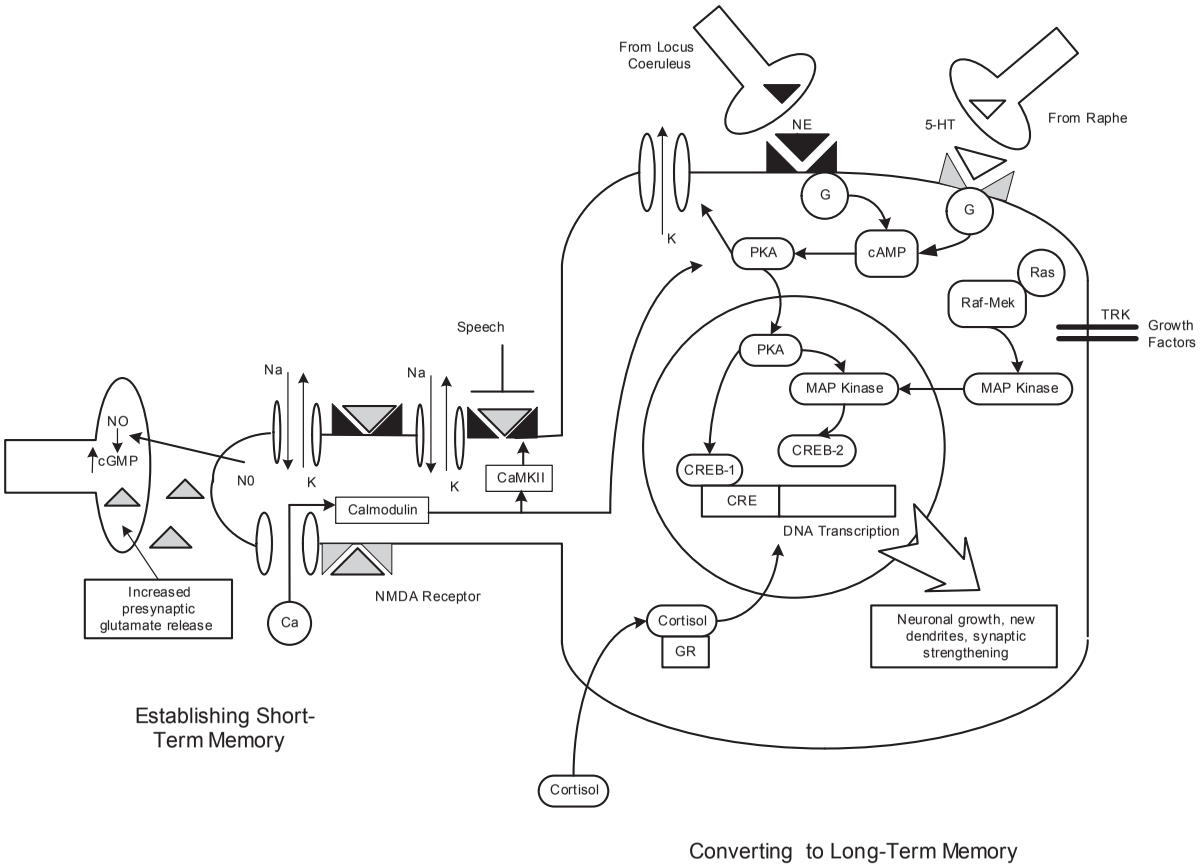


FIGURE 7.8. Maintenance of long-term potentiation.

when they heard that President John F. Kennedy had been killed on November 22, 1963, or where they were on September 11, 2001. In posttraumatic stress disorder, patients suffer from intrusive and unwanted memories of the traumatic event; it is possible that the high levels of arousal at the time of these painful events cause abnormalities in memory. Continuous activation of this hippocampal circuitry may be injurious to the brain tissue itself, as shown in the chapter on anxiety and depression (Chapter 11).

MEMORY NETWORKS

In the previous discussion, we saw how the hippocampus (via LTP) can associate two events. To understand memory fully, the hippocampus and Papez circuit must be placed within larger brain networks. The hippocampal circuit receives highly complex stimuli from the cortex, then transmits the processed information back to other cortical circuits. Ranganath and Ritchey (2012) examined the role of areas of the cortex around the hippocampus and proposed that there are two distinct memory systems: the anterior temporal (AT) and posterior medial (PM) systems. Each interacts with the hippocampal circuit just reviewed. Returning briefly to Figure 7.4, we now focus on three cortical areas with strong connections to the hippocampus: the PRC, the PHC, and the RSC. Figure 7.9 summarizes Ranganath and Ritchey's model.

The PRC is part of the AT memory system and connects not only to the hippocampus but also to the ventral tip of the temporal lobe, the orbitofrontal cortex, and amygdala. The AT system is concerned primarily with recognizing objects as familiar, as well as attaching emotional significance to them through its connections with the amygdala. (Recall the role of the amygdala in recognizing the biological significance of stimuli and fear learning.) This system is concerned with knowledge (semantics). It underlies remembering what things are, who someone is, and the significance of all these entities. Note that the memory described here is static, remembering something at a point in time. The experience of my trip to New York (described earlier) is much more than this; memory flows from one thing to another and from one point in time to another. This is the function of the PM memory system.

The PHC and RSC are both part of the PM memory system. These two areas are connected not only to the hippocampus but also to the default mode network: the precuneus, the posterior cingulate cortex, and the ventral prefrontal cortex. The default mode network is activated not only during a relaxed mental state but also during recall of an episodic memory. The PHC–RSC, hippocampal circuit, and default mode work together to put objects, people, and time in a larger context. Ranganath and Ritchey

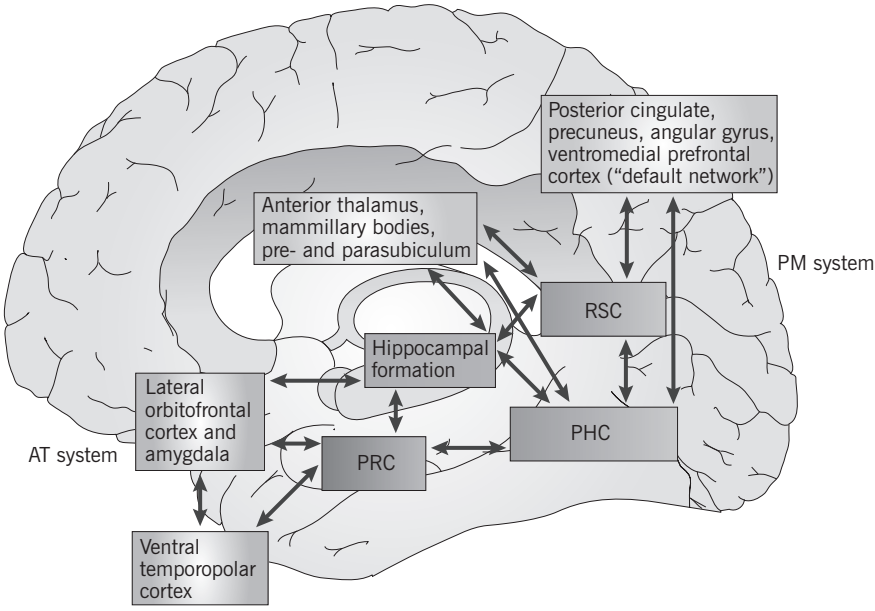


FIGURE 7.9. Two neural systems for memory-guided behavior. Reprinted from Ranganath and Ritchey (2012) with permission from Macmillan Publishers Ltd. Copyright 2012.

(2012) provide an example of how the two memory systems work together (Figure 7.10). Manoj is walking down the street, meets his friend Maria, and they go to a local coffee shop. The AT system allows recall of isolated concepts (Maria, beverage, coffee shop), as well as their significance (tastes good, friend). The PM system matches these cues to the larger context in space and time as described in Figure 7.10. Perhaps now it is clear why brain injury never destroys a discrete memory (e.g., of one's fourth grade teacher), leaving everything else intact. Like the Internet, memory is distributed across the AT and PM systems in networks.

SLEEP AND MEMORY

Dreams have long held significance for humans. In ancient times, dreams were thought to predict the future. For Freud, they were the "royal road to the unconscious," and psychotherapy relies heavily on dream interpretation. In spite of this, we do not fully understand why we sleep or dream. All mammals sleep, and it seems quite odd to spend one-third of one's life

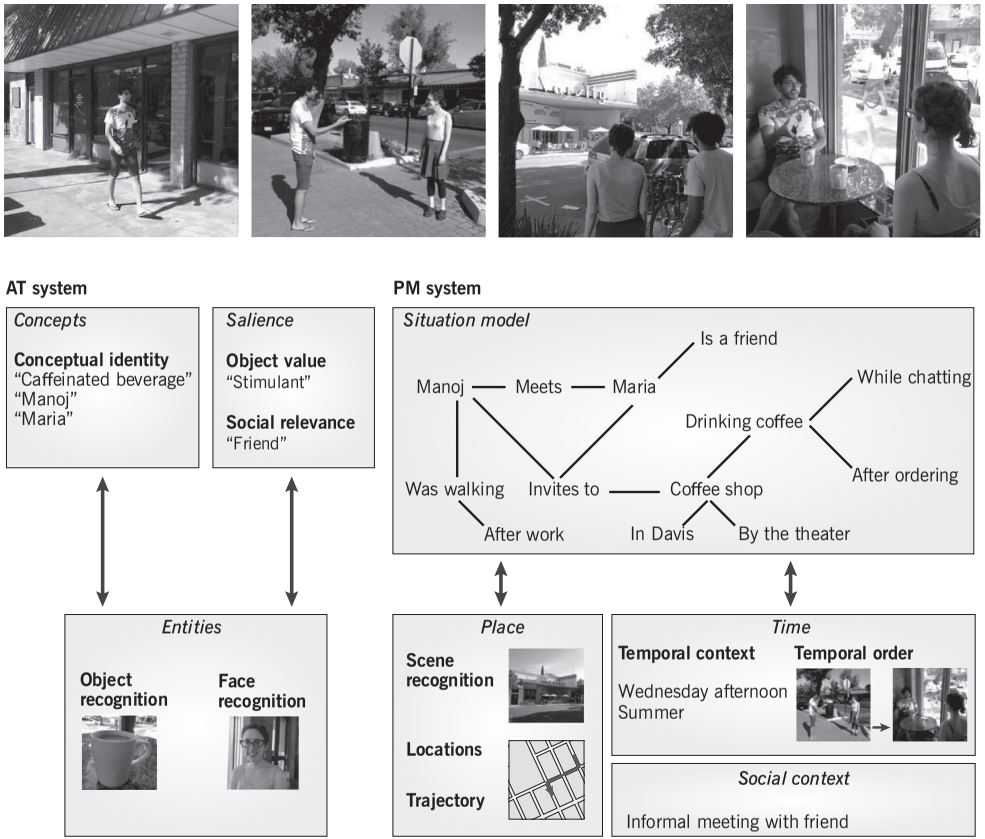


FIGURE 7.10. Different roles of the anterior temporal and posterior medial memory systems. Reprinted from Ranganath and Ritchey (2012) with permission from Macmillan Publishers Ltd. Copyright 2012.

unconscious and vulnerable to predators. Yet sleep is as great a necessity as food and water. Dolphins sleep one cerebral hemisphere at a time, so that they can continue swimming. Humans cannot go for more than 96 hours without sleep, or severe delirium and psychosis will set in.

Sleep has a very predictable pattern, as shown in Figure 7.11. It is divided into slow-wave sleep (SWS) and rapid-eye-movement (REM) sleep. SWS has four stages, each progressively deeper, with the deepest sleep occurring in the early part of the night. If awakened during SWS, people are groggy and disoriented, rarely report dreams, and fall back asleep quickly. During SWS, cortical and brain stem neuronal activity fall by 50%, as does cerebral blood flow. Cholinergic inputs to the cortex are reduced while noradrenergic activity remains at an intermediate level; cortisol levels in the hippocampus fall. Electroencephalographic (EEG) waves from the cortex become slow and synchronous as the cortical neurons drive the firing of hippocampal and thalamic neurons.

About 90 minutes into sleep, the first episode of REM sleep occurs. Cholinergic neurons become active, stimulating the visual cortex and limbic areas of the brain. Firing of the locus coeruleus decreases. The EEG during REM reveals ponto-geniculo-occipital (PGO) waves, the result of neurons from the brain stem stimulating the geniculate nuclei (a visual relay station that normally carries information from the retinas). The geniculate nuclei in turn stimulate the visual cortex, producing images. The eyes move in response to these images; hence the term "rapid eye movement." A person who is awakened during this period will invariably report a dream. After about 10 minutes, the first REM period ends, and there is a return

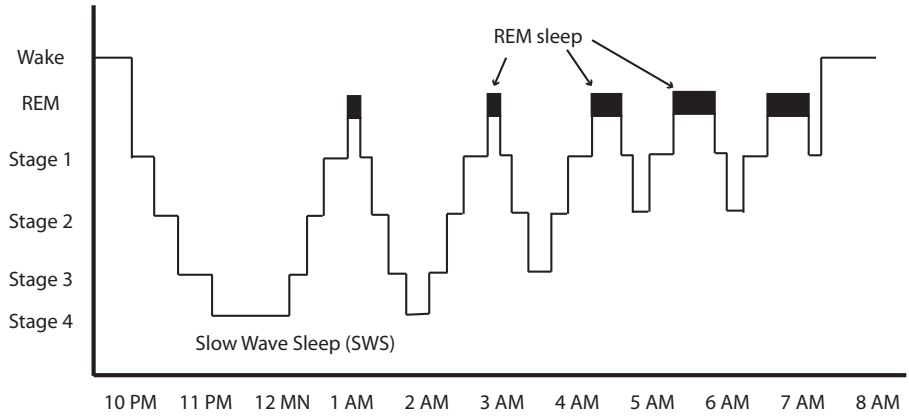


FIGURE 7.11. The structure of sleep.

to Stage 1 SWS; the person does not descend to the lower levels. People run through two to five cycles of sleep in this manner, but with each cycle, people do not descend into the deeper stages of SWS.

The alteration of SWS and REM sleep is key to the memory function of sleep (Diekelmann & Born, 2010). Throughout the day, the hippocampal circuit is rapidly encoding a great deal of information into memory; most of this is unlikely to be of value for the long term. There is a second, slower process that *consolidates* specific long-term memory into cortical regions (Frankland & Bontempi, 2005). During SWS, it appears that memories in the hippocampal circuit are replayed, and those destined for long-term memory are written into the patterns of neuronal synapse in the neocortex. This process of replaying takes place in the unconscious state; otherwise the brain would hallucinate. A rat can have electrodes placed in its hippocampus that record neuronal firing as the rat learns a maze. When the rat sleeps, the same sequence of hippocampal neuron firing is repeated, albeit in a compressed form (*http://web.mit.edu/org/w/wilsonlab/index.html*). After a sequence of SWS, the brain shifts to REM sleep. The hippocampal circuit is disconnected from the cortex, and the new synapses produced in SWS undergo synaptic strengthening or system consolidation. The brain is "backing up" the information remembered during the day for the long term, while "deleting" those files that have been deemed insignificant.

SUMMARY

The entire memory system is summarized in Figure 7.12. We began with the information about the external world entering the hippocampus through the input regions around it (1). LTP within this internal circuit is key to forming connections between events. This processed information travels through the Papez circuit to interact with the cingulate gyrus (2). Connections between the amygdala, orbitofrontal cortex, ventropolar temporal lobe, and PRC form the AT memory system. This system mediates the determination of "who, what, and why do I care?" (3). The hippocampal circuit next interacts with the PM memory system, which places these entities in their context in our internal representation of the world (4). Finally, sleep consolidates our memories. SWS replays our experiences, shifting information from temporary storage in the hippocampal circuits to the cortex (5), while REM sleep facilitates synaptic strengthening and pruning to make a long-term memory (6).

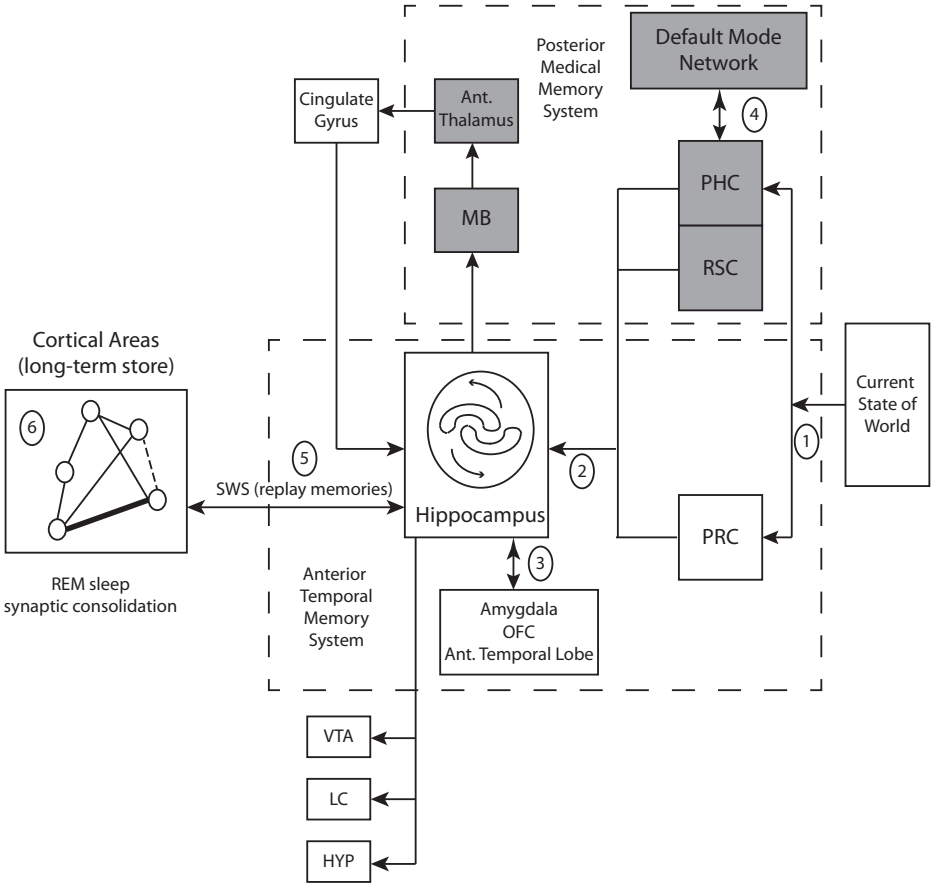


FIGURE 7.12. Integrating neuronal networks involved in memory.

CHAPTER 8

Higher Cognitive Functioning

In a sense, this chapter covers over a century of work on the understanding of how higher cognitive functions, such as language and executive function, are localized in the brain. In the late 19th century, neurologists such as Paul Broca, Carl Wernicke, and Jean-Marie Charcot studied patients with lesions in particular areas of the brain and were able to ascribe specific functions to a given area. This led to the well-established process of "localizing" lesions in the brain based on neurological examination functions or symptom presentation. These principles are still valid over 100 years later. The first part of this chapter reviews these principles, particularly in the area of language and visual–spatial skills. The previous chapter on memory and attention showed, however, that many complex functions are carried out by widely distributed networks in the brain. Today, neuroscientists are no longer dependent on looking at brain lesions at autopsy and instead can look at the connectivity of multiple regions of the brain. This approach gives us a new view of how the brain manages its complex array of functions.

In Figures 8.1 and 8.2, we return to Chapter 2, "Draw the Brain." The upper panel of Figure 8.1 is a sketch of the lateral side of the brain with the landmarks described in Chapter 2. In the lower panel, we sketch in key areas involved in cortical function. Let's start in the temporal lobe by drawing a line just below and parallel to the lateral fissure. This is the superior temporal gyrus. Now draw two more gyri (middle and inferior temporal) just below it. Next, draw two semicircles at the end of the lateral fissure and the superior temporal gyrus; these define the supramarginal and angular gyri. These areas are involved in auditory perception and language comprehension. In the inferior part of the frontal lobe, just anterior to the

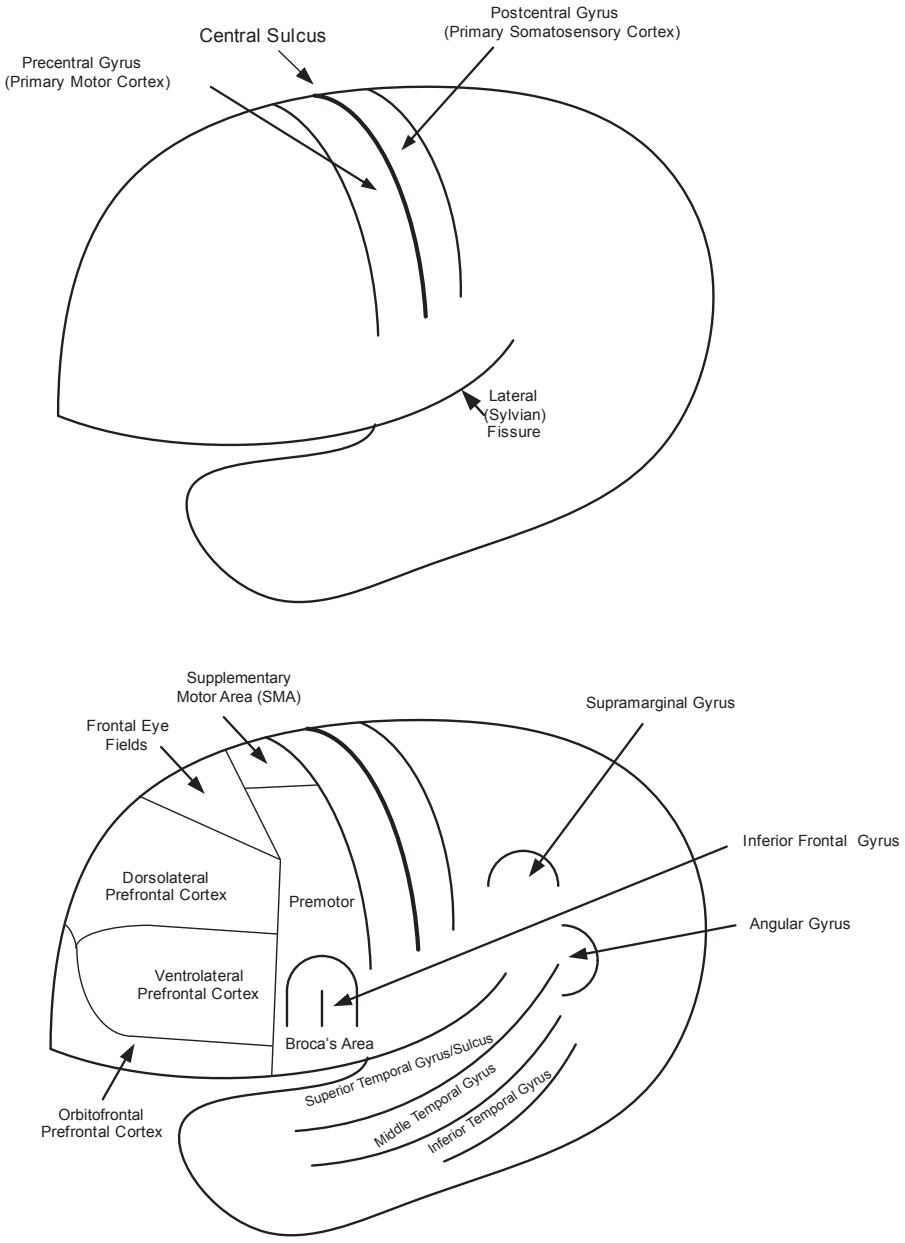


FIGURE 8.1. Overview of the cortex.

primary motor area, draw an upside-down U with a line down the middle. This is the inferior frontal gyrus (IFG). The area on the right side of the brain is part of the ventral (bottom-up) attention system. On the left side, the IFG contains Broca's area, a region critical for speech production and understanding grammar. Next, we subdivide the frontal lobe. Just anterior to the precentral gyrus are the supplemental motor area (SMA) and premotor cortex. These areas become active just before any type of motor movement; they also are activated during positron emission tomography (PET) studies if a participant simply imagines a motor act without actually moving a muscle. Anterior to the SMA are the frontal eye fields, which govern eye movements and are part of the dorsal (top-down) attention system. The prefrontal cortex encompasses the largest part of the frontal lobe. On the lateral view, we can see two major subdivisions of this region: the dorsolateral prefrontal cortex (DLPFC) and ventrolateral prefrontal cortex (VLPFC). Whereas the DLPFC is concerned with higher cognitive functions, the VLPFC is involved in motor inhibition. The edge of the orbitofrontal cortex (OFC) can be seen from this lateral view.

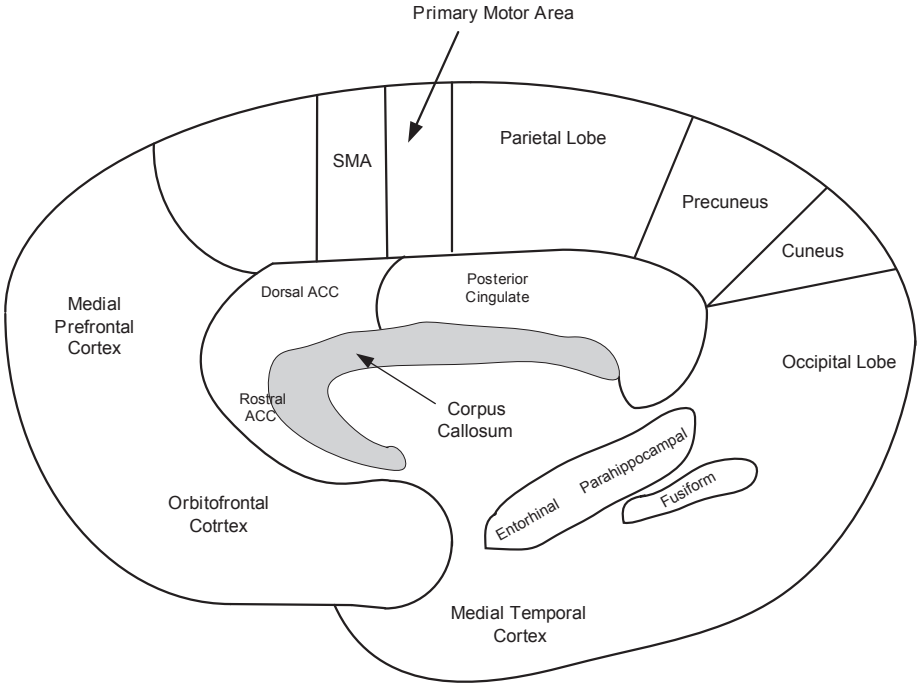


FIGURE 8.2. Medial view of the cortex.

Figure 8.2 shows the frontal lobe from the medial view of a sagittal section. The gray structure is the corpus callosum. The dorsal and rostral divisions of the cingulate gyrus can be seen at the anterior end of the corpus callosum. We discussed two of the major roles (conflict monitoring and error detection) of the dorsal anterior cingulate cortex (ACC) in Chapter 7. We also discussed the roles of the posterior cingulate, medial prefrontal cortex and precuneus as part of the "default mode" network. The OFC is more visible in the medial view. The hippocampus has been removed, but two of its input areas (parahippocampal cortex and entorhinal cortex) are shown. Ventral to this lies the fusiform cortex. This part of the temporal lobe contains the fusiform face area (FFA), which activates in response to the sight of human faces. This is a key area in the study of autistic spectrum and anxiety disorders.

Figure 8.3 is an overview of the "classic" localization of cortical functions. The predominant functions of the right and left hemispheres are shown. The adjectives "left-brain" and "right-brain" have found their way into popular culture to designate verbal, highly logical pursuits on the one hand and artistic, intuitive behavior on the other. This distinction, although overly simplistic in many ways, nonetheless is backed up by a significant body of work in both pathology and neuroimaging. We now examine cortical functions in terms of language, visual–spatial skills, and executive functions.

LANGUAGE

The primary auditory processing areas are in the superior temporal gyrus bilaterally. Speech sounds are quite different from the many other sounds we encounter in our daily lives. Our vocal cords are two strips of tissue in the larynx. On command, they beat together as we breathe out, setting the air in vibration. This creates sound waves, and as these sound waves travel through the throat and mouth, the motions of the palate, tongue, and lips shape them. This complex sound wave sets another individual's eardrum in motion. As the eardrum beats, the small bones of the middle ear transmit the frequency, amplitude, and pattern of these vibrations to the fluid of the cochlea of the inner ear. The movement of the fluid causes the hair cells of the cochlea to bend; this sets off neuronal firing. Information about the sound is carried first to the brain stem, then on to the primary auditory area in the superior temporal gyrus. Recently Mesgarani, Cheung, Johnson, and Chang (2014) showed how this gyrus is activated in response to speech sounds. A fascinating video of this process can be seen at *www.nih.gov/researchmatters/february2014/02102014speech.htm*.

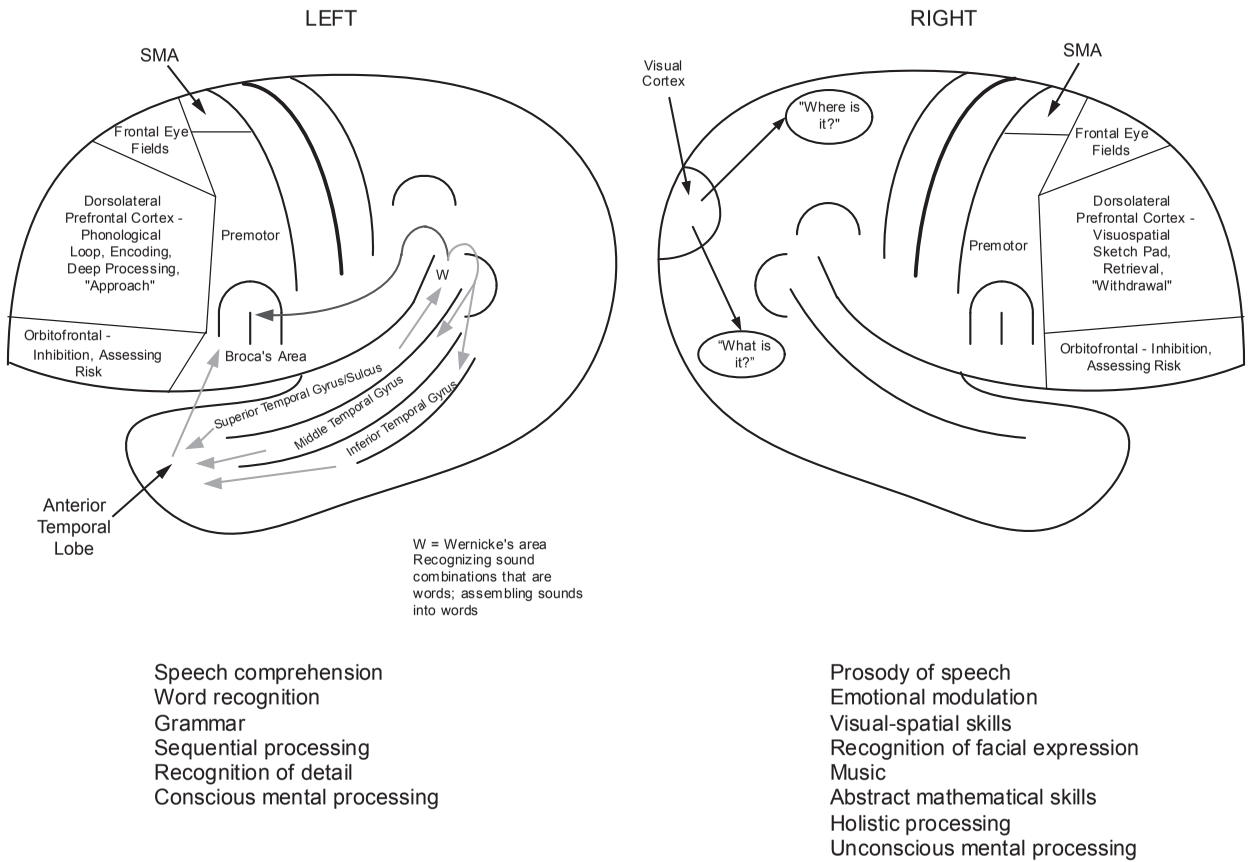


FIGURE 8.3. Language, executive and visual–spatial functions.

If we hear the word "baby," it consists of two sounds, or "phonemes": "ba" and "bee" (see Box 8.1 for a definition of language terms). Wernicke's area, which lies within the angular gyrus and supramarginal gyrus, recognizes those phonemes that are part of the languages we speak. Once Wernicke's area has recognized these sounds as speech, the information flows in both a dorsal stream (dark gray line in Figure 8.3) and a ventral stream (light gray lines) (Specht, 2014). The ventral flow proceeds to the middle and inferior temporal gyri, where the word sound is attached to meaning (semantics). More complex word meanings are stored in the most anterior parts of the temporal lobe. The dorsal stream appears to be more concerned with grammar (syntax) and motor action. As shown in Figure

BOX 8.1. Building Blocks of Language

- *Phoneme:* the smallest sound that can be a unit of language and combined into words. The sounds "ba" and "bee" can be combined to form the English word "baby." "Ooo" and "baa" can form the Spanish word "ova" (grape). Both English and Spanish speakers would experience activation of Wernike's area with spoken presentation of "baby" and "ova," since they represent language sounds.
- *Lexicon (semantics):* recognizing a combination of phonemes as a word with meaning. In the previous example, only the Spanish speakers would have a connection between the sound "ova" to the entity (a small green or purple, sweet fruit). Human beings maintain a large mental dictionary, which includes not only a one-to-one correspondence between a word and its meaning but also the ability to use context to assign meaning. For instance, "He's cool because he is in a band," and "He's cool because it is a chilly spring day," require the listener to assign very different meanings to the word "cool."
- *Morpheme:* the smallest unit of a word that can convey meaning. "Ju," "mmmm," and "p" are phonemes; when they are combined into "jump," the result is one morpheme that has meaning. The word "jumped" has two morphemes because the "ed" conveys past tense.
- *Syntax (grammar):* the language's rules for arranging subject, verb, object, and adjectives/adverbs. Broca's area appears to be key for understanding verbs and the grammatical relationship ("The boy hit the girl" and "The girl was hit by the boy" are equivalent statements).
- *Pragmatics:* integration of nonverbal cues (tone of voice, facial expression) into language for successful social communication, including the use of "slang" or understanding hidden meaning. For example, if you ask your spouse if he would like to see a movie and he replies, "I'm tired tonight," you implicitly know that the answer is negative. Pragmatics frequently is impaired in autism spectrum disorders.

8.3, Broca's area receives input both from the anterior temporal lobe and Wernicke's area. While the meaning of nouns may be found in the temporal lobe, the meaning of verbs and grammar are found in Broca's area.

These processes can be seen in two classic PET studies (Petersen, Fox, Posner, Mintun, & Raichle, 1988; Petersen, Fox, Synder, & Raichle, 1990). Plate 5 illustrates a study in which participants were given a PET scan while performing four tasks: eyes open, viewing nouns passively (and automatically reading them), reading nouns aloud, and generating a verb to go with a noun (Petersen et al., 1988). For example, in the last task, if a participant sees a picture of a car, he or she might say "drive." As can be seen, when a person is viewing words (upper right panel), the visual association cortex in the left temporal area is activated, in addition to the occipital visual areas activated by merely having one's eyes open. Reading nouns aloud (lower left panel) activates the primary motor area, but Broca's area is not strongly activated until the person *actively* uses grammar (e.g., when he or she generates a verb; lower right panel).

Plate 6 shows the results of another classic neuroimaging study in which participants viewed different types of reading stimuli (Petersen et al., 1990). In the far-left panel, participants viewed "false fonts," small geometric shapes that are the size of letters. Both right and left visual regions of the occipital lobe were equally activated, as these stimuli have no language meaning. The next panel to the right shows brain activation caused by strings of consonants such as "VSFFHT." There is no difference from the first panel because these stimuli also have no language meaning. In the third panel, the person viewed pseudowords, combinations of vowels and consonants that *could* be pronounced, such as "WOBBY." Note the stronger left-cortex activation compared with the letter-string condition. The amount of activation is the same as in the presentation of real words, shown in the far-right panel. This left-sided activation represents the brain's greater activation of the left temporal lobe in response to a visual stimulus (words or pseudowords) that might be meaningful to an English-speaking person. Consistent with this advantage of the left hemisphere for language, the superior part of the temporal lobe (called the "planum temporale") is larger on the left than on the right in most persons. Over 95% of right handers have language functions localized to the left hemisphere, but so do approximately 70% of left handers.

In reading, there is an interaction of the visual areas containing the representation of the letters of the word with Wernicke's area. The letter symbols ("b," "be," "ka") must be mapped onto the sounds they represent, a process referred to as phonemic analysis (see Box 8.1). The phonemes must be assembled into words, then words must access the respective language stream (noun-ventral or verb-dorsal) in order to be assigned meaning. As we read, the dorsal stream and Broca's area process the grammar (syntax)

of the evolving sentence. Reading involves more than just phonemic analysis, however. Take the words "threw" and "through." The first word can be perceived through phonemic analysis: the "th" and "rew" combinations of letters each stand for separate sounds. The brain needs only to decode them and recognize that, together, they form "threw," which means to have launched a projectile. In contrast, phonemic analysis is not helpful in decoding the word "through." English speakers simply must memorize the fact that the letter combination "ough" has been assigned arbitrarily to represent an "ew" or an "oh" sound, depending on which letters proceed it ("thr-ough" or "thor-ough"). The brain has two systems for analysis of the written word—phonemic analysis and whole-word recognition—and it can flexibly move back and forth between the two as we read.

The anatomy of language is further illustrated by the effects of brain injury on language. Persons who suffer a lesion in Broca's area ("Broca's aphasia") comprehend most aspects of language but have pronounced articulation deficits. They also cannot name a wide variety of objects because the motor programs that activate the sequence of lip, tongue, and mouth movements to produce the word are lost. Patients with Broca's aphasia also suffer "agrammatism." Verbs are most likely to be left out. If a patient with Broca's aphasia is asked to describe a picture that shows a car crashing into a wall, he or she will say something like "The car . . . car . . . there . . . the car and . . . the wall." The patient is unable to produce the verb "crash" at all, and each word is pronounced very haltingly. The patient can be shown two pictures, one of a boy hitting a girl and another of a girl hitting a boy. If he is asked to point to the picture in which "the boy hit the girl," he will get it right. But if he is told to point to the picture in which "the boy was hit by the girl," an error is much more likely. Broca's area appears key to understanding the grammatical construction of more complex sentences.

Patients with "Wernicke's aphasia" have a lesion in the left superior temporal lobe. These patients are completely fluent in their speech, but their speech makes no sense. They cannot comprehend speech and therefore cannot follow commands unless nonverbal cues attend them. The speech output of a Wernicke's patient might sound as follows: "Well, food is happening last night I went mooing, then he told is no good. Mary I don't know she righting the house and well, it just pessing." Curiously, the patient is unaware that anything is wrong. Each time the examiner asks a question, the patient responds with gibberish. In Wernicke's aphasia, not only is Wernicke's area itself damaged, but so are the connections to the ventral stream in the temporal lobe. When the patient hears words, Wernicke's area no longer recognizes them as words. With the connections to the anterior parts of the temporal lobe damaged, the brain can no longer attach a word to a concept. Thus, what is sent forward to Broca's area is meaningless (as in the computer jargon, "garbage in, garbage out").

When a stroke is less severe, only the ventral temporal area may be damaged, leaving Wernicke's area intact. This causes "transcortical sensory aphasia." These patients also do not comprehend what is said to them, yet they will repeat what they hear said around them. How is this possible? The sounds are processed in the primary auditory area, sent to Wernicke's area in which they are recognized as words, then sent directly to Broca's area through the dorsal stream, such that they can be repeated. Because the ventral temporal stream is damaged, however, the patient does not have access to the words' meaning. Although the patients repeat what they hear, they cannot understand it. "Conduction aphasia" is the opposite of this condition. The patient comprehends language and is fluent but cannot repeat things on command. Here, the direct connection between Wernicke's area and Broca's area (the arcuate fasciculus) is damaged. The sounds the patient hears move normally from the primary auditory cortex to Wernicke's area and through the ventral temporal stream; speech is thus comprehended. Since the ventral stream can still communicate with Broca's area, speech production is not impaired. The patient cannot, however, articulate a simple repetition because the direct route from Wernicke's area to Broca's area is disrupted. This direct pathway, called the "phonological loop," does not require us to know the meaning of a word. We use this loop when saying a word in a foreign language that we do not understand or when saying a pseudoword.

HEMISPHERIC ASYMMETRY

The right hemisphere plays a greater role in nonverbal, visual–spatial functions. Note in Figure 8.3 that two "streams" of information flow in the right cortical hemisphere from the occipital (visual) cortex. The ventral stream flows into the temporal lobe, in which representation of objects is the principal function. Assemblies of neurons activate when certain objects, animals, or persons are present. Unlike the left hemisphere, the right hemisphere produces primarily nonverbal, conceptual representations of the object or persons. Patients with right-sided lesions are more likely to exhibit "agnosia" (lack of knowing) about many objects, whereas patients with left-sided lesions tend to exhibit "anomia" (inability to name the object). A patient with a right temporal lesion, when shown a hammer, may state that he or she does not know what it is; when asked to demonstrate how to use it, he or she will fail to do so accurately. In contrast, the patient with a left temporal lesion will make pounding motions with his or her hands but be unable to access the correct word for the item. Patients in whom strokes have damaged the right temporal lobe also are more likely than those with left-temporal-lobe lesions to experience "prosopagnosia," that is, an

inability to recognize faces. Figure 8.2 shows the location of the fusiform gyrus on the ventro-medial side of the temporal lobe. Within this gyrus lies the FFA; the right FFA strongly activities in functional magnetic resonance imaging (fMRI) studies when subjects are viewing faces (McCarthy, Puce, Gore, & Allison, 1997). Perception and the recognition of faces depends on a network of brain regions (FFA, amygdala, superior temporal gyrus, and inferior occipital gyrus), which is bilateral but nonetheless has a right-sided bias. Brancucci, Lucci, Mazzatenta, and Tommasi (2009) noted that not only visual but also auditory, tactile, and even olfactory stimuli (how someone smells!) are processed more strongly in the right hemisphere. This network is part of the social brain, on which we focus in Chapter 13 on autistic spectrum disorders.

The dorsal stream feeds visual information into the parietal lobe, where it is integrated with other data (principally auditory) to determine where the object is in space. The parietal area deals both with the position of objects in space and our sense of our own bodies. Right–left discrimination is a critical part of this ability. Patients with right parietal strokes develop an array of interesting deficits. They often lose their sense of geography and are no longer able to navigate around their home or city. In severe cases, they may develop "hemineglect," a failure to recognize the left sides of their own bodies or the left side of their world. Asked to draw a picture of a clock, they draw only a semicircle, the right side of the clock. They may fail to wash their left hands or comb their hair on the left side. The right hemisphere appears predominant for a wide variety of visual–spatial functions. Whereas rote arithmetic seems more the province of the left hemisphere, the right hemisphere may handle more complex mathematical concepts, such as geometry and algebra.

