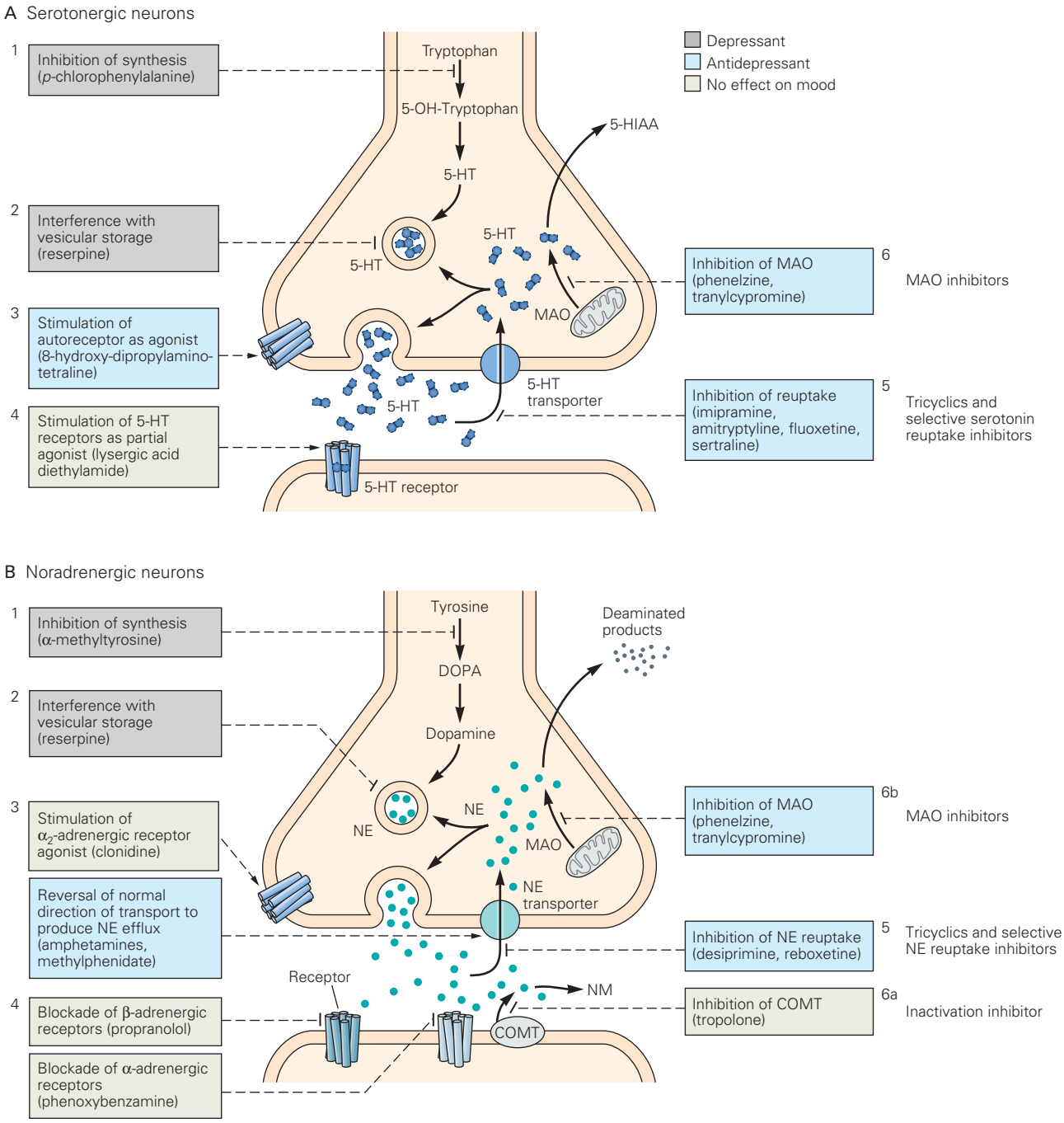
A Serotonergic neurons
Depressant
Antidepressant
No effect on mood
1
Inhibition of synthesis (p-chlorophenylalanine)
2
Interference with vesicular storage (reserpine)
3
Stimulation of autoreceptor as agonist (8-hydroxy-dipropylamino-tetraline)
4
Stimulation of 5-HT receptors as partial agonist (lysergic acid diethylamide)
Tryptophan
5-OH-Tryptophan
5-HT
5-HIAA
5-HT
5-HT
MAO
5-HT transporter
5-HT
5-HT receptor
Inhibition of MAO (phenelzine, tranylcypromine)
6
MAO inhibitors
Inhibition of reuptake (imipramine, amitryptyline, fluoxetine, sertraline)
5
Tricyclics and selective serotonin reuptake inhibitors
B Noradrenergic neurons
1
Inhibition of synthesis (α-methyltyrosine)
2
Interference with vesicular storage (reserpine)
3
Stimulation of α2-adrenergic receptor agonist (clonidine)
Reversal of normal direction of transport to produce NE efflux (amphetamines, methylphenidate)
4
Blockade of β-adrenergic receptors (propranolol)
Blockade of α-adrenergic receptors (phenoxybenzamine)
Tyrosine
Deaminated products
DOPA
Dopamine
NE
NE
MAO
NE transporter
Receptor
NM
COMT
Inhibition of MAO (phenelzine, tranylcypromine)
6b
MAO inhibitors
Inhibition of NE reuptake (desiprimine, reboxetine)
5
Tricyclics and selective NE reuptake inhibitors
Inhibition of COMT (tropolone)
6a
Inactivation inhibitor

