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## 462 Biology of Psychiatric Disorders

Counseling may help patients and their families cope with the long-term consequences of living with a chronic illness. Consulta tion with a physical or occupational therapist may identify energysaving strategies for activities of daily living as well as needed accommodations, such as a wheelchair for activities that require walking longer distances or prolonged standing. COURSE AND PROGNOSIS The illness severity varies from mild or moderate, with patients retaining varying degrees of pre-illness function, to severe, with patients essentially homebound. Most patients experience some improvement and stabilize, although return to their prior level of function is unusual. A continued decline in function should prompt evaluation for other illnesses. Patients should be re-evaluated at scheduled intervals to adjust treatments and detect any intercur rent disease. New or changing symptoms should be worked up to identify any new illnesses. Given the social isolation and loss of hope associated with a debilitating chronic illness, serious depres sion and an increased risk of suicide are reported for patients with ME/CFS. Clinicians should be prepared to screen for this and refer patients as needed. ■ ■FURTHER READING Centers for Disease Control and Prevention: Myalgic enceph alomyelitis/chronic fatigue syndrome (ME/CFS). Available from https://www.cdc.gov/me-cfs/about/index.html. Accessed June 4, 2024. Choutka J et al: Unexplained post-acute infection syndromes. Nat Med 28:911, 2022. Grach SL et al: Diagnosis and management of myalgic encephalomy elitis/chronic fatigue syndrome. Mayo Clin Proc 98:1544, 2023. Institute of Medicine: Beyond Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: Redefining an Illness. Washington, DC: The National Academies Press, 2015. Komaroff AL et al: ME/CFS and Long COVID share similar symp toms and biological abnormalities: Road map to the literature. Front Med (Lausanne) 10:1187163, 2023. Lapp CW: Initiating care of a patient with myalgic encephalomyelitis/ chronic fatigue syndrome (ME/CFS). Front Pediatr 6:415, 2019. Rowe PC et al: Myalgic encephalomyelitis/chronic fatigue syndrome diagnosis and management in young people: A primer. Front Pediatr 5:121, 2017. Vahratian A et al: Myalgic encephalomyelitis/chronic fatigue syndrome in adults: United States, 2021-2022. NCHS Data Brief 488:1, 2023. Walitt B et al: Deep phenotyping of post-infectious myalgic encepha lomyelitis/chronic fatigue syndrome. Nat Commun 15:907, 2024. Section 5 Psychiatric and Addiction Disorders Robert O. Messing, Eric J. Nestler,

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Biology of Psychiatric

Disorders Psychiatric disorders are central nervous system diseases characterized by disturbances in emotion, cognition, motivation, and socialization. They are highly heritable, with genetic risk comprising 20–90% of disease vulnerability depending on the syndrome. As a result of their

prevalence, early onset, and persistence, they contribute substantially to the burden of illness worldwide. All psychiatric disorders are broad heterogeneous syndromes that currently lack well-defined neuropa thology and bona fide biologic markers. Therefore, diagnoses continue to be made solely from clinical observations using criteria in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), of the American Psychiatric Association (see Chap. 463).

There is increasing agreement that the classification of psychiatric illnesses in the DSM does not accurately reflect their underlying biol ogy. Uncertainties in diagnosis complicate efforts to study the genetic basis and attendant neurobiological mechanisms underlying mental illness, though recent technologic advances along with the consoli dation of very large patient cohorts have, for multiple disorders, led to significant progress in these realms. In addition, there have been efforts to address the limitations of a categorical nosology directly through the development of an alternative diagnostic scheme, termed Research Domain Criteria (RDoC). This system classifies mental ill ness on the basis of core behavioral abnormalities shared across several syndromes—such as psychosis (loss of reality) or anhedonia (decreased ability to experience pleasure)—and the associated brain circuitry that controls these behavioral domains. Such classifications may assist in defining the biologic basis of key symptoms. Other factors that have impeded progress in understanding mental illness include the lack of access to pathologic brain tissue except upon death and inherent limitations of animal models for disorders defined largely by behavioral abnormalities (e.g., hallucinations, delusions, guilt, suicidality) that are inaccessible in animals. CHAPTER 462 Biology of Psychiatric Disorders Despite these limitations, the past decade has been marked by real progress. Neuroimaging methods are beginning to provide evidence of brain pathology; genome-wide association studies and high-throughput sequencing are reliably identifying genes and genomic loci that confer risk for severe forms of mental illness; and investigations of bettervalidated animal models, leveraging a host of new methods to study molecular, cellular, and circuit-level processes, are offering new insight into disease pathogenesis. There is also excitement in the utility of neurons, glia, and brain organoids induced in vitro from patientderived pluripotent stem cells, providing novel ways to study disease pathophysiology and screen for new treatments. There is consequently justified optimism that the field of psychiatry will better integrate behaviorally defined syndromes with an understanding of biological substrates in a way that will drive the development of improved treat ments and eventually cures and preventive measures. This chapter describes several examples of recent discoveries in basic neuroscience and genetics that have informed our current understanding of disease mechanisms in psychiatry. ■ ■NEUROGENETICS Because the human brain can only be examined indirectly during life, genome analyses have been extremely important for obtaining molecu lar clues about the pathogenesis of psychiatric disorders. Moreover, the identification of germline risk alleles and mutations provides potential traction on the question of cause versus effect. In other types of crosssectional studies, it may be impossible to determine whether a phe notype or biomarker observed in affected humans or model systems reflects an etiologic factor or a compensatory response. In contrast, germline genetic risk is present before the brain develops—at least theoretically allowing for experiments to address temporal sequencing. A wealth of new information has been made possible by two decades of advances subsequent to the sequencing of the human genome. These have enabled