Right-hemisphere mechanisms control "prosody," the changes in intonation and emphasis in speech that conveys emotion or meaning. For instance, the difference in the meaning of the sentences "Joe got a raise," and "Joe got a raise?" are conveyed by tone of voice. In the former, the tone of voice is even throughout the sentence, but in the latter, the voice rises at the end to indicate a question rather than a statement. Patients with damage to the right hemisphere have difficulties making such distinctions, and their speech takes on a flat, nonemotional tone. More broadly, the right and left hemispheres have different styles of processing information (Harmon-Jones, Gable, & Petersen, 2010). The left hemisphere is more language based, uses conscious processing, and is logical and rule based. In contrast, the right hemisphere is more abstract in its functioning, and its processing is unconscious. The left hemisphere concerns itself with details of stimuli in the world; the right interprets the global pattern. These differences can be seen most clearly in Figure 8.4. Participants are asked to

draw figures that consist of small stimuli embedded in larger stimuli. For instance, the large letter "A" is made up of small "X's." People without hemispheric damage have no difficulty including both the detail and the overall pattern. As the figure illustrates, patients with right-hemisphere damage lose the overall pattern, and patients with left-hemisphere damage lose sight of the detail.

R. J. Davidson and Nathan Fox (Davidson, 1992, 1994; Davidson & Fox, 1982, 1989; Fox, 1989; Fox & Davidson, 1986, 1988) performed a series of studies in the 1990s examining the amount of alpha wave activity in the frontal leads of subjects' electroencephalograms (EEGs). While somewhat of a simplification, greater alpha power may represent lower activity of the cortical hemisphere. These studies suggest that (1) people activate (produce less alpha) in the right frontal region when they experience a negative emotion, (2) people with higher baseline right frontal activity tend to be pessimistic and withdrawn, (3) infants with more right frontal activity cry more intensely in response to separation, and (4) temperamentally inhibited preschool children have greater right frontal activity. Moreover, right-sided frontal lobe tumors are more likely to result in mania (disinhibition) than are left-sided tumors, which are more likely to result in depression (Braun, Larocque, Daigneault, & Montour-Proulx, 1999; Starkstein et al., 1989). This suggests that the right hemisphere governs "withdrawal" and negative emotions (anxiety, fear, depression), whereas the left hemisphere is concerned with "approach" functions and positive emotions (elation). Aggression (particularly proactive aggression) is viewed as falling into the approach category (Harmon-Jones et al., 2010). This model may be of use in interpreting some neuroimaging studies of anger/depression, which often have lateralized findings in terms of brain activity.

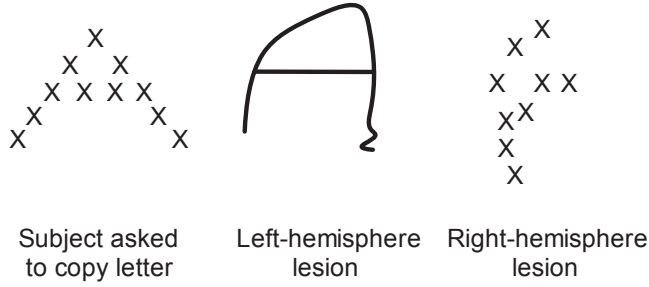


FIGURE 8.4. Stimuli requiring attention to both the fine details and the overall pattern that are processed differently by the right and left hemispheres.

EXECUTIVE FUNCTION

Behavior is not adaptive unless carried out according to a long-term plan; thus, there must be a capacity to wait to respond to stimuli in our environment until it is appropriate to do so. After perceiving information, we must hold the data in our minds, manipulate it, ponder what it means, and select a behavioral response. These abilities fall under the broad category of executive functioning. Take the following word problem:

> "Sally was walking down the street, carrying five apples. She walked five blocks north and met her friend. She gave her friend two apples, then walked four blocks west. She ate an apple and then walked one block south to her home. How many apples did she have left?"

Several cognitive functions are critical for solving this problem. Most obviously, language areas must be intact to understand all the elements of the problem; arithmetic skills are required as well. More than this is required to be successful, however. As you listen, you must keep track of the number of apples exchanging hands, and you must realize that the number of blocks walked is not relevant to the problem. This active, mental manipulation of information is done in *working memory*, in which the DLPFC plays a key role. Goldman-Rakic (1992) and colleagues illustrated this process in monkeys using a simple task. A monkey is shown a morsel of food, which is then placed in one of two wells. Both wells are covered, then a screen is lowered in front of the wells. After a delay, the screen is lifted, and the monkey must lift the cover of the well to find the food. Monkeys with DLPFC lesions have great difficulty doing this task. Goldman-Rakic then had the monkeys do a slightly different task. The covers of the wells had different symbols on them (a circle and a cross), and the food morsel was always placed under one of the symbols. After several trials, the monkeys learned which cover to lift. DLPFC lesions did not affect this skill. This finding tells us that long-term memory (associating the correct well with the symbol) was not impaired by frontal lobe damage. When the monkeys must hold the *location* of the well in their minds, however, the DLPFC is critical. The same task can be performed with monkeys who have indwelling electrodes in their frontal lobes. When the screen was lowered, particular DLPFC neurons fired during the delay, but they stopped once the response was made. Thus, the DLPFC is critical for "online" processing of information.

In Figure 8.3, slightly different executive functions are ascribed to the right and left DLPFC (Gazzaniga et al., 2014). The left DLPFC controls verbal working memory, which includes the "phonological loop" discussed earlier. Here, language information, such as the word problem

previously presented, is placed in a "mental buffer" and manipulated. The right DLPFC contains the "visual–spatial sketchpad," which manipulates objects in space. This area would be active when a person is thinking about a geometry problem or, more practically, trying to remember the directions to a place he or she has not been often. Patients with lesions in the DLPFC are quite different from those with lesions in the temporal or parietal lobes. They rarely exhibit overt language problems, and they recognize objects easily; indeed, in the initial conversation, they may appear quite normal. When tested, however, subtle impairments are detected. If given the problem described previously, they confuse the number of blocks with the number of apples. If a patient with a right parietal lesion and one with a DLPFC lesion are both given a maze to complete, they both have difficulties, but for different reasons. The patient with the parietal lesion, having lost his or her geographic sense, will fail to comprehend the task altogether. Instead of guiding the pencil through the maze, he or she makes stray marks on the paper that bear no relationship to the path. The patient finally just gives up, saying, "I can't do it, I don't understand." The patient with the DLPFC lesion will voice understanding, eagerly grab the pencil, and plow through the maze, taking the first path instead of taking time to consider routes that might be more successful. When at a dead end in the maze, he or she simply may keep drawing, ignoring the rule to stay within the walls.

O'Reilly (2010) integrated information about the function of the PFC in a wide variety of tasks to develop a "What, How, Abstract, Cold/Hot" (WHACH) model of its functioning, which is illustrated in Figure 8.5. From the anterior view, the PFC is laid out on a dorsal–ventral/medial–lateral grid. Parts of a mental task that are related to the "how" function activate the more dorsal aspect of the PFC, such as thoughts that relate to action (e.g., "How many apples did Sally give away?"). In contrast, the ventral aspect of PFC deals with the "what" function (e.g., "Is it apples or blocks I need to keep track of?"; "Who is Sally and why do I care?"). (The "what" system interacts with the anterior temporal memory system, discussed in Chapter 7.) "Hot" versus "cold" is distributed along the medial–lateral axis and refers to the emotional valence of the task. Sally's apple problem is fairly neutral from an emotional prescriptive; thus, medial areas of the PFC are not likely to play a role in this task. Trying to figure out when is a good time to ask a friend on a romantic date, however, would surely activate these medial regions. These lateral regions also integrate information from the immediate environment that is relevant to the problem, while medial areas of PFC allow internal information about the self (e.g., personal history, current emotional state) to influence the task. Finally, the lower panel shows the brain from a lateral view, illustrating the anterior–posterior gradient. The posterior aspect of the PFC deals with concrete concepts (count the apples), while the anterior pole is engaged as the task becomes more

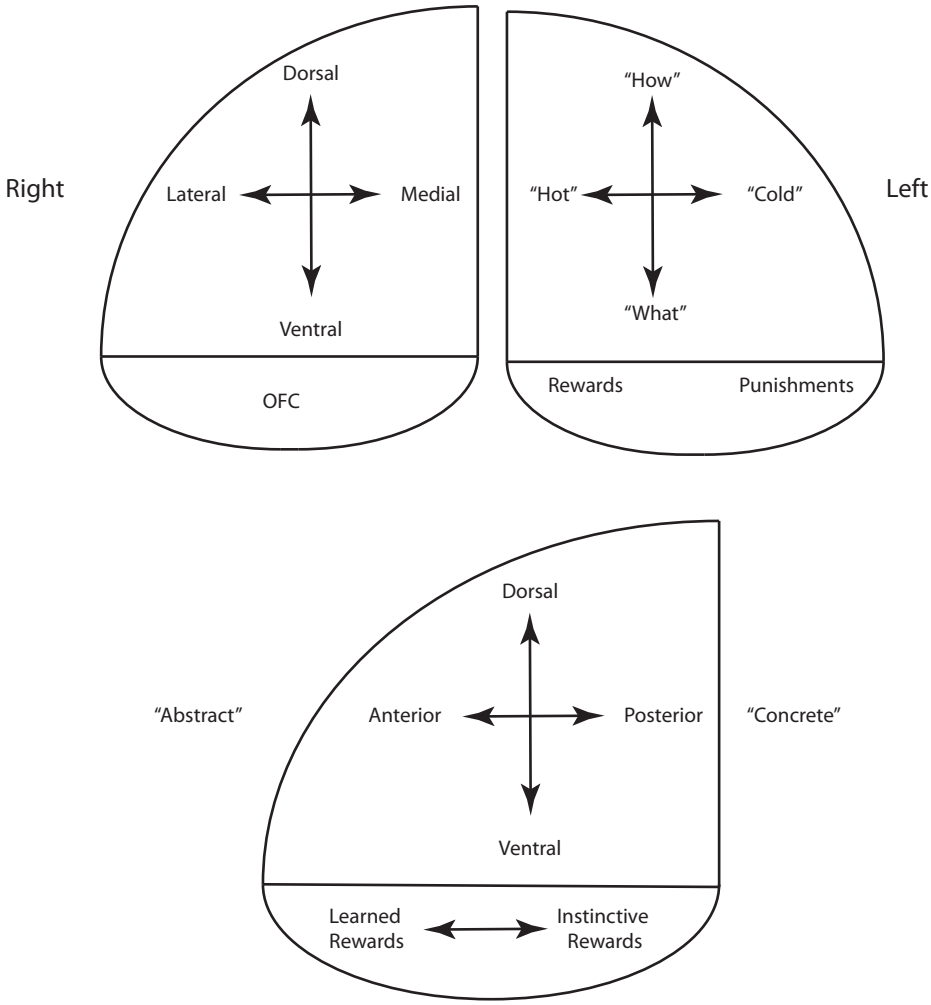


FIGURE 8.5. Processing of different types of cognitive information along the three-dimensional axes of the prefrontal cortex.

complex or abstract ("All men are created equal" does not mean that all men are of the same physical size but that they have equal political rights).

The OFC plays a key role in decision making and social behavior. Like the more dorsal part of the PFC, it also is organized along two axes. The lateral part of the OFC codes the value of *punishments*, while the medial OFC is concerned with the value of *rewards*. The OFC can both inhibit and activate the amygdala. In Chapter 6, I touched on the interaction between

the OFC and the amygdala. While the latter reacts to the current situation (physical needs, presence of rewards), the OFC contains information about *long-term* rewards and punishments. The OFC is strongly activated when subjects engage in tasks in which risk must be assessed, such as gambling games. Patients with OFC lesions have difficulty assessing risk and continue to take excessive risks even when they are losing. This is not due to a lack of awareness that they are doing poorly, but to an inability to assess risk anew on the next trial, even though they lost on the prior trial. Such patients are described as "impulsive," but it is due not to an inability to withhold a response per se, but rather to assess the risk and appropriateness of the response. Antonio Damasio (1994) described a patient, a well-adjusted professional in his 30s, who developed a brain tumor (a meningioma) that damaged his OFC. The tumor was removed, but the orbitofrontal areas did not recover. The patient could no longer hold a job, he spent money foolishly, and he began to collect meaningless pieces of junk. He divorced his wife of many years and remarried impulsively.

The posterior part of the OFC plays a role in rewards/punishments that are inborn or instinctive (sugar, sex, pain, social humiliation), while the anterior OFC is engaged for higher level, learned rewards (money, awards, fame). The OFC also plays a pronounced role in aggression. In one of the early neuroimaging studies examining the functioning of the OFC, 15 healthy volunteers listened to a script while cortical glucose metabolism was measured by PET scan (Dougherty et al., 1999). In the opening scenario, they heard about riding an elevator with their mothers. Next, came three other scenarios in which their mother was attacked physically by other men in the elevator. These scenarios differed in the following ways: (1) They could do nothing to help their mothers; (2) they tried to respond but were prevented from doing so by the other men in the elevator; and (3) they physically responded to the attackers. In all three of these aggressive scenarios, the activation of the OFC was *decreased* relative to the neutral condition, with the greatest deactivation occurring in the third (retaliation) condition. During the condition when aggression was restrained, other, more dorsal, frontal regions showed increases in activity.

Beyer, Münte, Göttlich, and Krämer (2015) used fMRI to assess OFC activity in 41 individuals who played a game against an opponent while in the scanner. They viewed the opponent as punishing them (delivering a loud noise into the scanner) for a losing response. The opponent would have either an angry or neutral expression. When the opponent had an angry expression, the OFC was more activated relative to the neutral expression. Subjects then had an opportunity to punish their opponent. Interestingly, those subjects who had the *greatest* difference in OFC activity between the angry and neutral faces delivered the *less* intense punishment, such that *decreased* OFC activity correlated with *more* aggressive

behavior. This complex relationship between the amygdala and OFC is illustrated in Figure 8.6A, which represents the average activity of these structures during both an anger-inducing stimulus and the response to that stimulus. The amygdala *recognizes* the threat (angry threat), whereas the OFC *assesses* the threat and weighs options (based on long-term assessment of risk/reward). If a decision is made to act aggressively, OFC activity decreases. Figure 8.6B shows the activity of these structures in less aggressive individuals. OFC activity jumps to a higher level at presentation of the threat and does not drop as sharply at the decision point to act aggressively. In contrast, Figure 8.6C shows that aggressive individuals tend to have less OFC activation in response to the threat; this may lead to a greater likelihood that they will trigger an aggressive response. OFC function is highly involved in disorders of anger and aggression.

THE SELF AND OTHERS

As humans, we have a remarkable ability to be aware of others' feelings and to understand their actions. Bird and Viding (2014) categorized the multiple brain systems involved in these processes. The "mirror neuron system" is generally localized to the premotor cortex and inferior parietal cortex (Molenberghs, Cunnington, & Mattingley, 2012). If we observe someone else performing an action (e.g., waving), motor areas of our own brain that would produce the same action are activated, even if we do not overtly

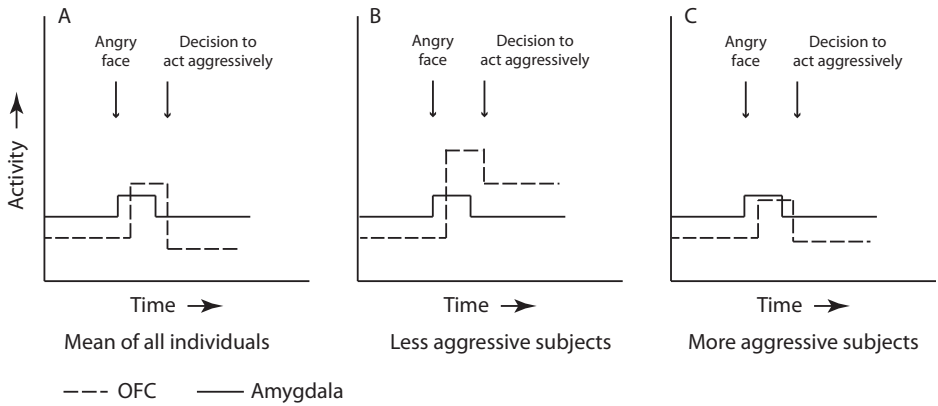


FIGURE 8.6. The role of the amygdala and orbitofrontal cortex (OFC) in assessing and responding to threat. (A) Mean response of all subjects. (B) Response of those who refrain from responding aggressively. (C) Response of those who respond aggressively.

perform the action. Parts of the default mode network (medial PFC and precuneus), temporoparietal junction (part of ventral bottom-up attention system), and the right superior temporal gyrus all form part of the *theory of mind* (ToM) system (Frith & Frith, 2003; Mills, Lalonde, Clasen, Giedd, & Blakemore, 2014). The default mode is active in imaging studies in which we must be introspective; through the other ToM connections, we are able to understand the actions of others by relating their actions to our own. The medial PFC is activated in fMRI when subjects must form impressions of other personalities based on their actions (Mitchell, Macrae, & Banaji, 2004). Thus, we can interpret the intentions of other people and guide our interactions with them by doing so. Empathy involves ToM as well as the understanding of how others feel emotionally. If we see a store clerk in uniform entering a store on Thanksgiving Day, ToM helps tell us that the clerk must have to work, not that he or she wants to work. If we have a sense of sadness that the person must work, that is empathy, which relies on an affective representational system located in the ACC, ventral striatum, and insula (Craig, 2009). Cikara, Botvinick, and Fiske (2011) recruited serious fans of the New York Yankees and Boston Red Sox to watch clips of plays between the two teams while undergoing fMRI. Subjects were exposed to plays in which their own team did well or failed. They then were exposed to plays in which the rival team did well or failed. The ventral striatum (reward center) was activated when one's own team was winning, while the insula and ACC were activated by the rival team winning or one's own team failing. The insula–ACC network also is active when seeing another in pain.

FROM PATHWAYS TO NETWORKS

I started this chapter with the framework that arose in the 19th century, when the localization of functions was discovered, particularly the location of language in the left hemisphere and the discovery of Broca's and Wernicke's areas. Up to now, we have taken a "pathway" approach, first following the axons of neurotransmitter neurons to their end points, then asking how information travels from one brain region to another. With memory and attention, we began to see how complex functions are not located in one area but are broadly spread out over multiple circuits. We now are ready to take the final step and look at "connectivity"—the way in which multiple areas of the brain talk to each other in networks. Perhaps fittingly, the techniques for discovering these brain networks emerged from the mathematics of the Internet and, specifically, the study of how social networks emerge (Bassett & Bullmore, 2014).

In functional neuroimaging, we often have the subject perform a task (e.g., viewing an angry face). Blood flow will increase or decrease to a

structure (e.g., the amygdala) that is likely to be involved in the task. Of course, the brain is not dormant before the task is executed. When "at rest," billions of neurons are active, but they are not randomly talking to each other. Neurons tend to talk to each other in networks that are close to them, occasionally communicating with far-away neurons. This is similar to our social networks. We have people, such as parents, siblings, or friends from high school, who are close to us, as well as people whom we see only rarely. Most of us have two large networks of associates: family or close friends *and* coworkers. In Figure 8.7A, "Dave" has a number of personal friends/family, as well as coworkers who have strong connections with each other, but only one coworker sees Dave outside of work. Figure

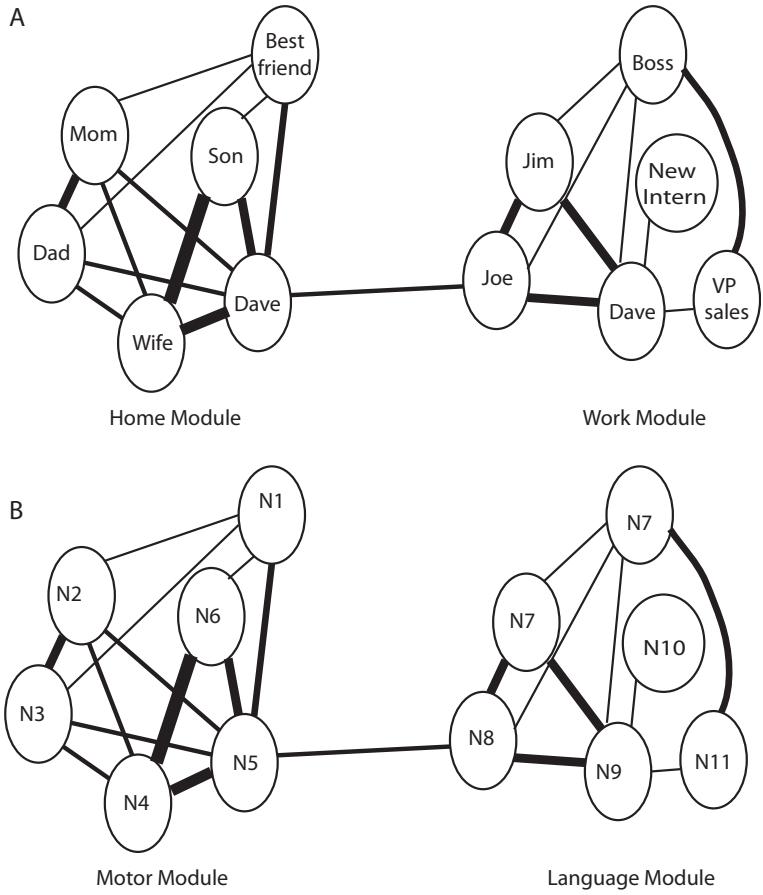


FIGURE 8.7. Analogous structure of social (A) and brain (B) networks.

8.7B shows that the neurons of the brain can function in an analogous manner. Neurons relate to each other in language and motor "modules." Neurons within modules are intensely connected with each other, while neurons between modules have fewer connections. This is referred to as a "small world" network (Bassett & Bullmore, 2014).

The lines between the circles represent the connections that may be assessed structurally by MRI (how strong the white matter connections are) or functionally. In the latter case, the individual is asked to lie in the scanner with his or her eyes open, thinking of nothing in particular. As the neurons spontaneously communicate, the minute fluctuations in the blood-oxygen-level-dependent (BOLD) signal are assessed and correlated across brain areas. The complex mathematics tells investigators which neurons are working together as modules. Yeo and colleagues (2011) performed this study on 1,000 healthy volunteers. The results showed seven distinct networks, as shown in Plate 7. These networks included the default mode (red in Plate 7), dorsal attention (green in Plate 7), and ventral attention (violet in Plate 7) that were discussed in Figure 7.1. In Plate 7, the somatomotor (blue) and visual (purple) involve primary motor/sensory processes; the limbic network (cream) and frontoparietal (orange) are frontal lobe networks key to the emotional and higher cognitive functions discussed in this chapter.

Plate 8 displays both the interconnectedness of these networks as well as their cross network connections (Baker et al., 2014). Three of the networks are illustrated: default mode, frontal–parietal ("control"), and the dorsal attention. Plate 8A represents the healthy controls. Note how each of the three networks has dense connections with each other and do not overlap, though they communicate with each other. Plate 8B shows the results from a group of psychotic patients with either schizophrenia or bipolar disorder. Note how the networks of the patients are far more diffuse, with fewer connections within the three networks and a greater distance (and therefore less efficient connections) between the networks. Thus, we should see serious psychiatric illness not as a "localized" lesion such as Broca's aphasia but as a condition affecting the totality of brain function.

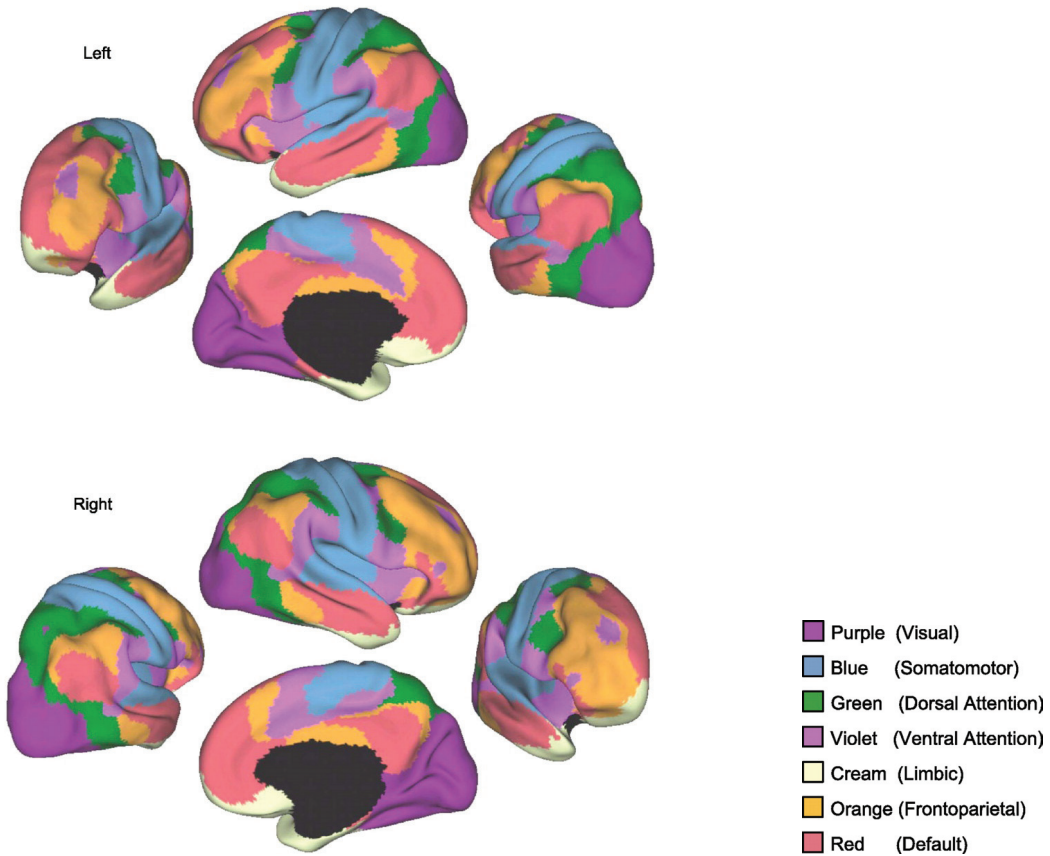


PLATE 7. A seven-network parcellation of the human cerebral cortex based on 1,000 subjects. Reprinted from Yeo et al. (2011) with permission from the American Physiological Society.

PART II

MENTAL DISORDERS

CHAPTER 9

Attention-Deficit/ Hyperactivity Disorder

Attention-deficit/hyperactivity disorder (ADHD) affects 5–7% of school-age children (Roberts, Milich, & Barkley, 2014) and 4% of adults (Kessler et al., 2006). The 2011 National Survey of Children's Health (NSCH) performed telephone interviews of nearly 100,000 parents of children ages 4–17 (Visser et al., 2014). Eleven percent of children had received a diagnosis of ADHD at some point in their lives, 8.8% were reported as having a current diagnosis of ADHD, and 6.9% (78% of those with ADHD) were taking medication for the disorder. For comparison, less than half of children with ADHD were taking medication in 2007. ADHD is related to many impairments, including poor school performance; oppositional and aggressive behavior; poor peer relationships; and earlier onset of delinquency, substance use, and sexual activity (including pregnancy). Relative to adults without ADHD, adults with ADHD show poorer job performance, greater lifetime substance abuse, and higher rates of depression and anxiety (Barkley, 2014a, 2014b). Yet some individuals with ADHD show resolution of their symptoms by adulthood and do well. Understanding the neurobiology of ADHD may shed light on the roots of a number of psychiatric disorders.

DSM-5 (American Psychiatric Association, 2013) lists the diagnostic criteria for the disorder. There are nine symptoms each of inattention and hyperactivity/impulsivity. Children must have six of nine symptoms in at least one of the two categories, whereas adolescents or adults must have five. DSM-5 describes three "presentations" of ADHD: combined (both inattentive and hyperactive–impulsive), predominantly inattentive, and predominantly hyperactive–impulsive. Most research has been conducted

on the combined type, particularly the studies to be reviewed here. Impairment from the symptoms must have started before age 12 and be present in at least two settings. At present, diagnosis is by clinical interview; typically, rating scales are obtained from the parent and school (or directly from the patient in the case of adults). The clinician must rule out other psychiatric disorders (psychosis, depression, mania, etc.), but this task is complicated by the fact that many patients with ADHD have comorbid disorders (Pliszka, 2009, 2014). The simple list of symptoms of ADHD belies the severe impairments that can be associated with the disorder (Weyandt & Gudmundsdottir, 2014), including the following:

- Many individuals with ADHD function poorly in everyday activities at home, at school, and on the job, usually as a result of poor focus, impulsive behavior, and impatience.
- Many individuals with ADHD display poor motor skills in strength, in visual–motor coordination, in adjusting motor speed, and in terms of manual dexterity (the handwriting of individuals with ADHD is notoriously poor).
- While many individuals with ADHD are very bright, average IQ is lower in those with ADHD relative to controls, and perhaps up to 45% of those with ADHD have coexisting learning difficulties. This latter estimate includes both individuals with a bona fide learning disability and those who fail to achieve because of poor concentration.
- Many individuals with ADHD lack introspection and are unable to see their own limitations. Children and adults with ADHD frequently think "everything is fine" even when they are performing poorly.
- A wide range of neuropsychological functions have been examined in individuals with ADHD and controls in laboratory settings. Willcutt (2014) has summarized this extensive body of over 250 studies. Those with ADHD have deficits in inhibitory control, working memory, planning, response variability (motor responses such as pressing a button when a light comes on are slower and more variable than controls), and processing speed (speed at which a mental task is completed). Yet not all people with ADHD have neuropsychological impairments. The Colorado Learning Disability Research Center (CLDRC) performed an extensive battery of neuropsychological tests in nearly 1,000 children and adults with ADHD (Willcutt, 2014). Surprisingly, nearly half of these individuals did not show deficits on any of the neuropsychological measures.
- Some individuals with ADHD are unable to delay gratification and exhibit excessive reward-seeking behavior, which is explored in more depth in the next section.

THE STANFORD MARSHMALLOW TEST

In the 1970s, Walter Mischel and Ebbe Ebbesen conducted the first "marshmallow test" at Stanford University (Mischel, Ebbesen, & Zeiss, 1972). Six hundred children ages 4–6 were placed in a room with a marshmallow on a table in front of them. An adult told them that they could eat the marshmallow right away or they could have two marshmallows in 15 minutes, when the adult returned. The adult left, leaving the child alone in the room. The children were filmed and the dependent variable was how many minutes they could wait before eating the marshmallow. (See videos of children at *www.ted.com/talks/joachim_de_posada_says_don_t_eat_the_marshmallow_yet?language=en*.) One-third of the children could resist eating the marshmallow (with the older children being more successful). As the children aged, the ability to delay gratification in this one setting showed surprising correlations with long-term outcome. Compared to those who ate the marshmallow, resisters were rated as more competent during adolescence (Mischel, Shoda, & Peake, 1988), had higher Scholastic Aptitude Test (SAT) scores (Mischel, Shoda, & Rodriguez, 1989), better educational achievement (Ayduk et al., 2000), and lower mean body mass index (Schlam, Wilson, Shoda, Mischel, & Ayduk, 2013). Kidd, Palmeri, and Aslin (2013) performed a variant of the study in which half of the children first interacted with an adult who broke a promise. When the children did the marshmallow test with this untrusted adult, they were far more likely to eat the marshmallow than children who had interacted with an adult who kept a promise. This shows that the ability to delay gratification should not be viewed as something hardwired to the individual, but as something affected by experience. McGuire and Kable (2013) elaborated on the idea that selecting a small reward early did not necessarily indicate a failure to delay gratification. They reanalyzed data from 931 children who did a variant of the marshmallow test (Belsky et al., 2007) and found that just over half of them waited the full 7 minutes for the examiner to return. Almost all of the remainder consumed the small reward in the first minute, with few of these giving in during the last 6 minutes. McGuire and Kable pointed out that if giving in to temptation was the main factor in failing to resist, more should have given in later, as their desire overcame inhibition. These youngsters who gave in early may have made a rational decision based immediately on their concept of how long they perceived they would have to wait.

The original Stanford subjects were followed up when they were in their 40s and underwent functional magnetic resonance imaging (fMRI; Casey et al., 2011). During the fMRI, the subjects performed a go/no-go task. Subjects were shown faces that were happy, neutral, or sad and instructed *not* to press the button depending on the gender of the faces. Adults who

were resisters as children showed greater right inferior frontal gyrus (IFG) during the no-go trials relative to those who had eaten the marshmallow. Recall from Chapter 7 that the right IFG is part of the bottom-up ventral attention system, critical for inhibitory control. When the faces in the task were emotional (happy or sad), the subjects who had been unable to wait showed greater activation in the ventral striatum (reward area) of the brain. Thus, this simple task at ages 4–6 years was predicting brain activity three decades later! Children with ADHD frequently show "delay aversion" (Sonuga-Barke, Bitsakou, & Thompson, 2010); that is, when offered the chance to have a small reward now or a larger reward later, they are far more likely than controls to choose the immediate reward.

BRAIN ANATOMY IN ADHD

Philip Shaw and his colleagues (2012, 2013) at the National Institute of Mental Health (NIMH) obtained structural MRI on children with ADHD and matched controls at age 8, then repeated these at various intervals until the subjects were in their 20s. He measured the thickness of the gray matter (neuronal bodies), as well as the cortical surface area in both groups to show changes over time. These results are illustrated in Figure 9.1. Figure 9.1A shows the development of cortical surface area. Note that in controls, cortical surface area increases until just before age 10; with the onset of adolescence, a process of normal "pruning" begins, and surface area declines as people enter young adulthood. Note that the children with ADHD begin with less cortical surface area and obtain their peak later in childhood. Interestingly, this pattern is most pronounced on the right side of the prefrontal cortex. A similar pattern is seen for cortical thickness, though an interesting trend emerges depending on long-term outcome (Figure 9.1B). Those persons whose ADHD persisted into adulthood showed less cortical thickness than controls both at age 8 and in adulthood, while those whose ADHD remitted caught up to the controls in cortical thickness growth.

While much focus in ADHD has been on the cerebral cortex, the cerebellum of those with ADHD is on average smaller in volume than that in controls; indeed, the magnitude of this effect is greater than that for the cerebrum (Valera, Faraone, Murray, & Seidman, 2007). This is important in view of the fact that, as noted earlier, children with ADHD show subtle motor deficits. In Chapter 6, we noted the role of the cerebellum in modulating ongoing motor activity. Both children and adults with ADHD have higher rates of accidental injury (Barkley, 2014e). Could motor problems resulting from a dysfunctional cerebellum be related to this phenomenon?

It also should now be clear that ADHD is not related to any highly localized brain region but affects brain development broadly. These

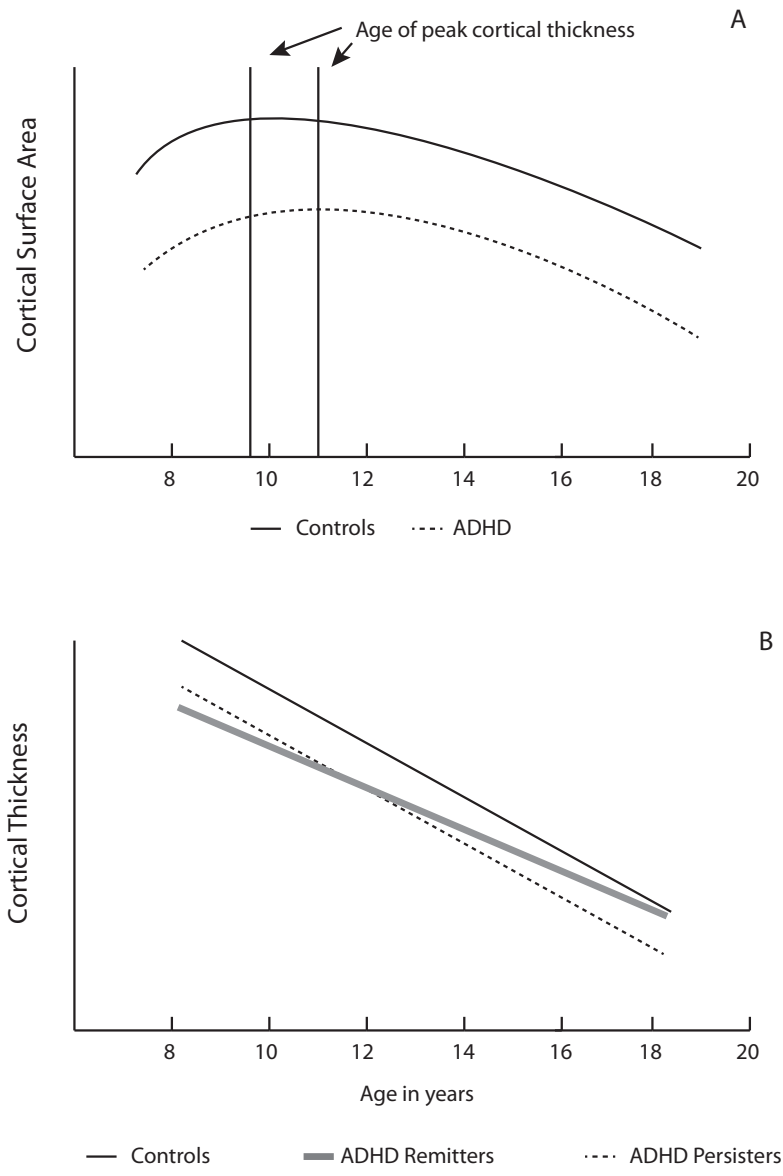


FIGURE 9.1. Changes in cortical thickness and cortical surface area over development in persons with ADHD and controls. Reprinted from Shaw et al. (2012) with permission from Elsevier Ltd.

anatomical findings are based on average differences between groups of individuals with ADHD and controls. There is a high degree of overlap between the control and ADHD groups; such volume changes cannot be seen on an individual MRI. Thus, as yet, MRI is not part of the clinical evaluation for ADHD.

fMRI IN ADHD

The attention networks described in Chapter 7 are logical places to look for deficits in patients with ADHD. Over the last several decades, many neuroimaging studies have been conducted in which patients with ADHD and controls performed tasks requiring inhibitory control during the scan. Hart, Radua, Nakao, Mataix-Cols, and Rubia (2013) conducted a meta-analysis of these studies; the results of which are shown in Plate 9. The brighter the orange color in the area of the brain, the greater that region is activated in controls relative to those with ADHD. The right IFC and the dorsal anterior cingulate gyrus (ACC), now well known to us as parts of the dorsal attention and control networks, were more active in controls, especially during inhibitory control tasks (Plate 9A). In Plate 9B, the cuneus is more *active* in ADHD than in controls during attention tasks.

Connectivity between brain regions appears altered in ADHD as well. As discussed in Chapter 7, the default mode and attention/control networks are in opposition to each other. Resting state MRI is assessed while the participant lies quietly with his or her eyes open, in contrast to the task-based MRI summarized in the Hart and colleagues (2013) meta-analysis. The correlations between different brain regions are studied to reveal the nature of brain networks (see Plate 7). A large-scale resting state fMRI study compared 481 controls with 276 adolescents with ADHD (Sripada et al., 2014). The results are shown in Plate 10. The dots are the nodes of the network: red = default mode network, blue = visual network, brown = frontal–parietal control network, and purple = ventral attention network. The brains of those with ADHD exhibited increased resting state connectivity between the default network and the ventral attention network, which means that there was a lack of the normal anti-correlation between these regions. As shown in Plate 10, there was a lack of connectivity *within* the various networks, as well as between the frontal–parietal control network and the other networks. The default mode network activity was further assessed in children with ADHD and controls while they performed a task under both high- and low-reward activity (Liddle et al., 2011). Control children strongly deactivated the default mode during the task, regardless of the magnitude of the reward. When children with ADHD were offered only a small reward, the default mode remained on during the task; only a large reward caused it to deactivate.

Tomasi and Volkow (2012) used a large public database containing de-identified resting state fMRI scans on 247 children and 307 controls. They examined correlations of activity between brains regions very close to each other, as well as long-range, cross-network correlations. Consistent with Sripada and colleagues (2014), children with ADHD had lower connectivity (short- and long-range) in regions of the dorsal attention and default-mode networks. In children with ADHD, the orbitofrontal cortex had *higher* connectivity with reward-motivation regions (ventral striatum and anterior cingulate) and *lower* connectivity with superior parietal cortex (part of the dorsal attention network). This indicates that people with ADHD may have less top-down control yet be more influenced by reward.

REWARD IN ADHD

Reward and punishment appear to work very differently in those with and without ADHD. Like the marshmallow eaters in the Stanford study, children and adults with ADHD have difficulty delaying gratification. They want an immediate reward and often cannot work for a long-term reward. Saying, "I will give you a dollar for every passing grade on your report card in 6 weeks" simply does not work for a child with ADHD. They often lose interest in rewards after they are given. Plichta and Scheres (2014) reviewed fMRI studies examining the activity of the ventral striatal reward network in individuals with ADHD versus controls. In these studies, participants performed tasks for which they earned a reward (usually monetary). Six of seven studies showed that when subjects with ADHD were anticipating a reward, they showed *less* activation of ventral striatum. Moreover, low ventral striatum responsiveness correlated with more severe ADHD symptoms (particularly those of impulsivity–hyperactivity). There is, however, a paradox to be unraveled. Note that in the study by Casey and colleagues (2011), the grown-up former marshmallow eaters had *increased* ventral striatal activity. Plichta and Scheres showed that in non-ADHD, healthy populations, activity of the ventral striatum is *positively* correlated with impulsivity, the exact opposite of what occurs in ADHD. They suggest that perhaps the dopamine input into the ventral striatum is genetically distinct in persons with ADHD compared to controls. That is, people with ADHD have abnormally low dopamine levels in the ventral striatum, reversing the normal, positive relationship between ventral striatal responsiveness and impulsivity. Alternatively, the negative correlation in patients with ADHD is actually between ventral striatal responsiveness and *symptoms* of ADHD, and not impulsivity per se. The subtleties of this latter argument are beyond the scope of this chapter. The main point of both arguments is that there are abnormalities in the way people with ADHD respond to reward at a neurobiological level.