Figure 61–7 (Opposite) Actions of antidepressant drugs at serotonergic and noradrenergic synapses. The figure shows the pre- and postsynaptic sides of serotonergic and noradrenergic synapses. Serotonin and norepinephrine are synthesized from amino acid precursors by enzymatic cascades. The neurotransmitters are packaged in synaptic vesicles; free neurotransmitter within the cytoplasm is metabolized by monoamine oxidase (**MAO**), an enzyme associated with the abundant mitochondria found in presynaptic terminals. Upon release, serotonin and norepinephrine interact with several types of pre- and postsynaptic receptors. Each neurotransmitter is cleared from the synapse by a specific transporter. The serotonin and norepinephrine transporters and MAO are targets of antidepressant drugs.

A. Important sites of drug action at serotonergic synapses. Not all actions described are shown in the figure.

1. *Enzymatic synthesis*. Inhibition of synthesis of the rate-limiting enzyme tryptophan hydroxylase by *p*-chlorophenylalanine initiates the cascade that converts tryptophan to 5-OH-tryptophan, the precursor of 5-hydroxytryptophan (**5-HT**, serotonin).

2. *Storage*. Reserpine and tetrabenazine interfere with the transport of serotonin and catecholamines into synaptic vesicles by blocking the vesicular monoamine transporter $VMAT_2$. As a result, cytoplasmic serotonin is degraded (see step 6 below), and thus, the neuron is depleted of neurotransmitter. Reserpine was used as an antihypertensive drug but commonly caused depression as a side effect.

3. *Presynaptic receptors*. Agonists at presynaptic receptors produce negative feedback on neurotransmitter synthesis or release. The agonist 8-hydroxy-diprolamino-tetraline (8-OH-DPAT) acts on $5\text{-}HT_{1A}$ receptors on the presynaptic neuron. The antimigraine triptan drugs (eg, sumatriptan) are agonists at $5\text{-}HT_{1D}$ receptors.

4. *Postsynaptic receptors*. The hallucinogen lysergic acid diethylamide (LSD) is a partial agonist at $5\text{-}HT_{2A}$ receptors on postsynaptic serotoninergic neurons. Second-generation antipsychotic drugs, such as risperidone and olanzapine, are antagonists at $5\text{-}HT_{2A}$ receptors in addition to their ability to block D_2 dopamine receptors. The antiemetic compound ondansetron is an antagonist at $5\text{-}HT_3$ receptors, the only ligand-gated channel among the monoamine receptors. Its key site of action is in the medulla.

5. *Uptake*. The selective serotonin reuptake inhibitors, such as fluoxetine and sertraline, are selective blockers of the serotonin transporter. The tricyclic drugs have mixed actions; some, such as clomipramine, are relatively selective for the serotonin transporter. Uptake blockers increase synaptic concentrations of serotonin. Amphetamines enter monoaminergic neurons via the uptake transporter and bind to the vesicular transporter found on the membranes of synaptic vesicles, causing reverse transport of the monoamine neurotransmitter into the cytoplasm. The neurotransmitter is then reverse-transported out of the neuron into the synapse via the uptake transporter.