affordable, very large-scale genome-wide association and high-throughput sequencing studies. A striking example of the impact of these developments has been progress in the genetics of autism spectrum disorders (ASDs), a phenotypically heterogeneous neurodevelopmental syndrome characterized by impaired social com munication and restricted, repetitive patterns of behavior. ASDs are highly heritable. Concordance rates in monozygotic twins range from 60–90%, a four- to sixfold increase compared to dizygotic twins and siblings. ASDs are also highly genetically heterogeneous and, like many psychiatric conditions, are mainly inherited in a polygenic fashion,

conferred by a conspiracy of alleles that are common in the population and carry small individual effects. Indeed, the increments of increased risk for any common ASD risk allele are so modest that studies of tens of thousands of individuals have identified only a handful of asso ciations meeting gold-standard genome-wide statistical thresholds. However, with increasingly large cohorts and an associated increase in statistical power, the number of identified risk loci is destined to continue to grow.

At the same time, the development of next-generation DNA sequencing has identified a substantial minority of ASD patients who carry rare, often spontaneous (de novo), heterozygous, proteindamaging mutations. This latter group has served as a powerful resource for the identification of specific ASD risk genes of very large effect (Fig. 462-1). To date, about 70–250 ASD genes have been identi fied by high-throughput sequencing analyses based on false discovery rates ranging from <0.001 to <0.1, respectively. In addition, approxi mately 10% of ASD-affected individuals carry rare, typically de novo, submicroscopic gains or losses of chromosomal material, known as copy number variations (CNVs), that also confer very large risks. All told, these mutations in individual genes or gene-rich genomic regions account for ~20–30% of cases of ASD seen in clinic, although none individually account for >1%. Importantly, as gene discovery in ASD has progressed, considerable overlap, both phenotypically and geneti cally, has been found among ASD, epilepsy, and well-established intel lectual disability syndromes. For example, individuals with fragile X syndrome or tuberous sclerosis (Chap. 95) show elevated rates of ASD, and mutations in the causal genes may be found in patients who pres ent with otherwise idiopathic ASD. PART 13 Neurologic Disorders The discovery of very large-effect ASD risk genes that are vul nerable to protein-damaging mutations has provided important opportunities to delve into pathologic mechanisms. From the earli est successes in gene discovery, several common biological themes have emerged. For instance, many of the identified pathogenic rare mutations are in genes that encode proteins involved in synaptic structure or function or in transcriptional and chromatin regula tion (Fig. 462-1). More recently, studies of high-confidence ASD risk mutations in model systems have confirmed these predictions and pointed to neurogenesis and neuronal migration as additional shared pathological mechanisms. Moreover, the availability of increasingly comprehensive maps of human brain gene expression has enabled studies of when and where ASD risk genes converge. These transcrip tomic studies have repeatedly pointed to glutamatergic neurons in the mid-fetal human cortex (Fig. 462-1) as one of several regions and cell types enriched for ASD genetic vulnerability. Given that many autism risk genes are biologically pleiotropic—that is, they serve multiple different functions—the identification of anatomic and temporal dimensions of risk should help narrow in on pathophysiologic mecha nisms and potential therapeutic targets. Moreover, as the number of large-effect ASD risk genes grows and the scale of transcriptomic, epigenomic, and proteomic mapping of human brain development expands, points of pathogenic convergence promise to be identifiable at single-cell resolution. A deeper