DOPAMINE, NOREPINEPHRINE, AND STIMULANT TREATMENT OF ADHD

Patients with ADHD are commonly treated with the stimulant medications methylphenidate and amphetamine, which are highly effective for reducing symptoms of inattention and hyperactivity (Pliszka, 2012). Acutely, stimulants bind to the transporters of norepinephrine and dopamine, blocking their reuptake and increasing their levels in the synaptic cleft. As we saw in Chapter 4, these neurotransmitters are very involved in both executive function and reward processing. Rubia and colleagues (2014) performed a meta-analysis of 14 fMRI data sets involving 212 children with ADHD who took a single dose of methylphenidate treatment while undergoing functional MRI and performing an inhibitory control task. The stimulant consistently was found to enhance right IFC/insula activation.

fMRI does not tell us directly about actions of dopamine or norepinephrine in the brain. In positron emission tomography (PET), the patient is injected with a positron-emitting substance such as raclopride that binds to dopamine receptors and the dopamine transporter. Compared to controls, adults with ADHD have fewer D_2 and D_3 receptors, as well as fewer dopamine transporter reuptake sites in the midbrain and in the dorsal and ventral striatum (Volkow et al., 2007). The lower levels of dopamine receptors correlate with lower ratings of motivation on a self-rating scale (Volkow, Wang, Newcorn, et al., 2011). Using a different positron-emitting substance, Vanicek and colleagues (2014) mapped norepinephrine transporters; no differences were found between medication-naive adults among individuals with ADHD and controls.

The effect of a stimulant on dopamine function also can be assessed with PET. After the raclopride binds to the receptors, the stimulant is given. As the stimulant enters the synaptic cleft and blocks the dopamine reuptake, the extra dopamine pushes the raclopride off the dopamine receptors. The drop in raclopride binding (measured as less "glow" on the PET image) is thus a measure of dopamine availability. Volkow and colleagues (2012) measured this effect in 20 adults with ADHD, first at baseline, before they had any treatment, then again after 12 months of treatment with methylphenidate. Both at baseline and at follow-up, the methylphenidate reduced raclopride binding (i.e., it made dopamine more available). The more dopamine was increased in the ventral striatum, the greater the clinical improvement of the patients' ADHD symptoms. This is not to say that only dopamine plays a role in stimulant action; norepinephrine probably does so as well. However, no method has been developed to assess stimulant effects on norepinephrine at the present time.

It would be tempting to conclude that increasing brain dopamine is the central event in the treatment of ADHD. As with all things in human neurobiology, it is not that simple. Drugs that directly affect norepinephrine (e.g., bupropion, atomoxetine, clonidine, or guanfacine) and have no direct

effect on dopamine are effective for ADHD. More curious is the fact that agents that are dopamine agonists but have no effect on norepinephrine are minimally effective in ADHD (Pliszka, McCracken, & Maas, 1996; Zametkin & Rapoport, 1987). Stimulants, which act on both norepinephrine and dopamine, remain the most effective agents, suggesting that dual action on both neurotransmitters is key.

The effects of stimulants on dopamine alone have an added layer of complexity. In the PET studies, it is the dopamine in the entire extracellular space around the neuron that is assessed. Figure 9.2 shows that dopamine in fact exists in two "pools" around the neuron: tonic dopamine (black circles) and phasic dopamine (open circles) (Grace, 1991, 1995, 2001). Tonic dopamine is released in response to glutamate binding to a glutamate hetereoreceptor on the end of the dopamine neuron (triangles, Figure 9.2A). As the name implies, tonic dopamine lingers in the extracellular space, where it attaches to the presynaptic dopamine receptors. Stimulation of these receptors results in *less* release of phasic dopamine when the dopamine neuron fires. Figure 9.2A shows a modest activation of the postsynaptic neuron when in this situation. In Figure 9.2B, there is a decreased input from the glutamate neuron, and thus less tonic dopamine, and the presynaptic dopamine autoreceptors are unstimulated. Now when the dopamine neuron fires, there is a massive release of phasic dopamine, leading to an exaggerated response in the postsynaptic neuron. In Figure 9.2C, the glutamate neuron is highly active, leading to an increased tonic pool of dopamine. With many more autoreceptors occupied, very little dopamine is released in response to neuronal firing, leading to a diminished response in the postsynaptic neuron. Based on the interaction between the tonic and phasic pools, it appears that with dopamine, "less is more" and "more is less." The decreased dopamine seen in the PET studies of individuals with ADHD might be due to a decreased tonic pool or a decreased phasic pool; the imaging technique is not sensitive enough to distinguish them.

LONG-TERM EFFECTS OF STIMULANTS ON THE BRAIN

Many patients with ADHD take stimulant medication for many years. What are the long-term effects on brain development? Shaw and colleagues (2009) followed 43 children with ADHD into adulthood; 19 of these stopped taking medication at some point based on their own (or their parent's) choice. Thus, it is important to bear in mind that this was not a controlled study. Patients underwent anatomical MRI at numerous intervals as they grew up. At age 16, patients who remained on stimulants had rates of cortical thinning indistinguishable from that of controls, while those who discontinued stimulants had greater rates of cortical thinning than that of controls. These findings particularly were marked in the left middle/IFG,

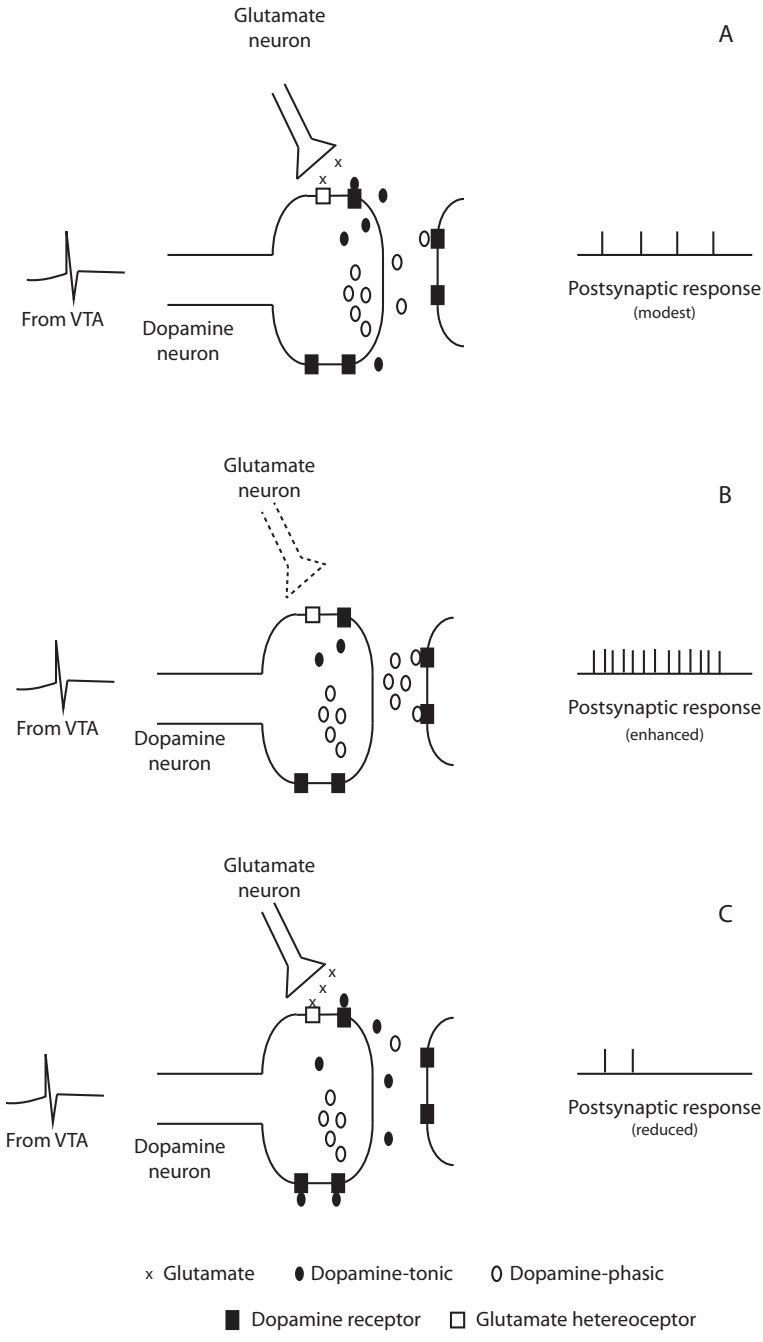


FIGURE 9.2. Tonic and phasic pools of dopamine and the modulation of dopaminergic neuronal firing.

the right medial frontal cortex, and the right posterior parietal–occipital cortex. While certainly not proving that stimulants are "good for the brain," the results argue strongly against any notion that long-term stimulants are harmful to brain development.

EMOTIONAL REGULATION IN ADHD

Patients with ADHD tend to be emotionally reactive, as well as cognitively impulsive (Barkley, 2014c). They are more likely to have bursts of irritability and lose their tempers more easily, and up to half of children with ADHD have a comorbid oppositional defiant disorder (ODD; Pliszka, 2009). Posner and colleagues (2011) asked adolescents with ADHD, as well as controls, to look at faces while undergoing fMRI. During the scan, angry faces were presented subliminally (so rapidly that they did not register in consciousness). The amygdala activates in response to such faces. Relative to controls, adolescents with ADHD have greater amygdala activity when looking at subliminal angry faces. Posner and colleagues also looked at connectivity between cortical regions and the amygdala. Adolescents with ADHD exhibited greater connectivity between the amygdala and the lateral ventral prefrontal cortex. In the same study, stimulants reduced the abnormal amygdala activity in response to subliminal angry faces, as well as normalized the excessive amygdala-lateral prefrontal cortex connectivity. In a study by another group (Hulvershorn et al., 2014), children with ADHD who had high ratings of emotional lability were found to have greater connectivity between the amygdala and ACC than controls or children with ADHD who were not emotionally labile. These two studies suggest an abnormally increased influence of the limbic system on cortical functions in patients with ADHD (particularly those with mood dysregulation).

GENETICS OF ADHD

Twin studies compare concordance rates for ADHD in monozygotic and dizygotic twins to determine the relative influence of genes and the environment on the variance in symptoms of a disorder, as discussed in Chapter 5. About 71–90% of the variance in ADHD traits is found to be attributable to genetics (Thapar, Cooper, Eyre, & Langley, 2013). Heritability estimates include the effects of gene–environment interaction; thus, the high heritability rates in ADHD do not minimize the effect of environment (see next section). Despite decades of studies, major genes for ADHD have not been identified. Risk alleles of candidate genes mainly involving the dopamine and serotonin systems are associated with ADHD but account for

only a small portion of the variance. In contrast, genome-wide association studies (GWAS) involving tens of thousands of subjects have *not* revealed any gene variant that passes the very high statistical threshold for genome-wide significance (Neale et al., 2010). There is evidence that small deletions or duplications of copy number variants (CNVs) are found more often in patients with ADHD, particularly those with comorbid developmental disabilities (Williams et al., 2010).

Since individual genes rarely passed the stiff threshold for genome-wide significance, a different approach is to examine the top-ranking genes in multiple ADHD genetics studies (Poelmans, Pauls, Buitelaar, & Franke, 2011). Single-nucleotide polymorphisms (SNPs) were identified in 85 genes. Forty-five of these genes code for proteins involved in neurodevelopmental and neuron growth (the other 40 could not be so linked). Many of these genes were found to overlap with those involved in dyslexia; several are known to have their transcription rates affected by stimulant medications. This will be an emerging theme in future studies—that psychiatric disorders are related to scores (if not hundreds) of genes that work together, as well as in conjunction with the environment, to produce a disorder. What does it mean to have 85 genes implicated in a disorder? Imagine how many different combinations of these risk genes (if they are validated in future studies) might result in ADHD or any other psychiatric disorder. If nothing else, it means there never will be a simple genetic test for ADHD. Also, it suggests that ADHD is a syndrome, just like "connective tissue disease" or "cancer," with many different causes and potential treatments.

ENVIRONMENTAL FACTORS

Twin studies also tell us something about the nature of the environmental factors affecting an illness (see Chapter 5). The amount of variance attributed to the environment can be parsed to shared factors (things the twins have in common, e.g., socioeconomic class) and nonshared factors (e.g., one twin has a head injury, the other does not). In ADHD, shared environmental factors do not appear to contribute anything of significance to the differences between the twins in heritability studies (Barkley, 2014d). In a group of twins "discordant" for ADHD (one has it and the other does not), we cannot attribute this discrepancy to things they share in the environment such as income level, school they attend, and general childrearing methods, unless we assume that parents are treating one member of the twinship differently. In contrast, twins can have different experiences of a neurobiological nature (e.g., birthweight, advantageous position in womb, head injury) that are not shared and these do seem to be related to ADHD.

Maternal smoking during pregnancy and pre/perinatal adversity also have been established as risk factors for ADHD (Mick, Biederman, Faraone, Sayer, & Kleinman, 2002; Mick, Biederman, Prince, Fischer, & Faraone, 2002). Children with ADHD exposed to smoking during pregnancy have more severe behavioral problems, lower IQ scores, and poorer neuropsychological test performance than nonexposed children with ADHD (Thakur et al., 2013), even when researchers control for income level, ethnicity, mother's age, and alcohol use. In an Australian population-based case–control study, over 12,000 children with ADHD were compared to over 30,000 controls on a wide variety of maternal, pregnancy, and birth data (Silva, Colvin, Hagemann, & Bower, 2014). Compared with the control group, mothers of children with ADHD were significantly more likely to be younger, single, or to have smoked in pregnancy. They also were more likely to have had induced labor and to have had preterm labor, preeclampsia, or an early-term delivery.

That these perinatal factors, especially maternal smoking, play a role in ADHD seem to be at odds with the earlier assertion that "shared" environmental factors are not important in the etiology of ADHD. Since the twins share the womb, do they not share the environment of exposure to maternal smoking? Here, things get complicated in two ways. First, maternal smoking could induce epigenetic effects, marking the epigenome of both twins in the same way. Second, women who cannot or do not quit smoking during pregnancy are likely to have addiction to nicotine and ADHD themselves; thus, their genetic loading is creating the environment. Once these factors are controlled, the contribution of maternal smoking to ADHD may itself turn out to be driven by genetics (gene-by-environmental correlation; see Chapter 5).

Given the rising rate of ADHD diagnoses, it is tempting to ask whether modern childrearing practices or cultural factors contribute to ADHD. This is particularly true given the early exposure of children and even infants to electronic media. This area is plagued by the classic "chicken and egg" problem. People with ADHD cannot delay gratification and are reward seeking; thus, they are more likely to want to watch television and play with their smart phones (Barkley, 2014d). Nonetheless, excessive interest in electronic media is likely detrimental to those with ADHD because it may distract from academic tasks or other important social experiences. A similar argument arises regarding childrearing practices. Are modern parents too permissive? Or conversely, are they too harsh? Given genetics, many parents of children with ADHD have the disorder themselves, leading to distracted parenting and an impulsive parenting style. It was shown many years ago that when children with ADHD are treated with stimulants, parents reduce their negative parenting behavior as their child's behavior improves (Barkley & Cunningham, 1979). There also is some evidence that

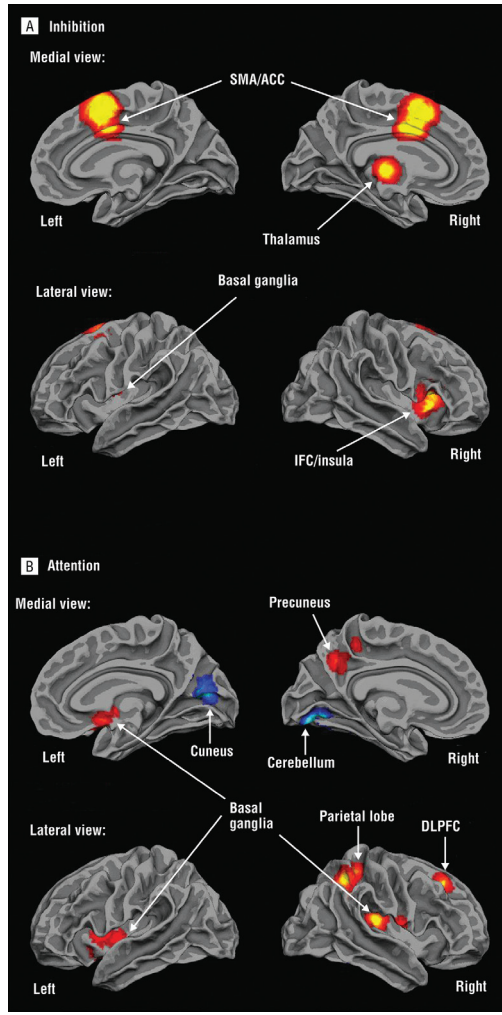


PLATE 9. Inhibition tasks and attention tasks. (A) All inhibition tasks together. Regions of decreased (red and orange) and increased (blue) activation in patients with ADHD compared with healthy controls. Decreased activation in patients with ADHD relative to healthy controls is shown in the right inferior prefrontal cortex (IFC) extending into the insula, in a cluster comprising the supplementary motor area (SMA) and the cognitive division of anterior cingulate cortex (ACC), in the left caudate extending into the putamen and insula, and in the right midthalamus. (B) Attention tasks. Decreased activation in patients with ADHD is shown in the right dorsolateral prefrontal cortex (DLPFC), in the left putamen and globus pallidus, in the right posterior thalamus (pulvinar) and caudate tail extending into the posterior insula, in the right inferior parietal lobe, and in the precuneus and superior temporal lobe. Increased activation in patients with ADHD relative to healthy controls was seen in the left cuneus and in the right cerebellum. Reprinted from Hart, Radua, Nakao, Mataix-Cols, and Rubia (2013) with permission from the American Medical Association.

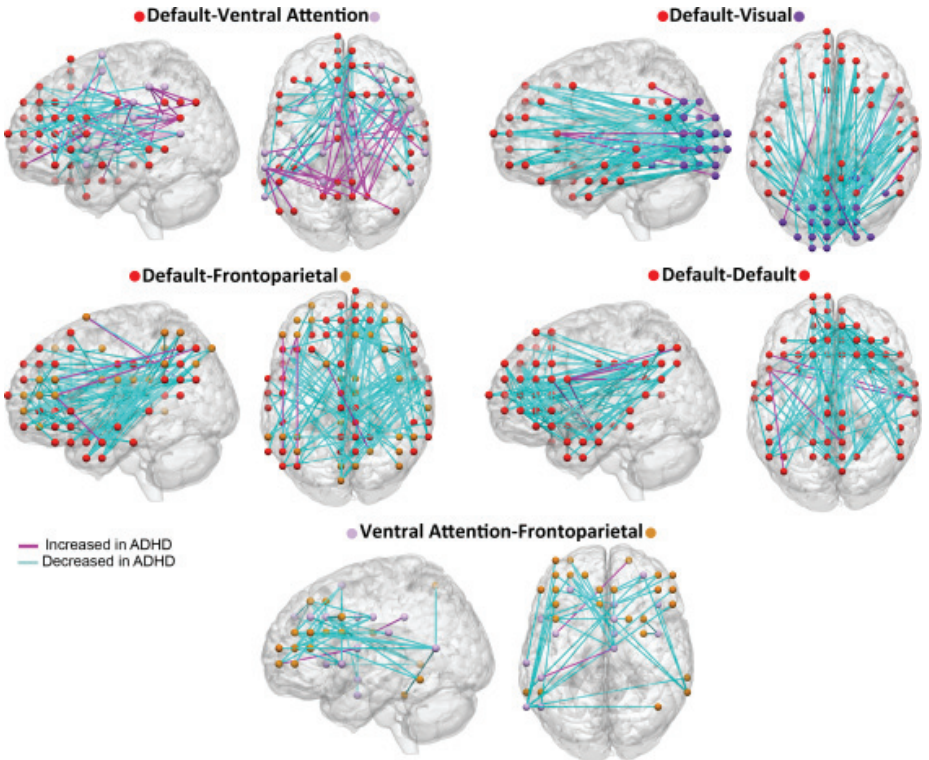


PLATE 10. Three-dimensional visualization of abnormal network interconnections. ADHD brains exhibited abnormal network-to-network interconnections involving five network pairs. Each of these five sets of abnormal network-to-network interconnections is rendered separately on sagittal and axial views of a canonical brain. ADHD, attention-deficit/hyperactivity disorder. Reprinted from Sripada et al. (2014) with permission from John Wiley & Sons, Inc.

when parents with ADHD are treated, they also improve their childrearing skills (Wang, Mazursky-Horowitz, & Chronis-Tuscano, 2014).

Nonetheless, an environment filled with distractions and opportunities for sensation seeking may be a world in which it is more difficult for individuals with ADHD to live. A child with mild ADHD in the 1950s might have had nothing but his or her toys and the three television networks (mostly showing adult shows) to distract from doing his or her homework. Perhaps, no need for treatment would have been perceived, since impairment was minimal. In today's world, the child must resist temptation from the computer, the smartphone, the video game, and the endless entertainment available online. In this model, the overstimulating environment is not causing the ADHD. Rather, it is much more difficult for the child with ADHD to cope, and this triggers greater impairment and referral for treatment.

SUMMARY

The genetic, neuroimaging, and treatment research suggests broad deficits in attention, default mode, and reward networks. As shown in Figure 9.3, there is likely an impairment of "top-down" attention networks and an excessive connectivity of reward and emotional regulation networks. Default mode is inappropriately connected to attention networks. This results in an individual who does not utilize "top-down" attention control. Intrusion of default mode network into active attention produces erratic and variable performance on tasks. The ventral striatum may be hyporesponsive to anticipation of reward (possibly due to low dopamine), leading to motivation deficits. Paradoxically, however, those reward networks are overconnected to the cortical areas, making the individual unable to delay gratification. Not shown in Figure 9.3 but potentially also important in the disorder are cerebellar deficits that may lead to subtle deficits in motor coordination and timing.

Not every individual with ADHD has every one of these deficits. Importantly, all of the disturbances illustrated in Figure 9.3 are not unique to ADHD. As we study other disorders, we will find problems in attention, inhibitory control, response to reward, etc. This is a good time to review Table 1.3 and be reminded of the fact that the neurobiology is linked to these broad functions rather than to the disease per se. It is the combination of deficits in the various circuits that leads to the expression of disease in a given individual. Since ADHD is a major risk factor for substance abuse and maladaptive aggression, it is logical to examine those issues next.

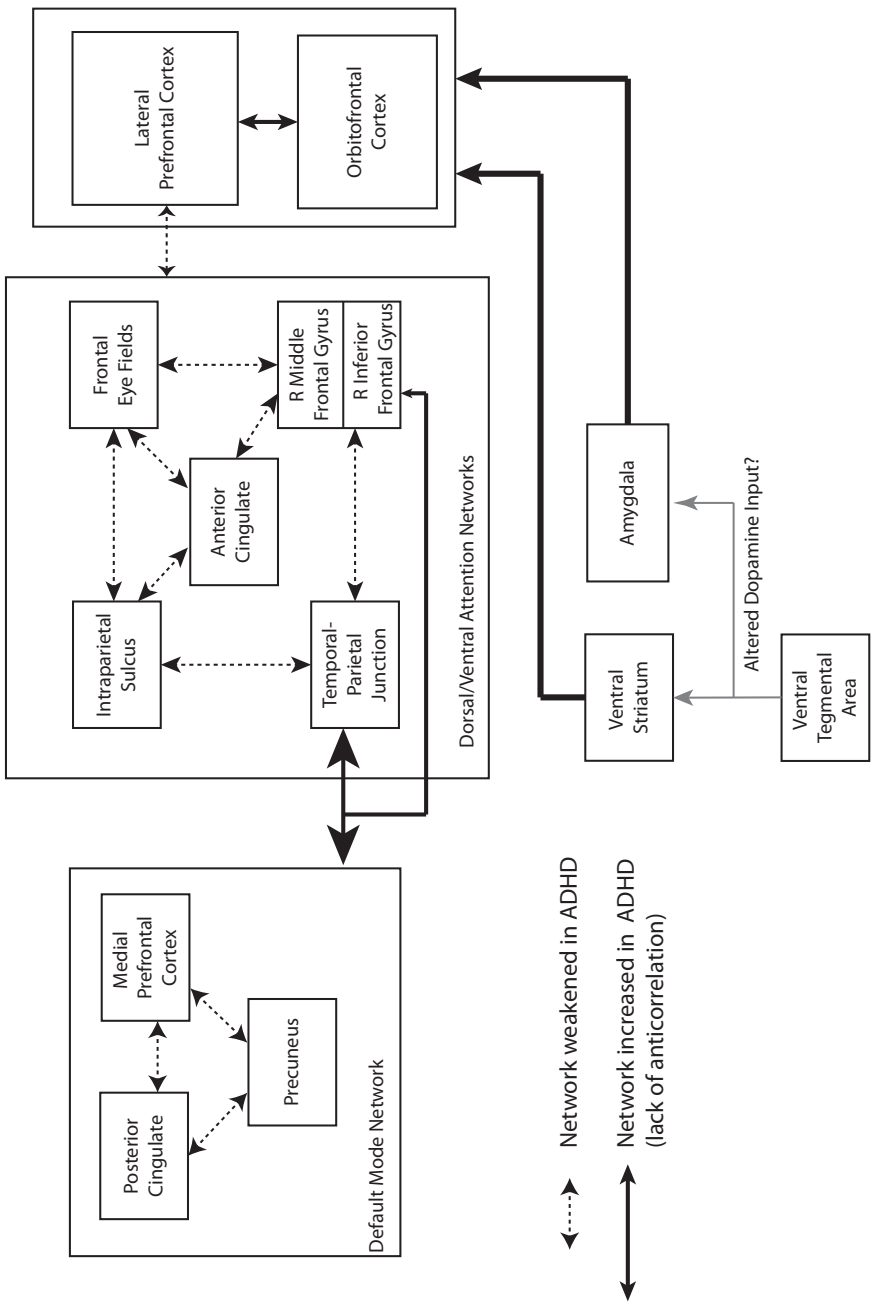


FIGURE 9.3. Hypothesized neural networks thought to be disturbed in ADHD.

CHAPTER 10

Aggression, Antisocial Behavior, and Substance Abuse

Human beings commonly engage in a wide range of maladaptive behaviors that violate societal standards, are harmful to others, or involve consuming pleasure-inducing substances to the point of addiction. These behaviors often occur in the same individual, and the neurobiological research on them tends to implicate similar systems, making it logical to address them in the same chapter. "Psychopathy" (antisocial personality in DSM-5) comprises a subset of persons who engage in antisocial behavior; psychopaths lack empathy for others and any sense of remorse regarding their behavior. The study of neurobiological factors in crime and antisocial behavior is referred to as "neurocriminology" (Glenn & Raine, 2014; Raine, 2013) and may play a greater role in the future in both the court system (in adjudicating individual cases) and in making criminal justice policy. (See Box 10.1 for a discussion of the ethical and political issues on this matter.)

Crime rates in the United States and Western Europe have undergone enormous swings in the last 50 years (*www.bjs.gov*; *www.fbi.gov/about-us/ucr/ucr*). In the United States, the total crime rate was about 2,000/100,000 persons in 1960. It then began a sharp rise to a peak of 6,000/100,000 and has been falling ever since, dropping to less than 4,000 in 2012. In 1990, 2,245 people were murdered in New York City, whereas in 2014, there were only 328 homicides, a drop of 85%! There is no consensus among criminologists as to the reason for this drop. In the United States, there was a dramatic increase in the number of people sent to prison, but similar drops in crime rates have been seen in Europe and Canada, where prison populations have not risen (*http://ec.europa.eu/eurostat/web/crime/database*; *www.statcan.gc.ca*). Part of this drop is

BOX 10.1. Ethical and Political Issues in Neurocriminology

Perhaps even more so than other mental disorders, the concept of biological factors in criminal behavior raises ethical and political issues. Unfortunately, the discussion is rarely well informed, and many social commenters argue from the incorrect premise that "biological" means "genetic," which means the condition is permanent and the person is inferior. The far right endorses this idea; the far left fears it. Of course, no scientist is saying this; we have seen already that the environment can work through biology and if something is genetic, there certainly can be treatments for it. Today, this is mostly a "straw man," erected by those who oppose any study of biology in criminology and behavior in general. Why should this be so?

People with very severe mental disorders (chronic psychosis, intellectual disability) may be found "not guilty by insanity" when charged with a crime. This means that they did not have the capacity to know that what they did was wrong (or cannot participate in their defense). This is to be distinguished from "capacity." An "incapacitated person" is an individual who, for reasons other than being a minor, is unable to receive and evaluate information or to make or communicate decisions to such an extent that he or she lacks the ability to meet essential requirements for physical health, safety, or self-care, even with appropriate technological assistance. Such persons are appointed guardians by the court. These people are generally very cognitively impaired (e.g., those with intellectual disability or dementia). Beyond this, our society grants autonomy or free will to persons, and they are held accountable in the event of wrongdoing.

The question in neurocriminology is whether the kinds of brain changes we have discussed (whether they arise from either genetics or environment) constitute a type of diminished capacity. For instance, if changes in the frontal lobe due to child abuse result in increased impulsivity, what are we to do with this knowledge in the legal setting? The person knows what he or she did was wrong (and therefore is not insane), but finds it *more difficult, if not impossible*, to resist the impulse. Should the person be found not guilty or be given a reduced sentence, since this would be a mitigating factor? Here, those on the right fear the breakdown of moral order, while those on the left, who were so fearful of "genetic" theories, have no problem using neuroscience arguments to help end the death penalty, because the person "was not responsible."

There is no easy answer to this conundrum. We should, however, be aware that we cannot have both diminished capacity and full autonomy. If a person cannot control his or her impulses because of a brain disorder (and we cannot yet cure the disorder), then his or her autonomy must be curtailed, for example, by the appointment of a guardian or mandatory residential placement. Yet we increasingly live in a "disability" culture in which persons want to be free of responsibility and even be compensated by the state for their condition, yet have no restrictions on their right to do whatever they want, which includes engaging in maladaptive behavior!

related to the aging of the population in the developing world: People tend to commit crimes during their teens and 20s. However, crime has dropped within the younger age cohort itself. Nonetheless, in 2013, 2.6% of people in the United States reported being a victim of a violent crime (*www.bjs.gov/index.cfm?ty=pbdetail&iid=5111*). Much antisocial behavior, particularly domestic violence, goes unreported. In children and adolescents in the United States, most antipsychotic medication is prescribed not for psychosis but for severe aggressive behavior. The rate of such prescriptions has risen markedly in the last several decades (Patel, Crismon, & Shafer, 2006). In 2012, 9,445,000 people were arrested: 13% of these were for drug offenses, and 14% were for alcohol-related offenses. Thus, a better understanding of the root of antisocial and addictive behaviors would have a marked impact on public health.

AGGRESSION AND ANTISOCIAL BEHAVIOR

Age of Onset, Attention-Deficit/Hyperactivity Disorder, and Criminal Behavior

A number of studies have shown that attention-deficit/hyperactivity disorder (ADHD) in early childhood, particularly when combined with family adversity and learning disability, is highly predictive of delinquent behavior during the teenage years. Loeber, Brinthaupt, and Green (1988) examined the number of multiple criminal offenders in a sample of adolescents. Only 1.7% of adolescents without ADHD or conduct disorder were multiple offenders; among those with ADHD without conduct disorder, 3.4% were so classified. In contrast, 20.7% of adolescents with conduct disorder but no history of ADHD were multiple offenders. In the comorbid ADHD–conduct disorder group, nearly one-third (30.8%) had committed multiple crimes. Farrington, Loeber, and Van Kammen (1990) collected data on hyperactivity and conduct problems in a large, nonreferred sample of schoolchildren and followed up on the number of juvenile convictions the participants acquired over time. Again, hyperactivity and conduct problems independently predicted delinquency. About 24% of children with ADHD had juvenile convictions (compared to 12.6% of controls), but 46% of the children with ADHD–conduct disorder had become delinquent. Thirty-five percent of children with conduct disorder in the absence of ADHD were later convicted of juvenile offenses. Thus, it is not ADHD alone but ADHD in conjunction with the early onset of conduct disorder that particularly predisposes individuals to later criminal behavior.

Moffitt (1993) reviewed the neuropsychology of conduct disorder and delinquency. She pointed out that delinquents showed an overall deficit of one-half standard deviation (about 8 IQ points) compared with

nondelinquent peers. For delinquent samples as a whole, neuropsychological tests showed statistically significant but clinically mild impairments in cognitive functioning. Few children with conduct disorder or delinquency are identified as brain damaged, as defined by the presence of severe signs such as aphasia or sensory loss. In the Dunedin (New Zealand) Multidisciplinary Health and Development study, Moffitt noted that IQ differences between offenders and controls varied greatly based on the seriousness of the offenses. Those adolescents who engaged in transient delinquency showed only a one point mean IQ difference relative to controls, whereas those aggressive delinquents who had been antisocial since early childhood showed a 17 point mean difference relative to controls. Many other studies have shown that low IQs predispose individuals to antisocial behavior; persons with above-average IQs are far less likely to engage in criminal activity, even when raised in high-risk environments.

As part of the Dunedin study, neuropsychological tests were administered to a large epidemiological sample of 13-year-olds (Moffitt & Silva, 1988). The sample was subdivided as follows: children with no history of ADHD or delinquency (n = 558), children with ADHD who had no history of delinquency (n = 14), delinquents with no history of ADHD (n = 87), and delinquents with ADHD (n = 19). The authors controlled for the effects of family adversity factors on test performance. Overall, the delinquents performed more poorly than the nondelinquents on the verbal, visual–motor integration, and visual–spatial measures, but the two delinquent groups had very different neuropsychological profiles. Delinquents with ADHD scored significantly below the delinquents without ADHD on the verbal and visual–motor integration measures. Children with ADHD who did not become delinquent, as well as delinquents without ADHD, were not markedly different from controls on the neuropsychological measures.

Moffitt (1990) then examined longitudinal data for 435 boys divided into the four groups mentioned previously. Delinquent boys without a history of ADHD did not begin their antisocial behavior until around age 13, whereas delinquent boys with ADHD showed antisocial behavior as early as age 5. Controls, delinquents without ADHD, and boys with ADHD but without delinquency were similar in Verbal IQ and reading ability, whereas delinquents with ADHD showed deficits in both of these areas. Delinquent boys with ADHD had experienced much greater family adversity than those in the other three groups. At follow-up at age 15, delinquents with ADHD had committed more aggressive acts of delinquency. Overall, there was a distinct pattern of symptoms in the boys with ADHD who would become delinquent. Low Verbal IQ was noted as early as age 3; ADHD was then diagnosed at age 7. These children also experienced greater family adversity. They then went on to commit more aggressive delinquent acts by age 15.

Family Environment, Aggression, and Crime

There is a voluminous literature examining a wide variety of environmental factors that contribute to crime (Farrington, 2011). These include (1) criminal or antisocial parents, (2) large family size, (3) childrearing methods, (4) abuse and neglect, (5) parental conflict/family disruption, and (6) other parental factors such as young age, substance abuse, or depression. Sixty-three percent of boys with a father convicted of crime have a conviction themselves by midadulthood (Farrington, Coid, & West, 2009). In terms of child rearing, the most important dimensions are supervision and monitoring of the child's behavior, consistent rewards and punishments for behavior, parental warmth, and parental involvement. Twenty-one percent of white males who were physically punished by slapping or spanking had a criminal conviction in adulthood compared to 8% of those who were not (Farrington, Loeber, & Stouthamer-Loeber, 2003). Interestingly, families that produce children who become criminals tend to have both high rates of physical punishment and a lack of supervision or low parental involvement.

Childhood victims of abuse or neglect were more likely than controls to have a juvenile or adult arrest for any nontraffic offense (49 vs. 38%) and for a violent crime (18 vs. 14%); almost half the victims of child abuse were arrested for a nontraffic offense by age 32 (Widom & Maxfield, 1996). Abuse and neglect turn out to be major factors in mood and anxiety disorders as well. Abuse is associated with all of the other five factors reviewed earlier; more importantly for our purposes is that abuse may have direct toxic effects on the brain. I discuss this in more detail in Chapter 11 on posttraumatic stress disorder (PTSD). Note that many abused children do not grow up to commit crimes or become violent. A major factor, of course, is the severity of the abuse and the age at which the abuse occurred. Another factor is gene-by-environment interactions, which I discuss shortly.

How Aggressive Children See the World

When we face conflictual situations with others, we must process the complex information about the other person's intent and determine our response, a process referred to as "social information processing." There are various stages of social information processing (Dodge, 2006). First, we must *encode* information about a social situation. This includes information about tone of voice, facial expression, and the type of setting in which we are involved. Often a social cue is subtle, such as the raising of an eyebrow. Once encoded, social cues must be interpreted as friendly, neutral, or hostile. Next, we select a goal for our interaction (to obtain something or stop a hostile action) and generate possible responses (walk away, talk with the person, or be aggressive). Finally, we choose from among the responses. In choosing a response, we also have certain expectations about how successful those responses will

be in getting us what we want. In Dodge's studies, children viewed videotapes of social interactions in which possible conflict exists. Children were asked to interpret what went on in the tape and to discuss how they would respond, and what they think the consequences of their actions would be. When looking at social situations, aggressive children encode fewer relevant cues and do not seek out additional information when the situation is ambiguous. They are more likely to interpret ambiguous cues as hostile. As for goal selection, aggressive children seek dominance and control, and generate fewer potential responses to a problematic social situation. There is a negative correlation between the number of responses and the child's rate of aggression. In terms of response decision, aggressive children view aggression as producing more desirable outcomes; they are more likely to see aggression as leading to tangible rewards and peer-group approval, and do not see their victims as suffering any real harm. The encoding and the response–decision phases are key because these may differ in children with different subtypes of aggression.

Aggression has been subtyped in the research literature as proactive versus reactive. Although many aggressive children show aspects of both types of aggression, certain children can be reliably classified as having predominantly "proactive" (well planned, instrumental, and affectless) or "reactive" (impulsive, hostile, and affective) aggression (Vitiello & Stoff, 1997). Dodge, Harnish, Lochman, and Bates (1997) classified both a large population of third graders and a group of adjudicated juvenile offenders as showing either proactive or reactive aggression. Participants viewed videotapes of social interactions. Each student was asked to imagine being the protagonist. In the community sample, encoding errors were found in the reactive aggressive children, whereas the proactive aggressive children were more likely to anticipate positive outcomes for aggression. Similar results were found for the offender sample. Reactively aggressive offenders (who also had suffered more abuse as children) made more encoding errors, whereas the proactively aggressive offenders expected aggression to reduce aversion.

Genetics of Antisocial Behavior

Adoption studies show a modest genetic effect on antisocial behavior. Decades ago, Schulsinger (1972) found, in studying adoptees with "psychopathy" (antisocial personality), a higher rate of psychopathy among the adoptees' biological relatives (14.4%) than among their adoptive relatives (7.6%). Adopted-away offspring of antisocial parents show higher rates of antisocial behavior than adopted-away offspring of noncriminal biological parents (Cadoret, Cunningham, Loftus, & Edwards, 1975; Crowe, 1978). Mednick, Gabrielli, and Hutchings (1984, 1987) performed a major "cross-fostering" study. All Danish adoptions between 1924 and 1947

were reviewed. Cases fell into four groups, as shown in Table 10.1: children for whom neither the biological nor adoptive parent was antisocial (control group), children for whom *both* the biological and adoptive parent were antisocial (high-risk group), children of antisocial biological parents who were reared by non-antisocial parents, and children of non-antisocial biological parents who had antisocial adoptive parents. It was then determined whether the adoptees had criminal records of any kind. Examining the bottom row of Table 10.1, we can see that simply having an antisocial parent is not sufficient to increase the risk of having a criminal conviction; the two groups in the bottom row are not statistically different from each other. It is in the high-risk group, having both genetic and environmental risks for antisocial behavior, that a statistically significant increase of criminal convictions is found. This suggests that a gene-by-environment interaction is required to express antisocial behavior. It is important to note that even in the high-risk group, nearly 75% still did not have a criminal conviction.

Twin studies also have been informative on the genetics of antisocial behavior. In general, monozygotic (MZ) twins are more similar than dizygotic (DZ) twins in antisocial behavior, though heritability is lower than that found for ADHD. In a large twin study, the heritability for juvenile antisocial personality was quite low (.07), whereas it was significant for adult antisocial personality (.43) (Lyons et al., 1995). DiLalla and Gottesman (1991) reviewed the literature on twin similarity for antisocial behavior. The concordance rate (how often the twins were both antisocial) differed in adult and juvenile studies. For juvenile studies, the concordance rates were .87 and .72 for MZ and DZ twins, respectively. For adult studies, the concordance rates were .51 for MZ twins and .22 for DZ twins. Again, the genetic effect was stronger for adult than juvenile antisocial behavior. At first, this seems at variance with the earlier statement that early-onset conduct disorder is associated with persistence of antisocial behavior into adulthood. In these twin studies, juvenile delinquency was most often assessed. These studies would include many individuals with adolescent-onset conduct disorder in whom genetic factors were less likely to be prominent. These individuals often desist in their antisocial behavior

TABLE 10.1. Rate of Criminal Records of Adoptees in a Cross-Fostering Study (Mednick et al., 1984, 1987)

	Adoptive parents with antisocial history	Adoptive parents with no antisocial history
Biological parents with antisocial history	24.5%	20.0%
Biological parents with no antisocial history	14.7%	13.5%

by adulthood. The more "genetically loaded" individuals will have early onset in childhood, then persist in their antisocial acts through adolescence and into adulthood. In contrast to ADHD, in which shared environment appears not to play a major role, shared environment such as family and neighborhood are important factors in the etiology of crime and aggression, which is not surprising in view of the studies reviewed previously.

As with ADHD, there have been multiple genome-wide association studies (GWAS) attempting to discover genes linked to aggression or violence (Raine, 2013). A meta-analysis of 185 studies constituting 277 independent associations on 31 genes found *no* association of any polymorphism and aggression (Vassos, Collier, & Fazel, 2014). Two genes stood out as possibly interacting with environment to influence aggressive behavior. Both are genes for enzymes influencing the catecholamine and serotonin systems: catechol-*O*-methyltransferase (*COMT*) and monoamine oxidase A (*MAOA*). *COMT* breaks down dopamine and norepinephrine in the brain; it represents another mechanism in addition to reuptake for controlling the levels of these neurotransmitters in the brain. Human beings have a variation in the gene called the Val158Met polymorphism. This single-nucleotide polymorphism (SNP) results in a substitution of a valine amino acid for a methionine amino acid at position 158. The Val form can break down dopamine at four times the rate of the Met form ("Val = V = very fast" is a good way to remember it). The *COMT* gene is found on chromosome 22, on the long (q) arm at position 11.21 (hence its name 22q11.21). If a piece of the gene is deleted (copy number variant [CNV]), even in one copy, the person develops a variety of disorders characterized by intellectually disability, facial defects, and heart problems (see Chapter 13). Such individuals are at high risk for various mood and psychotic disorders as well. Although the Val form of *COMT* also is associated with a variety of mental disorders, here we focus on antisocial behavior. Caspi and colleagues (2008) genotyped several large samples of children with respect to the form of *COMT* and assessed both their level of antisocial behavior and ADHD status. Children homozygous for the Val variant had more symptoms of conduct disorder, were more aggressive, and were more likely to be convicted of criminal offenses compared to those who had the Met/Met or Val/Met form. The combination of ADHD and Val/Val status resulted in even higher levels of criminality, but *COMT* status was not associated with ADHD itself.