6. *Degradation*. Phenelzine and tranylcypromine, both of which are effective for depression and panic disorder, block MAO-A and MAO-B. Moclobemide, effective against depression, is selective for MAO-A; selegiline, which has been used to treat Parkinson disease, is selective for MAO-B in low doses. (Abbreviation: **5-HIAA**, 5-hydroxyindoleacetic acid.)

B. Important sites of drug action at noradrenergic synapses.

1. *Enzymatic synthesis*. The competitive inhibitor α-methyltyrosine blocks the reaction catalyzed by tyrosine hydroxylase that converts tyrosine to DOPA. A dithiocarbamate derivative, FLA-63 (not shown), blocks the reaction that converts DOPA to dopamine.

2. *Storage*. Reserpine and tetrabenazine interfere with the transport of norepinephrine (**NE**), dopamine, and serotonin into synaptic vesicles by blocking the vesicular monoamine transporter $VMAT_2$. As a result, the cytoplasmic neurotransmitter is degraded (see below), and thus the neuron is depleted of neurotransmitter.

3. *Presynaptic receptors*. Agonists at presynaptic receptors produce negative feedback on neurotransmitter synthesis or release. Clonidine is an agonist at α_2-adrenergic receptors, inhibiting NE release. It has anxiolytic and sedative effects and is also used to treat attention deficit hyperactivity disorder. Yohimbine is an antagonist at α_2-adrenergic receptors; it induces anxiety.

4. *Postsynaptic receptors*. Propranolol is an antagonist at β-adrenergic receptors that blocks many effects of the sympathetic nervous system. It is used to treat some forms of cardiovascular disease but is commonly used to block anxiety during performance situations. Phenoxybenzamine is an agonist at α-adrenergic receptors.

5. *Uptake*. Certain tricyclic antidepressants, such as desipramine, and newer NE selective reuptake inhibitors, such as reboxetine, selectively block the NE transporter, thus increasing synaptic NE. Amphetamines enter monoaminergic neurons via the uptake transporter and interact with the vesicular transporter (the transporter on synaptic vesicles) to release neurotransmitter into the cytoplasm. The neurotransmitter is then pumped out of the neuron into the synapse via the uptake transporter acting in reverse.

6. *Degradation*. At the postsynaptic neuron, tropolone inhibits the enzyme catechol *O*-methyltransferase (**COMT**), which inactivates NE (**step 6a**). Normetanephrine (**NM**) is formed by the action of COMT on NE. At the presynaptic neuron, degradation by MAO is blocked by the MAO inhibitors phenelzine and tranylcypromine.

and also suggests new interpretations of such stimuli that help the patient cope with the experience. Where possible and when tolerable to patients, gradual transition to real-world exposures to phobic stimuli can be employed.

Exposure therapy produces extinction learning in analogy with studies of animal behavior. The memory of the phobic stimulus is not erased, but the fearful response is suppressed by new information that the stimulus and the context in which it is experienced are not dangerous. Animal physiology and lesioning studies and human imaging studies demonstrate that the prefrontal cortex is required for extinction learning and that the hippocampus is required for learning new contexts for familiar events or stimuli (eg, that a helicopter flying overhead does not portend an attack).

Electroconvulsive Therapy Is Highly Effective Against Depression

Although it still conjures up negative images in the popular imagination, electroconvulsive therapy (ECT) administered with modern anesthesia is medically safe and a tolerable patient experience, and it remains a highly effective intervention for the acute treatment of serious major depressive disorder. It is most often used when depressive symptoms are severe and medications and psychotherapies have proven ineffective. It is also effective in both the depressed and manic phases of bipolar disorder. It is not effective for anxiety disorders in the absence of a mood disorder and is not used to treat them clinically.

Generally, six to eight treatments are given, most commonly on an outpatient basis. Patients are anesthetized, and electrical stimulation is administered just above the threshold to produce electroencephalographic evidence of a generalized seizure. The major side effect is a variable degree of anterograde and retrograde amnesia. Amnesia can be minimized, but not eliminated, by placing the electrodes unilaterally and using the lowest level of electrical stimulation needed. Rodents given ECT exhibit massive release of neurotransmitters, which causes significant activation of gene expression, presumably leading to large-scale neural plasticity. However, the precise molecules, cells, and circuits involved in the therapeutic response remain unknown.