understanding of disease pathogenesis and the identifica tion of genetic subtypes is ultimately aimed at developing more effec tive, rational, and personalized therapies, particularly for those who are most severely affected. In this regard, in humans, increasing attention has turned to nucleic acid targeting to treat severe phenotypes in cases in which a highly penetrant coding mutation is present, for example, with CRISPR-based therapies or the use of antisense oligonucleotides (ASOs). Remarkable success with very early intervention in spinal muscular atrophy using these strategies has piqued interest in their utility in a range of brain-based conditions. Currently, among neuro developmental disorders, these approaches are being actively pursued for well-known intellectual disability syndromes that may also manifest core features of or elevated risk for ASD, such as Angelman syndrome and SHANK3 deletion/Phelan-McDermid syndrome. If successful, such efforts would be transformational, and potentially not only for the individuals carrying mutations that may be amenable to nucleic acid–targeting approaches.

The ability to catalog common genetic variants and assay them on array-based platforms and carry out whole exome sequencing has also allowed investigators to leverage large patient cohorts to reliably detect risk loci for schizophrenia and bipolar disorder. In contrast to ASD, where the lion’s share of early success resulted from the study of rare, large-effect, de novo mutations, much of gene discovery for these syn dromes has resulted from genome-wide association studies of common inherited polymorphisms. To date, several hundred distinct genomic regions, marked by associated single nucleotide polymorphisms, have been identified in schizophrenia, some of which show risk as well for bipolar disorder. Several identified genes are parts of molecular complexes, such as voltage-gated calcium channels (in particular, CACNA1C and CACNB2) and the postsynaptic density of excitatory synapses. Notably, as the scale of high-throughput sequencing studies has expanded, rare large-effect mutations have also been identified in schizophrenia. To date, 10 high-confidence genes have been identified. Genes that promote risk for addiction and depression have also begun to emerge from large studies. One susceptibility locus for addic tion is the CHRNA5-A3-B4 nicotinic acetylcholine receptor gene clus ter on chromosome 15 associated with nicotine and alcohol addiction. Genome-wide association studies of depression and addiction have required hundreds of thousands of cases and controls to identify the first statistically significant loci using state-of-the-art approaches. For example, a meta-analysis of >1 million individuals was able to identify 110 unique genetic variants associated with problematic alcohol use. Such findings collectively point to the tremendous heterogeneity of these disorders as well as the very small biological effects conferred by any individual common allele. A recurrent theme in genetic studies of psychiatric disorders is phenotypic pleiotropy, namely, that individual risk genes may be asso ciated with multiple psychiatric and neurodevelopmental syndromes. For example, functionally identical heterozygous deletions of the gene NRXN1 are associated with ASD, schizophrenia, intellection disability, epilepsy, and other neurodevelopmental phenotypes. Common poly morphisms in CACNA1C are associated with both schizophrenia and bipolar disorder. Rare mutations in this same gene may lead to severe neurodevelopmental syndromes and congenital heart disease, includ ing Timothy syndrome, which may include autistic features. Likewise, there is striking overlap among the phenotypes associated with largeeffect CNVs, including ASD, schizophrenia, and bipolar disorder, as well as epilepsy and intellectual disability. For example, duplication of chromosome 16p is associated with both schizophrenia and autism, whereas deletions in the DiGeorge’s (velocardiofacial) syndrome region are associated with schizophrenia, autism, and bipolar disorder. These findings attest to the complexity of psychiatric disorders, the very large gap between molecular mechanisms and the current categorical diag

nostic schemes, and the influence of additional factors that combine to specify the ultimate phenotype. The latter might include polygenic “background,” stochastic events, epigenetic effects, and environmental factors. This pleiotropy of consequences for a given genetic mutation in psychiatry is akin to the pleiotropy seen for neurodegenerative dis orders as well as for many cancer-causing mutations, where the same mutation can lead to very different disorders across the population. ■ ■SIGNAL TRANSDUCTION Studies of signal transduction disturbances in psychiatric disorders have provided insight into development of new therapeutic agents. For example, lithium is a highly effective drug for bipolar disorder and competes with magnesium to inhibit numerous magnesium-dependent enzymes, including GSK3β and several enzymes involved in phos phoinositide signaling that lead to activation of protein kinase C. These findings have led to discovery programs focused on developing GSK3β or protein kinase C inhibitors as potential novel treatments for mood disorders, although none have demonstrated clinical efficacy to date. The observations that tricyclic antidepressants (e.g., imipramine) inhibit serotonin and/or norepinephrine reuptake and that mono amine oxidase inhibitors (e.g., tranylcypromine) are effective anti depressants initially led to the view that depression is caused by a deficiency of these monoamines. However, this hypothesis has not