MAOA also is an enzyme involved in the breakdown of norepinephrine and serotonin; the gene is located on the X chromosome. Like *COMT*, it is has both low- and high-activity variants in humans; the low-activity variant would presumably lead to higher levels of norepinephrine activity in the neuronal cleft. As males have only one X chromosome, the activity of *MAOA* is determined by the single allele (high or low) the boy inherits. The situation in females is more complex because they can have both a high or

low allele (heterozygous). Thus, most of the findings on *MAOA* are related to boys and men. A family in the Netherlands has been identified that has an X-chromosome-linked behavior disorder and mild mental retardation (Brunner, Nelen, Breakfield, Ropers, & van Oost, 1993). The males in this family are extremely aggressive. A mutation was identified in the *MAOA* gene, resulting in severe deficiency of enzyme activity. As far as can be determined, this is the only family in the world with this disorder. The two members of the family with the mutation who were studied showed higher levels of serotonin and lower levels of 5-HIAA, a main metabolite of serotonin. The *MAOA* gene can be knocked out of rodents; these rats show high levels of aggression, and their brains show low levels of 5-HIAA and very high levels of serotonin (Cases et al., 1995). Thus, we should be careful not to interpret the low 5-HIAA studies as always indicating that serotonin is decreased in aggressive–impulsive disorders. Factors that interfere with the breakdown of serotonin could lead to decreased 5-HIAA, while the serotonin amounts are in fact increased in the brain.

In a now classic study, Caspi and colleagues (2002) assessed antisocial behavior, history of child abuse, and *MAOA* activity in the children from the Dunedin study discussed earlier. They found that child abuse was very strongly related to future antisocial behavior. *MAOA* type did not have any effect on the antisocial behavior of children who had not been abused. However, if a boy suffered severe maltreatment, those with low *MAOA* activity showed a marked increase in a wide variety of measures of antisocial behavior relative to those with high *MAOA* activity. Male carriers of the low-*MAOA* allele were more likely to use a weapon or be involved in gang violence (Beaver, DeLisi, Vaughn, & Barnes, 2010). Byrd and Manuck (2014) performed a meta-analysis of 27 studies that examined this relationship between MAOA activity and abuse and found a robust effect in males, but not females. Intriguingly, this relationship holds for white European American males, but not for African American males (Widom & Brzustowicz, 2006). There are two possible explanations for this. Measures of antisocial behavior are highly based on arrest records, and it is a sad reality that African American boys and men are more likely to be the victims of biased policing; that is, if police are arresting African Americans for trivial or non-offenses, then arrest record is not an accurate measure of antisocial behavior. Alternatively, there could be subtle differences in the DNA sequence around the gene in African Americans relative to European Americans such that activity level of the gene is not being accurately classified in African Americans.

The relationship between low-*MAOA* activity and aggression holds true even in those who do not have criminal records (McDermott, Tingley, Cowden, Frazzetto, & Johnson, 2009). College students were genotyped with regard to *MAOA* activity, then brought into a laboratory setting to play a game with an imaginary opponent in another room. The opponent

"stole" money from the subject, and the subject was given the opportunity to punish the person by feeding the person hot sauce. Men with low-*MAOA* activity fed a significantly higher amount of hot sauce to their opponents than did the high-*MAOA* subjects.

Serotonin in Aggression and Impulse Control

In Chapter 4 we discussed how extensively serotonin is distributed in the brain. After its release from neurons, serotonin is converted by a series of enzymes into 5-hydroxyindoleacetic acid (*5-HIAA*). Does *5-HIAA* level in brain or spinal fluid indicate the level of serotonergic activity? It may be hard to say. On one hand, the more serotonin released, the more *5-HIAA* should be produced. On the other hand, if the activity of the *MAOA* enzyme is reduced, then serotonin cannot be turned into *5-HIAA* and low *5-HIAA* might represent "too much serotonin." It is instructive to look at some nonhuman primate data before examining the human data. In rhesus monkeys, *5-HIAA* levels are under substantial genetic control (> 50% of the variance) and are highly consistent within individuals over time, although environmental factors can affect the development of the serotonin system (Higley, King, et al., 1996). In adult rhesus monkeys, cerebrospinal fluid (CSF) *5-HIAA* is highly associated with measures of both aggression and social competence. Low-CSF *5-HIAA* is associated with high rates of prolonged, inappropriate aggression in both males and females. In rhesus monkeys living in the wild, CSF *5-HIAA* is positively correlated with prosocial behaviors such as grooming and physical proximity to other monkeys, whereas low-CSF *5-HIAA* is associated with increased intensity of aggression, more physical wounds, and greater risk taking (Higley, Suomi, & Linnoila, 1991). Monkeys low in CSF *5-HIAA* were more likely to take long leaps from trees at dangerous heights (Mehlman et al., 1994, 1995). Higley, Mehlman and colleagues (1996) collected CSF *5-HIAA* from monkeys and followed them in the wild over a 3-year period; 46% of the monkeys in the low-*5-HIAA* group were dead at follow-up, most likely because of increased aggression.

Chapters 1 and 5 introduced epigenetic effects of the environment on gene expression. Kraemer, Ebert, Schmidt, and McKinney (1989) first studied the effects of social rearing on the development of norepinephrine, serotonin, and dopamine systems ("biogenic amines") in rhesus monkeys. Twelve infant, male rhesus monkeys were reared by their mothers until age 10–14 months. This group was subdivided into those who continued to live with their mothers but were peer deprived and those who continued to live with their mothers and had contact with peers. Another group of six infant monkeys was deprived of both mother and peer contact. These monkeys were finally introduced to peers at age 15–21 months. The mother-reared, peer-deprived monkeys also were introduced to peers at age 21–22 months.

Serial measurements of CSF *5-HIAA,* norepinephrine, and homovanillic acid (HVA; the main metabolite of dopamine) were made throughout the monkeys' development. *5-HIAA* declined steadily from birth to 24 months for all the infant monkeys, regardless of social-rearing group. The effects of social rearing were most pronounced on the correlations of serotonin indices with the measures of the dopamine and norepinephrine systems. By 22 months, monkeys reared with mothers showed strong, positive correlations of *5-HIAA* with HVA, whereas no such correlation was noted in the other two groups of monkeys. These correlations suggest that social deprivation may disrupt the "entraining" of the dopamine and serotonin systems.

Studies of *5-HIAA* in adult personality disorders show a striking consistency with those in nonhuman primates. A high negative correlation (–.78) between CSF *5-HIAA* and ratings of aggression and suicide attempts has been found in men dishonorably discharged from the military (Brown, Goodwin, Ballenger, Goyer, & Major, 1979). Linnoila and colleagues have performed a large number of studies of *5-HIAA* in aggressive individuals (Linnoila & Charney, 1999; Linnoila et al., 1983; Virkkunen & Linnoila, 1992). Lower *5-HIAA* levels were found in impulsive personality disorders relative to paranoid or passive–aggressive personality disorders. Men who had impulsively murdered a sex partner or their own children had lower CSF *5-HIAA* levels than other violent criminals. CSF *5-HIAA* correlates negatively with ratings of hostility in normal volunteers. Criminals with high rates of recidivism and a history of suicide attempts had lower CSF *5-HIAA* levels than less chronic offenders. Impulsive offenders with early-onset alcoholism and arsonists also show low levels of CSF *5-HIAA*. Virkkunen and colleagues (1994) compared four groups of individuals: 23 men with antisocial personality disorder (APD), 20 men with intermittent explosive disorder (IED) (both of these groups were highly impulsive), 15 nonimpulsive offenders, and 21 control participants. CSF *5-HIAA* was significantly lower in the group with APD than in the control group, whereas the nonimpulsive offenders were significantly higher in CSF *5-HIAA* than the controls. This does not mean that "serotonin is low" in antisocial individuals; with the advent of modern neuroimaging (see below), we can begin to answer this question.

Recall from Chapter 4 (Figure 4.14) that when monkeys were performing tasks (Nakamura, 2013), serotonin neurons fired over the course of the task trial, but different sets of neurons fired according to the expectation of reward (one set for low reward, another for high reward). Through its massive projections in the brain (Figure 4.12), serotonin can influence multiple systems that include the immune and stress (hypothalamic–pituitary–adrenal [HPA] axis) systems. Thus, it would be a grave error to associate serotonin with aggression per se; rather, disturbances in the serotonin system might leave an individual unable to respond to "changing situations."

Recall the sea slug we discussed previously—how serotonin aids its response to threats to its gills. Is there a human analogue? We become aggressive when we are frustrated (cannot get what we want) or when we are threatened. From life experience, our serotonin neurons are trained to respond to different situations, and this sets the tone for our response. If the serotonin neurons cannot respond due to genetic changes (low *MAOA* activity level) and a highly stressful situation (abuse) is encountered, then the management of emotion becomes impaired.

The Autonomic Nervous System, Testosterone, and Crime

In Chapter 4, we also examined the interrelatedness of the central norepinephrine system and the peripheral autonomic nervous system (ANS). The Papez circuit included the hypothalamus, which can activate both the HPA (leading to increased cortisol) and the ANS (Figure 4.7). The ANS governs heart rate and skin conductance, a measure of activity of the sweat glands in the skin. In the face of threat or when we are anxious or afraid, our heart rate rises and skin conductance increases. The level of ANS activity in both controls and offenders has been assessed with these two measures for decades, both by examining resting rate and by looking at how heart rate and skin conductance responds in stressful situations. Four longitudinal studies have shown that low resting heart rate in childhood is associated with future antisocial behavior (Ortiz & Raine, 2004). Lower heart rate response to a stressor in teenage offenders predicts a greater number of new offenses 5 years later (De Vries-Bouw et al., 2011), a relationship that holds even at age 50 (Jennings, Piquero, & Farrington, 2013). If a person is subjected to a noxious stimulus, skin conductance increases. If the noxious stimulus is paired with a light (classical conditioning), then skin conductance will increase in response to the light after a few trials. Even at age 3 years, poor skin conductance conditioning is associated with more convictions for criminal offenses at age 23 (Gao, Raine, Venables, Dawson, & Mednick, 2010).

Increased autonomic activity proved to be a protective factor against developing antisocial behavior. A group of adolescents was identified that was already engaging in antisocial behavior at age 15 but desisted and never obtained criminal convictions. They were compared with the criminals-to-be and with controls (Raine, Venables, & Williams, 1990). The desistors showed even higher resting heart rates and more nonspecific skin conductance than the normal controls. Brennan, Raine, and Mednick (1994) obtained heart rate and skin conductance data in 50 men at risk for crime because they had criminal fathers. About half of these men became criminals themselves. They were compared with a group of criminals that had no family histories of crime and with a control group (neither fathers

nor sons were criminals). Higher skin conductance and heart rates were found in the men who did not commit crimes in spite of having criminal fathers (Raine, Venables, & Williams, 1995). In contrast, the lowest heart rates and skin conductance were found in those who committed crimes despite coming from intact homes in higher social classes.

Secretion of cortisol is the end result of the HPA axis. Low levels of cortisol (suggesting a decreased fear response) in childhood are predictive of later adolescent aggression (McBurnett, Lahey, Rathouz, & Loeber, 2000). Conversely, higher levels of testosterone have a modest relationship to crime and cannabis use (Tarter et al., 2009; van Bokhoven et al., 2006). A key issue here is that testosterone levels are not fixed but vary in response to events, particularly in competitive situations (Archer, 2006).

If a child does not have a strong fear response, he or she may be tempted to engage in antisocial behavior at an early age. In contrast, a child with a strong ANS response may be temperamentally more fearful and prone to avoid situations in which he or she might get in trouble. Indeed, such a child might be scorned by antisocial peers as cowardly, and this might exclude him or her from their antisocial pursuits. ANS hyporesponsiveness is not necessarily a lifelong event; an environmental enrichment program for 3- to 5-year-old children yielded not only lower offending rates at age 23 but increases in ANS activity and electroencephalographic (EEG) activity (Raine et al., 2001).

Brain Imaging and Antisocial Behavior

In our study of ADHD, we emphasized the role of both cortical control ("cool") and limbic ("hot") networks (Figure 9.3). We hypothesized a lack of sufficient activity/connectivity in the cortical control networks and excessive activity/connectivity of the emotional limbic networks. Young children with antisocial behavior invariably have ADHD, suggesting a close link between the two. Thus, imaging studies in antisocial behavior have focused on similar brain regions and networks. However, before reviewing these studies, an important caveat is in order. Several studies have shown that traumatic brain injury in childhood or early adulthood is associated with a marked increase in both violent and nonviolent crimes (Fazel, Lichtenstein, Grann, & Langstrom, 2011). Such brain injury is most likely accidental, though it is often secondary to child abuse. In imaging research studies of antisocial behavior, persons with a clear-cut history of traumatic brain injury are generally excluded. Nonetheless, clinicians must be aware of the role of acquired brain dysfunction in antisocial behavior.[1]

[1]Brain injury is distinct from epilepsy, which is not associated with criminality (Stevens & Hermann, 1981).

A meta-analysis of 43 neuroimaging studies (Yang & Raine, 2009) determined that the largest reductions in structure and function in persons with antisocial personality were found in the orbitofrontal cortex (OFC), anterior cingulate cortex (ACC), and dorsolateral prefrontal cortex. In particular, patients who experienced injury to the ventral prefrontal cortex are far more likely to exhibit aggressive behavior (Grafman et al., 1996) and show reduced ANS activity in response to socially meaningful stimuli (Damasio, 1994). Non-brain-injured individuals with psychopathy show reduced cortical gray matter volume, which correlates with reduced ANS activity as well (Raine, Lenz, Bihrle, LaCasse, & Colletti, 2000). These findings are more pronounced in "unsuccessful psychopaths," that is, criminals who engaged in impulsive, poorly-planned crimes (Yang, Raine, Colletti, Toga, & Narr, 2010). Such individuals also are more likely to show the intellectual and neuropsychological deficits found by Moffitt (1993).

Persons with antisocial behavior show different levels of emotional reactivity. Some coldly commit crimes and show little emotion, while others show rage attacks and irrational aggression (as in domestic violence). "Cold" psychopaths show reduced amygdala volume (Yang, Raine, Narr, Colletti, & Toga, 2009) and reactivity (Birbaumer et al., 2005; Glenn, Raine, & Schug, 2009; Jones, Laurens, Herba, Barker, & Viding, 2009), while men with IED (and not necessarily psychopathic) show both increased amygdala and decreased OFC activity when viewing angry faces (Coccaro, McCloskey, Fitzgerald, & Phan, 2007). Reduced ACC activity during a task requiring inhibitory control in prisoners doubled the risk of repeat offending 3 years later (Aharoni et al., 2013), as did reduced amygdala volume in high-risk males at age 26 (Pardini, Raine, Erickson, & Loeber, 2014).

Earlier, we noted a relationship between low cortisol and criminal behavior. Neuroimaging research also has drawn a link between brain function and the activity of the ANS and HPA. Mujica-Parodi, Carlson, Cha, and Rubin (2014) studied a group of 22 young adults who volunteered for skydiving class, seeking to study neurobiological factors that distinguished between those who show "brave" versus "reckless" behavior. Before their first jump, subjects underwent an fMRI in which they looked at threatening stimuli known to activate the amygdala. Their cortisol levels were measured on a baseline day and on the day of their jump (it is markedly elevated at the moment of the jump from the airplane, a normal response to an acute stress). There was a strong correlation between activity in the amygdala and the subjects' cortisol response. Jumpers who showed a decreased cortisol response (suggesting they did not appreciate the danger) showed inferior frontal cortex (IFC) thinning and a dysregulation of the circuitry connecting the IFC, the hippocampus, and the amygdala. (Recall these from Chapter 9 on ADHD?)

Testosterone blood levels are positively correlated with reactivity of both the amygdala and the hypothalamus. Goetz and colleagues (2014) performed a study in which healthy men were given a drug that temporarily reduced their testosterone levels. They were randomized to receive either placebo or a testosterone infusion, then underwent fMRI while they looked at angry faces. Administration of testosterone was associated with heightened reactivity of the amygdala, hypothalamus, and periaqueductal gray in response to angry facial expressions.

Imaging studies also are beginning to yield information about the role of serotonin in aggression and antisocial behavior. Meyer-Lindenberg and colleagues (2006) obtained fMRIs in healthy volunteers classified by *MAOA* status. Those subjects with low activity had smaller cingulate gyri and amygdala volume but *greater* activation of the amygdala in response to emotional faces. Similarly, men with high levels of childhood aggression who had low *MAOA* activity had increased levels of activity in the amygdala, hippocampus, and ACC (Holz et al., 2014). Low levels of MAO (regardless of activity type) in the brain are related to higher levels of anger/hostility (Soliman et al., 2011).

Positron emission tomography (PET) now can be used to study the level of serotonin in the brain, number of serotonin reuptake sites (serotonin transporter), and density of serotonin receptors. Such studies are complicating the view of serotonin and aggression further. Men with high levels of childhood aggression had lower indices of serotonin synthesis in the brain than controls, yet "there were no group differences in plasma tryptophan levels, genotyping, aggression, emotional intelligence, working memory, computerized measures of impulsivity, psychosocial functioning/adjustment, and personal and family history of mood and substance abuse disorders" (Booij et al., 2010, p. e11255). The density of the major postsynaptic serotonin receptors ($5\text{-}HT_{2A}$) did not relate to measures of aggression in healthy men (da Cunha-Bang et al., 2013). The availability of serotonin transporters has a complex relationship to aggression in that it is negatively related to irritability and positively related to callousness (lack of remorse) in aggressive patients with personality disorders (van de Giessen et al., 2014). Lower availability of serotonin transporters might lead to more serotonin in the synapse and thus greater anger, consistent with the effect of low *MAOA* activity. Patients with borderline personality disorder, when given a serotonin agonist drug, do not activate the prefrontal cortex as strongly as do controls (Soloff, Meltzer, Greer, Constantine, & Kelly, 2000).

Epigenetics and Aggression

In Chapter 5, we examined the role of environmental events impacting gene expression, or "epigenetics." Recall that environmental events can lead to changes in gene expression either by methylation (silencing) of DNA or by

histone modification. Early adversity and child abuse can clearly induce these changes, as covered in the next chapter. While epigenetic changes in the brain are likely most critical in mental disorders, they cannot be studied in humans for the obvious reason that we would never biopsy brains to examine the neuronal epigenome (though this can be done postmortem). In humans, epigenetic changes are usually studied in peripheral blood cells. We can determine how relevant the alterations are by comparing them to epigenetic changes in animal brains. If they are very similar, we can conclude there is a close parallel between brain and periphery. Epigenetic changes in individuals with a history of childhood aggression have been reviewed (Provencal, Booij, & Tremblay, 2015). Table 10.2 summarizes these changes. Persons with a history of childhood aggression (and often abuse) show epigenetic modifications in genes governing the HPA (as in the neglected rats discussed in Chapter 5); the serotonin, dopamine and immune systems; the hormone arginine vasopressin (*AVP*); and hundreds of other genes (Guillemin et al., 2014; Provencal et al., 2014).

TABLE 10.2. Epigenetic Changes in Individuals with a History of Childhood Aggression (a Partial List)

Gene	Function	Finding
Dopamine D_1 receptor	Mediates effect of dopamine	More methylated in aggression
Glucocorticoid receptor	Mediates effects of cortisol	More methylated in aggression; may alter stress response
Corticotropin-releasing factor binding protein (CRH)	Controls release of ACTH	More methylated in aggression; may alter stress response
Multiple cytokines	Immune system	More methylated in aggression (common to findings in mood and anxiety disorders); early stress in animals alters the immune response
Serotonin transporter	Reuptake of serotonin	Increased methylation may lead to decreased transporter activity, altering serotonin transmission
Tryptophan hydroxylase 2	Rate-limiting step in synthesis of serotonin	More methylated in aggression
5-HT_{1D} receptor	Mediates pre- and postsynaptic serotonin effects	Less methylated in aggression
Vasopressin	Salt and water balance in kidneys, but plays role in social bonding	Less methylated in aggression

ALCOHOL AND SUBSTANCE ABUSE

Mechanisms of Euphoria and Withdrawal

Extensive work over the last several decades has shown that alcohol and drugs of abuse exert their effects by altering dopamine (DA) input to the nucleus accumbens (NA; Volkow & Baler, 2014). In PET, adult volunteers are given intravenous stimulant or cocaine that is labeled with positron-emitting atoms that allow imaging of where the drug binds in the brain. Other PET studies using raclopride clearly show that DA levels rise rapidly when the drugs of abuse are infused. Interestingly, the "high" is experienced only during the period in which the drug is acutely blocking DA reuptake, that is, within a minute or so of administration (see Figure 10.1). Although the drug remains bound to the reuptake site for several minutes, the "high" fades much more quickly. This suggests that it is the *rate of change* of DA in the NA that accounts for the "high." When stimulants such as methylphenidate are given by mouth rather than intravenously (IV), the rate of binding to the DA receptor is much slower and euphoria is not experienced, even though the methylphenidate ultimately reaches the same level of reuptake site binding as the IV-administered drug. This explains why treatment of ADHD with low-dose oral methylphenidate is not associated with a risk of abuse or addiction, whereas snorting or injecting the drug is.

Opiate drugs, such as heroin or morphine, exert their effects at the mu receptor, mimicking the effects of the endogenous opioid peptides. Small opioid peptide neurons are found around the ventral tegmental area (VTA) and the locus coeruleus (LC). Opiates appear to have different effects on these two neurotransmitter systems. As shown in Figure 10.1, opiate neurons inhibit the release of gamma-aminobutyric acid (GABA) from the small GABA interneurons around the VTA. With the VTA neuron released from GABA inhibition, VTA neuron firing rate increases and more DA is released into the NA. Opiate neurons also can directly stimulate the NA neuron. The opposite effect occurs in the LC. Opioid drugs directly stimulate the mu receptors on the LC, resulting in the stimulation of G proteins. The G_i protein reduces the production of cyclic adenosine monophosphate (cAMP), which in turn leads to a reduction in protein kinase A (PKA). Among its many functions, PKA stimulates CRE-binding (CREB) protein, such that this protein, critical for controlling multiple genes, is diminished. The G_o protein will activate a K channel, with more K leaving the cell and prolonging the after-hyperpolarization. This leads to a more refractory, less active neuron. The opiates, in summary, reduce the activity of the LC. Because the LC normally promotes arousal and anticipatory anxiety, this action accounts for the opiates' antianxiety and sedating effects, whereas the increased activity of the VTA may account for some of the euphoria. Opioid peptide neurons occur throughout the brain, and part of

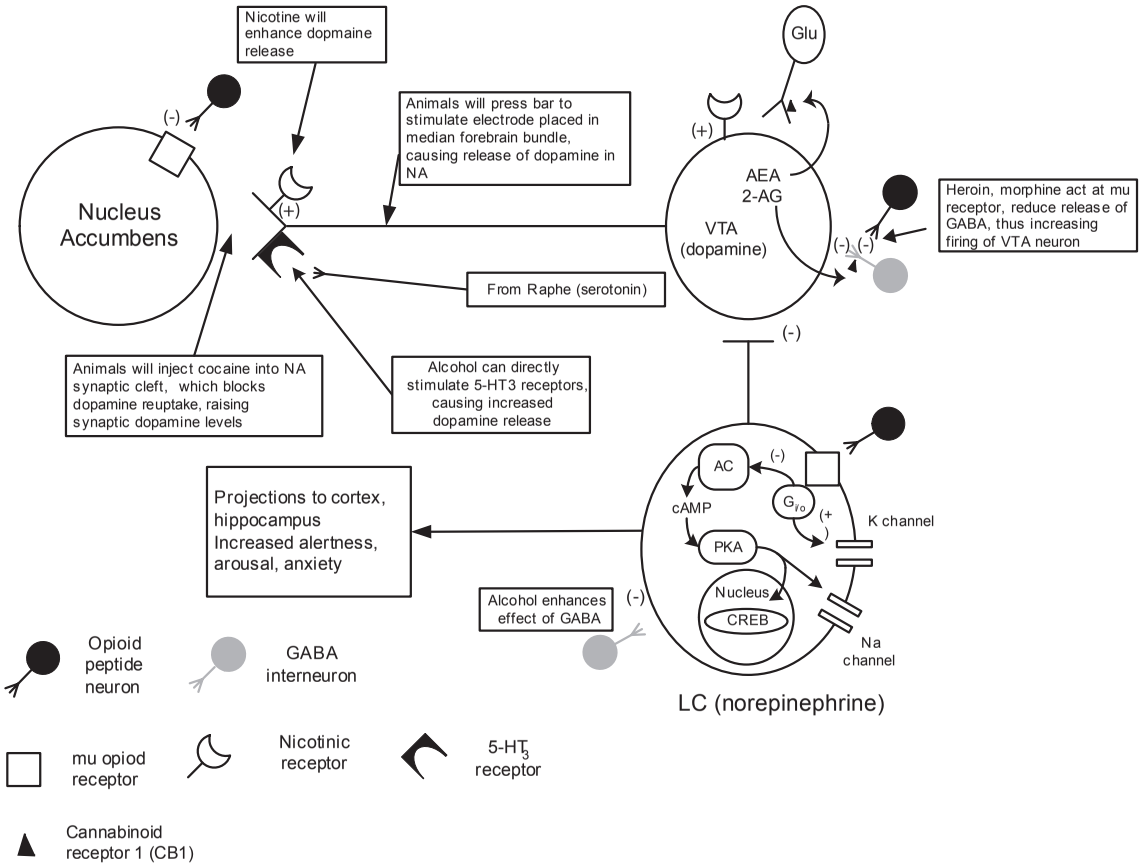


FIGURE 10.1. Mechanisms of production of euphoria by alcohol and other substances.

the euphoria that is characteristic of opiate drugs is produced through DA-independent mechanisms. The LC also is thought to be responsible for the mechanisms of withdrawal. The LC neuron somehow adapts to the chronic stimulation of the mu receptor. The activity of the cAMP-stimulated PKA pathway is up-regulated in an attempt to counter the effects of the opiate. First, this leads to tolerance. Larger doses of opiates are needed to achieve the same effect. When opiates are discontinued, this up-regulated cAMP–PKA pathway now surges into action, massively increasing the firing of the LC and other sympathetic neurons. This increase causes the typical opiate withdrawal signs of excessive sympathetic nervous system activity: severe anxiety, sweating, dilated pupils, and a runny nose.

Although they do not produce a "high" per se, cigarettes give much pleasure to chronic smokers and are highly addicting. Nicotine stimulates the VTA through nicotine receptors on the cell body, and it enhances the release of DA through similar receptors on the axon terminal. The active agent in marijuana (cannabis) is delta-9-tetrahydrocannabinol (THC). It acts at specific cannabinoid receptors (CB_1) in the brain to produce relaxation and mild euphoria. As shown in Figure 10.1, CB_1 is stimulated by the endogenous neurotransmitters anandamide (*N*-arachidonoylethanolamine [AEA]) and 2-arachidonoylglycerol (2-AG). Increases in calcium in the VTA neuron trigger the production of these substances, which diffuse back across the synapse in a retrograde fashion to stimulate presynaptic CB_1 receptors on both glutamate and GABA neurons (Melis & Pistis, 2012). The net effect is to enhance VTA firing. THC is much more potent than these endogenous compounds. CB_1 receptors are found only in the brain; CB_2 receptors are found on immune system cells, where they play a role in regulating the inflammatory response. This may account for the many effects of "medical marijuana" (Pacher & Mechoulam, 2011).

The effects of alcohol on the brain are diffuse. It enhances the effects of GABA, and this, as shown in Figure 10.1, will decrease LC firing. Through direct stimulation of serotonin ($5\text{-}HT_3$) receptors on the DA nerve terminals, DA release is increased. Alcohol inhibits glutamate and *N*-methyl-D-aspartate (NMDA) receptors, leading to sedation. In toxic amounts, alcohol blocks sodium and calcium channels, which can lead to coma and death. In many alcoholics, acute withdrawal of alcohol leads to sudden rebound of neuronal excitability (due to reactivation of glutamate and NMDA receptors). This excess neuronal activity can lead to psychosis (delirium tremens, or "DTs") and seizures. If not treated with benzodiazepines, death may often ensue.

Withdrawal from opiates, marijuana, or cocaine is not life threatening, but it is very uncomfortable. Cocaine withdrawal is associated with increased activation of the NA and amygdala, even after controlling for the general agitated state that withdrawal induces (Kilts et al., 2001). When patients are withdrawing from cocaine, methamphetamine, or alcohol, they showed a marked reduction in the number of DA (D_2) receptors (Goldstein

& Volkow, 2002). Paradoxically, when cocaine users are in withdrawal, they show *decreased* DA release in response to an IV infusion of methylphenidate relative to controls but an *increased* release of DA in the dorsal striatum while watching a video containing cocaine cues (Volkow, Wang, Fowler, Tomasi, & Telang, 2011). This is consistent with the cycle of drug addiction: The drug itself becomes less rewarding, but being without it induces intense craving. Thus, more and more drug is needed to satisfy the craving. Cocaine users in the Volkow, Wang, Fowler, and colleagues (2011) study who later relapsed during treatment had lower levels of DA release in response to the methylphenidate infusion.

Genetics of Alcohol and Substance Abuse

Alcohol and substance abuse problems run in families. Cloninger (1989) defined two subtypes of alcoholism. Type 1 is characterized by a later age of onset, low levels of antisocial behavior and personality disorder, and high levels of guilt about alcohol abuse. These individuals often "lose control" of their drinking; they do not set out to get intoxicated, but one drink leads to another, then another. In contrast, Type 2 alcoholsm is characterized by early age of onset (often in the teen years), high levels of antisocial behavior, and deliberate alcohol-seeking behavior. These individuals show little guilt about their drinking behavior except in cases when some consequence is harmful to them (e.g., being arrested for driving under the influence). Type 1 alcoholics tend to be anxious and to shy away from stimulation; they may drink to reduce their social anxiety, whereas Type 2 alcoholics are often risk takers, have low anxiety, and are easily bored. The similarity of Type 2 alcoholics to the impulsive, aggressive personality already discussed in this chapter should be apparent.

The two types of alcoholism show very different patterns of inheritance, as shown in a study of over 1,700 adoptees in Sweden (Bohman, Cloninger, Sigvardsson, & Van Knorring, 1983; Bohman, Sigvardsson, & Cloninger, 1981). For Type 1 alcoholism, a gene × environment interaction was necessary for the adoptee to show the disorder. If a child with a Type 1 alcoholic parent was adopted by a Type 1 alcoholic, the child had about a 12% chance of developing Type 1 alcoholism (as opposed to the 4% rate in the general population). In contrast, children of Type 1 alcoholics did not show an increased risk if raised by nonalcoholic parents, and children with no genetic risk did not have an increased rate of alcoholism even if they were raised by a Type 1 alcoholic adoptive parent. The pattern for Type 2 alcoholism was quite different. Children of Type 2 alcoholics had a much greater rate of Type 2 alcoholism (17–18%) regardless of the alcoholism of the adoptive parent. Children of nonalcoholics did not have a higher rate of Type 2 alcoholism even when raised by a Type 2 alcoholic; that is, only genetics appeared to play a role in Type 2 alcoholism.

Heritability of alcohol and abuse disorders has been found to range from 0.45–0.65 (Edenberg & Foroud, 2014). A number of candidate genes (See Table 10.3) have been associated with alcoholism or substance abuse. However, it is important to note that these genes only convey a very small degree of risk, in that many individuals carrying the risk alleles do not develop drug or alcohol problems. As in both ADHD and aggression, GWAS studies have not identified any major risk genes for substance abuse. The abuse of drugs may in fact be related to the same genetic factors related to impulsivity and sensation seeking (Volkow & Baler, 2014).

Neurobiology of Alcohol and Substance Abuse

Figure 10.2 summarizes a model of addiction developed by Nora Volkow and her colleagues over the last several years (Volkow, Wang, Fowler, et al., 2011; Volkow, Wang, Tomasi, & Baler, 2013). Before going into the details of the model, I introduce two brain structures not previously discussed. Note the output of the globus pallidus to the habenula, which in turn exerts influence over the VTA. The habenula is a small structure located at the posterior medial end of the thalamus. Stress, signals in the environment indicating punishment, and the failure of an expected reward all activate the habenula, which inhibits the VTA and leads to less DA being released in the NA (Hikosaka, 2010). Thus, the habenula serves as an "anti-reward" center. The insula and amygdala have reciprocal connections with each other (not shown in Figure 10.2). Both structures are involved in "interoception," that is, the perception of internal states such as hunger, pain, disgust, and craving (Naqvi & Bechara, 2009). Interestingly, smokers who have experienced damage to the insula are more easily able to quit smoking because they do not experience intense cravings (Naqvi, Rudrauf, Damasio, & Bechara, 2007).

Figure 10.2A shows the circuitry of the nonaddicted brain. Before the acute abuse of the drug, the circuit is in balance, with the ACC and lateral OFC in control. Recall the topographical organization of the OFC from Chapter 8—the lateral aspect of the OFC deals with nonemotional and punishment related processes, thus enhancing behavioral inhibition. When drugs are acutely abused, there is a marked increase in DA in the nucleus accumbens/ventral striatum (NA/VS) that leads to a marked sense of pleasure ("Like"). Chronic substance abuse leads to changes in this circuitry as shown Figure 10.2B. (Thickened borders and arrows represent structures/pathways with increased influence.) Dopamine input to the dorsal striatum is enhanced, leading to increased output of the globus pallidus (left side of Figure 10.2B), which in turn strongly activates the habenula. This "anti-reward" area inhibits the VTA, leading to decreased DA in the NA/VS. As a result, there is a reduction in "Like" but an increase in craving. This sense of craving is worsened by increased input to the NA/VS by the insula and amygdala. Finally,

TABLE 10.3. Candidate Genes for Drug and Alcohol Use Disorders

Drug	Chromosome	Gene	Function	Phenotype
Alcohol	4	*ADH1B*	Major form of alcohol dehydrogenase in liver that breaks down alcohol	*ADH1B*2,*3* increase metabolism of alcohol, provide protective effect (persons get no high since alcohol does not reach high levels in most people). Also associated with esophageal cancer.
	12	*ALDH2*	Mitochondrial version of alcohol dehydrogenase	*ALDH2*2* enzyme has very low activity; person develops severe flushing, cannot drink alcohol. More common in Asian populations.
	4	*GABR2*	Variation in alpha subunit of $GABA_A$ receptor, altering impact of alcohol on GABA receptor	*GARBR2* variant associated with greater "high" when drinking (Arias et al., 2014).
		GABRG1	Variation in gamma subunit of $GABA_A$ receptor	3 nucleotide single-nucleotide polymorphism (SNP) variant associated with higher alcohol dependence (Ittiwut et al., 2012).
Nicotine	15	*CHRNA5* *CHRNA3* *CHRNA4*	Subtype of nicotinic receptor alpha subunit	Variants in these three genes are associated with heavy daily smoking, later age of smoking cessation, greater likelihood of relapse after smoking cessation, and poorer response to treatment for nicotine dependence (Chen et al., 2012).
Opioid	6	*OPRM1*	Gene codes for mu-1 opioid receptor	Some variants in noncoding region of opioid receptor may increase risk for opioid addiction (Levran et al., 2008).
	1	*OPRD1*	Gene codes for delta-1 opioid receptor	Several SNPs associated with opioid addiction. AA or AG allele have worse response to opioid dependence treatment than those with GG SNP (Clarke et al., 2014).

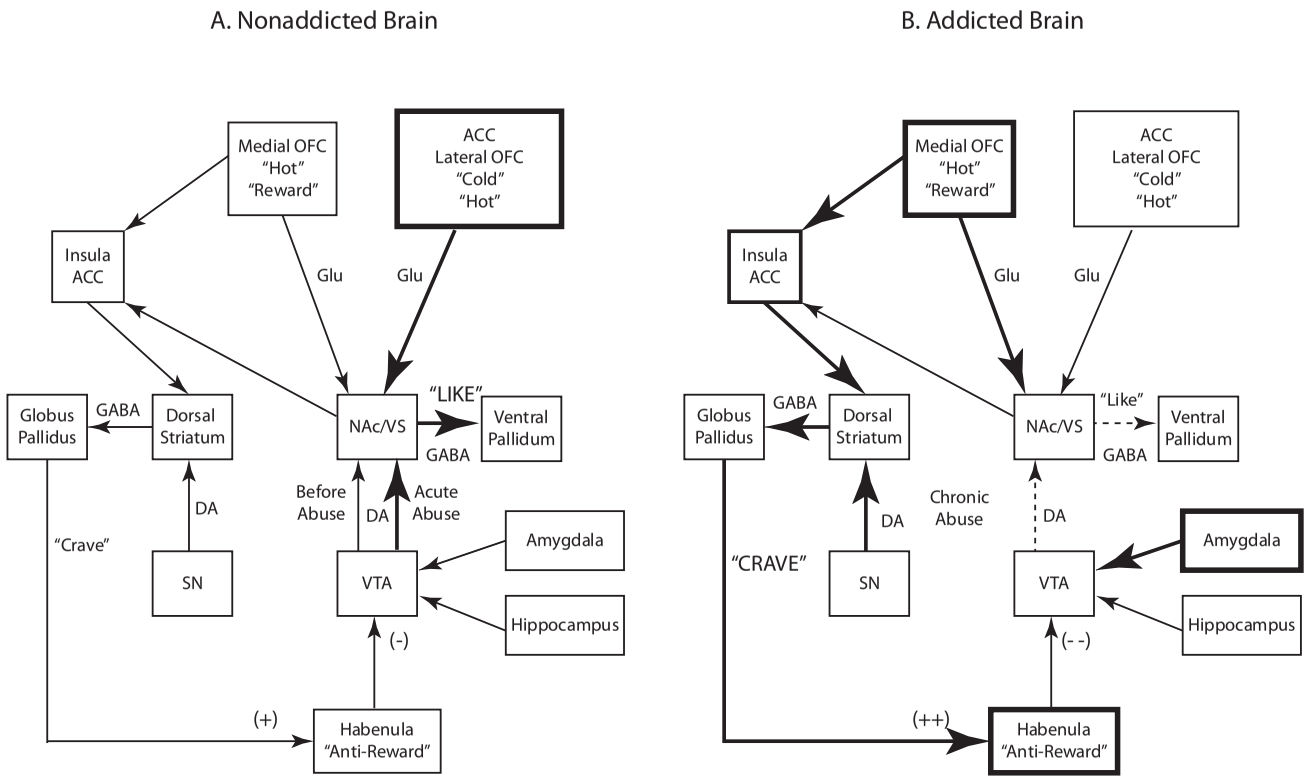


FIGURE 10.2. Volkow's model of how brain reward and risk circuitry is rewired by substances to produce addiction. Adapted from Volkow and Baler (2014) with permission from Elsevier Ltd.

the OFC circuitry is shifted, leading to enhanced influence of the more medial areas, which are attuned to emotional ("hot") and reward processes. The result is a continuous increase in drug-seeking and impulsive behavior.

It is sobering (no pun intended) to see the major rewiring of the brain induced by substances of abuse. How is this accomplished? Here, we must turn to epigenetic mechanisms (see Chapter 5). Recall that gene expression often depends on whether the histone that the DNA is wrapped around carries an acetyl group, and that this process is controlled by histone acetyltransferases (HATs) or histone deacetylases (HDATs). Cocaine increases DA levels in the NA/VS synapse, increasing stimulation of DA receptors. As described in Chapter 4, this can lead to activation of PKA, which ultimately elevates levels of the CREB transcription. CREB elevates levels of a key protein DeltaFosB (Nestler, 2014). DeltaFosB recruits an HDAC that, by deacetylating histone, turns off c-Fos, a key protein in regulating neuronal growth. In contrast, DeltaFosB also recruits a HAT that acetylates histones around the *Cdk5* gene, activating it. In animals, *Cdk5* activation increases learning. In addiction, excessive activation of this enzyme may underlie the cravings because the addict has learned too well the association between the substance and the pleasure it induces. It also is clear from animal studies that these epigenetic changes can occur in sperm or ova, which means that the effects can be passed onto the next generation (Vassoler, White, Schmidt, Sadri-Vakili, & Pierce, 2013).

Treatment of Alcohol and Substance Abuse Disorders

Table 10.4 lists the current established treatments of alcohol and substance abuse disorders. Most of these treatments either replace or block the effect of the substance in the hope of reducing the motivation to use it. New approaches on the horizon include attempting to adjust the glutamate–GABA reward circuity balance with agents such as *N*-acetylcysteine, glutamate metabotropic receptors agonists, and transmagnetic stimulation (Volkow & Baler, 2014). Medications can be blunt instruments, however, and Figure 10.2 shows the intricate interconnection of the circuits. Affecting GABA or DA in one part of the circuit may be beneficial for substance abuse treatment, whereas simultaneously perturbing it in another part of the circuit might worsen the condition. Review the distribution of D_1 and D_2 receptors in the striatum in Chapter 6 (Figures 6.2 and 6.3). In the ventral striatum, there is a similar separation of the GABA neurons into those with D_1 and D_2 receptors. In addition to being simulated by DA, these neurons have cholinergic input from the basolateral amygdala. Review the discussion of optogenetics in Box 4.1 in Chapter 4. Channelrhodopsin can be introduced into these cholinergic neurons in animals (Tye & Deisseroth, 2012). Mice will work to stimulate D_1-bearing GABA neurons but will

TABLE 10.4. Treatments for Alcohol and Substance Use Disorders and Their Hypothesized Mechanisms

Substance	Agent	Mechanism
Alcohol	Naltrexone	Antagonist at mu, kappa, and delta opioid receptor. Persons with the G polymorphism of the *OPRM1* gene for the mu receptor respond better to naltrexone.
	Disulfiram	Blocks degradation of alcohol resulting in production of acetaldehyde, which in turn leads to unpleasant flushing reaction, discouraging drinking.
	Acamprosate	Acts on the gamma-aminobutyric acid (GABA) and glutamate neurotransmitter systems and is thought to reduce symptoms of protracted withdrawal, such as insomnia, anxiety, restlessness, and dysphoria.
	Topiramate	Topiramate is thought to work by increasing inhibitory (GABA) neurotransmission and reducing stimulatory (glutamate) neurotransmission.
Nicotine	Bupropion	Also known as the antidepressant Wellbutrin®; may affect dopaminergic reward circuitry.
	Varenicline	Partial agonist at nicotinic receptors, leads to modest dopamine release in NA/VS. Reduces urge to smoke.
Opiates	Methadone	Full agonist at the mu opioid receptor, but also has some affinity for the NDMA ionotropic glutamate receptor. Maintains dependency (without euphoria) until person can be gradually weaned off.
	Naltrexone	Antagonist at mu, kappa, and delta opioid receptor.
	Buprenorphrine	Buprenorphine is a synthetic opioid medication that acts as a partial agonist at mu, kappa, and delta opioid receptors. It does not produce the euphoria and sedation caused by heroin or other opioids but is able to reduce or eliminate withdrawal symptoms; less risk of overdose than methadone.