Newer Forms of Neuromodulation Are Being Developed to Treat Depression

Other forms of therapeutic electrical stimulation of the brain are being explored, motivated by the desire to improve upon the therapeutic effects of ECT while diminishing its side effects. These approaches are often described as "neuromodulation."

Transcranial magnetic stimulation (TMS) employs a device on the scalp to deliver brief pulses of rapidly alternating magnetic stimulation. This induces currents to flow within axons in regions of cerebral cortex beneath the device. Daily administration of TMS over the left prefrontal cortex is safe and was effective enough to have received regulatory approval by the US Food and Drug Administration. Nonetheless, in subsequent trials, its efficacy appears to be only modest. Additional clinical experiments are under way aimed at improving efficacy.

Alternative therapies under development include magnetic seizure therapy, an alternative to ECT in which a magnetic field is the used to produce a seizure. The hope for this experimental therapy is to reproduce the efficacy of ECT with less anterograde and retrograde amnesia.

Deep brain stimulation (DBS), mentioned above, is an invasive neuromodulatory treatment in wide use for treatment of the motor symptoms of Parkinson disease and of essential tremor. For treatment of Parkinson disease, an electrode is typically placed within the subthalamic nucleus, a component of basal ganglia circuitry involved in motor control that is well understood compared with circuits that regulate mood. A DBS electrode is connected by a wire that exits the skull and travels under the scalp and skin of the neck to a controller and battery pack that resides in the chest, much like a cardiac pacemaker battery. The rate at which the electrode stimulates its target can be controlled externally and is typically adjusted by the treatment team to optimize the therapeutic response. During the past decade, clinical trials of DBS have been extended from Parkinson disease and other movement disorders to psychiatric disorders. In addition to its use in treatment-refractory depression, DBS is being studied for the treatment of obsessive-compulsive disorder.

Several locations in the brain have been targets for DBS to treat depression. As described in Figure 61–4, the rostral anterior (subgenual) cingulate cortex is activated by sadness. Accordingly, it has been used as a DBS target for treatment-resistant depression (Figure 61–8). In some clinical series, 60% of treatment-resistant patients achieved stable improvement with stimulation of the subgenual cingulate cortex. However, similar levels of efficacy using this target could not be replicated in a large multisite clinical trial. Differences in patient selection, interindividual differences in brain anatomy, or small differences in electrode placement may account for the disparate results seen to date. To

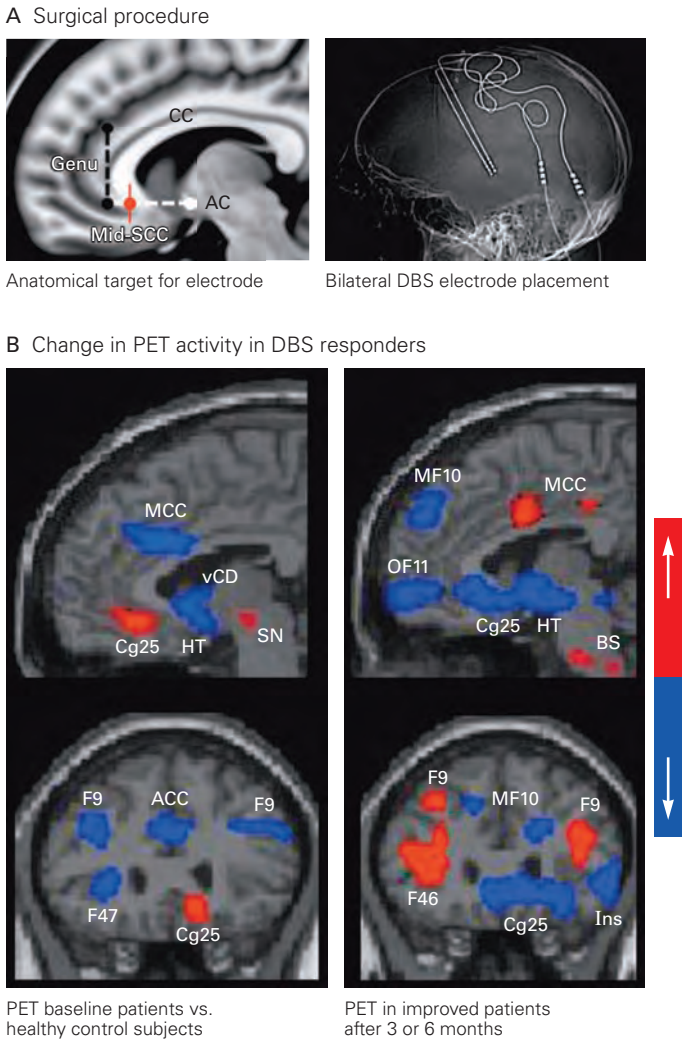

Figure 61–8 Electrode placement for deep brain stimulation (DBS) in the rostral anterior cingulate cortex and measurement of response by [18F] fluoro-2-deoxyglucose positron emission tomography (PET). (Reproduced, with permission, from Helen Mayberg.)