Note. Data from *www.drugabuse.gov/publications/principles-drug-addiction-treatment/evidence-based-approaches-to-drug-addiction-treatment/pharmacotherapies*.

not work to stimulate D_2-bearing GABA neurons. While very far away at present, this work holds promise that specific sets of neurons in the reward circuitry could have channelrhodopsin inserted into them, then surgically implanted optic fibers could activate specific circuits to reduce craving. Vaccines are also being developed that will allow the addicted person's body to form antibodies to cocaine or nicotine. Improved treatments could greatly reduce the enormous costs of substance abuse to society.

CHAPTER 11

Mood and Anxiety Disorders

Chapters 9 and 10 dealt primarily with overt characteristics such as hyperactivity, antisocial behavior, and aggression, but we clearly have seen that emotion plays a role in these disorders. In this chapter, the emphasis shifts to a discussion of disorders of emotion, but without losing track of the fact that these emotions influence behavior. DSM-5 continues the long tradition of Emil Kraepelin with regard to dividing the major psychiatric illnesses into schizophrenia and manic–depressive illness, or bipolar disorder. DSM-5 subdivides the mood and anxiety disorders into an extensive array of subdisorders (major depressive episode, persistent depressive disorder, bipolar I and II disorder, panic disorder, generalized anxiety disorder, etc.). In the DSM-5 field trials, Regier and colleagues (2013) found that most of these disorders overlap with each other, as well as with other psychiatric disorders outside the mood/anxiety spectrum (see Figure 11.1).

"Mood" and "affect" are elementary concepts in the mental status examination that are taught to every medical student and beginning mental health professional. It is often said that "affect is to mood as weather is to climate." "Mood" is a sustained emotional state (elated, depressed, irritable, and anxious) over a given period of time, whereas "affect" is the emotional state at any given moment. These time periods can be arbitrary. We may speak of mood as occurring over the hour of a clinical interview, the past day, or even the past year, whereas affect refers to feelings at a given moment. Thus, clinicians speak of the "range and intensity" of affect; that is, how much affect changes over the course of the period in which the mood is assessed. The range of affect may be "labile" (constantly changing from sad to happy), "normal" (appropriate to thought content) or "blunted" (hardly changing at all). At a conceptual level, it appears that the

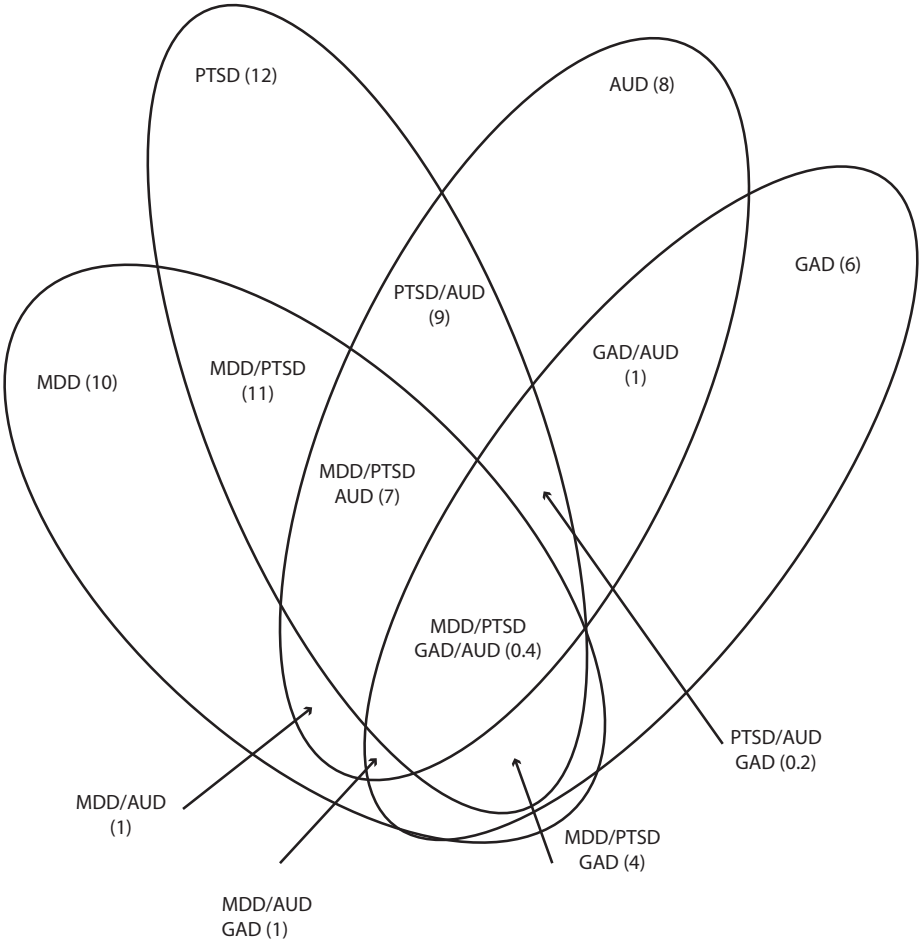


FIGURE 11.1. Overlap of mood and anxiety disorders in the DSM-5 field trials. AUD, alcohol use disorders; GAD, generalized anxiety disorders. Numbers in parentheses indicate percent of sample. Adapted from Regier et al. (2013) with permission from the American Psychiatric Association. Copyright 2013.

brain must have some mechanism for both determining and altering our affect from second to second in response to events in the environment. If someone says to us, "I am sad," it is our natural inclination to respond with "What's the matter?" We assume that some event has caused the person to feel this way. Whether the sad affect is "normal" will depend on the associated event. If the person tells us his parent died last week, we expect him to be sad not only at the moment (affect) but for some extended period of time

(weeks, months). Thus, the person has a depressed mood. The brain must have an "affect thermostat" that interacts with the environment, such that we experience the full range of affect: sadness, happiness (elation), calmness, anxiety, fear, irritability, anger. A "mood disorder" emerges when the mood change (elation, depression, irritability) becomes extreme and persistent, causes deterioration in function, and is associated with various other physical and cognitive symptoms. In extreme cases, the patient may become delusional or have hallucinations.

According to the National Institute of Mental Health (NIMH) (*www.nimh.nih.gov/health/statistics/index.shtml*), about 10% of U.S. adults meet criteria for a mood disorder in any given year; the lifetime prevalence of depression (a person ever having been depressed in his or her life) is 20%. The 12-month and lifetime prevalence of mood disorder in adolescents (ages 13–17) is 4.7 and 14%, respectively. Whereas the lifetime prevalence of bipolar disorder in adults is about 4%, the rate in children is controversial. The last decade has seen an explosion of research into the genetics, epigenetics, neuroimaging, and treatment of mood disorders.

GENETIC AND ENVIRONMENTAL RISK IN MAJOR MENTAL ILLNESS

While this chapter focuses on mood disorders, the next chapter on schizophrenia is a close companion to it; we are learning that these diseases have more in common than Emil Kraepelin thought. At a clinical level, there always have been patients who do not fit easily into either the mood disorder or schizophrenia category because they share symptoms of both; DSM-5 refers to these individuals as having "schizoaffective" disorders. Uher (2014) reviewed environmental risk factors related to bipolar disorder (BP), major depressive disorder (MDD), and schizophrenia (see Table 11.1). These disorders share a number of common risks. Note that for MDD, risks related to child abuse, social disadvantage, and stress are stronger than in BP. With regard to the loss of a parent, parental death is not associated with depression to the same degree as parental separation (Agid, Kohn, & Lerer, 2000). Persons who were sexually or physically abused during childhood are up to four times more likely to develop major depression or commit suicide; child abuse is associated with an earlier age of onset of depression and greater chronicity of the depression. Twin studies also have shown that the tendency to experience negative life events is itself influenced by genetics, separate from the genetic risk for the affective disorder itself (Kendler, Makowsy, & Prescott, 1999). Uher (2014) reviewed twin studies showing the heritability of BP to be 70–80%, while that of MDD is much lower (~50%). As discussed in Chapter 5, the effects of genes and the environment interacting (G × E) is expressed in the heritability term (i.e., the 80% of

TABLE 11.1. Common Risk Factors Shared Across Mood Disorders and Schizophrenia

Exposure	Schizophrenia	Bipolar disorder	Major depressive disorder
Prenatal			
Season of birth	+++	++	+
Poor nutrition	++	++	+
Vitamin D levels	+++		
Lead	+		
Herpes simplex-2	++		
Rubella	+		
Prenatal stress		+	+
Perinatal			
Preterm birth	++	+++	+
Obstetric complications	+	–	
Hypoxia			
Childhood			
Cytomegalovirus	+		
Child abuse	+++	+	+++
Loss of a parent			++
Social disadvantage	+++	–	+++
Bullying	++		+
Urban living	+++		
Adolescence			
Cannabis use	+++	+	+
Adulthood			
Stressful life events	+	++	+++

Note. +++, consistent evidence from multiple studies or metanaylsis; ++, evidence from several studies; +, evidence from one study or multiple low-quality studies; –, evidence for no association; blank cell indicates lack of studies. Reprinted from Uher (2014).

heritability includes the G × E effects). Newer molecular biology techniques allow us to subtract out the pure genetic effects. In BP and MDD, this leaves 50–60% of the heritability unaccounted for ("missing heritability"). G × E effects, as well as epigenetic effects, may account for this finding.

Approximately 10 genome-wide association studies (GWAS) focusing on BP have been completed (Craddock & Sklar, 2013; Kerner, 2014). Table 11.2 shows major single-nucleotide polymorphism (SNP) variations that have been associated with BP, although there are many others that are less well replicated. While it can be determined which gene is near the variation, this does not mean the gene itself is altered in its function. Note that the odds ratio (OR) for each gene is quite small. If the risk for BP in the general population is 2.6%, then having a risk SNP with an OR of 1.14 means

TABLE 11.2. Genome-Wide Significant Association in European-Origin Samples for BP

Disorder	Chromosome	Odds ratio	Nearest gene	Function
BP, schizophrenia, autism, ADHD	11q14.1	1.14 (for BP)	*ODZ4*	During brain development, gene regulates neuron synaptic connectivity.
BP, schizophrenia, autism, ADHD	12p13.3	1.14 (for BP)	*CACNA1C*	*A* allele in gene associated with BP but not coding region. Gene codes for voltage-gated calcium channel.
BP	19p12	1.17	*NCAN* (neurocan)	Codes for a large secreted protein found in extracellular space; influences cell adhesion, migration, and axon guidance.
BP	12q13.12	0.9	*RHEBL1*, DHH	Ras homolog enriched in brain-like protein 1 (activator in RTK signaling system). Desert hedgehog (DHH) protein—the hedgehog signaling pathway transmits information to embryonic cells required for proper development.
BP	20q11.22	1.16	*TRPC4AP*	Gene codes for a cation (+ charge) channel, including calcium.
BP	6q25	1.10	*SYNE1*	May be involved in postsynaptic glutamate receptor modulation.
BP + schizophrenia	2q32.1	1.11	*ZNF804A*	Gene codes for zinc finger protein which stabilize the DNA helix.
BP + schizophrenia	3p21.1	1.12	*ITIH3-ITIH4*	Inter-alpha-trypsin inhibitor heavy-chain H_3 and H_4. Trypsin breaks down proteins in the gut and is involved in the inflammatory response.
BP + schizophrenia	10q21	1.22	*ANK3*	Ankyrins play key roles in activities such as cell motility, activation, proliferation, contact, and the maintenance of specialized membrane domains.
BP + schizophrenia	16p11.2	1.08	*MAPK3*	Mitogen-activated protein kinase 3. Part of the RTK activated signaling system.
BP + recurrent depression	3p21	0.87	*PBRM1*	The polybromo 1 protein coordinates key features common to all remodeling complexes and has an important role in transcriptional regulation.

Note. Adapted from Craddock and Sklar (2013) with permission from Elsevier Ltd.

the person's risk increases to only 2.6 × 1.14 = 2.96% (i.e., 97% of the people with the risk SNP do not have the disorder). An OR of less than one means the variant is protective. Note that many of these risk variants are not unique to BP and they are associated with other major disorders as well. It also should be noted that the genes implicated often regulate calcium in neurons or are involved in very basic neurodevelopmental processes, suggesting that vulnerability to BP begins during fetal development. Genetic variations in the serotonin transporter and in brain-derived neurotropic factor (BDNF) have been the focus of much research in mood disorders.

THE SEROTONIN TRANSPORTER

The serotonin transporter (5-HTT) governs the reuptake of serotonin into the neuron (see Figure 4.13 in Chapter 4). The gene for the 5-HTT is named *SLC6A4*. Within the promotor area of the gene is a region in which a segment of the DNA may be repeated a variable number of times; this region is call the 5-HTT-linked polymorphic region (5-HTTLPR). It has two major variants: short and long. The short form is associated with reduced 5-HTT protein availability and function (Canli & Lesch, 2007). Based on animal studies, this would suggest that individuals with the short allele have higher levels of serotonin in the synaptic cleft. In a seminal study, Caspi and colleagues (2003) genotyped the 5-HTTLPR status of over 1,000 children and followed them to age 26, assessing rates of child abuse and stressful life events prospectively. As shown in Figure 11.2, individuals with the short allele were more prone to depression if they were exposed to stressful life events. While controversial at first, a meta-analysis has confirmed this relationship (Karg, Burmeister, Shedden, & Sen, 2011). Compared to those with the long allele, individuals with the short allele activate the amygdala more strongly in response to angry faces (Caspi, Hariri, Holmes, Uher, & Moffitt, 2010), have larger startle responses (Brocke et al., 2006), and experience increased distress or fear when exposed to threatening situations (Homberg & Lesch, 2011). Possessing the short allele is not all negative, however. In their review, Homberg and Lesch (2011) reviewed a wide variety of studies showing that short allele carriers also responded more positively to emotional stimuli, showed enhanced cognition relative to long allele carriers, and demonstrated better response inhibition. Interestingly, the short allele, in combinations with other gene variants, is associated with more creative dancing ability (Bachner-Melman et al., 2005). Homberg and Lesch hypothesized that the short allele simply does not convey vulnerability to depression or anxiety but in combination with other genes governs the responsiveness of cortical–limbic circuits. In combination with a stressful environment, affective/anxiety disorders may result. However,

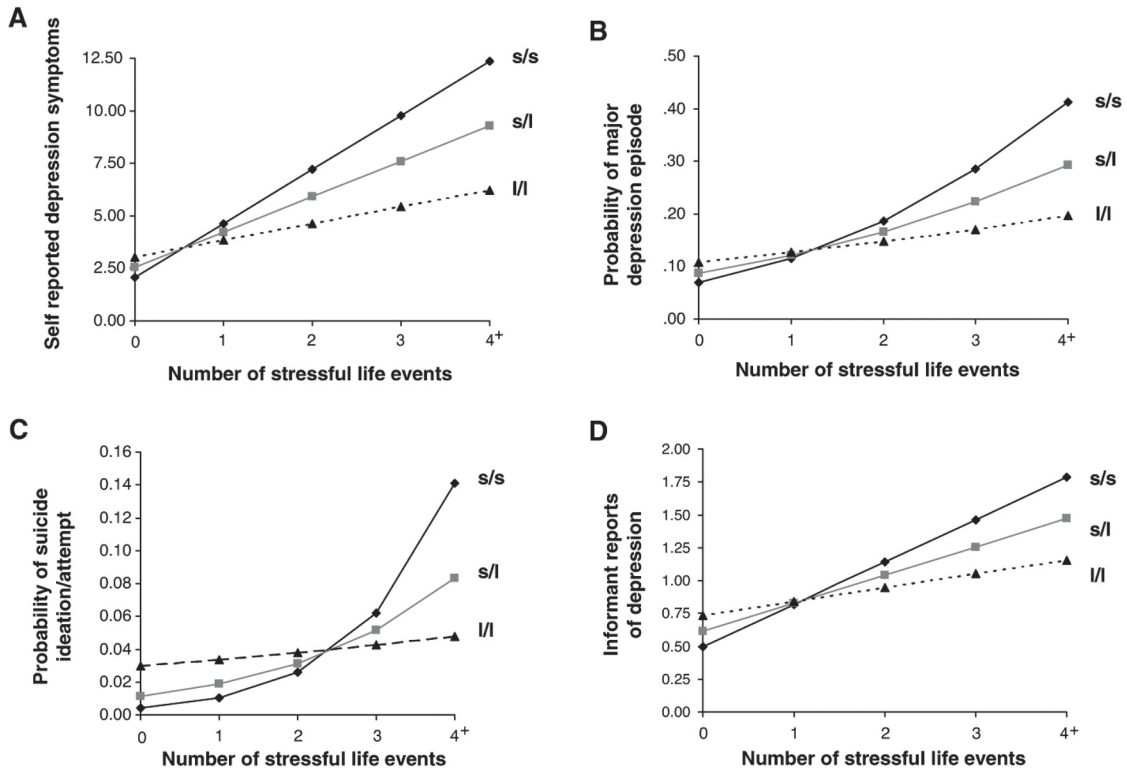


FIGURE 11.2. The interaction between serotonin transporter genotype and enviromental stress in the risk for depression. Reprinted from Caspi et al. (2003) with permission from the American Association for the Advancement of Science.

in combination with a nurturing environment, the person may be more creative, enjoy life more, or have enhanced cognition.

BRAIN-DERIVED NEUROTROPIC FACTOR

Please review Figure 3.11 regarding the action of growth factors at the receptor tyrosine kinase (RTK). BDNF works through RTK-B, one of the RTK receptor subtypes to activate the PI3K, which in turn increases the activity of protein kinase B (Akt). BDNF leads to activation of the phospholipase C (PLC) system, resulting in changes in intracellular calcium levels; it also activates the Ras/mitogen-activated protein kinase (MEK)/extracellular signal-regulated kinase (ERK) system. All of these events lead to the transcription of messenger RNA (mRNA) for a wide variety of proteins and enzymes related to neural development and survival (Duman & Voleti, 2012). Stress, in both animals and humans, leads to increased levels of BDNF in the prefrontal cortex and hippocampus. In animal models, antidepressant treatment also leads to increased BDNF in these areas. Humans show a polymorphism in BDNF referred to as Val66Met, an SNP in which a methionine (Met) is substituted for a valine (Val). The Met variation is found in 25–30% of humans and is associated with decreased BDNF in dendrites (Duman & Voleti, 2012). Duncan and Voleti (2012) also reviewed studies showing that Met carriers have reduced hippocampal volume and decreased executive function, and are less likely to forget a fearful response. As with the 5-HTTLPR, an interaction with stressful life events appears to mediate the relationship between the gene and depression. A meta-analysis of 22 studies involving over 14,000 patients showed that carrying the Met allele and exposure to stressful life events or childhood adversity lead to greater depression relative to those with the Val allele (Hosang, Shiles, Tansey, McGuffin, & Uher, 2014). We return to how altered BDNF is involved in depression later in the chapter.

THE AFFECTIVE CIRCUMPLEX AND BRAIN MECHANISMS OF EMOTION

The term "affective circumplex" may be quite unfamiliar to clinicians, but it has a long history in experimental psychology (Barrett & Bliss-Moreau, 2009). As humans, we see emotions as occurring in discrete categories: sad, mad, happy, excited, or irritated. These are so natural to us that we may think that the brain has specific regions for producing each of these emotions. Perhaps these areas are either "overactive" or "underactive" in depression, mania, or anxiety. In contrast, the affective circumplex model hypothesizes that all emotion can be mapped onto a two-dimensional axis

system, as shown in Figure 11.3. The *x*-axis represents the valence of the emotion (positive or negative), while the *y*-axis represents the intensity of arousal (high vs. low). Under such a model, there might be just two brain systems (arousal and valence) that produce a wide array of emotions based on their relative activation to each other. There might also be different brain systems for positive and negative valence, or perhaps one brain system that might activate for positive and deactivate for negative valence (or vice versa).

Lindquist, Satpute, Wager, Weber, and Barrett (2015) attempted to resolve this issue with a meta-analysis of 397 neuroimaging studies of emotion involving nearly 7,000 subjects. In these studies, the subjects performed tasks that contrasted negative versus neutral emotion or positive versus neutral emotion. From this analysis, there was *no evidence at all* that the brain had different systems for producing positive and negative emotions, nor did it appear that there was one brain system that reacted in opposite directions from each other depending on the valence. Rather, as shown in Figure 11.4, there was a set of brain regions that activated for *both* positive and negative valences. These regions, mainly in the medial ("hot") part of the brain, should be familiar to you from prior chapters. The amygdala and insula react to all emotions but seem more primed to

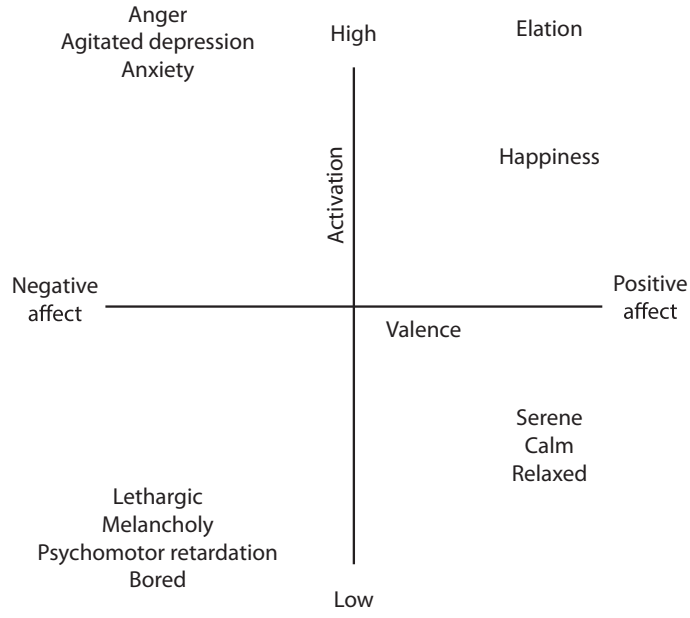


FIGURE 11.3. The affective circumplex.

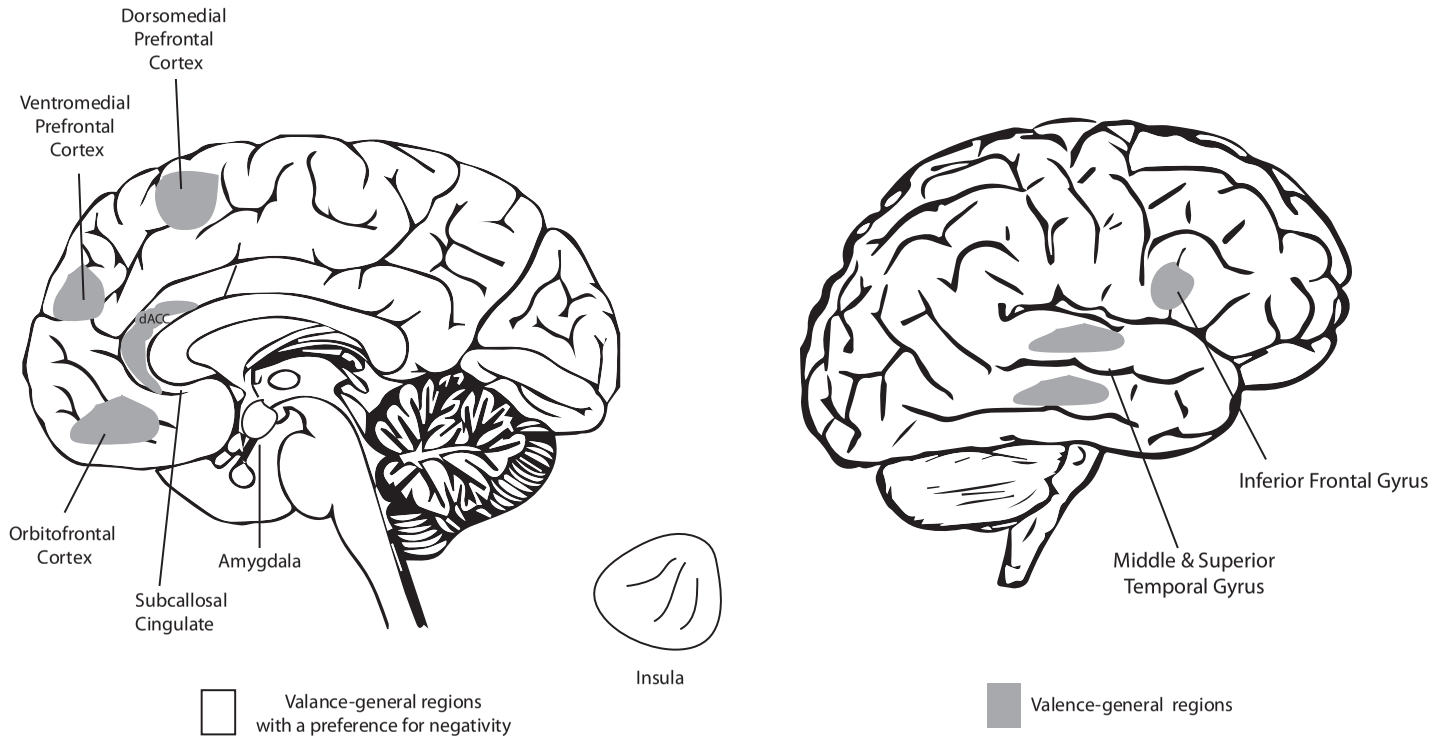


FIGURE 11.4. Region of the brain activated by negative and positive valence emotions.

react to negative emotions. This will be key to understanding neuroimaging studies of mood disorders.

NEUROIMAGING OF MOOD DISORDERS

The literature on the neuroimaging of mood disorder is by now voluminous and complex. Studies generally compare persons with BP to controls, persons with MDD to controls, and also contrast MDD and BP. In the vast majority of these studies, individuals have been ill for many years, making it difficult to determine whether the differences seen are causes or effects of the illness. Person with both MDD and BP are scanned in a variety of mood states (manic, depressed, and euthymic); most of the time, the subjects remain on their antidepressant or mood stabilizing medication because it would be unethical to withdrawn them just for a research study. In BP, studies tend to focus on persons with a history of full-blown mania (BP I) rather than those with a history of only hypomanic disorders (BP II). Participants have been studied using structural magnetic resonance imaging (MRI), functional MRI (fMRI), and diffusion tensor imaging (DTI); the latter studies the integrity of the white matter of the brain. Since the advent of neuroimaging, literally thousands of patients and controls have been studied and numerous meta-analyses of this data have been performed (Chen, Suckling, Lennox, Ooi, & Bullmore, 2011; Delvecchio et al., 2012; Houenou et al., 2011; Kupferschmidt & Zakzanis, 2011). Phillips and Swartz (2014, p. 830) summarized the findings of this data around four themes. Their review suggests that relative to controls, patients with BP show the following brain abnormalities:

1. Abnormally *decreased* ventrolateral prefrontal cortex (including inferior frontal cortex [IFC]) activity during emotional processing, emotion regulation, and response inhibition.
2. Abnormally *increased* amygdala, striatal, and medial prefrontal cortical activity and *decreased* functional connectivity between amygdala and prefrontal cortex to *positive* emotional stimuli.
3. Abnormally *increased* amygdala, orbitofrontal cortex, and temporal cortical activity during *nonemotional* cognitive task performance.
4. Abnormally *increased* left ventrolateral prefrontal cortex and orbitofrontal cortex and ventral striatal (nucleus accumbens) during reward processing.

Phillps and Swartz (2014) found that these themes, which emerged from the fMRI studies, were supported by structural MRI and DTI studies

that have shown decreased gray and white matter volume, particularly in the right ventrolateral (and IFG) and orbitofrontal cortex. The volume of the amygdala and hippocampus is decreased, and white matter connections within the frontal lobe are decreased.

These themes are collapsed across all mood states (mania, euthymia, depression). When patients with BP in depressed, manic, and euthymic states are compared, the reductions in frontal activity are most decreased during mania, while the limbic activity is even more increased. When individuals with BP are depressed, they show more marked reduction in anterior cingulate cortex (ACC) and subgenual prefrontal cortex (Kupferschmidt & Zakzanis, 2011). How do patients with MDD who have never had a manic or hypomanic episode compare to patients with BP on neuroimaging measures? Consistent with the idea that the brain does not have distinct systems for mania and depression, patients with MDD alone and BP are more similar than different. Both disorders show increased activation of the limbic areas (Delvecchio et al., 2012). BP had more reductions in IFG activity than did MDD, while patients with MDD showed greater cortical reactivity to viewing negative facial expressions. Patients with MDD did not show increased ventral striatal activity during reward processing as did the patients with BP. This makes sense because patients with MDD do not experience pleasure in the same way as controls, whereas manic patients are pleasure seeking.

Lindquist and colleagues (2015) found that the insula has a tendency to be activated by negative valence emotions, although it can be activated by pleasurable stimuli such as music (see Plate 4). The insula is just underneath the temporal and frontal lobes; it sits on top of the caudate–putamen and interacts with the amygdala (see Figure 11.5). The insula plays a role in intereroception, which matches our emotional state with the physical sensations in our body. The insula would be strongly activated if we smelled or ate rancid food, and its activity would be linked to our sense of disgust. It plays a major role in our perception of pain (Hashimoto et al., 2015). Mutschler, Ball, Wankerl, and Strigo (2012) performed a meta-analysis of 11 fMRI studies on emotion and MDD (n = 209 patients), 44 studies on emotion in healthy subjects (n = 756 subjects), and 57 studies on physical pain in healthy individuals (n = 690). Emotion-related brain activation in depressed patients was shifted to the dorsal anterior insula, where regions related to physical pain in healthy subjects are located. This indicated that when depressed patients were experiencing emotion, they were using the pain centers of the insula. This may explain why depressed patients experience negative emotional events as being so *painful*.

Mood disorders frequently have an onset during childhood or adolescence. Sufficient neuroimaging studies have been done in both youth and adults with BP to examine differences between the age groups (Wegbreit et al., 2014). In general, youth with BP, relative to adult patients, have more

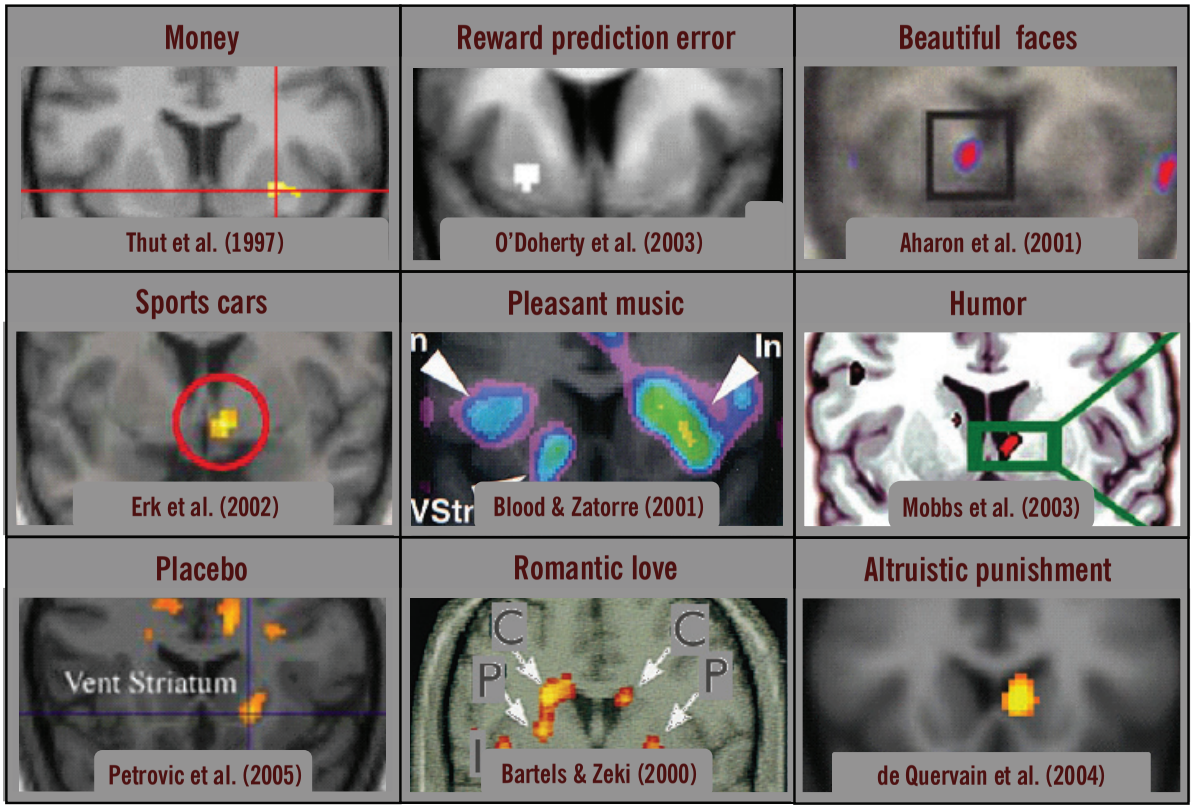


PLATE 4. The ventral striatum responds to a wide variety of rewards. Reprinted from Schultz (2007) with permission from Wolfram Schultz.

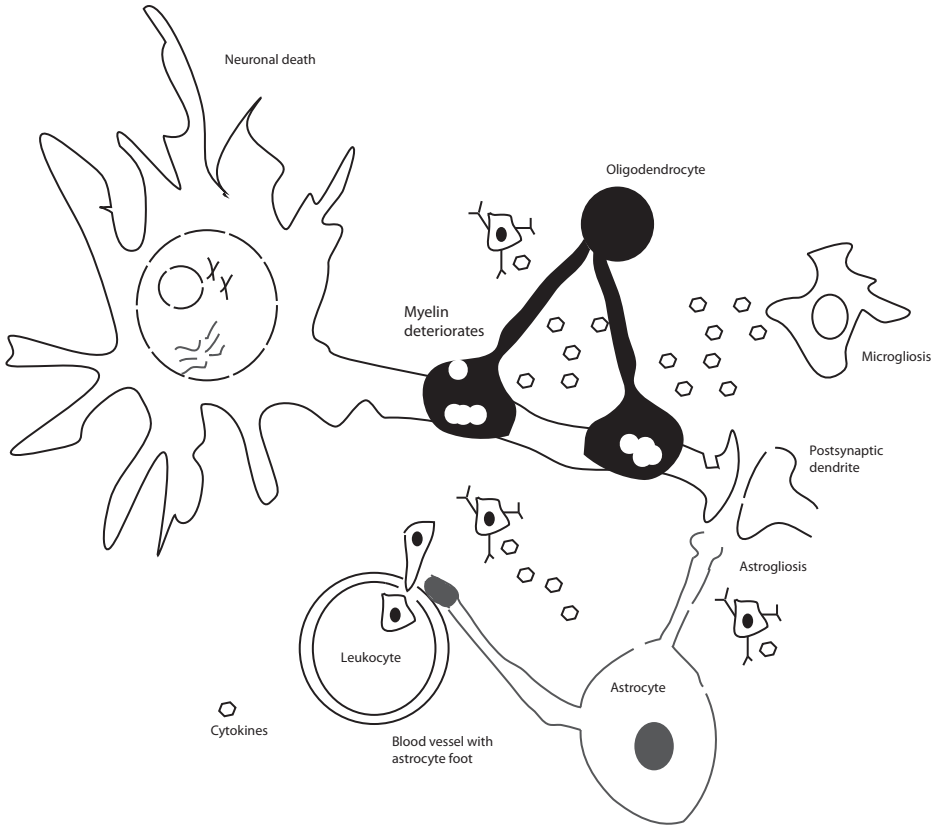


FIGURE 11.5. Delterious effects of inflammatory cytokines in the central nervous system.

pronounced abnormalities along the four themes described earlier. Analyses of emotional face recognition fMRI studies show significantly greater amygdala hyperactivation among youth with BD than among adults with BD, while analyses of fMRI studies using emotional stimuli showed significantly greater hyperactivation in the inferior frontal gyrus and precuneus among youth with BD than among adults with BD. In contrast, analyses of fMRI studies using nonemotional cognitive tasks show significantly greater hypoactivation in the ACC among youth with BD than among adults with BD.

It is highly likely that many of these imaging changes in mood disorder are the result of lifelong illness. This is shown by "high-risk" studies in which the offspring of parents with mood disorder are imaged prior to showing any illness themselves. In another meta-analysis, data from 37

studies involving 996 individuals at high risk for BP and 1,258 controls revealed very few differences between the groups (Fusar-Poli, Howes, Bechdolf, & Borgwardt, 2012). No significant differences were detected between high-risk individuals and controls in the selected emotional circuit noted to be disturbed in mood disorder: striatum, amygdala, hippocampus, pituitary gland, and frontal lobe. So far, no biomarker has emerged that can be said to be a predictor of future mood disorder.

INFLAMMATION AND MOOD DISORDERS

The body's immune system reacts with inflammation to injury or infection. Immune cells produce a wide variety of small proteins called cytokines, which are listed in Table 11.3. The pro-inflammatory cytokines assist in clearing infection and repairing damage to tissues; when the damage is controlled, the anti-inflammatory cytokines dampen the response (Sankowski, Mader, & Valdes-Ferrer, 2015). When we have an infection such as the flu, it is notable that we experience malaise, fatigue, and problems sleeping; we exhibit many of the symptoms of depression. Excessive inflammatory action is key to the pathophysiology of disorders such as Crohn's disease or rheumatoid arthritis. Cytokines are released by cells in the tissue and bloodstream but can cross the blood–brain barrier to have neurotoxic effects, as shown in Figure 11.5. Once leukocytes enter the brain, release of cytokines can disrupt astrocytes, leading to decreased neuronal support and deterioration of synapses. White matter is attacked and myelin deteriorates; ultimately, neuronal death can ensue.

A wide variety of psychosocial insults unrelated to physical injury or infection can trigger these effects (Audet, McQuaid, Merali, & Anisman,

TABLE 11.3. Pro- and Anti-Inflammatory Cytokines

Pro-inflammatory	Anti-inflammatory
TNF-alpha	IL-4
IL-1	IL-10
IL-8	IL-11
IFN-gamma	IL-13
IL-15	IL-18BP
IL-16	IL-1RA
IL-17	sTNF-R monoclonal antibody to TNF
	TGF-beta

Note. IFN, interferon; IL, interleukin; TGF, tumor growth factor; TNF, tumor necrosis factor.

2014). These include bereavement, care of a spouse with dementia, isolation from others, poverty, and excessive work for low reward. Despite the association between cytokines and depression, antidepressant medications do *not* have anti-inflammatory effects, and current anti-inflammatory drugs are not effective antidepressants. Exposure to abuse or trauma during either childhood or adulthood is associated with higher levels of interleukin-1 beta (IL-1beta), IL-6, and tumor necrosis factor (TNF)-alpha (but not of IL-2, IL-4, IL-8, or IL-10), particularly in those with psychiatric disorder (Tursich et al., 2014). Thus, the role of trauma in mood and anxiety disorders requires in-depth examination.

TRAUMA AND EPIGENETICS IN MOOD AND ANXIETY DISORDERS

In Chapter 5, we discussed the epigenetic effects of neglectful maternal rat behavior on both cortisol receptors in the cytoplasm of neurons and oxytocin receptors in pups. These actions affect adult rat behavior in terms of stress response and maternal behavior, respectively. Roth, Lubin, Funk, and Sweatt (2009) exposed rat pups to mothers who were aggressive (abusive) toward pups (rather than just neglectful) and compared them to pups raised by control mothers. They found that pups exposed to abuse had lower levels of the BDNF protein itself and greater methylation (silencing) of the BDNF gene. More significantly, the pups of the grown abused rats also had excessive methylation of the BDNF gene, showing intergenerational transmission of the effects of abuse.

People exposed to severe stress (including genocide and combat) show altered methylation levels of the *NR3C1* glucocorticoid receptor gene (Vukojevic et al., 2014; Yehuda et al., 2015). *NFKPB5* is a gene coding for a "chaperone" protein that binds to the cytosol glucocorticoid receptor and dampens the effect of cortisol (Klengel & Binder, 2015). *FKPB5* is activated by stress; certain individuals have a polymorphism in the gene that leads to increased cortisol levels. These individuals are not at risk for psychiatric disorder unless they are exposed to childhood (but not adult) trauma. With stress, the glucocorticoid receptor gene becomes demethylated, leading to even greater expression of these receptors and an exaggerated cortisol stress response. Regardless of the history of depression, women with a history of childhood abuse show an exaggerated adrenocorticotropic hormone (ACTH) to a psychological stressor than do controls (Heim, Shugart, Craighead, & Nemeroff, 2010). Evidence that abuse and neglect induce lifelong changes in gene expression that may even be transmitted to the next generation brings up serious ethical issues when discussing public policy regarding the prevention of child abuse (see Box 11.1).

BOX 11.1. Implication of Epigenetics for Public Policy on Child Abuse and Neglect

What is the best public policy to combat child abuse and prevent its obvious negative effects in terms of future criminal behavior, substance abuse, PTSD, and mood disorder? The lay public and even many mental health professionals tend to view abuse and neglect as "psychological" or "environmental" stressors, which means that its effects can be reversed once the abuse is stopped. It is accepted that the child would need a course of psychotherapy, but he or she should be "fine." Child Protective Services (CPS), when encountering abuse and neglect cases, must balance the risks of leaving the child in the abusive home (and hoping the parent will change) and disrupting family bonds by removing the child. Across the United States, there has been a concerted effort over the last decade to decrease the number of children removed from their homes. Any health professional has experienced the frustration of making a child abuse report and discovering that not only is the child not removed from the home, but little real intervention is provided to the family. Of course, it is not possible to conduct a study randomizing children exposed to abuse to stay in their home or be placed in foster care to determine the best long-term outcome. Simply following those who are placed in the home versus foster care is not helpful, since who suffer the worst abuse are more likely to be placed out of the home and therefore invariably have the worst outcome.

We have data now, however, from both animal and human studies that early neglect and abuse may produce long-term damage to the brain. It is possible that this damage cannot be undone and may even be transmitted to the next generation. Does this not shift the risk–benefit ratio in terms of stopping child abuse as early as possible? Does this not suggest that leaving a child in an abusive home for "6 months" to "see how the parent will do" is unwise? Within this decade, the epigenetic research on the effects of trauma will need to trump political views about "kinship placements" and "family reunification." Facts, as John Adams observed, are stubborn things.

NEUROIMAGING OF TRAUMA AND POSTTRAUMATIC STRESS DISORDER

The lay public and even many clinicians may view childhood trauma as a psychological issue if there is not some actual damage to the brain by physical abuse. It is now clear, however, that early trauma of all kinds leaves its mark on both the structure and function of the brain (Teicher & Samson, 2013). Multiple studies have indicated reductions in the size and integrity of the corpus callosum, the white matter tracks connecting the two hemispheres. This may account for the wide variety of cognitive deficits often seen in survivors of child abuse. The hippocampus also is decreased in size in adults with a history of abuse, while generally studies have not shown a difference between abused and nonabused individuals in the size of the

amygdala. The volume of the ACC and the ventromedial prefrontal cortex also are reduced (Kuhn & Gallinat, 2013). fMRI studies, however, consistently show hyperreactivity of the ACC, amygdala, and hippocampus, and lower reactivity of the ventromedial prefrontal cortex, particularly when exposed to negative or traumatic stimuli (Hayes, Hayes, & Mikedis, 2012; Patel, Spreng, Shin, & Girard, 2012). The default mode network also was overactive; this is important because the default mode is active during self-referential tasks, which suggests that persons exposed to abuse are reexperiencing their past abuse. The valence emotional network was strongly activated in persons with a history of abuse and/or posttraumatic stress disorder (PTSD), similar to that seen in mood disorder. It is notable that the amygdala and insula (part of the negative valence network) were also strongly activated. These overactivations are not seen as reliably in trauma-exposed individuals who did not develop PTSD (Sartory et al., 2013).