A. *Left:* The rostral anterior (subgenual) cingulate cortex, Brodmann area 25 (**Cg25**), is an anatomic target for DBS for patients with treatment-resistant depression. (Sagittal section; electrode site in **red**; corpus callosum is just superior and shown in **white**; **dotted line**, position of the electrode relative to the AC-genu line.) (Abbreviations: **AC**, anterior commissure; **Mid-SCC**, mid-subcallosal cingulate.) *Right:* A PET scan shows placement of the electrodes in the brain of a patient undergoing stimulation of the rostral anterior cingulate cortex. (Sagittal section.)

B. PET scans show the changes in activity in patients with treatment-resistant depression who have improved with stimulation of the rostral anterior cingulate cortex. The **top** panels are sagittal sections; the **bottom** panels are coronal sections. *Left:* Pretreatment metabolic activity in patients with treatment-resistant depression. **Red** pseudo-color denotes elevated metabolic activity compared with healthy control subjects (note elevated activity in Cg25 before DBS); **blue** denotes lower metabolic activity. *Right:* Averages of patients who have improved at 3 or 6 months after initiation of DBS. Activity in Cg25 is decreased (**blue**) in patients who have had a positive response to stimulation. (Abbreviations: **ACC**, anterior cingulate cortex; **BS**, brain stem; **F9**, dorsolateral prefrontal cortex; **F46**, prefrontal cortex; **F47**, ventrolateral prefrontal cortex; **HT**, hypothalamus; **Ins**, insula; **mF10**, medial frontal cortex; **MCC**, middle cingulate cortex; **OF11**, orbital frontal cortex; **SN**, substantia nigra; **vCD**, ventral caudate.)

put it simply, depression is highly heterogeneous, and it should not be surprising that a single DBS target is not useful for all treatment-resistant patients.

Lacking good animal models of mood disorders, human DBS treatment trials may provide a particularly important source of information about the brain circuitry responsible for the symptoms of mental disorders. Although careful attention must be paid to obtaining informed consent and to safety, especially when the judgment of patients is influenced by severe depression, DBS may provide an opportunity to learn about mood regulation. In particular, newly developed electrodes not only stimulate a DBS target but can also record extracellular neuronal activity. Such "read–write" electrodes, currently being used in research settings only, may not only improve clinical results but also advance our knowledge of circuit dysfunction and therapeutic modulation in psychiatric disorders.

Bipolar Disorder Can Be Treated With Lithium and Several Anticonvulsant Drugs

In 1949, John Cade discovered the calming effects of lithium in guinea pigs and, soon thereafter, in a small clinical trial in bipolar patients. Cade's observations initiated the modern era of psychopharmacology in which drugs, ultimately subjected to randomized, blinded clinical trials, were used to treat specific symptoms of mental disorders. Lithium eventually proved to be effective in treating acute episodes of mania and in stabilizing mood by reducing the frequency of cycling into mania and depression.

Several drugs initially developed to treat epilepsy, such as valproic acid and lamotrigine, have also been shown to be effective in treating acute mania and for mood stabilization and can serve as substitutes for lithium. In addition, antipsychotic drugs effectively

ameliorate symptoms of acute mania and, at low doses, can also help stabilize mood. None of these drugs exerts therapeutic effects rapidly; improvements in mental state and behavior may take several weeks.

The mechanisms by which lithium and anticonvulsant drugs exert beneficial effects on mania and on mood cycling are not known. Unlike the antidepressant and antipsychotic drugs, however, there remain open questions about the initial molecular target of lithium in the nervous system relevant to the initiation of its therapeutic effects. This lack of certainty reflects the many actions of lithium at therapeutic concentrations in the brain. The most likely molecular target is inhibition of glycogen synthase kinase type 3β (GSK3β), a component of the Wnt signaling pathway that has many functions in the nervous system. As in the case of other drugs to treat psychiatric disorders, investigation of the therapeutic mechanism of lithium and of the mood-stabilizing properties of anticonvulsants is impeded by the lack of an animal model of bipolar disorder.

Whatever the molecular mechanisms of lithium or the anticonvulsants, mood stabilizers appear to dampen the dynamics of mood regulatory systems. Mood is regulated by the external environment as well as several internal inputs, including the internal hormonal milieu, immune modulators, and circadian controls (eg, both the serotonergic and noradrenergic systems show diurnal variations closely coupled with the sleep–wake cycle). The integration of these systems is complex, involving dynamic interactions that are still poorly understood.

Second-Generation Antipsychotic Drugs Are Useful Treatments for Bipolar Disorder

All antipsychotic drugs act by blocking D_2 dopamine receptors, but these drugs have long been recognized to have therapeutic effects not only in the treatment of the psychotic symptoms of schizophrenia, severe mood disorders, and many other conditions, but also in the treatment of acute manic episodes. The side effects of first-generation antipsychotic drugs are severe, most prominently Parkinson-like motor side effects that result from D_2 dopamine receptor antagonism.

Most second-generation drugs have somewhat lower affinity for D_2 dopamine receptors than first-generation drugs and, in addition, have other receptor effects, such as blocking serotonin 5-HT_{2A} receptors, resulting in a lower liability for severe motor side effects. These drugs are by no means free of serious side effects; most cause weight gain and associated metabolic conditions. However, their relative tolerability and their effects on serotonin receptors have made them an important treatment for the depressed phase of bipolar disorder as well as the treatment of acute mania. They have gained an important role in therapeutics because bipolar depression is less likely to respond to antidepressant drugs than unipolar depression.

Highlights

1. Mood disorders are divided into unipolar and bipolar disorder based on whether depression occurs alone (unipolar) or whether a person also suffers from episodes of mania. Unipolar and bipolar disorders have different familial patterns of transmission.
2. Clinically significant unipolar depression, often denoted as major depressive disorder (major depression), differs from normal sadness by its persistence, pervasiveness, and association with physiological, cognitive, and behavioral symptoms.
3. Major depression is common (15%–20% lifetime prevalence) and disabling, making it a leading cause of disability worldwide. Bipolar disorder is less common (1% lifetime prevalence worldwide) but tends to produce severe symptoms that often require hospitalization.
4. Anxiety disorders are the most common psychiatric disorders. They range in severity from highly disabling cases of panic disorder and posttraumatic stress disorder (PTSD) to simple phobias. They often co-occur with major depression.
5. Mood and anxiety disorders have both genetic and nongenetic components of risk. Bipolar disorder is more heritable than major depression or anxiety disorders. Childhood adversity and later environmental stressors play a significant role in susceptibility to major depression and anxiety disorders. Genetic analyses of bipolar disorder, major depression, and PTSD are beginning to yield molecular clues to pathogenesis.
6. The neural circuitry of fear and anxiety disorders involves the amygdala and its interconnections with the prefrontal cortex. The neural circuitry of major depression and bipolar disorder is less well understood. However, neuroimaging in humans with major depression implicated circuits involved in the processing of emotional salience and in cognitive control.
7. Bipolar disorder can be treated with lithium, certain anticonvulsant drugs such as valproic acid, and second-generation antipsychotic drugs, although many patients have residual symptoms, most commonly depression.

8. Major depression and anxiety disorders can be treated with diverse antidepressant drugs and by cognitive and behavioral therapies. Electroconvulsive therapy is effective for major depression that is unresponsive to medications.
9. Experimental treatments such as deep brain stimulation are being investigated for treatment of major depression and other psychiatric disorders. The development of electrodes that can record as well as stimulate promise greater insight in human neural circuit function in disease and its treatment.

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Disorders Affecting Social Cognition: Autism Spectrum Disorder

Mental retardation, now referred to widely as *intellectual disability*, is currently defined as having an IQ below 70 accompanied by marked deficits in adaptive functioning. Both terms have been broadly used to label a variety of cognitive impairments linked to prenatal or early postnatal brain abnormalities. For decades, subsets of individuals with rare intellectual disability syndromes, such as Rett syndrome or fragile X syndrome, have been characterized by their genetic etiologies. We are now beginning to elucidate the complex genetics of more prevalent neurodevelopmental disorders without distinct physical features that distinguish them, including so-called *idiopathic* or *nonsyndromic* forms of autism spectrum disorder (ASD). The combination of insights resulting from the intensive study of rare genetic syndromes coupled with successes in unraveling the genetics underlying idiopathic ASD has transformed our understanding of normal and pathological development of the human brain.