HOW DO ANTIDEPRESSANTS WORK?

Since their discovery, it has been known that antidepressants can block the reuptake of norepinephrine and/or serotonin. However, while this reuptake blockade occurs immediately, the therapeutic effects of antidepressants require 4–6 weeks to obtain full therapeutic results. There is no difference in efficacy between antidepressants that are selective for serotonin or norepinephrine, nor are there any clinical predictors of who will respond to which class of antidepressants. Tianeptine, a drug that enhances rather than blocks serotonin reuptake, is also an efficacious antidepressant (Kasper & McEwen, 2008). Thus, theories of antidepressant action have gone beyond monoamine transmitters per se to focus on other long-term mechanisms (Krishnan & Nestler, 2010; Willner, Scheel-Krüger, & Belzung, 2013).

As we have reviewed, stress, depression, and anxiety all may have neurotoxic effects, with chronically increased cortisol-activating processes that can lead to cell death (see Figure 11.6). Antidepressants may set in place mechanisms that prevent cell death and encourage neurogenesis. By blocking serotonin or norepinephrine reuptake, the monoamines can increase the transcription factor cyclic adenosine monophosphate (cAMP) response element binding protein (CREB-P), which can then trigger the production of BDNF. BDNF, acting through the RTK receptor system, activates the microtubule-associated protein (MAP) and phosphatidylinositol 3-kinase (PI3K) systems. The MAP system will trigger processes that lead to neurogenesis, while the PI3K system inhibits three enzymes that are anti-apoptotic ("against death"). Thus, BDNF maintains the health of current neurons and helps generate new ones. Serum BDNF rises in patients treated with antidepressants, though this is not currently a clinically useful measure (Wolkowitz et al., 2011). Rats administered the antidepressant

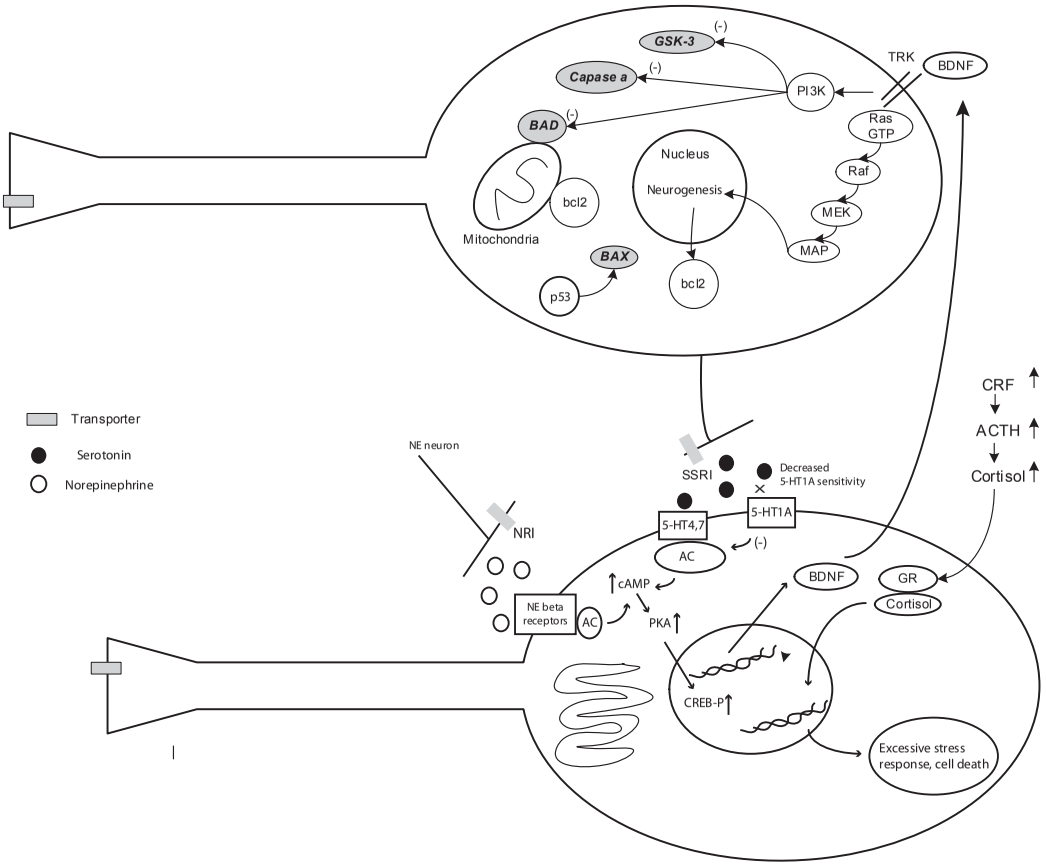


FIGURE 11.6. Neuroprotective and apoptotic factors in mood disorders.

fluoxetine for 4 weeks show increased numbers of new neurons in their hippocampi (Santarelli et al., 2003). Mice exposed to a social defeat (attack by a more aggressive rat) show increased methylation of the BDNF gene with decreased BDNF, but antidepressants acetylate the histones on the BDNF gene, leading to increased BDNF production (Tsankova et al., 2006).

It has been shown that increased BDNF has been found not only with antidepressants but also with lithium and electroconvulsive treatment of affective disorder. It would be tempting to see BDNF as the final common pathway for antidepressant treatment, though this would be premature. BDNF does not cross the blood–brain barrier easily, so an analogue would need to be developed. Furthermore, BDNF's beneficial action is most likely in the hippocampus; in the ventral tegmental area, it may have a depressive rather than an antidepressive effect (Krishnan & Nestler, 2010).

NEUROIMAGING OF AFFECTIVE DISORDER TREATMENT

Through what mechanisms do treatments for affective disorder exert their effect? This issue has been most studied with regard to antidepressant treatments, both pharmacological and psychosocial. It is a well-established fact that, on average, antidepressant pharmacotherapy and cognitive-behavioral therapy (CBT) show similar efficacy in the treatment of MDD (De Rubeis, Gelfand, Tang, & Simons, 1999; Hollon et al., 1992); although some patients may respond better to one or the other, other patients may require both concurrently. The biological mechanisms of both types of treatment have been studied primarily using PET scans of brain regional glucose metabolism (Goldapple et al., 2004; Mayberg et al., 2005). The first step in this line of work was to look at general changes in brain metabolism induced by each of these classes of treatment. Interestingly, despite the similar efficacy of antidepressants and CBT in depression, the brain effects of each are quite different, as shown in Table 11.4. In higher-level circuits related to executive function, memory, and the default mode network, CBT and antidepressants appear to have opposite effects, with CBT reducing metabolism in these networks while antidepressants increase it. CBT has unique effects in the medial, frontal and cortices. Interestingly, medial frontal and orbital frontal areas, which may be involved in emotional, ruminative behaviors, decrease in activity, while the ACC increases in activity. This might represent the process of CBT shifting the individual's thought patterns in a different, more positive direction. Given the effects of antidepressants on norepinephrine and serotonin, it is not surprising that these agents have unique effects on limbic and brain stem mechanisms. Effects on the subcallosal cingulate cortex (SCC) and the insula have subsequently been found to play a role in predicting response to treatment.

TABLE 11.4. Changes in PET-Measured Glucose Brain Metabolism during Antidepressant or Cogntive-Behavioral Treatment of MDD

Region of brain	CBT	Antidepressant
Drug and CBT have opposite effects		
Dorsolateral prefrontal cortex	↓	↑
Hippocampus	↓	↑
Inferior parietal cortex	↓	↑
Posterior cingulate	↓	↑
Effects of CBT only		
Medial frontal cortex	↓	
Anterior cingulate cortex	↑	
Orbitofrontal cortex	↓	
Effects of antidepressant only		
Subcallosal cingulate cortex		↓
Insula		↓
Brain stem		↑
Hypothalamus		↑
Thalamus		↓

Given the role of the insula in negative valence emotion (although this is clearly not its only role in the brain), it is an interesting target for antidepressant treatment. McGrath and colleagues (2013) used PET to measure brain glucose metabolism in 82 adults with MDD prior to treatment randomization to either the selective serotonin reuptake inhibitor (SSRI) escitalopram or CBT for 12 weeks. They were able to analyze scans from 38 patients with clear outcomes: 12 remitters to CBT, 11 remitters to escitalopram. They examined the ratio of insula activity to the whole-brain metabolism; those with a high ratio (hypermetabolism) showed a better response to the antidepressant and a poorer response to CBT, while those with hypometabolism were more likely to show the reverse pattern. This work would need to be replicated in a larger sample in which the insula/whole-brain metabolism ratio was assessed and those with high and low metabolism were then randomized to the two treatments. If such a study not only confirmed these results but also found an effect large enough to be useful at the level of an individual patient, then assessing insula function in MDD might be of clinical relevance.

NOVEL TREATMENTS FOR DEPRESSION

Ketamine is an anesthetic drug that is often abused due to its tendency to cause vivid hallucinations. Administered intravenously in low doses, it can

induce near-immediate remission of depressive symptoms, even in patients with chronic depression who have not been helped with traditional antidepressants (Kavalali & Monteggia, 2015). Ketamine is an *N*-methyl-D-aspartate (NMDA) receptor antagonist that works when the magnesium ion is blocking the NMDA channel. It also requires the presence of BDNF. These two facts give clues to its mechanism of action (see Figure 11.7). Note that when the NMDA receptor is blocked, more glutamate is available to stimulate the alpha-amino-3-hydroxy-5-methylisoxazole-4-proprionic acid (AMPA)/kainate receptors. This fast excitation leads to the opening of voltage-gated calcium channels, which can trigger the release of BDNF, possibly at much greater rates and amounts than triggered by traditional antidepressants. This BDNF induces activation of the same neurogenesis promoting genes shown in Figure 11.6, but in this case activation of PI3K may be more critical (Duman & Voleti, 2012). PI3K activates Akt, which in turn activates the mechanistic target of rapamycin (mTOR). mTOR turns on S6 kinase (S6K), which inhibits eukaryotic elongation factor-2 kinase (eEF2K). This enzyme has been related to several cancers, and it also prevents translation of certain messenger RNAs. Thus, when it is inhibited, new glutamate receptor complexes are translated and moved to the neuronal membrane. The final step is enhanced synaptogenesis in the hippocampal circuits.

In deep brain stimulation (DBS), electrodes are inserted into the brain and high-frequency electrical current is delivered to a specific brain region. The current is left on all the time after surgery; the electrode is attached to a wire that runs outside the skull to a battery pack. Mayberg and colleagues (2005) first placed the electrode in the SCC (also known as Brodmann's area 25), the part of the ACC that wraps around the corpus callosum, then bends under it (see Figure 11.4). Some of the patients receiving DBS had lifelong depression and for many multiple treatments had failed. The patient is awake during the procedure; one woman reported that when the current was turned on, she felt an immediate lifting of the depression. Three to 6 years later, over half of the patients undergoing DBS remained much improved (Kennedy et al., 2011).

Mayberg and colleagues (2005) hypothesized that the SCC is a key region for DBS because it is part of the negative valence network (along with insula and amygdala) and is overactive in people with depression relative to controls (Mayberg, 2007). When awake patients in surgery have the electrodes planted in the SCC and are shown various pictures, the SCC responds primarily to disturbing or unhappy scenes (Laxton et al., 2013). High activity in the SCC in depressed patients at baseline predicts nonresponse to traditional antidepressants and psychotherapy (McGrath et al., 2014). The high-frequency stimulation provided by DBS actually turns off the SCC (Benabid, 2015). Thus, DBS has great promise. Most

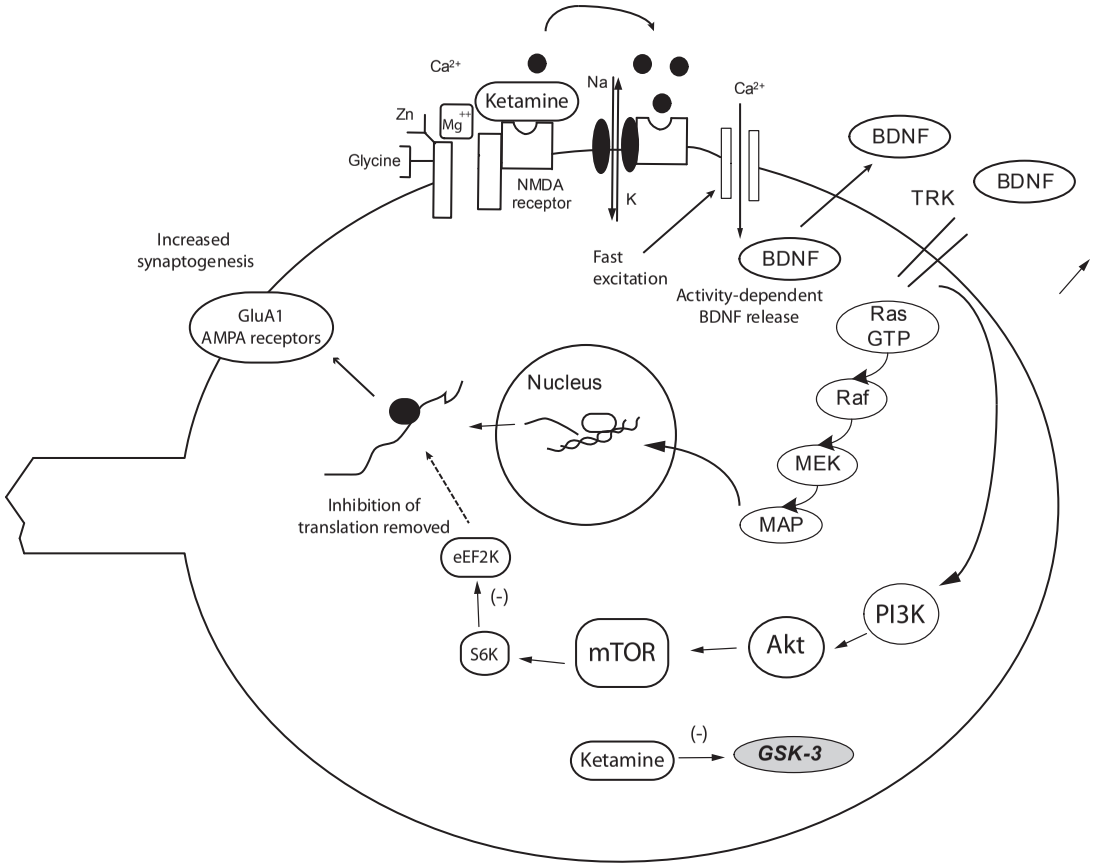


FIGURE 11.7. Possible mechanisms of antidepressant action.

of the studies done, however, have been open trials (Galvez et al., 2015). In a sham-controlled trial, the electrodes are placed but the current is not turned on in one group; the other group receives the current (patients cannot physically perceive the difference). The BROADEN (BROdmann Area 25 DEep brain Neuromodulation), a sham-controlled clinical trial at St. Jude's Medical Center, was halted due to the failure of patients to improve in the actual DBS over the sham (*www.neurotechreports.com/pages/publishersletterdec13.html*). While discouraging, some recent work suggests additional layers of complexity of DBS that need to be examined.

Preoperative high-resolution MRI data, including DTI (which assesses white matter tracts), were acquired in 16 patients with treatment-resistant depression who then received SCC DBS (Riva-Posse et al., 2014). This allowed the investigators to determine what tracts in the brain the DBS was impacting. The striking results are shown in Plate 11. The DBS must reach beyond the SCC itself to reach three areas: (1) medial frontal cortex, (2) rostral and dorsal cingulate cortex, and (3) subcortical nuclei, including the ventral striatum. This suggests electrode placement must be individualized in each patient. These results need to be confirmed by further sham-controlled studies.

OBSESSIVE–COMPULSIVE DISORDER

Obsessive–compulsive disorder (OCD) is actually out of place in a chapter on mood and anxiety disorders, but it is placed here because of its traditional grouping with these disorders. DSM-5 now places OCD in its own category of disorders, along with tic disorders and hoarding or other compulsive behaviors such as kleptomania (American Psychiatric Association, 2013). OCD and tic disorders are genetically related (Pauls, 1992; Pauls, Leckman, & Cohen, 1993). Both might even be viewed as movement disorders. Recall from Chapter 6 how the basal ganglia are involved in the initiation of motor movement, with the direct pathway providing the "gas" and the indirect pathway providing the "brake." In both OCD and tic disorders, the direct pathway appears to be in overdrive, leading to repetitive activation of tics, compulsions, or obsessions (Pauls, Abramovitch, Rauch, & Geller, 2014). People with compulsive disorders pull their hair out, pick at their skin, are unable to stop checking to see whether a door is locked, or hoard newspapers from the last 30 years. Why would humans develop such strange obsessions and compulsions?

Examining the behavior of animals helps us to take an evolutionary perspective. Primates such as apes and monkeys spend a great deal of time grooming each other and picking insects out of each other's hair, but mostly making physical contact. Cats and dogs lick their fur to keep it clean and as

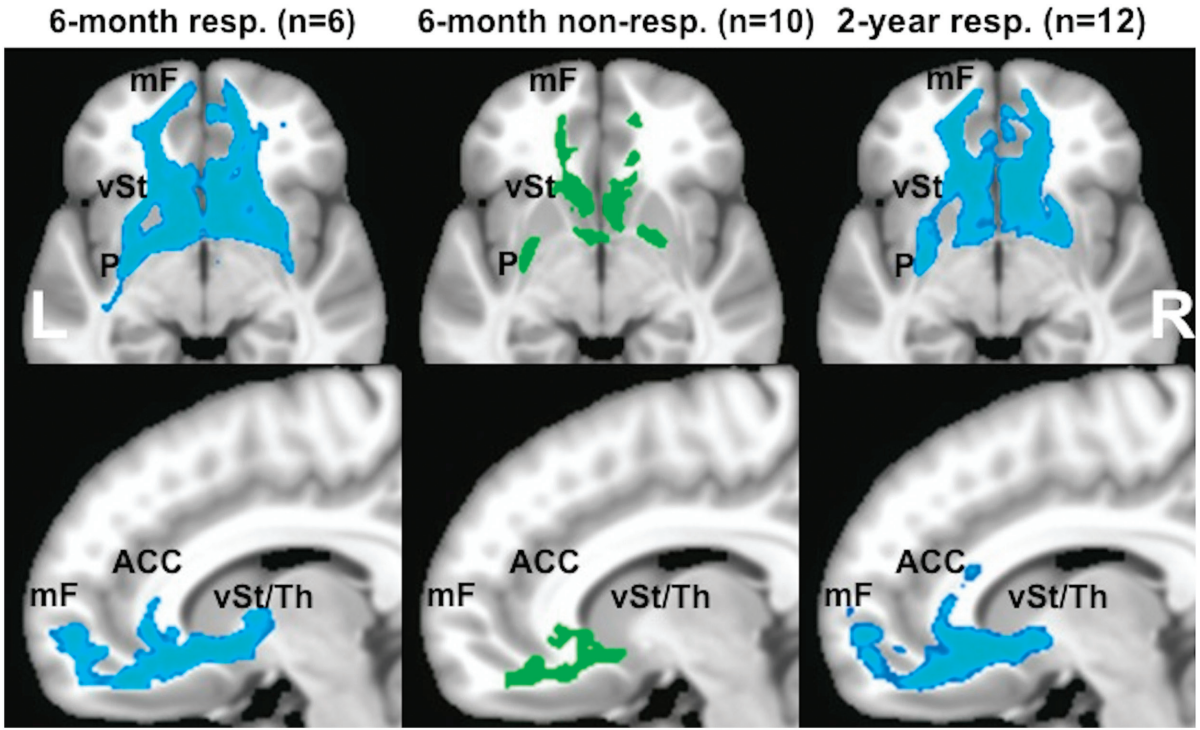


PLATE 11. Activation of patient-specific brain pathways may be needed for success of deep brain stimulation in the treatment of severe depression. Reprinted from Riva-Posse et al. (2014) with permission from Elsevier.

a self-soothing mechanism. Humans also seek physical contact with each other for emotional connection: Parents and children, as well as those who are romantically linked, will stroke each other's hair. It appears that such behaviors have been conserved by evolution in humans for emotional regulation, since we are hairless and do not need them to keep us clean! Yet the programs for these behaviors most likely still exist within the basal ganglia. When the direct pathway becomes overactive, they are initiated without reason. Hoarding may well be a remnant of the behavior of squirrels and other small mammals who gather nuts in anticipation of winter.

Depending on which cortical–striatal–thalamic loop is overactivated (see Figure 6.6), a particular obsession or compulsion is activated. If the limbic loop is overactivated, a sexual or religious obsession may result. Multiple neuroimaging studies have shown gray matter abnormalities, white matter tract dysconnectivity, and altered functional activity in the cortical–striatal–thalamic circuits (Chamberlain, Blackwell, Fineberg, Robbins, & Sahakian, 2005; Del Casale et al., 2011). The caudate nucleus and the ACC show pronounced hyperactivity relative to controls in fMRI studies; this may represent the striatum driving the excessive initiation of movement, while the ACC is engaged in excessive monitoring of behavior and cognition (e.g., the urge to check).

Two GWAS studies have been conducted in OCD, identifying several genes of interest (Pauls et al., 2014). These include Fas apoptotic inhibitory molecule 2 (*FAIM2*), which, as its name implies, is involved in neuronal death, particularly in glutamate neurons. Also of note is *BTBD3,* part of a large family of transcription factors. It is involved in the regulation of transcription, ion channel assembly and gating, and posttranslational modification and degradation of protein. As with *FAIM2,* several other genes were implicated that play a role in the glutamate system. The role of Streptococcus A and other infectious phenomena in OCD and tics has been controversial for many years (Murphy, Kurlan, & Leckman, 2010). While some children with pediatric autoimmune neuropsychiatric disorders associated with Streptococcus (PANDAS) can clearly develop OCD (as well as chorea or other motor disorders), the studies are equivocal as to how common autoimmune phenomena generally are in OCD or tic disorder.

SUMMARY

Mood and anxiety disorders share many features, including genetic vulnerabilities and early psychosocial stress. The serotonin and BDNF systems may be dysregulated with subsequent neurotoxic events leading to decreased hippocampal volume. The emotional valence brain network appears to be more strongly activated in persons with these disorders, particularly the

amygdala, insula, and SCC. The SCC may be a key region in moderating response to treatment. Future treatments may involve reestablishing brain circuitry that modulates negative emotion through enhanced neurogenesis and synaptogenesis. Child abuse and other trauma should be viewed as injurious to the brain itself. Since the days of Kraepelin, mood disorders have been seen as distinct from schizophrenia. As we move to the study of schizophrenia, we will see that these disorders in fact may not be so separate.

CHAPTER 12

Schizophrenia

Schizophrenia affects about 1% of the U.S. population (National Institute of Mental Health, 2015). People with schizophrenia suffer high rates of disability, homelessness, and early death (Saha, Chant, & McGrath, 2007). While it is well known that higher levels of creativity and artistic accomplishment are found among people with bipolar disorder, it is less well known that families of people with schizophrenia also contain individuals of considerable accomplishment. Bertrand Russell had both a son and a granddaughter with schizophrenia. Albert Einstein's son by his first marriage suffered from the disorder, as did James Joyce's daughter Lucia. In the United States alone, over $20 billion is spent on care for schizophrenia every year (Knapp, Mangalore, & Simon, 2004). Since the closing of many state hospitals in the mid-20th century, many people with schizophrenia end up in prison for a wide variety of crimes, from disorderly conduct to murder (often while psychotic or delusional). In 1959, nearly 559,000 mentally ill patients were housed in state mental hospitals (Lamb, 1998). After deinstitutionalization, the number of persons housed in public psychiatric hospitals dropped to around 70,000 by the 1990s. In a 2006 Special Report, the Bureau of Justice Statistics (James & Glaze, 2006) estimated that 705,600 mentally ill adults were incarcerated in state prisons, 78,800 in federal prison, and 479,900 in local jails. Thus, the burden of schizophrenia to both the individual and society is great.

Schizophrenia often has a long, premorbid course that consists of gradual withdrawal and decline in functioning. An acute episode of psychosis often occurs during late adolescence or early adulthood, with "positive" symptoms that include hallucinations, delusions (including paranoia), and illogical/incoherent thought (loose associations or "thought disorder"). Positive symptoms often resolve with antipsychotic medication, but people with schizophrenia more prominently suffer from "negative" symptoms,

such as a lack of emotion (blunted affect), low motivation, poor social skills, and lack of interest in others. Cognitive impairment also is noted; accomplished people who develop schizophrenia rarely obtain their original level of functioning after disease onset. These negative symptoms often produce greater impairment in daily functioning than do positive symptoms.

GENETICS OF SCHIZOPHRENIA

The heritability of schizophrenia is around 80% (Sullivan, Kendler, & Neale, 2003), and it is now clear that the genetic risks for schizophrenia are shared with affective disorder (Cardno & Owen, 2014). A large schizophrenia genome-wide association study (GWAS) of 36,989 patients and 113,075 controls recently has been published (Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014). The study identified 108 loci that met genome-wide significance (83 had not been previously found). The loci were spread throughout the chromosomes, with the most robust findings on chromosome 6, near the loci for the major histocompatibility complex (MHC), which plays a role in the immune response. This is relevant to our discussion of environmental insults related to schizophrenia in the next section. In the supplementary discussion to the article, the authors listed the genes thought to be implicated in schizophrenia. The major ones are summarized in Table 12.1.

Of note, variations in genes for calcium channels are involved not only in schizophrenia but also in attention-deficit/hyperactivity disorder (ADHD), bipolar disorder, autism spectrum disorder, and major depressive disorder (Cross-Disorder Group of the Psychiatric Genomics Consortium, 2013). Gatt, Burton, Williams, and Schofield (2015) examined multiple meta-analyses of GWAS of psychiatric disorders and also found the following genes shared across these disorders: the dopamine transporter, dopamine receptor 4, serotonin transporter, *COMT*, *BDNF*, *APOE* (also linked to Alzheimer's disease), and the methylene tetrahydrofolate reductase (*MTHFR*, the enzyme involved in processing folate). At the present time, our "leads" in the pathophysiology of schizophrenia are (1) altered dopamine, glutamate, and cholinergic functioning; (2) impaired early neural development; (3) impairments in neuroplasticity and pruning of synapses; and (4) altered calcium signaling.

ENVIRONMENTAL RISK FACTORS IN SCHIZOPHRENIA

Early abuse and neglect, poverty, and urban living all have been linked to schizophrenia, as with other mental illnesses (Uher, 2014). Although

TABLE 12.1. Genes Implicated in the Pathophysiology of Schizophrenia

Domain	Gene (chromosome)	Function
Dopamine	*DRD2* (11q23.2)	Dopamine receptor, long known to be one of the main targets of antipsychotic medication.
Glutamate neurotransmission	*GRM3* (7q21.12)	mGluR3 is a metabotropic glutamate receptor predominantly expressed in astrocytes; may be a target for future therapeutic drugs.
	GRIN2A (16p13.2)	NMDA receptor subunit *GRIN2A* (NR2A) is a key mediator of synaptic plasticity. NMDA receptor channel blockers such as ketamine and NMDA autoantibodies mimic the symptoms of schizophrenia in humans.
	GRIA1 (5q33.2)	Glutamate receptor 1 (GluR1, GluA1) is a subunit of an AMPA (non-NMDA) receptor that mediates fast synaptic transmission, involved in synaptogenesis in the hippocampus.
	SRR (17p13.3)	Serine racemase catalyzes L-serine racemization (switching from right- to left-handed molecule) to D-serine, which is an essential coagonist and activator of NMDA receptors.
	CLCN3 (4q33)	CLC-3 is a voltage-gated chloride channel localized to glutamatergic synapses in the hippocampus, where it modulates plasticity.
Nicotinic acetylcholine receptors	*CHRNA3*, *CHRNA5*, and *CHRNB4* (15q25.1)	Nicotinic acetylcholine receptors (nAChRs) are on both pre- and postsynaptic neurons (see Figure 4.6). Abnormal Ach transmission can impact cognition. Schizophrenics have high rates of smoking nicotine relative to controls.
Neuron calcium signaling	*CACNA1I* (22q13.1)	*CACNA1I* is the pore forming alpha subunit of a calcium channel. Activation triggers synaptic plasticity and long-term potentiation when co-activated with NMDA receptors.
	RIMS1 (6q12-13)	RIMs are multidomain proteins that tether calcium channels to synaptic active zones, dock and prime synaptic vesicles for release, mediate presynaptic plasticity, and facilitate neurotransmitter release.
	CACNA1C, *CACNB2*, *CAMKK2*, *NRGN*, and *ATP2A2*	Multiple calcium channels. These loci also linked to other major psychiatric disorders (ADHD, bipolar, autism spectrum disorders).

mood disorders have been described back to antiquity, descriptions of schizophrenic-like behavior only have been noted with the onset of intense urban living, which began in 1300–1500. The prevalence of schizophrenia (dementia praecox or insanity, as it was called then) rose markedly in the 1850s with the onset of industrialization (Liberman, Musgrave, & Langlois, 2003).

Consistent findings over three decades have linked adverse events during pregnancy and delivery to schizophrenia. Obstetrical complications appear to be particularly likely to increase the risk for schizophrenia; these include low birthweight, prematurity, the need for resuscitation after birth, or perinatal brain damage (Nosarti et al., 2012). People who develop schizophrenia are somewhat more likely to be born in the winter and early spring, when the mother is more likely to have been exposed to the influenza virus during pregnancy (Mortensen et al., 1999). Indeed, prenatal infection with herpes (Buka, Cannon, Torrey, & Yolken, 2008) and rubella (Brown et al., 2001) are linked to the disease.

During World War II, in the winter of 1944, the Netherlands was blockaded, producing a famine. Women who were in the second trimester of pregnancy during this period were more likely to bear children who later developed schizophrenia, indicating that poor nutrition during critical phases of brain development is a risk factor (Susser & Lin, 1992). Low maternal weight gain during pregnancy, small head circumference at birth, and low placenta weight also contribute to the risk of schizophrenia. During brain development, neurons migrate from the center of the brain to the periphery, where they establish networks with each other. Reelin, a key protein in brain development, serves as a stop signal for neuronal migration. Studies have shown that reelin is reduced by 30–50% in the prefrontal cortex and hippocampi of people with schizophrenia (Fatemi, Earle, & McMenomy, 2000; Folsom & Fatemi, 2013; Guidotti et al., 2000). Finally, people with schizophrenia show a higher than expected rate of minor physical anomalies in various areas of their bodies. These include minor alterations in fingers, ears, mouth, and feet that do not affect function but suggest a degree of fetal maldevelopment (McNeil, Cantor-Graae, & Ismail, 2000). These minor anomalies are not specific to schizophrenia; however, they are found in a number of psychiatric disorders, including fetal alcohol syndrome, autism, and learning disabilities.

SCHIZOPHRENIA AS A NEURODEVELOPMENTAL DISORDER

It is important to note that the vast majority of people who have any of these early risk factors do not go on to develop schizophrenia. This fact has led to the "double-hit" hypothesis, which suggests that a genetic risk is

necessary but not sufficient for the development of schizophrenia. A genetic risk combined with one of the early insults just discussed would then lead to the expression of the disorder. Those who do not suffer an early brain insult might go on to develop mild schizotypal symptoms or perhaps show no disorder at all. Genetic and perinatal insults operate early in life, but schizophrenia rarely has full onset before adolescence. What accounts for this? Children who ultimately develop schizophrenia do show subtle behavioral differences in a number of areas. Examination of home movies of people with schizophrenia as children revealed that compared with their normal siblings, children who were preschizophrenic showed more abnormal limb movements during the first 2 years of life (Schiffman et al., 2004). These abnormal movements correlated with the degree of brain abnormality in adulthood (Walker, Lewine, & Neuman, 1996). During the elementary school years, persons who will develop schizophrenia already show lower IQs and increased social withdrawal. These early signs are generally not noticeable to parents and teachers at the time. The development of schizophrenia may require a "triple hit"; that is, in addition to genetic risk and early brain insult, some factor triggered during adolescence may cause the final progression to schizophrenia.

McGlashen and Hoffman (2000) reviewed data strongly suggesting that people with schizophrenia show reduced synaptic connectivity. Gray matter volume (e.g., neurons and their support cells) normally increases until age 5, when it begins to decline. During adolescence, it begins a sharp decline, as synapses are "pruned"; this process is most marked in the frontal and parietal lobes. In a normal individual, this pruning eliminates unnecessary connections and optimizes brain flexibility to deal with new learning. McGlashen and Hoffman proposed that in a vulnerable individual with too few synapses to begin with, the onset of the normal pruning process can cause a severe impairment in information processing and the subsequent onset of schizophrenia. Alternatively, they proposed that some individuals with schizophrenia have an overly aggressive pruning process (the "third hit"). Their model is consistent with the neuroimaging data.

BRAIN STRUCTURE IN SCHIZOPHRENIA

There now have been many decades of structural magnetic resonance imaging (MRI) studies of schizophrenia, with several meta-analyses available to examine the overall results (Adriano, Caltagirone, & Spalletta, 2012; Shepherd, Laurens, Matheson, Carr, & Green, 2012). There is strong evidence for gray matter reductions of the anterior cingulate, frontal medial and inferior and temporal lobes, hippocampus/amygdala, thalamus, and insula in persons with schizophrenia relative to controls. These deficits are

present at first episode and become worse over time. The deficits are particularly pronounced in those with childhood-onset schizophrenia (Rapoport, Giedd, & Gogtay, 2012). While the gray matter is reduced, more neurons are packed into a smaller space. The neurons are smaller and have fewer dendrites, resulting in less connectivity (Glantz & Lewis, 2000). Diffusion tensor imaging shows decreased structural integrity of the large white tracks, such as the cingulum bundles, uncinated fasciculi, internal capsules, and corpus callosum (Wheeler & Voineskos, 2014). Relative to controls, persons with schizophrenia have fewer oligodendrocytes, leading to decreased maintenance of the white matter (Hof et al., 2003).

Numerous studies show evidence of excessive "apoptosis" (programmed cell death) in schizophrenia (Jarskog, Glantz, Gilmore, & Lieberman, 2005). Postmortem studies and magnetic resonance spectroscopy (MRS) studies in individuals with schizophrenia show reduced dendritic spines on neurons, decreased glutamate and gamma-aminobutyric acid (GABA) release, and decreased synaptic protein messenger RNA (Jarskog et al., 2005). Persons with schizophrenia are more likely to express a less functional version of the *N*-methyl-D-aspartate (NMDA) receptor (Meador-Woodruff & Healy, 2000). They have reduced *N*-acetyl aspartate (NAA) in the dorsolateral prefrontal cortex, implying decreased neuronal integrity. The amount of glutamic acid decarboxylase (the enzyme that is key to the synthesis of GABA) is reduced in the brains of persons with schizophrenia, and there are derangements in the GABA transporter that governs its reuptake (Akbarian et al., 1995).

A particularly useful strategy in studying brain structure in schizophrenia is to compare the brains of monozygotic (MZ) twins discordant for schizophrenia. This allows the investigators to separate influences of genetic and other factors on brain structure. Barre and colleagues (2001) studied 15 MZ and 14 dizygotic (DZ) twins who were discordant for schizophrenia and compared them with 29 twin pairs, neither of whom had schizophrenia (the controls were matched for zygosity). In general, the correlation of the size of brain regions was higher for the MZ twins than for the DZ twins; that is, brain structure was more similar in the MZ twins. The investigators studied both intracranial volume (space inside the skull, which is set by early brain growth) and volume of the brain itself (whole-brain volume). First, intracranial volume was reduced in *both* of the MZ twins discordant for schizophrenia relative to the twin pairs in which both were healthy. Second, frontal lobe size was decreased in ill MZ twins, relative to their healthy co-twins, in excess of the decrease in whole-brain volume. This suggests that both the ill and healthy MZ twins had reduced early brain growth (particularly in the frontal lobe) but that only one of them developed the illness (see Figure 12.1). Thus, reduced early brain growth is a risk factor for schizophrenia, but it does not itself cause the

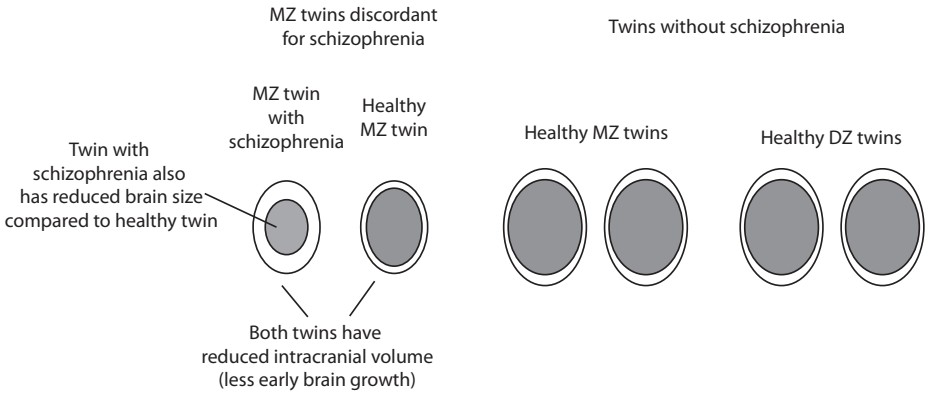


FIGURE 12.1. Illustration of the findings of Barre et al. (2000) of intracranial and whole-brain volume in monozygotic twins discordant for schizophrenia.

disorder. In contrast, whole-brain volume, as well as hippocampal volume, was reduced in the twins with schizophrenia regardless of zygosity. This additional decrease in brain size may be due to the schizophrenia disease process itself. The imaging data are consistent with the triple-hit hypothesis: A genetic factor impairs early brain development in both twins, while in the affected twin some other factors lead to decreased brain volume.

FUNCTIONAL NEUROIMAGING IN SCHIZOPHRENIA

Give the widespread structural deficits in the brains of persons with schizophrenia and the cognitive problems of the disorder, it is not surprising that functional MRI (fMRI) also shows widespread abnormalities, particularly during cognitive tasks (Belger & Dichter, 2006). Morey and colleagues (2005) studied four groups: controls, persons with recent-onset schizophrenia, persons with chronic schizophrenia, and persons at high risk who already were showing premorbid symptoms. The subjects performed a cognitive task in the scanner that activated the control networks (by now familiar to the reader): anterior cingulate gyrus (ACG), medial frontal gyrus (MFG), inferior frontal gyrus (IFG), basal ganglia, and thalamus. This network was underactivated relative to the controls in all three groups in the following order: controls > high risk > early > chronic. This study showed that the cognitive decline may begin before the acute onset of the illness. Deficits in this control network are seen in all of the other disorders we have examined so far. What can imaging tell us specifically about schizophrenia?

People with schizophrenia have difficulty connecting to others emotionally. Ursu and colleagues (2011) had both controls and patients view angry, pleasant, or neutral faces while obtaining fMRI. After a delay of 12.5 seconds, the participants rated how energized, positive, or negative the pictures made them feel. There were no differences in brain activation during the presentation of the faces, with both groups activating a broad network of prefrontal, limbic, and paralimbic structures. After the delay, however, those with schizophrenia showed a marked decrease in activation of the dorsolateral prefrontal cortex and the decrease correlated with the patients' rating of their anhedonia. This implies that schizophrenia does not cause the inability to recognize emotion, but that there are deficits in downstream appraising and experiencing of emotion.

In Chapter 7, we discussed the role of both the hippocampus and the default mode network (DMN) in memory. We discussed the anterior and posterior systems of memory, with the posterior memory system working to put current experience into a larger context. During this process, the brain must clearly segregate the current perception from what has occurred in the past or what is imagined. This process clearly breaks down in schizophrenia, wherein patients both perceive stimuli that are not present (hallucinations) or make connections between events that are clearly false (e.g., "The garbage man works for the city, so the government is spying on me"). Tamminga, Southcott, Sacco, Wagner, and Ghose (2012) have reviewed the extensive neuroimaging work on the hippocampus in schizophrenia. They point out that resting cerebral blood flow, blood volume, and perfusion measures of nonstimulated neuronal activity are elevated in persons with schizophrenia relative to controls. In contrast, during cognitive tasks, fMRI studies show *decreased* activation of the hippocampus of persons with schizophrenia relative to controls. They hypothesize that the increased activity at baseline is due to increased activity in the CA3 field of the hippocampus, while task-related deficits are related to reduced glutamate signaling in the dentate gyrus (DG). Their hypothesis is illustrated in Figure 12.2A. A glutamate signaling lesion in the DG leads to an imbalance in the hippocampal circuit. With greater long-term potentiation (LTP) occurring at the CA3 site, this may lead to improper associations between events and thus exaggerated associations (review LTP in Chapter 7). If disturbed interactions in the hippocampal circuit spread to the posterior memory system, there will be difficulties in placing current experience in context and matching the external world to internal memories. It is not difficult to see how such deficits would lead to a delusional experience.