Common to all of these disorders are mental impairments that persist throughout life, hampering development and learning. Generally speaking, even if all mental functions seem to be affected, conditions with distinct etiologies and natural histories can be differentiated because some cognitive domains tend to be

more impaired than others. And indeed, these differences are reified in diagnostic schemes that draw distinctions between developmental abnormalities that affect primarily general cognition, social cognition, or perception. These differential cognitive and behavioral vulnerabilities may provide useful clues about the origin and developmental time course of specific mental functions in normal development.

In this chapter, we focus principally on neurodevelopmental disorders that include abnormalities in social functioning, including ASD, fragile X syndrome, Williams syndrome, Rett syndrome, and Angelman and Prader-Willi syndromes. These conditions all impair highly sophisticated brain functions including social awareness and communication. ASD is a prime focus for several reasons: the high prevalence in the population; the overlap in genetic risks with other common neuropsychiatric conditions, including schizophrenia; and the absence of a defining neuropathology. They are also exemplars of the etiological and phenotypic heterogeneity common to many psychiatric syndromes. In this respect, ASD is a paradigmatic neuropsychiatric syndrome.

Autism Spectrum Disorder Phenotypes Share Characteristic Behavioral Features

Profound social disability has probably always been with us, but the characterization of autism as a medical syndrome was first described in the literature in 1943 by Leo Kanner and in 1944 by Hans Asperger. Today, clinicians and researchers think of autism as a spectrum of disorders with two defining but highly variable diagnostic features: impaired social communication and stereotyped behaviors with highly restricted interests.

Until recently, the term "Asperger syndrome" was used to describe individuals who met these two diagnostic criteria, but in whom language acquisition was not delayed and IQ was in the normal range. In the most recent edition of the standard psychiatric diagnostic manual, *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (DSM-5), Asperger syndrome along with a distinct disorder known as pervasive developmental disorder not otherwise specified—designed to capture individuals with deficits in social communication who did not meet full criteria in other areas—were eliminated in favor of including variations within a single spectrum construct.

Autism spectrum disorder is present in at least 1.5% of the population. Rigorous epidemiological studies estimate prevalence as high as 2.6% for the full spectrum of social disability, far higher than estimated only decades ago. The reasons for the increase in the prevalence over a relatively short time frame are of considerable interest and active debate, particularly among the lay public. Within the scientific community, a consensus has emerged that this increase reflects a combination of changing diagnostic criteria, increased awareness among families and health care professionals, "diagnostic substitution" (in which individuals who formerly would have been diagnosed with intellectual disability are now more likely to be identified as socially disabled), and some true increase in incidence. These issues will be discussed below with regard to genetic risks.

Autism spectrum disorders occur predominantly in males, although the typically cited 4:1 male-to-female ratio has recently been called into question based on concerns about male bias in the approaches used to ascertain the diagnosis, including the diagnostic instruments. Even accounting for these challenges, however, the cumulative evidence suggests a ratio bias of at least 2:1 to 3:1 male excess. Individuals across the IQ spectrum are affected, and based on current diagnostic practices, about half of all individuals with ASD also have intellectual disability. By definition, ASD must be detectable before 3 years of age, but recent studies have shown that it is possible to identify affected children in high-risk families well within the first year of life. ASD occurs in all countries and cultures and in every socioeconomic group.

Although ASD clearly affects the brain, no definitive biological markers have yet been identified; thus, diagnosis is based on behavioral criteria. This does not mean that there are not strong biological correlates, including specific gene mutations and neuroimaging findings, but none of these are sufficiently specific or predictive to be useful as an alternative to the gold standard of clinical assessment. Moreover, because behavior is variable during development and depends on a number of factors—age, environment, social context, and availability and duration of remedial help—no single behavior is likely ever to be conclusively diagnostic.

Like other neurodevelopmental syndromes, ASD typically endures throughout life. However, in recent longitudinal studies, approximately 10% of clearly affected children showed improvement, with little or no evidence of social disability later in life. Autism is not progressive. On the contrary, special educational programs and professional support often lead to improvements in behavior and adaptive functioning with age.