Over the last few decades, there have been multiple neuroimaging studies of hallucinations per se. These studies are difficult because they require the patient to be scanned at the time of the hallucinations. Consistently, auditory hallucinations are associated with activation of the primary

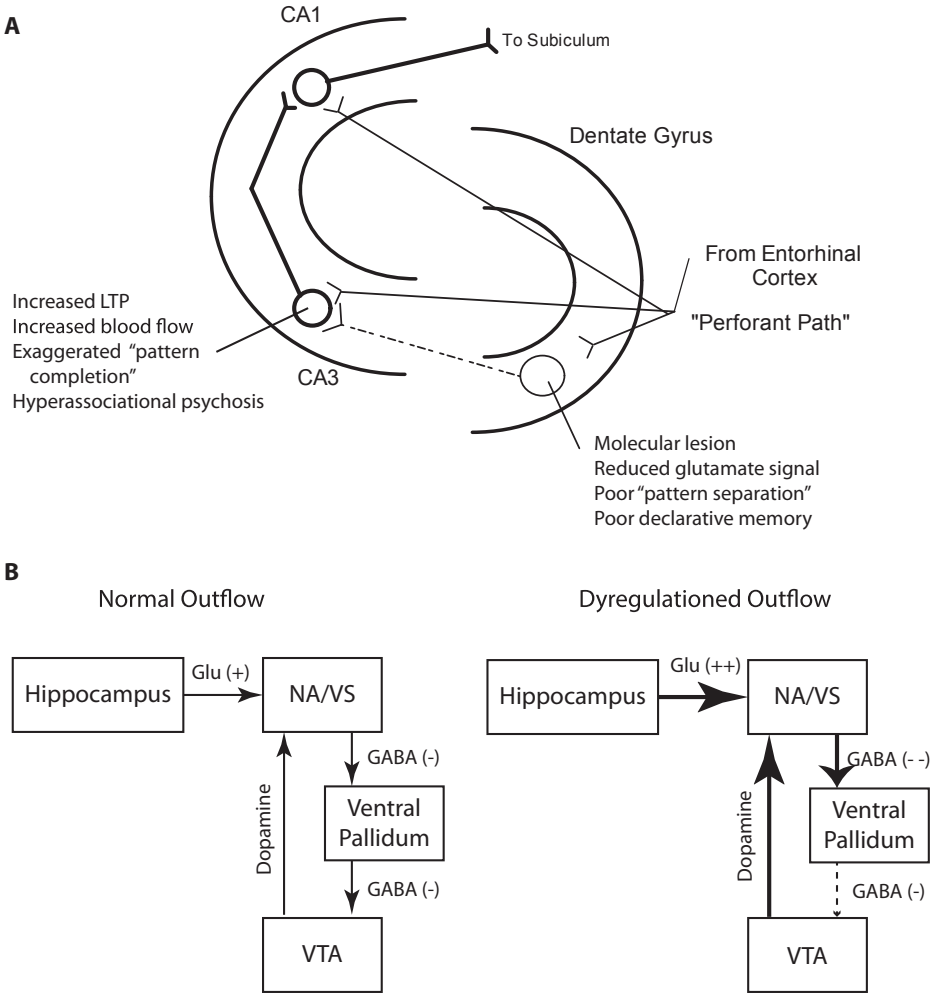


FIGURE 12.2. Neurochemistry of the hippocampus and ventral striatal circuits in schizophrenia.

auditory cortex and Wernike's area, just as with normal, external auditory stimuli (Allen et al., 2012). What causes the abnormal activation of these areas? As with other disorders, investigators are shifting their focus to disturbances in brain networks (Rashid, Damaraju, Pearlson, & Calhoun, 2014; van den Heuvel & Fornito, 2014). Look again at Plate 8 (Baker et al., 2014). The patients all had a history of psychosis, including those with schizophrenia, schizoaffective disorder, and bipolar disorder. Interestingly,

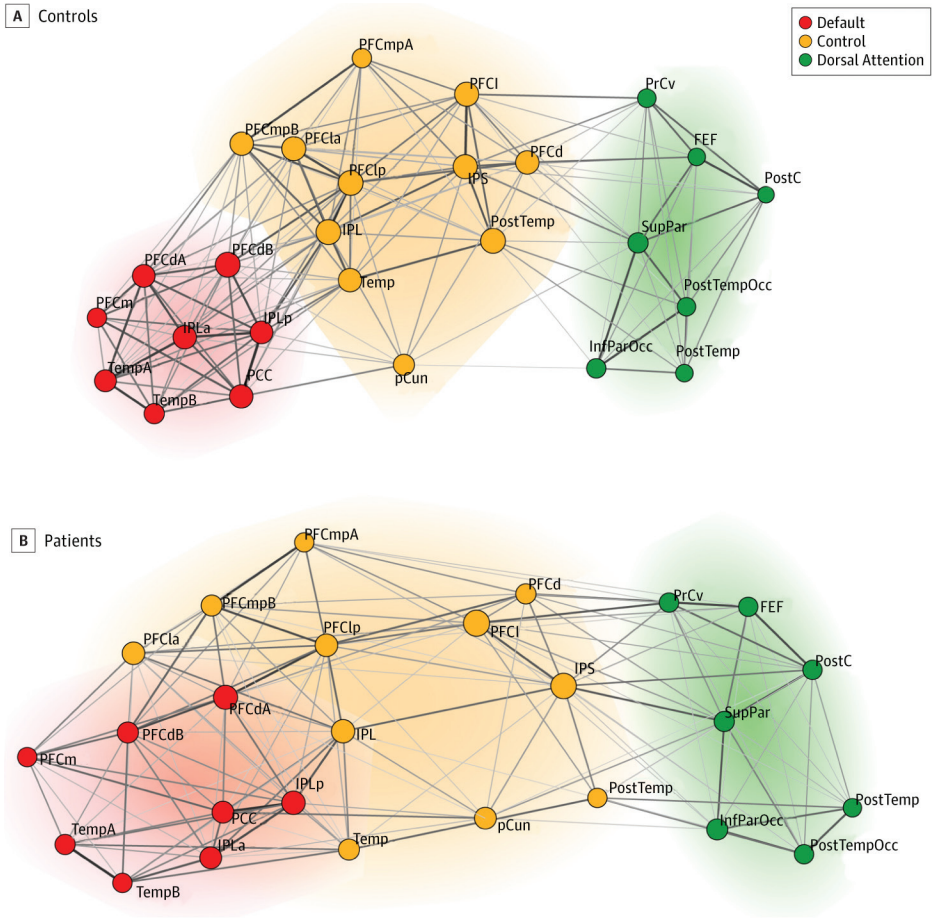


PLATE 8. Spring-loaded graphs showing selected nodes of the frontal–parietal control network, dorsal attention network, and default network in controls (A) and patients (B). Node size is based on nodal degree; edge connection strength is represented by gray-scale value and line thickness. Controls had a more segregated pattern clustering of frontal–parietal and default networks (represented with nonoverlapping colored halos); by contrast, patients had less clustering within default and frontal–parietal control networks and evidence of extension of frontal–parietal nodes into the default cluster (represented with blended red–orange halos). FEF, frontal eye fields; InfParOcc, inferior parietal–occipital; IPL, inferior parietal lobule; IPLa, lateral inferior parietal lobule; IPLp, posterior inferior parietal lobule; IPS, intraparietal sulcus; PCC, posterior cingulate; pCun, precuneus; PFCd, dorsal prefrontal cortex; PFCdA, dorsal anterior prefrontal cortex; PFCdB, B component of dorsal prefrontal cortex; PFCl, lateral prefrontal cortex; PFCla, lateral anterior prefrontal cortex; PFClp, lateral posterior prefrontal cortex; PFCm, medial prefrontal cortex; PFCmpA, A component of medial posterior prefrontal cortex; PFCmpB, B component of medial posterior prefrontal cortex; PostC, postcentral gyrus; PostTemp, posterior temporal; PostTempOcc, posterior temporal occipital; PrCv, ventral precentral gyrus; SupPar, superior parietal lobule; Temp, temporal cortex; TempA, A component of temporal cortex; TempB, B component of temporal cortex. Reprinted from Baker et al. (2014) with permission from the American Medical Association.

differences in the networks did not distinguish these three groups. What is of particular note is the manner in which, in the patients, the DMN is not clearly segregated from the other networks. Peeters, van de Ven, and colleagues (2015) obtained resting-state fMRI scans from 73 patients with psychotic disorder, 83 nonpsychotic siblings of patients with psychotic disorder, and 72 healthy controls. They also assessed the subjects for their history of exposure to a variety of psychosocial stressors. Both the patients and siblings had increased connectivity of the DMN to other networks relative to controls. These network studies suggest that the daydreaming, self-referential DMN network may intrude into other networks that receive stimuli from the external world, creating false perceptions. Another group found decreased connectivity between reward regions of the brain (nucleus accumbens) and frontal networks, suggesting a reason for the low motivation in schizophrenia (Peeters, Gronenschild, et al., 2015).

NEUROCHEMISTRY IN SCHIZOPHRENIA

Given that antipsychotic medications block dopamine-2 (D_2) receptors, the hypothesis of excessive dopamine in schizophrenia has been long-standing. Interestingly, only in the last 20 years have we been able to address the question definitely, with the advent of positron emission tomography (PET) and the ability to image dopamine release and dopamine receptors in the brain. In an extensive review of PET studies, Brunelin, Fecteau, and Suaud-Chagny (2013) concluded that there is evidence for excessive dopamine in schizophrenia. Relative to controls, persons with schizophrenia show an increase in dopamine synthesis presynaptically, coupled with a modest increase in the density of postsynaptic D_2 receptors. Persons with schizophrenia also show increased release of dopamine in response to administration of amphetamine. It is increasingly apparent, however, that disturbance in dopamine is likely a secondary effect in the disorder.

Insight into the neurochemistry of schizophrenia comes from a mouse model of the disorder, which results from administration of mitotoxin methylazoxymethanol (MAM) to pregnant rats on day 17 of gestation. At adulthood, these rats show a number of behavioral and physiological deficits akin to schizophrenia (Lodge & Grace, 2009), as well as increased dopamine activity of ventral tegmental area (VTA) and substantia nigra neurons (Winton-Brown et al., 2014). Similar to humans with schizophrenia (Tamminga et al., 2012), these rats show increased activity in the CA3 field of the hippocampus (Lodge & Grace, 2011; Modinos, Allen, Grace, & McGuire, 2015). The consequences of this are shown in Figure 12.2B. The increased glutamate output from the hippocampus leads to overstimulation of the nucleus accumbens, with resultant increased GABA input to

the ventral pallidum. This excessive inhibitory input results in less GABA output to the VTA, which in turn is disinhibited, resulting in abnormally increased dopamine input back to the accumbens. The circuit is put into "overdrive," and this may underlie the positive symptoms of schizophrenia.

In Chapter 6 we noted that reward-associated dopamine release into the accumbens was associated with an increase in the fMRI signal in that region (see Plate 4). Brunelin and colleagues (2013) showed dopamine activity to be increased in schizophrenia, yet in human studies, patients with schizophrenia showed *reduced* activity in the ventral striatum during montery reward tasks (Winton-Brown et al., 2013). This complex disturbance in the dopmaine circuitry may suggest an abnormality in how schizophrenics process "salience." In this hypothesis (Winton-Brown et al., 2013), people with schizophrenia (as well as others in a psychotic state), have abnornal dopamine input into the ventral striatum, which causes an abormal coding of a random event or stimuli as being salient, that is, as having meaning. This leads to an abnormal or even paranoid view of events being connected in some way. Why this would result in dopamine decreasing vental striatal activity is not clear, but it may involve a complex interaction between phasic and tonic release of dopamine (see Figure 9.2 in Chapter 9) that current neuroimaging techniques cannot resolve.

PSYCHOPHARMACOLOGY OF SCHIZOPHRENIA

Older, first-generation (or "typical") antipsychotic medications (FGAs), such as haloperidol, block D_2 receptors and eventually induce "depolarization block" in which the dopamine neurons decrease their firing. Decreased dopamine input to the striatum can mimic the effects of Parkinson's disease. Generally, the negative symptoms of schizophrenia are left untouched. In the early 1990s, the group of "atypical" or second-generation antipsychotic medications (SGAs) that emerged appeared to have fewer Parkinson's-like side effects and possibly more effectiveness against negative symptoms. The SGAs generally had more potency at blocking serotonin 2_A ($5\text{-}HT_{2A}$) receptors than FGAs, and this was hypothesized to underlie their increased benefit (Kapur & Remington, 1996). However, $5\text{-}HT_{2A}$ antagonist drugs do not have any beneficial effect on schizophrenia (de Paulis, 2001). A major National Institute of Mental Health study challenged the idea that the SGAs have any benefit over the older drugs (Lieberman et al., 2005); this lack of difference in efficacy between the two classes is confirmed by more recent work (Nielsen, Jensen, Friis, Valentin, & Correll, 2015). Meta-analyses of antipsychotic treatment studies suggest a more nuanced picture, with some SGAs showing modest superiority over FGAs, with no clear line demarcating the two classes (Leucht et al., 2009, 2013). Thus, it seems pointless to

try to discern neurochemical differences between the two drug classes in an effort to understand the pathophysiology of schizophrenia.

More interest is currently focused on the glutamate and GABA systems as future targets for schizophrenia drugs. The GABA receptors in the hippocampi carry a specific alpha-5 subunit of the chloride channel (Lodge & Grace, 2011). A new agent (SH-053-2′F-R-CH_3) is a positive allosteric modulator of this channel, enhancing its function. Since these GABA interneurons appear to be deficient in schizophrenia, this agent might reduce aberrant hippocampal activity in people with schizophrenia. Figure 12.2 clearly shows a role for glutamate in schizophrenia. Phencyclidine (PCP) and ketamine can worsen schizophrenia or induce psychosis in normal individuals. These drugs work by blocking the NMDA receptor, but a variety of agents that enhance NMDA receptor activity have not proven effective in schizophrenia (Goff, 2015). Agonists of the glutamate metabotropic receptors are currently being studied, but development has been difficult (Matosin & Newell, 2013).

SUMMARY

Schizophrenia remains a serious mental disorder with marked mortality and morbidity. Treatments are very limited, and deinstitutionalization has resulted in increased homelessness and incarceration for this population. In many ways, deinstitutionalization is a crime against humanity: There is no other disease in which needed inpatient care is denied for political reasons. In addition to advances in basic science, a shift in attitude is needed to improve care for people with schizophrenia. Those on the political right wing must accept that a vast investment in the public mental health sector (including long-term residential care) is required to treat the disorder. Those on the left must disabuse themselves of their antipsychiatry ideology and accept that schizophrenia is a chronic brain disorder that often robs people of their sense of reality and ability to make decisions. The “right to refuse treatment” and the “least restrictive environment” are outmoded legal constructs that the courts need to abandon. Treatment of psychosis is not a denial of liberty; it is its restoration.

CHAPTER 13

Autism Spectrum Disorders

Several years ago my wife and I took our son to a local gym to practice basketball. The gym was filled with parents and youth of various ages, all practicing dribbling and shooting; a pickup game between some high schoolers was underway. At one end of the gym, a man was standing with a boy about 12 years old. The boy was slightly overweight, and moved slowly and oddly; he walked around the court following the penalty line, looking down at the floor. The father shot baskets and dribbled. At one point, he held the ball out and offered it to the boy. The boy immediately tilted his head to the left against his shoulder, straightened his left arm out, and pointed it down at the floor. He then began walking in circles, repeating in a loud, nasal, robotic voice, "No ball, no ball, no ball!" People in the gym stopped and looked for a second, then continued on with their activities. The father took the ball back. His son relaxed and resumed walking the court.

Even without a psychiatric evaluation, it was clear the child had autism spectrum disorder (ASD). In that 5-minute observation, one could see its two DSM-5 core features: (1) deficits in social interaction and (2) restricted, repetitive patterns of behavior, interests, and activities. The boy also exhibited the language and gross- and fine-motor abnormalities often associated with ASD. Looking at the father's face, one also could see the heartbreaking toll this disease imposes on families. The father could not have the simple joy of shooting hoops with his son on a Saturday afternoon. ASD robs people of one of the fundamental gifts of being human—our ability to have close social bonds with each other. Autism was first described by Leo Kanner (1943, p. 220), who noted that when one of his patients went into a room, "he completely disregarded the people and went for objects."

The following year, Hans Asperger described four cases of children who were very verbal but lacked social skills; he further noted the occurrence of stereotypic movements and habits (Asperger, 1991). Whereas DSM-IV made a distinction between autistic disorder and Asperger syndrome, DSM-5 recognizes that these disorders are not separate but lie on the same spectrum. Two qualifiers are added after the diagnosis of ASD: the severity of intellectual disability, and the severity of language disturbance. An individual diagnosed as having Asperger syndrome under DSM-IV would be diagnosed as having ASD with no (or minimal) intellectual disability or language disorder.

EPIDEMIOLOGY AND CLINICAL PRESENTATION OF ASD

Through the end of the 20th century, estimates of the prevalence of ASD were relatively low, as few as 1 in 1,000 (Fombonne, 2001; Lotter, 1966). Recent studies have put the prevalence at 1 in 68 children in the United States (Developmental Disabilities Monitoring Network Surveillance Year 2010 Principal Investigators, 2014), with worldwide estimates as high as 1–2% of the population (Lai, Lombardo, & Baron-Cohen, 2014). A good deal of this increase is due to the introduction of Asperger syndrome in DSM-IV, allowing the diagnoses of less impaired individuals who had no diagnostic home prior to then. Also, people with intellectual disability often may be given the concurrent diagnosis of ASD more now than in the past. The increased prevalence continues, however, despite consistent use of DSM-IV criteria in the last decade (Keyes et al., 2012). Thus, it appears that there are more new cases arising in the population now than in previous generations.

People with ASD have a wide variety of concurrent psychiatric and medical problems (Lai et al., 2014). Twenty-eight to 44% have attention-deficit/hyperactivity disorder (ADHD), while about 45% have intellectual disability. Up to 80% have tics or motor abnormalities such as motor delays, hypotonia, deficits in coordination, movement preparation and planning, and gait and balance. Two-thirds show aggressive behavior and up to half may show self-injurious behavior (SIB). SIB can result in injury through head banging, repetitive self-biting, and cutting (with its subsequent wound infections and lacerations). Medical problems noted to be more common in ASD than in the general population include epilepsy (8–30%), gastrointestinal problems (9–70%), immune dysregulation (38%), and sleep problems (50–80%) (Lai et al., 2014). Mortality for people with autism is two to eight times higher than that in the general population (Woolfenden, Sarkozy, Ridley, Coory, & Williams, 2012). There is a tendency in the media and the lay public to take a romantic view of ASD, with celebration of

the tiny numbers of persons with ASD who function well or have unusual talents. In fact, the vast majority of individuals with ASD are on disability as adults; fewer than 20% are rated as having a good outcome in later life, and none show remission of their ASD (Howlin, Goode, Hutton, & Rutter, 2004). Thus, it is important to see ASD not as a "gift" but as a serious disease.

"SYNDROMIC" ASD

A number of remarkable advances have occurred in the genetics of ASD in the last decade. One of the most important findings is the awareness of "syndromic" ASD, which occurs in the context of a known chromosomal/genetic abnormality (Miles, 2011). These disorders often are associated with physical anomalies and specific medical conditions, and they show a higher rate of intellectual disability than nonsyndromic ASD. This may account for as much as 25% of ASD cases. The major syndromes are listed in Table 13.1, but Coleman and Gillberg (2012) list hundreds of such conditions, each of which is very rare by itself. One should think of these syndromes as being "associated with" and not "causing" ASD because not all affected persons with a given syndrome have ASD. There is an asymmetric overlap between these conditions and ASD, in that whereas only 1–2% of people with ASD have a particular syndrome, 50–100% of people with that syndrome have significant symptoms in the autistic spectrum.

Fragile X syndrome results from a mutation in the fragile X mental retardation 1 (*FMR1*) gene. The mutation results in duplication (repeats) of the nucleotide triplet CGG at the start of the gene. As a result, it cannot be transcribed, and the *FMR1* protein levels in the neuron are reduced to nearly zero. Bear, Huber, and Warren (2004) proposed the "mGluR theory of fragile X," which is illustrated in Figure 13.1. During neuronal activity, glutamate can stimulate the metabotropic receptor subtype-5 (mGlu5), which in turn leads to the stimulation of phospholipase C and phosphatidylinositol 3-kinase (PI3K) (see Figures 3.9 and 3.11). This leads to the synthesis of a variety of proteins that decrease the number of alpha-amino-3-hydroxy-5-methylisoxazole-4-proprionic acid (AMPA) glutamate receptors on the surface of the neuron. *FMR1* inhibits this process. Think of mGlu5 stimulation and *FMR1* as being in balance with each other to regulate the number of AMPA receptors and thus the neuron's receptivity to stimuli. When *FMR1* is deficient, the mGlu5 influence becomes excessive and there is excessive reduction of AMPA receptors, decreasing synaptic plasticity and leading to reduced connectivity. This has led to attempts to use mGlu5 antagonists as possible therapeutic agents in fragile X; regrettably, trials

TABLE 13.1. Some Major Syndromes Associated with ASD

Syndrome	Chromosomal abnormality	Prevalence of autism in condition	Prevalence of condition in autism
Fragile X syndrome	> 200 repeats of CGG in *FMR1* gene, reduced level of FMR1 protein, excessive internalization of AMPA receptors	46% of males 16% of females	1–2%
Prader–Willi syndrome (PWS)	Up to seven genes on the paternal chromosome 15 (q11–13) are deleted	12% strict autism 36.5% autism traits	Rare
Angelman syndrome	Deletion of genes on the maternal chromosome 15 (q11–13); a gene for the regulatory protein ubiquitin is implicated	50%	Rare
Timothy syndrome	Mutation in calcium ion channel gene *CACNA1F* at Xp11.23	60–80%	1–2%
PTEN macrocephaly syndrome	*PTEN* is a tumor suppressor gene; mutations may lead to suppression of phosphatidylinositol 3-kinase (PI3K) enzyme pathway		1–17% depending on sample
Smith–Magenis syndrome (SMS)	Deletion or mutation of retinoic acid induced-1 (RAI1) gene on chromosome 17p11.2; RAI1 is a protein involved in neurodevelopment	~90%	Very rare
Potocki–Lupski syndrome	Duplication of 17p11.2	~66%	Unknown
Williams syndrome	Deletion of 26 genes on chromosome 7q11.23	Excessive social interactions and eye contact	N/A
Williams–Beuren syndrome	Duplication of region in 7q11.23	High rates of ADHD and ASD	Very rare
Rett syndrome	De novo mutation MECP2 on X chromosome	18% of females	4% of females

of six medications of this type have not shown therapeutic benefit (Scharf, Jaeschke, Wettstein, & Lindemann, 2015). Mouse models of Fragile X show decreased $GABA_A$ and $GABA_B$ receptors in the brain (Lozano, Hare, & Hagerman, 2014). Arbaclofen (STX209) is a GABA receptor agonist. It was hoped that activating these GABA receptors would be therapeutic in fragile X, but clinical trials results have been equivocal (Frye, 2014). As a result, U.S. Food and Drug Administration approval for this compound to treat either fragile X or ASD is not likely.

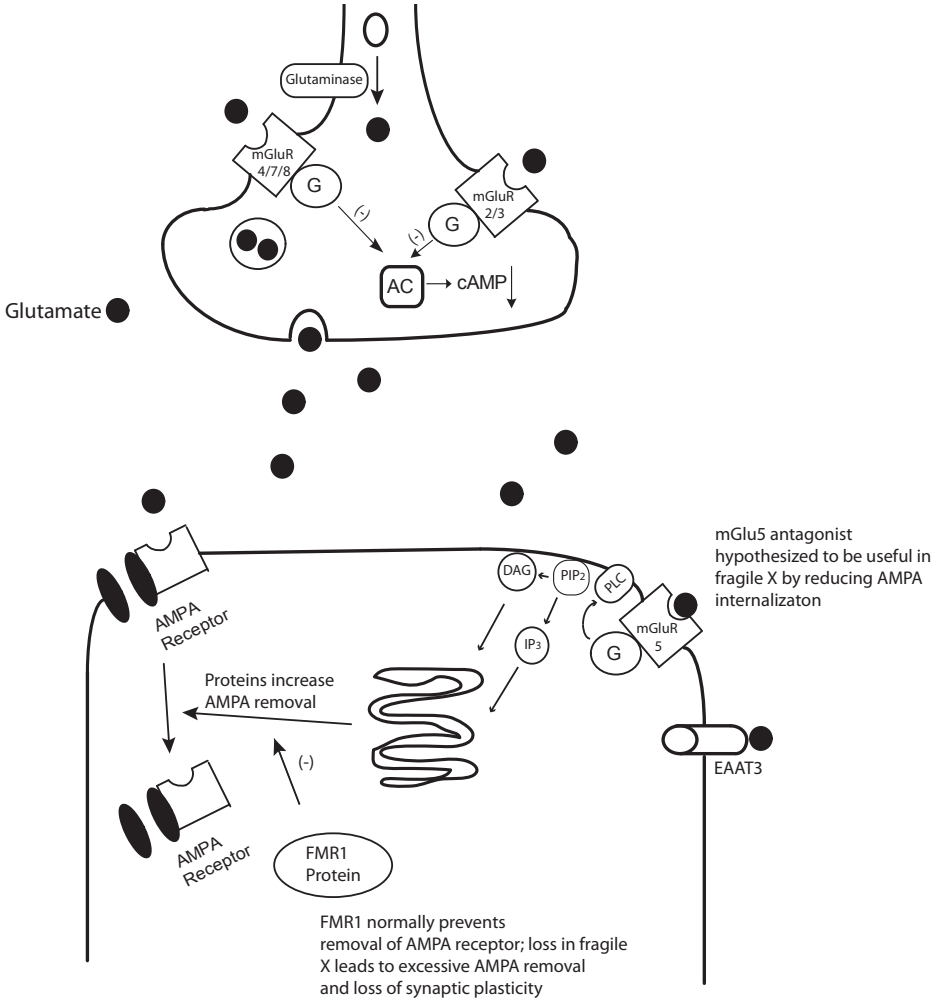


FIGURE 13.1. A theory of the role of glutamate metabotropic receptors in ASD.

Several of the syndromes in Table 13.1 are of interest because *both* deletions and duplications of a given region can lead to ASD or at least to social communication deficits. Well-known examples of this phenomena are Williams syndrome (deletion on chromosome 7) and Willams–Beuren syndrome (duplication on chromosome 7). Deletions and duplications on chromosome 17 are responsible for Smith Magenis syndrome and Potocki–Lupski syndrome, respectively. Increasingly, chromosomal microarray (CMA) is viewed as a routine part of a work up for ASD or intellectual disability (Schaefer & Mendelsohn, 2013). If a specific syndrome is found, it does provide an explanation for the family and may lead to treatment for other medical comorbidities. Specific syndromic diagnosis does not, as yet, provide any specific treatment recommendations for the ASD itself.

ADVANCES IN THE GENETICS OF ASD

In Chapter 5, I discussed two major forms of genetic variation. Single-nucleotide polymorphisms (SNPs) are caused by a change in one "letter" of the DNA code, while copy number variants (CNVs) result from either a duplication or deletion of a "chunk" of DNA. The syndromes in Table 13.1 are caused by CNVs, which may be either inherited or de novo. In de novo mutations, the parents and other children in the family do not carry the mutation; rather, the patient who experiences a spontaneous mutation is often the first person in the family to show the disorder. As with other psychiatric disorders studied so far, genome-wide association studies (GWAS) in autism have focused on SNPs, particularly those that are commonly inherited. Although specific genes have not been identified with this method, yet-to-be discovered common variants may explain the majority of the variance in ASD (Gaugler et al., 2014). In contrast, the study of de novo CNVs has brought about some major understanding of the genetics of ASD (Chen, Penagarikano, Belgard, Swarup, & Geschwind, 2015; Iossifov et al., 2014). Such studies have found around 1,000 of these de novo mutations, which may account for as much as 30% of the genetic variance of "simplex" cases in which the child with ASD has no family history of the disorder.

The possible role of specific genes in ASD has been enhanced by the study of the Simons Simplex Collection, a group of over 1,000 families (Willsey et al., 2013). This study identified mutations in nine high-risk ASD genes (See Table 13.2) identified as part of a network that is highly active during fetal brain development. This network is involved the initial establishment of synaptic connections, particularly in the frontal cortex. A quick scan of Table 13.1 is enough to reveal that the genes involved in ASD are very basic to brain function. The involvement of these de novo

TABLE 13.2. High-Risk ASD Genes Identified in the Simons Simplex Collection

Gene	Chromosome	Name and function
ANK2	4q25–q27	Ankyrin 2, neuronal. Ankyrins are proteins that ensure ion channels are guided to the proper location in neurons and other cells.
CHD8	14q11.2	Chromodomain helicase DNA binding protein 8. Encodes a DNA helicase that functions as a transcription repressor by remodeling chromatin structure.
CUL3	2q36.2	Cullin 3. Cullin proteins play a critical role in ubiquitin pathway. Ubiquitin plays a role in modifying protein after they have been translated from mRNA.
DYRK1A	21q22.13	Dual-specificity tyrosine-(Y)-phosphorylation regulated kinase (RTK) 1A. It may play a significant role in a signaling pathway regulating cell proliferation and may be involved in brain development. It is localized in the Down syndrome critical region of chromosome 21.
GRIN2B	12p12	Glutamate receptor, inotropic, *N*-methyl-D-aspartate 2B. Gene for NDMA receptor subtype, involved in long-term potentiation and other key functions of the glutamate system.
KATNAL2	18q21.1	Katanin p60 subunit A-like 2. Part of the process for degrading and reorganizing microtubules in neurons.
POGZ	1q21.3	Pogo transposable element with ZNF domain. A "zinc finger" protein involved in controlling DNA replication and chromosome segregation in cell division.
SCN2A	2q23–q24	Sodium channel, voltage-gated, type II, alpha subunit. Sodium channel involved in the neuron action potential.
TBR1	2q24	T-box brain protein 1. A major transcription factor, TBR1 is involved in the differentiation and migration of neurons during normal brain development.

mutations in ASD is sobering because of a basic fact: Such mutations in sperm increase as a function of the father's age. There is now clear evidence that advanced age of the father is a major risk factor for ASD. Men excluded from military service in Israel due to ASD were 8.75 times more likely to have been fathered by a man over 40 years old (Reichenberg et al., 2006), a result confirmed by a more recent meta-analysis (Hultman, Sandin, Levine, Lichtenstein, & Reichenberg, 2011). In the Western world, there has been a significant delay in marriage and procreation since the 1960s; perhaps, this most parsimoniously explains the increase in the prevalence of ASD.

Epigenetics (changes in gene expression) also are likely to be highly relevant to ASD. Ning and colleagues (2015) performed a meta-analysis of 10 studies involving 364 individuals with ADHD and 248 controls; eight of the studies looked at gene expression in blood cells, while two examined it in postmortem brain. For the blood cells, one must be cautious, since gene expression in these cells may not reflect what is occurring in the brain. Postmortem brain samples may be influenced by the events that led to the individual's demise. The investigators identified 3,105 genes that were differentially expressed in ASD (1,425 up-regulated and 1,680 down-regulated genes) relative to controls. Seven of these genes were associated with phospholipase A2; up-regulation of this gene could lead to an increased inflammation response. The greatest alteration was found in a ribosome pathway, suggesting that widespread changes in translation of messenger RNA (mRNA) to proteins are possible.

EARLY ENVIRONMENTAL INSULTS IN ASD

As in schizophrenia, early perinatal insults increase the risk for ASD (Gardener, Spiegelman, & Buka, 2011). Multiple perinatal factors that induce risk for ASD include abnormal presentation, umbilical cord complications, fetal distress, birth injury or trauma, multiple birth, maternal hemorrhage, summer birth, low birthweight, small for gestational age, congenital malformation, low 5-minute Apgar score, feeding difficulties, meconium aspiration, neonatal anemia, *ABO* blood type gene or Rh incompatibility, and hyperbilirubinemia. Perinatal factors *not* shown to be related to ASD risk are anesthesia, assisted vaginal delivery, postterm birth, high birthweight, and large head circumference. Whereas maternal depression and use of antidepressant medication during pregnancy induce a small risk of ASD (Rai et al., 2013), exposure to the medication valproate *in utero* appears to be a substantial risk factor (Christensen et al., 2013). Infection during pregnancy may interact with the presence of CNVs and, through a gene × environment interaction, further raise the risk for ASD (Mazina et al., 2015).

There has long been debate regarding any link between environmental pollution and ASD. Exposure to air pollution *in utero* and in early childhood increases the risk of ASD by an odds ratio of 1.5–2.0 (i.e., if the base rate of ASD is 1%, it rises to 2%; Volk, Lurmann, Penfold, Hertz-Picciotto, & McConnell, 2013). The closer a mother lives to a field where pesticides are applied, the greater the risk of ASD (Roberts et al., 2007). Removing the multiple confounds in this sort of research is difficult, however. These environmental agents may interact with preexisting genetic risk factors (Rossignol, Genuis, & Frye, 2014). As Rossignol and colleagues (2014) stated in their review, "Notably, many of the reviewed studies had

significant limitations, including lack of replication, limited sample sizes, retrospective design, recall and publication biases, inadequate matching of cases and controls, and the use of nonstandard tools to diagnose ASD" (p. 1). Moreover, while much work remains to be done in cleaning up the environment, the fact is that the rise in ASD prevalence occurred during a period in which pollution, in general, has been declining (U.S. Environmental Protection Agency, 2015).

INFLAMMATION AND CYTOKINES IN ASD

As in affective disorders, inflammatory processes have been implicated in ASD (Zantomio et al., 2015). A special positron emission tomography (PET) ligand ([^{11}C](R)-PK11195) can be used to image inflammatory microglia activation. The binding of this ligand was found to be significantly higher in multiple brain regions in young adults with ASD than in controls (Suzuki et al., 2013). Higher levels of the pro-inflammatory cytokines (tumor necrosis factor [TNF]-alpha, interferon [IFN]-gamma, interleukin [IL]-6 and IL-8) were found in the cerebrospinal fluid of participants with ASD than in that of controls (Vargas, Nascimbene, Krishnan, Zimmerman, & Pardo, 2005). Mice with high levels of IL-6 show impaired social interaction and poor synapse formation (Wei et al., 2012). It is unclear whether such inflammatory responses are a cause or an effect of ASD; genetic alterations related to ASD might secondarily overactivate inflammatory responses.

The role of gastrointestinal (GI) factors in ASD has long been controversial. Since parents, after the diagnosis of ASD in their child, may focus on GI symptoms due to publicity about the role of toxins and diet in the disease, prospective studies are critical. Bresnahan and colleagues (2015) followed mothers during pregnancy and into the child's early years, resulting in information on GI symptoms from three groups of participants: children with ASD (n = 195), children with developmental delays (n = 4,636), and children with typical development (n = 40,295). Infants whose mothers reported a history of constipation or food intolerance were 1.5–2.7 times more likely to develop ASD. A major hypothesis of GI involvement in ASD is that excessive intestinal permeability (a "leaky gut") allows dietary proteins to enter the body and activate neuroinflammatory processes (Liu, Li, & Neu, 2005). (A corrupted variant of this theory also was cited by the infamous Andrew Wakefield in his bogus claims that the measles, mumps, rubella [MMR] vaccine disrupted the intestinal barrier and therefore caused ASD.) Just over one-third of children with ASD, compared to none of the controls, showed abnormally increased intestinal permeability (de Magistris et al., 2010). Interestingly, there was no difference in GI symptoms in individuals with ASD based on intestinal permeability levels. The lack of

controlled studies of the effect of diet on ASD to date leaves the meaning of these findings subject to further debate.

Recent work on GI aspects of ASD has focused on the role of the gut–brain axis, which involves bidirectional communication between the central and enteric nervous systems (Carabotti, Scirocco, Maselli, & Severi, 2015). Human beings have more non-disease-causing bacteria on and in their bodies than actual cells, and a large portion of these colonize the gut (the microbiome or microbiota). The type and actions of these bacteria can influence the functioning of the nervous system, including levels of serotonin, brain-derived neurotropic factor (BDNF), and GABA receptor mRNA. Children with ASD have been found to have altered microbiota (Mayer, Padua, & Tillisch, 2014; Song, Liu, & Finegold, 2004). This is likely to be a fruitful area of research not only for ASD but also for many GI, autoimmune, and neuropsychiatric disorders.

OXYTOCIN AND ASD

In Chapters 4 and 5, I discussed the role of oxytocin in maternal relationships and social bonding. It will therefore come as no surprise that the role of oxytocin in ASD has been much researched; the human oxytocin gene has several dozen variations caused by SNPs (De Dreu & Kret, 2016). LoParo and Waldman (2014) performed a meta-analysis of 16 of these polymorphisms in 11 independent studies of 3,941 individuals with ASD. They found associations between ASD and four of these polymorphisms: (1) rs7632287 ("A" allele is risk-inducing), (2) rs237887 ("A" allele is risk-inducing), (3) rs2268491 ("T" allele is risk-inducing) and (4) rs2254298 ("A" allele is risk-inducing). At present, the functional nature of these polymorphisms (i.e., more or less oxytocin produced in the brain) is not known.

Oxytocin can be administrated intranasally to humans. Administered to healthy humans, it can, relative to placebo, increase feelings of trust, foster cooperativeness among unrelated individuals, improve recognition of emotional facial expression, and promote eye gaze to the eye region of the face (De Dreu & Kret, 2015). Preti and colleagues (2014) reviewed data from seven randomized controlled trials of intranasal oxytocin involving 101 subjects. The studies were too heterogeneous to combine in a traditional meta-analysis, and the median sample size for the studies was 15. Only one study had negative results, with other studies showing improvements in various measures of social cognition. None of the studies rigorously examined the effect of oxytocin on the core symptoms of ASD, nor have studies of the long-term safety of oxytocin administration been performed. Thus, although oxytocin is a promising agent for future research trials, it is not currently considered a standard treatment.

STRUCTURAL BRAIN IMAGING IN ASD

Chen and colleagues (2015) reviewed studies of postmortem neuronal changes in small groups of individuals with ASD and controls. They found that the brains of people with ASD, relative to controls, have more astrogliosis in subcortical white matter, excessive microglial activation in various cortical regions, as well as increased levels of pro-inflammatory cytokines (in both brain and cerebrospinal fluid). In contrast to schizophrenia, in which white and gray matter loss is widespread in the brain, studies of total and regional brain volume show a complex pattern of losses in some regions and increases in others (Aoki, Abe, Nippashi, & Yamasue, 2013; Cauda et al., 2011; Dickstein et al., 2013; Via, Radua, Cardoner, Happe, & Mataix-Cols, 2011). For both gray and white matter, these reviews reveal a pattern of gray matter decreases in limbic/language areas (amygdala, hippocampus, temporal lobe, angular gyrus), as well as posterior cortical areas (anterior cingulate cortex, cerebellum, lateral occipital). In contrast, gray matter increases were found in superior frontal, the precentral gyrus, and tips of the frontal and temporal cortices. No areas of increased white matter were found, but white matter volume decreases were noted in the internal capsule, anterior cingulate, and corpus callosum.

Fractional anisotropy (FA) and mean diffusivity (MD) are assessed by diffusion tensor analysis (DTI) to determine the integrity of the white matter. Increases in FA and decreases in MD indicate maldevelopment or injury to white matter tracts. Aoki and colleagues (2013) analyzed DTI data on several hundred individuals with ASD and controls. They found significant FA reductions in the corpus callosum, left uncinate fasciculus, and left superior longitudinal fasciculus. They also found significant increases of MD in the corpus callosum and superior longitudinal fasciculus bilaterally in subjects with ASDs compared with controls.

These changes were noted when subjects of all ages were combined in the analysis. Brain growth trajectory is likely altered in ASD from childhood to adulthood. While macrocephaly has long been associated with ASD, increased brain volume occurs only in a minority of children with ASD and is associated with a greater regression of skills (Nordahl et al., 2011). Very young children (ages 2–4 years) have enlarged amygdala volume relative to controls (Nordahl et al., 2012). Brain growth is influenced by a variety of environmental factors (e.g., nutrition, social class) that often are not controlled in these studies. Moreover, some samples may be enriched by individuals with syndromic autism (e.g., phosphatase and tensin homolog [PTEN] mutation), in which macrocephaly is more common. Nonetheless, there does seem to be a pattern of early brain overgrowth in ASD relative to controls followed by normal total brain volume

in adulthood, with only the regional differences remaining. This pattern of growth alteration suggests that there are alterations in the rates of neuronal proliferation and cell death in ASD. Wei, Alberts, and Li (2014) compared the expression of genes for pro- and anti-apoptotic factors in the peripheral cells of person with ASD and controls. They noted that several of these proteins (Bcl-2, cathespin D, p53, caspase) are differentially expressed in ASD, possibly throwing off the timing of neuronal proliferation and elimination.

FUNCTIONAL MRI IN ASD

fMRI studies in ASD are generally done with high-functioning individuals who do not have significant medical comorbidities such as epilepsy or congenital malformations. A great deal of fMRI work has focused on face perception studies and other measures of social interactions. fMRI more recently has been performed in toddlers at risk or already diagnosed with ASD (Pierce, 2011). In these procedures, children ages 12–48 months of age are brought to the MRI scanner at night, when they are naturally very tired and ready for bed. They are placed in the scanner and read a typical bedtime story. Typically developing toddlers clearly activated the left temporal language areas during this social speech; those with ASD (who already showed language delays) did not. This can be seen clearly in Plate 12. Eyler, Pierce, and Courchesne (2012) found that at-risk toddlers later diagnosed as autistic displayed deficient left-hemisphere response to speech sounds, as well as abnormally right-lateralized temporal cortex response to language. This defect worsened with age, becoming most severe at follow-up in 3- and 4-year-olds with autism.

Early imaging studies in high-functioning adults with ASD showed that they were unable to detect emotional state from just looking at pictures of eyes (something persons without autism do easily); moreover, the participants with ASD showed lower activation of the amygdala (Baron-Cohen et al., 2000). Recall that the fusiform face area (FFA) is a region in the temporal lobe involved in facial perception (Figure 8.2). The FFA (in the fusiform gyrus) is a major hub of the large facial processing network shown in Figure 13.2. Faces are preferentially processed by a subcortical network consisting of the superior colliculus, pulvinar (part of the thalamus), and amygdala. The amygdala can react to faces (and engage an emotional response) before the face is consciously perceived. Faces activate both the FFA and the occipital face area far more strongly than do other objects. The amygdala, FFA, and occipital area are linked to an extended face network that includes the superior temporal sulcus (STS), insula, and parts of the attention control

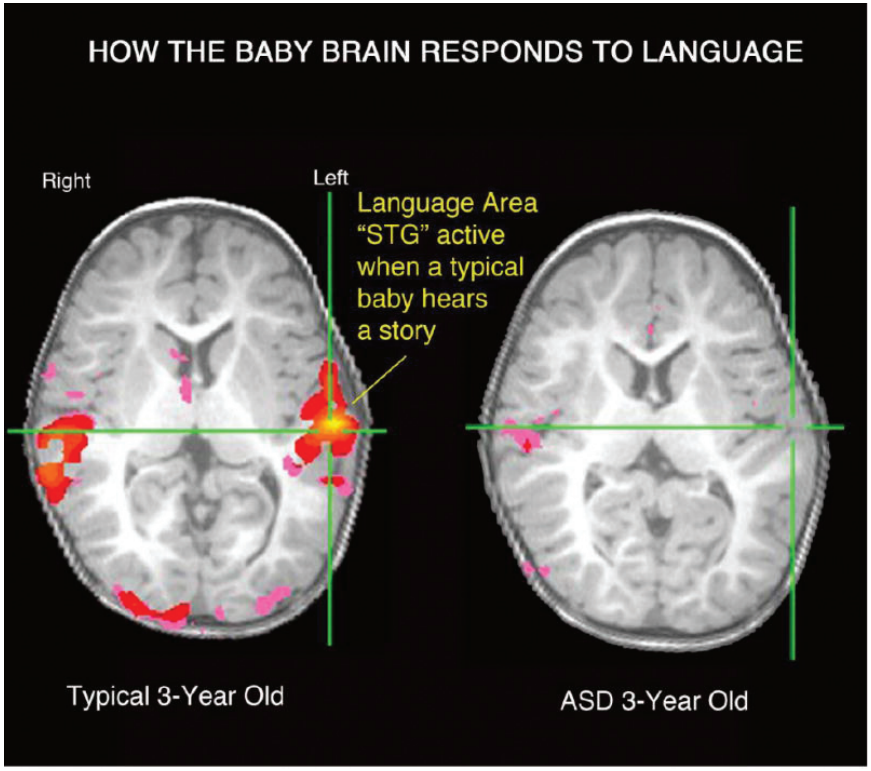


PLATE 12. Functional activation map of a typically developing 3-year-old in comparison to a 3-year-old with ASD during a sleep fMRI experiment. In this experiment, the child was presented with the bedtime story "It's Time for Bed." Reprinted from Pierce (2011) with permission from Elsevier Ltd.

network (the anterior cingulate cortex [ACC] and inferior frontal gyrus [IFG]). Whereas the occipital area processes static faces, the amygdala and STS process changing face features (Haxby, Hoffman, & Gobbini, 2000). The medial prefrontal cortex (MPFC) joins the ACC, IFG, STS, and insula to form the empathy network that is active when subjects look at an emotional face and attempt to say how the person feels. The MPFC is not active when people imitate a facial expression (imitation network).

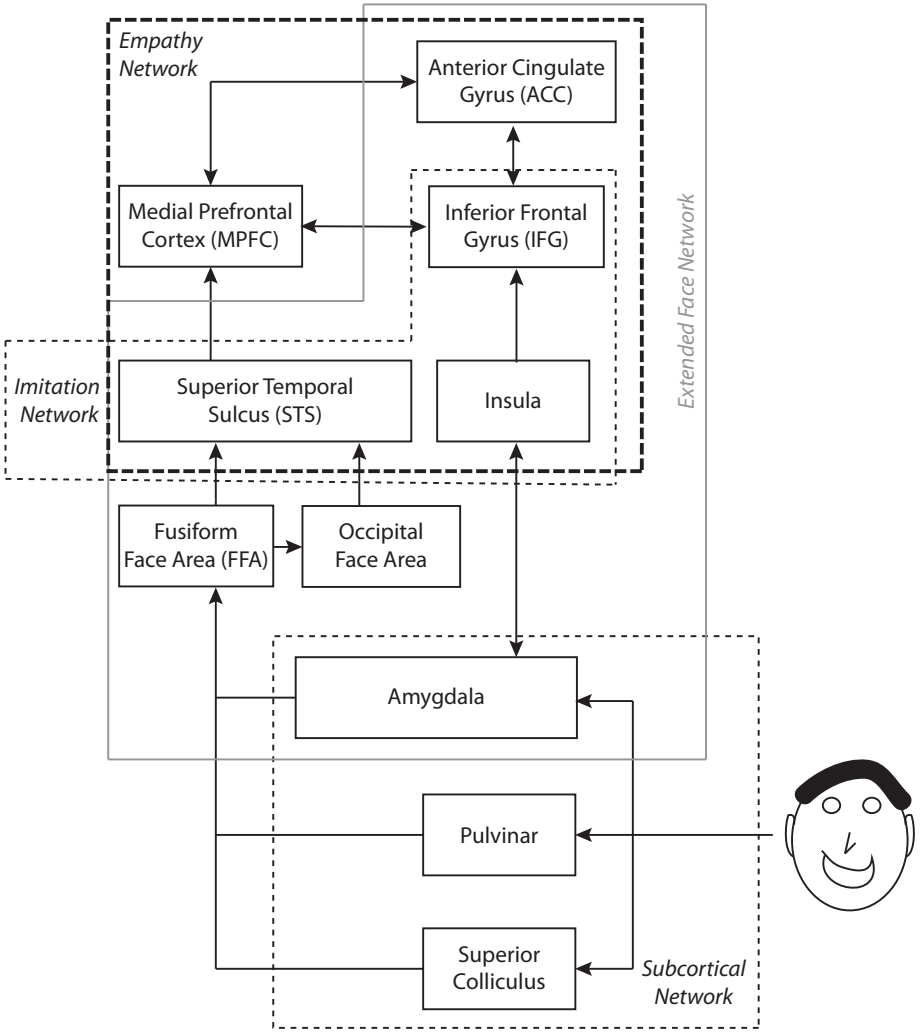


FIGURE 13.2. Brain networks for perception and evaluation of facial expression.

Two meta-analyses of fMRI studies of face processing in individuals with ASD and controls (Nickl-Jockschat et al., 2015; Nomi & Uddin, 2015) have reached broadly similar conclusions:

- Persons with ASD show hypoactivation of the subcortical face network when looking at faces, which suggests deficits in face perception at a very early stage of face processing.
- The FFA and its connections to other face processing networks are hypoactive in ASD, and this hypoactivation is more pronounced for emotional faces (or in tasks requiring judgment of emotion in faces) than for neutral faces. The FFA also shows reduced connectivity to other networks in persons with ASD relative to controls.
- When individuals with ASD are given explicit instructions to attend to the faces, activation of the FFA increases to levels similar to those of controls. In a fascinating experiment Grelotti and colleagues (2005) found that two boys with ASD strongly activated the FFA in response to cartoon faces but not to photos of actual human faces.
- When exposed to faces, persons with ASD tend to activate regions of the brain that are utilized more for object identification in controls (Koshino et al., 2008; Scherf, Luna, Minshew, & Behrmann, 2010).
- Individuals with ASD tend to fixate on areas of the face other than the eyes, but forcing those with ASD to fixate on the face increases activity in the FFA.

Recent work in ASD has moved beyond perception of faces to examine deficits in more complex social cognition (Lombardo & Baron-Cohen, 2011). The MPFC is part of the default mode network and is particularly active in tasks that require individuals to be self-referential. It is also key in interpreting the actions and feelings of others. During social tasks, typically developing adolescents (who are highly focused on their own self as well as the views of others) activate the MPFC much more strongly than do adults (Blakemore, 2012). Thinking through how you or others might feel in a given situation is referred to as "mentalizing." fMRIs on individuals with high-functioning ASD and on controls were obtained while they were asked questions such as "How likely are you to think that keeping a diary is important?" (Lombardo et al., 2010). They were asked the same question but were asked to say how Queen Elizabeth II might respond. (The study was done at Cambridge University in England.) Controls preferentially recruited the ventromedial prefrontal cortex in response to *self*-compared with *other*-referential mentalizing. In autism, however, the ventromedial prefrontal cortex responds *equally* to self and other mentalizing. This suggests that persons with ASD do not, at a neural level, distinguish between self and other, and this may underlay their social difficulties.

TREATMENT OF ASD

Psychosocial interventions are the principal means of alleviating the core symptoms of ASD, though evidence for effectiveness remains in the low to moderate range, based on reviews and meta-analyses (Lai et al., 2014). Applied behavioral analysis (ABA) is perhaps the best known of the psychosocial approaches. It focuses on intensive (often daily) behavior management to decrease stereotypies, poor social behaviors, and repetitiveness while increasing prosocial behavior. The Early Start Denver Model (ESDM) integrates ABA with a "relationship-focused developmental model" that places a greater emphasis on emotional development. These treatments are difficult, often expensive, and take many years. Media fascination with so-called "cures" for ASD, often through some magical therapy that "releases" children from their condition, often clouds public judgment and limits public investment in the treatment of ASD. More insidious are notions that ASD is some sort of gift (*http://thegiftsofautism.com*) that does not need treatment, or that ASD is not that big a problem. Notions that we should "accept" people as they are is often a code word for "Let's not spend any money on those people." People with severe ASD often benefit from residential treatment, but, as with schizophrenia, these options are limited.

Psychopharmacology plays an adjunctive role in the treatment of ASD (Pliszka, 2009). Stimulants, alpha agonists, and atomoxetine are effective for the treatment of ADHD in individuals with ASD, whereas risperidone and aripiprazole are effective for irritability and aggression. While selective serotonin reuptake inhibitors (SSRIs) have a long tradition of use in ASD based on clinical experience, controlled studies show that they are *not* effective for repetitive and compulsive behaviors, and instead may have adverse effects on mood (King et al., 2009). There is a long road to developing new agents that will work on the diverse neurobiological pathways to ASD. It is also likely that such agents will need to be deployed early in the disease process to be effective, a phenomenon that ASD may share with the dementias, which are the focus of the final chapter.

CHAPTER 14

Dementia

Alois Alzheimer, a German psychiatrist and neuropathologist, observed a 51-year-old patient named Auguste Deter in a Frankfurt asylum in 1901. She had a variety of severe behavioral problems, as well as severe memory loss. When examined by Alzheimer, she stated, "Ich hab mich verloren" ("I have lost myself"). Alzheimer maintained contact with her over the years; after her death at the age of 55, he obtained her medical records and brain. Using Franz Nissal's new silver staining techniques for visualizing neurons in postmortem brain samples, Alzheimer noted plaques and neurofibrillary tangles in the sections of Deter's brain. On November 3, 1906, he presented her case at a medical meeting. This marks a rare time in science, when the first patient and exact date of discovery of a disease process are known. Alzheimer's findings were included in Emil Kraepelin's famous textbook of psychiatry and by 1911, the term "Alzheimer's disease" (AD) was in common medical use.

Deter had what today we call "early-onset Alzheimer's." At the turn of the 20th century, this was the only dementia thought to be a disease. Then, few people lived into their 70s and 80s, and senility within this age group was viewed as "normal." It is important to distinguish between the broad clinical diagnosis of dementia and the subset of those individuals with AD. Although AD is the most common cause of dementia, there are various other subtypes (see Figure 14.1A). Dementia is a progressive, long-term decline in alertness, orientation, memory, and cognitive skills. Long-term memory tends to be preserved to the end of the illness. Dementia should be differentiated from "delirium," which is an acute, short-term deterioration in cognition, usually caused by a specific medical condition such as intoxication, infection, fever, or brain injury. In this chapter, our focus is on AD,

which in 2014 affected over 5.2 million people (Alzheimer's Association, 2014). Figure 14.1B shows that AD affects only about 4% of those under 65 years of age, while prevalence rises to 44% of those of ages 75–84 years. Many in this latter age group die of the disorder (or related conditions), so that paradoxically the percentage of those over age 85 years with AD declines to 38%. The key point here is that the vast majority of older adults enter their 80s and 90s without ever suffering dementia. AD and other forms of dementia will be an enormous burden on the world's health care

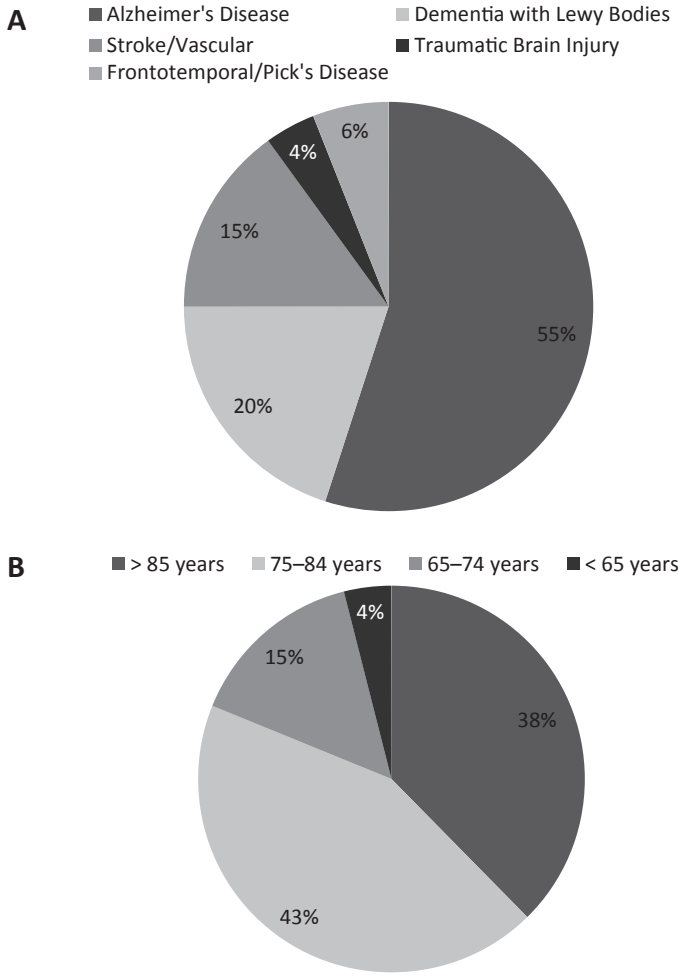


FIGURE 14.1. Prevalence of types of dementia (A) and rate of AD among different age groups (B).

systems as the proportion of older adults in the population grows. Most people in the United States think of Medicaid as a health care program for the poor, but in reality, 62.2% of nursing home costs are paid by Medicaid. While older adults constituent only 9% of Medicaid enrollees, they account for 20% of its costs, with 31.5% of Medicaid funds going to nursing homes (Bernstein, 2012). Thus, a cure for AD will be critical to avoid a crisis in health care spending in the coming decades.

GENETICS OF AD

The genetics of the rare, early-onset form of AD need to be discussed separately from that of the more common, late-onset form. As noted in Figure 14.1, the early-onset form of AD accounts for only about 6–7% of cases of AD; only 13% of these early-onset cases show a clearly autosomal dominant pattern (Campion et al., 1999). Three genes clearly have been identified as causative in these forms (Guerreiro et al., 2015). The first is a mutation in amyloid precursor protein (*APP*) located on chromosome 21. This is the same chromosome that is duplicated in Down syndrome, and it is of note that people with Down syndrome have a very high rate of early-onset AD. The two other genes that cause familial early-onset AD are *presenilin*-1 (on chromosome 14) and *presenilin-2* (on chromosome 1). In each of these mutations, *APP* is cut abnormally into segments, which leads to a by-product called amyloid-beta peptide. These segments clump together to form the amyloid plaques that Alzheimer originally saw. The accumulation of amyloid plaques is thought to be neurotoxic. This process led to the amyloid-beta cascade hypothesis of *all* forms of AD, on which I elaborate later in this chapter (Hardy & Higgins, 1992). In families that have one of these mutations for early-onset AD, 30–70% of the mutations are in the *presenilin-1* gene, 10–15% are in the *APP* gene, and less than 5% are in the *presenilin-2* gene (Patterson et al., 2008). It should be noted that there are nearly 100 mutations of the *APP* gene and about 20 mutations of the *presenilin* genes, complicating the genetics of even this small subset of AD. Verlinsky and colleagues (2002) described the case of a woman who carried one of the mutations of the *APP* and was certain to develop early-onset AD. His team was able to prescreen her fertilized embryos and implant one that did not carry the mutation, ensuring that her child would not suffer the mother's fate.

The more common cases of AD (~94%) have *no* relationship to any of the three genes mentioned earlier. Late-onset AD is referred to as "sporadic," because there is never a clear Mendelian inheritance pattern. The most studied gene in the late-onset form is the *apolipoprotein E* (*APOE*) gene. In the central nervous system, *APOE* is produced by astrocytes and

transports cholesterol to neurons by the use of *APOE* receptors. There are three forms of the gene: epsilon 2, epsilon 3, and epsilon 4. In white populations, epsilon 3 is the most common allele (75%), and being homozygous for it provides a risk of AD at the level of the normal population. Having the epsilon 2 allele is modestly protective (risk is 60% of that in the general population), while having one epsilon 4 allele triples the risk of AD. Being homozygous for the epsilon 4 allele results in an 11-fold increase in the risk (Hsiung & Sadovnick, 2007). The strength of the effect is greater for women than for men. Interestingly, these effects only hold for those of European ancestry. While persons of African ancestry have higher rates of having an epsilon 4 allele than do Europeans, it does not translate into a higher risk of AD (Teruel et al., 2011). The function and role of *APOE* in AD is discussed below.

Genome-wide association studies (GWAS) more recently have identified other loci that are risk factors for late-onset AD (Guerreiro et al., 2015). These risk factors, listed in Table 14.1, fall into three major categories: (1) the formation of "vesicles" (small membrane-wrapped spheres containing key substances for the neuron), as well as neuronal membrane recycling;

TABLE 14.1. Risk Alleles for Late-Onset AD Identified by GWAS

Domain	Gene	Functional relevance
Endosomal vesicle recycling	*BIN1*	A nucleocytoplasmic adaptor protein that assists neurons in forming endocytes. May activate apoptotic (cell death) processes.
	SORL1	Sortilin-related receptor 1: one of the cytoplasmic receptors for *APOE*.
	PICALM	May govern the amount of neuronal membrane that is recycled.
Innate immune system	*TREM2*	Triggering receptor expressed on myeloid cells 2: involved in chronic inflammation by triggering the production of neurotoxic cytokines.
	CR1	Complement component (3b/4b) receptor 1: part of the "complement system" in the immune process that distinguishes "self" from "other."
	CLU	Clusterin: clears cellular debris, involved in apopotic cells process.
Cholesterol metabolism	*ABCA7*	Adenosine triphosphate (ATP)-binding cassette subfamily A7: transports proteins across extra- and intracellular membranes. Plays a role in lipid transport.
	APOE	See text.
	CLU	Involved in lipid transport.

(2) genes governing the immune response, suggesting that inflammatory response plays a role in AD; and (3) genes involved in cholesterol metabolism, which are of great interest given the nongenetic risk factors in AD.

ENVIRONMENTAL RISK FACTORS IN AD

Figure 14.2 shows an array of factors that have been found either to increase risk of or protect against AD (Patterson et al., 2008). Given the role of genes that handle cholesterol in AD, it is not surprising that increased serum cholesterol, obesity, and elevated blood pressure enhance the risk for AD; there is modest evidence that controlling hypertension can reduce this risk (Forette et al., 1998). On the other hand, treatment of hyperlipidemia with statins does not reduce the risk for AD (Heart Protection Collaborative Study Group, 2002). Protective factors include higher level of education, physical activity, moderate wine consumption, and use of nonsteroidal anti-inflammatory medications. Oddly, a double-blind placebo-controlled trial of celecoxib (Celebrex) failed to show any preventive effect

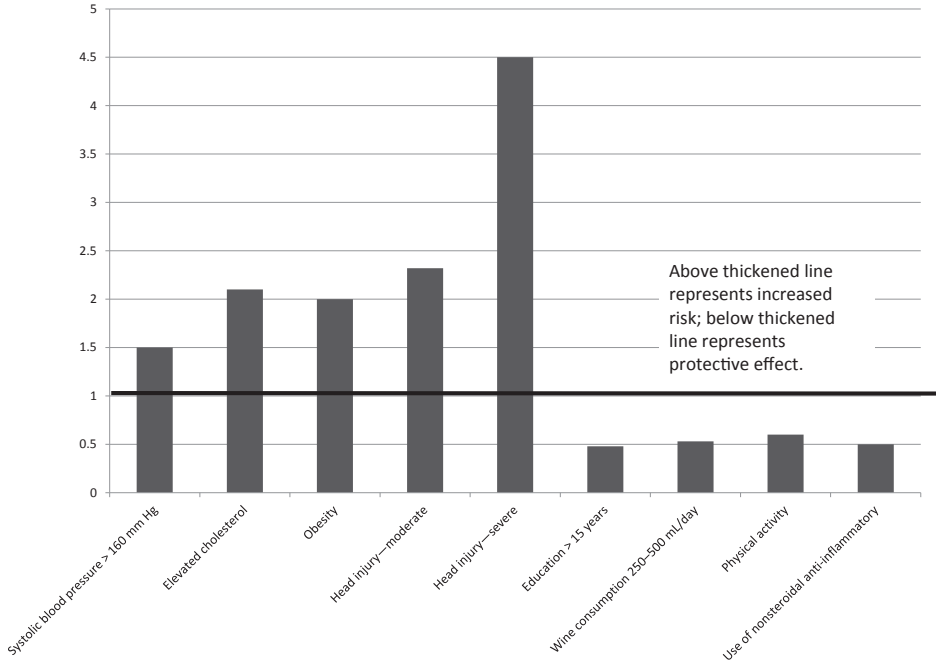


FIGURE 14.2. Environmental risk factors in AD.

of the anti-inflammatory drug for AD (Lyketsos et al., 2007). Such findings suggest that results from naturalistic epidemiological studies need to be interpreted cautiously. It may be that education, wine drinking, and exercise are things pursued by highly intelligent people who have a greater degree of "cognitive reserve," which in turn protects them from AD. A randomized controlled trial found that cognitive training with older adults results in an increase in specific cognitive performance 5 years later, but it has yet to be demonstrated whether this will result in a reduced risk of AD (Huntley, Gould, Liu, Smith, & Howard, 2015).

THE AMYLOID-BETA CASCADE HYPOTHESIS

APP is a protein than spans the neuronal membrane (see Figure 14.3) and is critical in both neurodevelopment and synapse formation, though its specific roles remain to be defined (O'Brien & Wong, 2011). Cholesterol is needed for synapse formation, and *APP* may play a role in cholesterol transport into neurons (van der Kant & Goldstein, 2015). *APP* can be cleaved into a number of different fragments that also play roles in neuronal function; the amyloid-beta fragment is the most relevant to AD. For the last two decades, the belief that abnormal accumulation of amyloid-beta is the prime cause of AD has driven research into this condition (Hardy & Higgins, 1992). Figure 14.3 summarizes this amyloid-beta cascade hypothesis (Kanekiyo, Xu, & Bu, 2014).

APP can be cleaved by a nonamyloidogenic pathway (1). *APP* is first cut by alpha-secretase into a soluble *APP*-alpha (sAPP-alpha) segment that is released into the cytoplasm while the remaining alpha-C terminal fragment (alpha-CTF) continues to be attached to the membrane. Alpha-CTF is then cut by gamma-secretase to *APP* intracellular cytoplasmic domain (AICD), which moves to the nucleus of the cell and acts as a transcription factor. The remaining p3 fragment is released into the cytoplasm. sAPP-alpha stimulates neural growth and is generally neuroprotective (van der Kant & Goldstein, 2015). In the amyloidogenic pathway (2), the order of secretase cleavage is different. Beta-secretase splits APP into beta-CTF and sAPP-beta; the latter can be neurotoxic. Next, gamma-secretase splits beta-CTF into AICD and amyloid-beta is released to the cytoplasm. Amyloid-beta has normal physiological functions, but in certain circumstances it can aggregate into amyloid plaques.

In early-onset, familial AD, there are mutations in the genes for *APP* or in the *presenilin 1 and 2* genes that lead to an abnormal production of amyloid-beta, particularly for the 42 amino acid form. Amyloid-beta chains clump together (3) to form amyloid plaques. In late-onset AD,

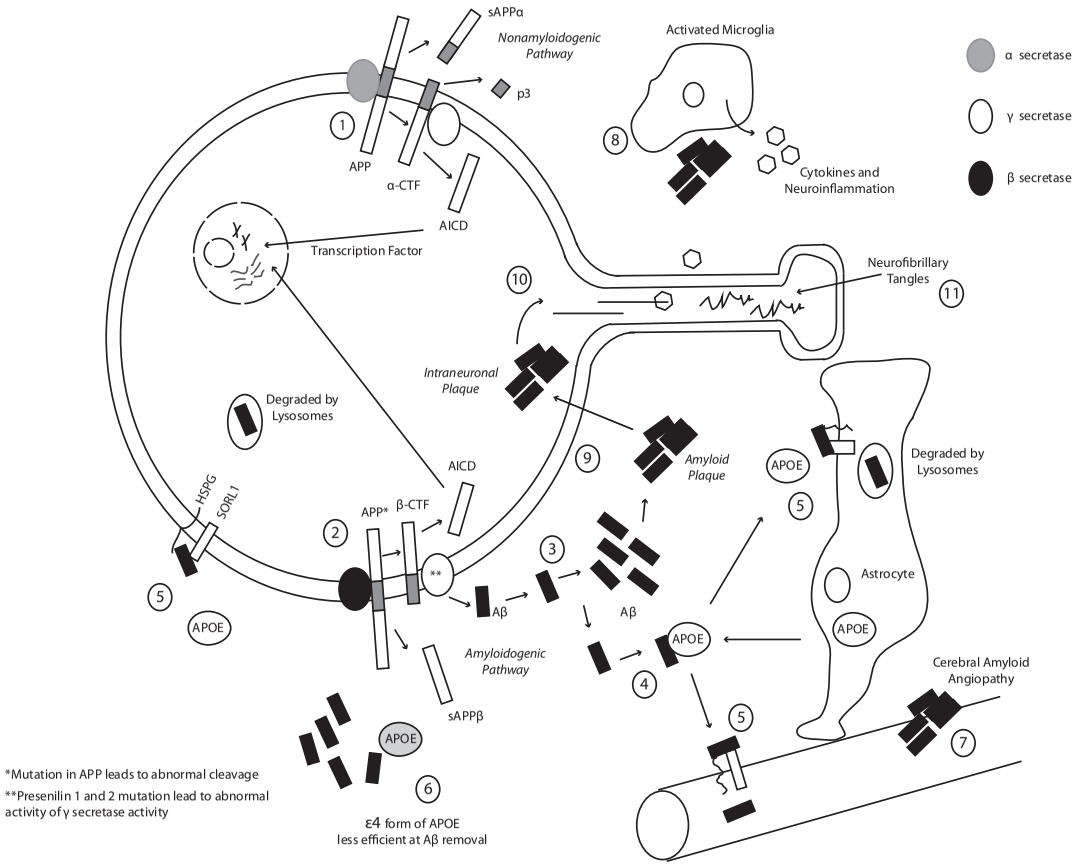


FIGURE 14.3. The amyloid-beta cascade hypothesis of AD. See text for details.

amyloid plaque formation is thought to occur via a different route. *APOE* is produced in astrocytes and binds when it enters the cytoplasm amyloid-beta (4). The *APOE*–amyloid-beta complex is then transported to lipid-protein receptors on the astrocytes, neurons, and blood vessels (5). Once absorbed into neurons or astrocytes, the amyloid-beta is placed into vesicles and degraded by lysosomes. APOE–amyloid-beta also may be carried to the blood vessels, where the amyloid-beta is drained away. As noted earlier, one risk factor for AD is having the epsilon form of *APOE* (gray in Figure 14.3). This form may not efficiently bind amyloid-beta, allowing it to accumulate (6).

The accumulation of amyloid plaques has a number of downstream effects. Plaques may form on the cerebral arteries, leading to cerebral amyloid angiopathy and interference with the brain's blood supply (7). Plaques also may cause the activation of microglia and the release of inflammatory cytokines (8). Amyloid plaques can be absorbed into neurons (9), where they may activate a number of abnormal cellular processes that damage microtubules (10). Microtubules carry nutrients and building blocks through the neuron and, in particular, to synapses. Tau proteins are a critical component of these microtubules. In AD, the tau protein becomes hyperphosphorylated, causing the microtubules to twist into neurofibrillary tangles. The end result of all these processes is neuronal death and shrinkage of gray and white matter.

Limitations of the Amyloid-Beta Cascade Hypothesis

As compelling as the amyloid cascade hypothesis is, it is sobering that treatments based on its central thesis (the accumulation of amyloid plaques) have not proven helpful. Inhibiting the action of gamma-secretase, in an attempt to lessen the accumulation of amyloid-beta, actually worsened cognitive function in AD (Doody et al., 2013). Medications designed to prevent amyloid-beta from aggregating into plaques were not effective relative to placebo (Aisen et al., 2011; Salloway et al., 2011). Another approach was to vaccinate patients in the hope that they would develop antibodies against the amyloid, and that the body's immune system would remove it (Wisniewski & Goni, 2015). An active vaccine, AN1792, showed that some patients with AD had clearing of plaques, along with some possible cognitive improvement, but no overall change in cognition relative to placebo (Devanand, 2014). Six percent of the patients in this trial also developed meningoencephalitis. A different vaccine (CAD106) does not have such serious side effects and may decrease long-term cognitive decline (Farlow et al., 2015). Emphasis was then switched to agents that would directly deliver the antibodies to the brain (human monoclonal antibodies) in the hope of inducing the immune system to attack the plaques. Solanezumab was not

superior to placebo in AD. Indeed, a worsening of the symptoms was seen at higher doses, though a post hoc analysis indicated that milder patients may have benefited (Doody et al., 2014). A similar agent, bapineuzumab, also failed in clinical trials (Salloway et al., 2014). Trials of immunotherapy for the hyperphosphorylated tau are currently underway (Pedersen & Sigurdsson, 2015).

What could explain these disappointing results? One clue is the more positive results seen in the milder patients in the Doody and colleagues (2014) study. Perhaps in more advanced disease, the damage done by the plaques is already so great that clearing amyloid is no longer helpful. It has long been known that the amyloid begins to accumulate years before any symptoms of AD appear. Would anti-amyloid agents prevent the onset of AD if given to at-risk individuals? A group of 26 remarkable extended families in Columbia is helping to answer this question (Acosta-Baena et al., 2011). These unfortunate families have an unusually high incidence of an autosomal-dominant mutation in the *presenilin-1* gene (nicknamed the Paisa mutation), leading to a tragically high rate of early-onset AD. Many members of these families have volunteered to participate in a large international clinical trial of another human monoclonal antibody drug, cernezumab. The drug is being administered to 100 individuals with the mutation, while placebo is administered to 100 carriers and 100 noncarriers. Thus, these individuals are taking a risk that the drug might hasten the onset of their dementia or have other side effects, in the hope of obtaining benefit. If this approach works, the whole world will owe a debt of gratitude to these families.

On the other hand, there are a number of facts about AD for which the amyloid-beta cascade hypothesis does not account (Moreno-Trevino, Castillo-Lopez, & Meester, 2015). These include (1) uncertainty as to whether there really is a link between the accumulation of amyloid plaques and the development of neurofibrillary tangles, since these two pathological signs do not always occur in the same place in the brain (Jucker & Walker, 2011); (2) the fact that many healthy individuals without dementia are found to have plaques and tangles equivalent to that of patients with AD (though without cortical atrophy) at autopsy (Cummings, Ringman, & Vinters, 2014); (3) accumulation of phosphorylated tau predicts cognitive symptoms of AD better than accumulation of amyloid-beta; and (4) the amyloid-beta cascade hypothesis does not account for the fact that AD begins in the hippocampus and spreads to other areas of the brain, while amyloid plaques are more evenly distributed. Alternatives to the amyloid-beta cascade hypothesis include broader abnormalities of lipid (including cholesterol) metabolism, reactivation of the herpes simplex 1 virus, as well as other forms of neuroinflammation and disturbance of immunity (Heneka, Carson, et al., 2015; Heneka, Golenbock, & Latz, 2015).

NEUROIMAGING IN AD

By the time the average patient with AD presents for diagnosis, structural MRI shows marked atrophy, particularly in the hippocampus (Johnson, Fox, Sperling, & Klunk, 2012). Hippocampal volumes begin to decline at a rate of 3% per year several years before symptoms appear, with reductions of 25% of volume at the time of diagnosis. Whole-brain volume will decline about 0.3% per year, with reductions of 6% by the time the patient presents. The atrophied gray matter and enlarged ventricles seen on MRI are obvious even to the non-radiologist. Given the early damage to the hippocampus, it will not be surprising that that fMRI studies show widespread deactivations in the anterior and posterior memory systems (see Chapter 7), as well as aberrant activation of the default mode network (Johnson et al., 2012). Positron emission tomography (PET) scans show marked reductions in glucose metabolism throughout the brain (Mattson & Magnus, 2006).

Given the (possibly misplaced) primacy of amyloid plaques in AD, much research has gone into the development of imaging methods that show the deposit of amyloid in the brain. Pittsburgh Compound B (PiB) is a dye that binds to amyloid (Klunk et al., 2004). By placing a positron emitting ^{11}carbon (^{11}C) in the compound, the amount of amyloid in the brain can be directly measured. Since ^{11}C has such a short half-life, it is not practical for clinical use, so other amyloid binding agents that use ^{18}fluorine (^{18}F) as the positron emitter have been developed (Johnson et al., 2013). Those positron emitters currently approved by the U.S. Food and Drug Administration (FDA) for clinical use include florbetapir (Amyvid), flutemetamol (Vizamyl), and florbetaben (Neuraceq). PET imaging for neurofibrillary tangles is under development; the key methodological issue is to develop a tracer that binds to the excessively phosphorylated tau protein and not to amyloid. Seven different tau binding agents are in development, with ^{18}F-AV-1451 currently in FDA Phase II trials (James, Doraiswamy, & Borges-Neto, 2015).

Plate 13 shows the distribution of amyloid in the brain measured with PiB. Note how even control subjects show some degree of amyloid deposits. This can be shown more clearly in Plate 14, which compares levels of florbetapir in the brain to cerebrospinal fluid (CSF) levels of amyloid-beta (Blennow, Mattsson, Schöll, Hansson, & Zetterberg, 2015). Interestingly, because patients with AD deposit excess amyloid-beta in the brain, they have *lower* levels of amyloid-beta secreted into the CSF, such that levels of amyloid-beta in CSF correlate *negatively* with levels of amyloid (Mattsson et al., 2014). Note that in Plate 14B, most patients with AD have florbetapir levels above the cutoff value, but so do a substantial number of controls.

This creates a practical and ethical dilemma as to when to use amyloid PET scanning in the clinical setting (Johnson et al., 2013). Examine the

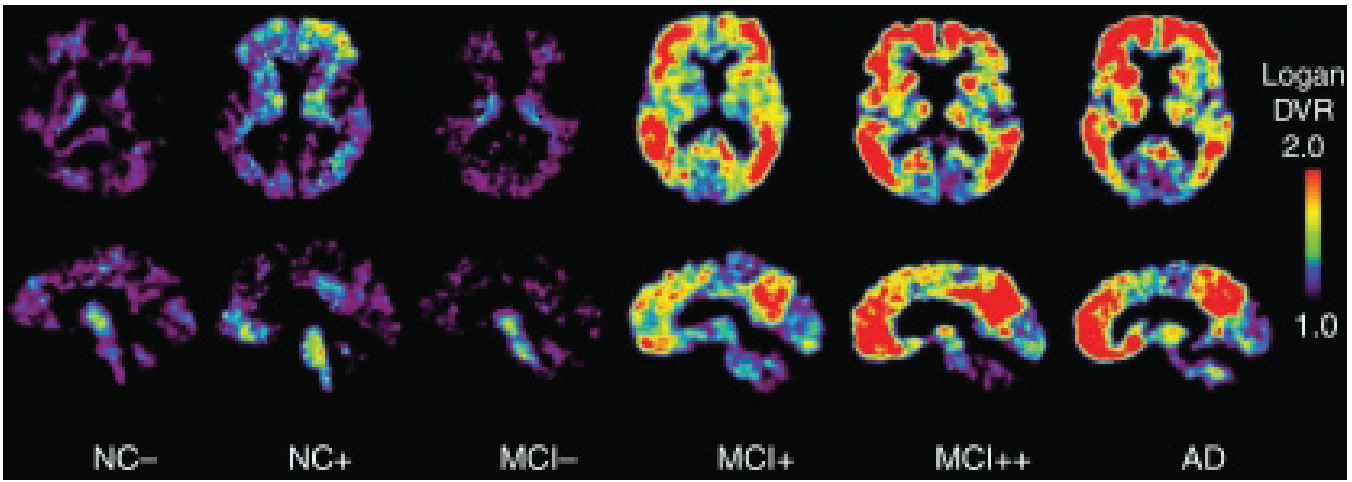


PLATE 13. PiB PET images of normal control, mild cognitive impairment (MCI), and AD subjects, showing a range of amyloid-beta deposition. Most controls show no evidence of amyloid-beta deposition (NC–), but a substantial portion (25%) do (NC+). Most patients with MCI show moderate (MCI+) or severe amyloid-beta deposition (MCI++), but as many as 40–50% show no evidence of amyloid-beta pathology (MCI–). The vast majority of clinically diagnosed patients with AD show heavy amyloid-beta deposition (AD). Reprinted from Johnson, Fox, Sperling, and Klunk (2012) with permission from Cold Spring Harbor Laboratory Press.

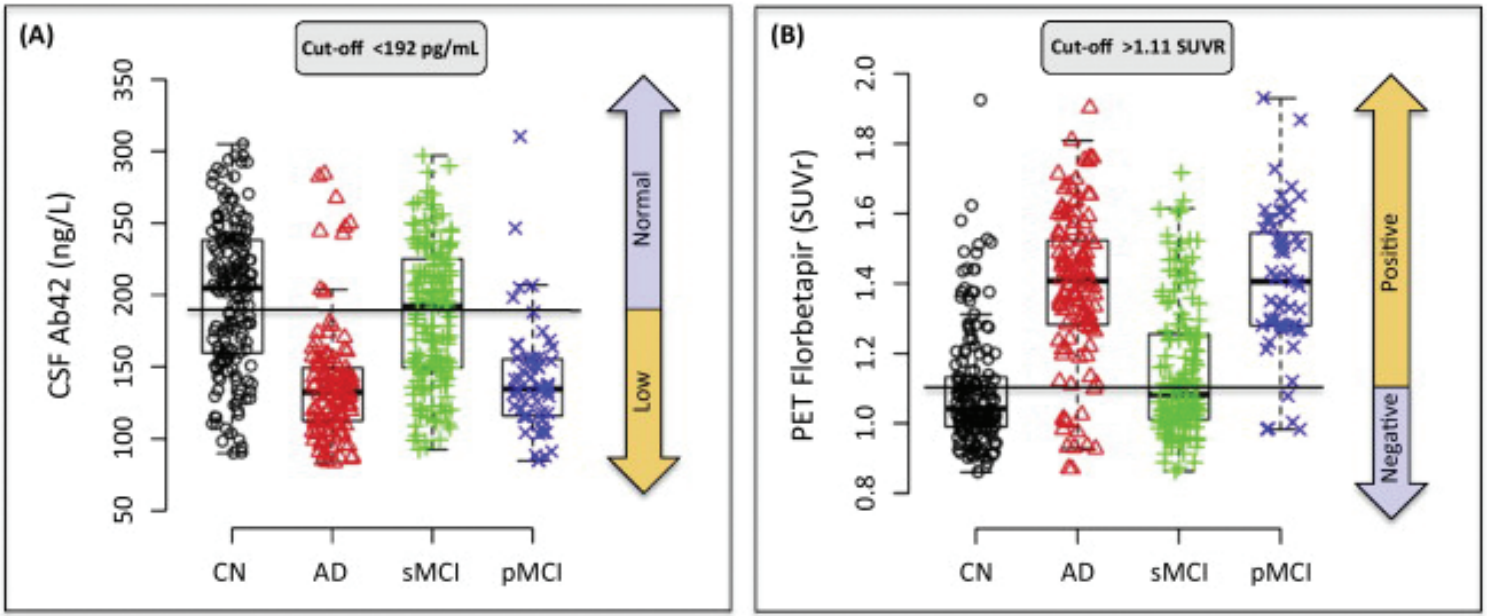


PLATE 14. Raw values for cerebrospinal fluid (CSF) and positron emission tomography (PET) amyloid biomarkers. (A) CSF amyloid-beta (Ab) 42 levels in picograms per milliliter (analyzed using the AlzBio3 Luminex assay). (B) Florbetapir amyloid PET as global standardized uptake value ratio (SUVr). Lines represent established cutoffs for AD, with a CSF Ab42 level below 192 picograms per milliliter and a global florbetapir SUVr above 1.11 (normalized to whole cerebellum) indicative of AD. Diagnostic groups: C, controls; AD, AD dementia; sMCI, stable mild cognitive impairment; pMCI, progressive MCI. Based on data from the Alzheimer's Disease Neuroimaging Initiative (ADNI) study. Reprinted from Blennow, Mattsson, Schöll, Hansson, and Zetterberg (2015) with permission from Elsevier Ltd.

amyloid findings in Plate 14B more closely. Note the control participant who has the highest level of amyloid; his level is actually higher than the participant with the highest level in the AD group. Suppose this control individual came to the clinician and said, "I have a family history of dementia and I want to know if I might get it." Should he receive an amyloid PET scan? If so, what should he be told about the results? Bear in mind that he might never develop AD. Should he spend his life worrying about it because he is aware that he has high levels of amyloid? On the other hand, suppose he changes his lifestyle: He stops smoking, loses weight, and lowers his cholesterol. Would these changes enable him to lower his risk of AD, and would he be more motivated to do so knowing his amyloid levels? More vexing, should he enroll in a clinical trial of an anti-amyloid agent in the hope of preventing the onset of AD? Again, recall that in some of the clinical trials of prior agents, patients got worse. These questions do not have easy answers. Clearly, amyloid PET should not be viewed as a simple "test" of AD or as a predictor of who is going to get AD.

In view of these dilemmas, the Society of Nuclear Medicine and Molecular Imaging and the Alzheimer's Association have issued guidelines for the appropriate use of amyloid imaging (Johnson et al., 2013). They have listed the following indications for scanning:

- Patients with persistent or progressive, unexplained mild cognitive impairment (MCI).
- Patients satisfying core clinical criteria for possible AD because of unclear clinical presentation, either an atypical clinical course or an etiologically mixed presentation.
- Patients with progressive dementia and atypically early age of onset (usually defined as 65 years or less in age).

In contrast, the Task Force regards the following situations as inappropriate for scanning for amyloid:

- Patients with core clinical criteria for probable AD, with typical age of onset.
- To determine dementia severity.
- Based solely on a positive family history of dementia or presence of APOE epsilon 4 allele.
- Patients with a cognitive complaint that is unconfirmed on clinical examination.
- In lieu of genotyping for suspected autosomal mutation carriers.
- In asymptomatic individuals, nonmedical use (e.g., legal, insurance coverage, or employment screening).

These cautionary notes probably will apply to the use of neuroimaging in any psychiatric disorder. We are currently caught in the bind of "If the case is obvious, you don't need the neuroimaging, but if the case is not obvious, the scan does not really help."

SUMMARY AND CONCLUSIONS

Perhaps it is appropriate to close this book with a chapter on an end-of-life disorder such as dementia. In the work on AD, we see both the hope and the pitfalls for research into the biological roots of mental disorder. In AD, we have a clearly defined brain lesion and a fairly complete understanding of the biology underlying it, yet this has not led us, as yet, to effective treatments. Genetics clearly play a role but we find a great impact of lifestyle factors. The latter should be of some concern given both the aging of the populations and the simultaneous increase in rates of obesity. Exercise, diet, and mental activity will do more to prevent AD than the development of a new anti-AD drug, as welcome as that development will be.

We should see this as a paradigm for neuroscience research for all of the mental disorders. Genetics will surely play an important role in all of the major disorders (attention-deficit/hyperactivity disorder, affective disorder, autism spectrum disorders), but it is likely that these genes will first set the stage. We will then need to understand how environment produces epigenetic forces that lead to gene expression. Our definition of environment must be very broad, to include the womb, nutrition throughout life, parent–child interactions, interactions with everyone around us, and our socioeconomic environment (e.g., poverty, pollution, social justice). In this work, we must be prepared to face the sobering reality that damage done early might be undone or can only be undone with the most expensive and dramatic of interventions. We must accept again the reality that mental disorders can be as serious as cancer or diabetes, deserving of similar societal investments.

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