DPYSL2 cAMP Ca2 + Ch. ANK2 Spectrin Network L1 DYNC1H1 AP2S1 Ca2 + Ch. MINT CASK NRNX1 ?+ SCN2A GRIN2B MGluR KCNQ3 NMDARs NLGNs CAMKII CK2 PSD95 CNTNAP2 Homer SHANK3 CAMKII PI3K PSD95 GKAP1 SYNGAP1 GKAP1 PTEN Ras-GTP SHANK2/3 Ras-GDP Endoplasmic Reticulum CTNNB1 AGO1-4 SRPR TNRC6B** DSCAM Membrane/ Vessicle Targeting GIGYF1 2EHP A ASH1L KMT2C SETD5 KDM6B KDM5B ARTKQTARKSTGGKAPRKQLATKAARKSAPATGGVK CHD8 SGRGKGGKGLGKGGAKRHRKVLRDNIQGITKPAIR SUV420H1 Methyl group Ubiquitine ligase Lysine demethylase Lysine methyltransferase Other chromatin remodeler B Convergence of Autism Associated Genes & Co-expression Network Analysis Mid-fetal Development Prefrontal and Primary Motor-Somatosensory Cortex C Co-expression of Autism Associated Genes FIGURE 462-1 Functional characteristics and developmental convergence of autism spectrum disorder (ASD) associated genes. A representative selection of genes associated with ASD based on recurrent rare coding mutations is shown in A and B. Those genes encoding proteins with a false discovery rate (FDR) <0.01 in Sanders et al, Neuron 2015, and Satterstrom et al, Cell 2020, are highlighted with respect to their putative functions. Genes meeting the highest confidence criteria in Sanders et al 2015 and showing either an FDR >0.01 or an FDR >0.3 in Satterstrom are noted (* and **, respectively). Additional interacting and functionally related molecules that do not meet the above criteria are shown in green. FMR1, TSC1, and TSC2 are syndromic ASD genes included in the figure (A). Multiple gene ontology analyses of ASD genes have highlighted both pre- and postsynaptic molecules (A) and chromatin modifiers (B) as points of enrichment. In C, an alternative strategy for grouping ASD risk genes is highlighted (Willsey et al, Cell 2013), based on their spatiotemporal expression patterns as opposed to putative functions. One analytic strategy, illustrated in C, leveraged only high-confidence ASD genes and examined their developmental expression patterns using the BrainSpan data set. Convergence for ASD risk was identified in deep layer (V and VI) excitatory neurons in mid-fetal human cortex. Multiple analyses have similarly found glutamatergic neurons in mid-fetal prefrontal cortex as one point of convergence, with somewhat less agreement on layer specificity and potential additional spatiotemporal points of convergence.

Microtubule SCN2A KATNAL2** DYRK1A MAP1A Presynaptic Phos. localizes RBX1 CUL3** CK2 Channels KCT13 Ubiquitin Ligases Ub Cell Adhesion Proteins Scaffolding Proteins RhoA GABRB3

Phosphatase SLC6A1 Kinases GABRB3 Other Transcription Factors Adaptor Proteins Actin Cytoskeleton FDR>0.01 CAMKII CHAPTER 462 PIKE-L RAC1 Postsynaptic Δ NCKAP1** FMR1 WRC Nucleus MBD5 AKT CYFIP1 PAX5 MKX MED13L CYFIP1 TBR1* MYT1L BCL11A FMR1 Biology of Psychiatric Disorders TCF7L2* POGZ RORB WAC MEK TSC1 TSC2 TTT-Pontin/ Reptin complex FOXP1 DEAF1 CTNNB1 MAPK mTORC1 Transcription Δ Δ Translation RNF20 RNF40 WAC Ub TRIP12* H3 H2B RNF168 Ub H4 H2A ARID1B ADNP DNMT3A SIN3A RAI1 ANKRD11 Reader TLK2 CHD2 FDR > 0.01 TBL1XR1 Map of Gene Expression in the Developing Human Brain

been substantiated. A cardinal feature of these drugs is that long-term (weeks to months) administration is needed for their antidepressant effects. This means that their short-term actions, namely promotion of serotonin or norepinephrine function, are not per se antidepressant but rather induce a cascade of adaptations in the brain that underlie their slowly developing clinical effects. The nature of these therapeutic druginduced adaptations has not been identified with certainty. A subset of depressed patients display upregulation of the hypothalamic-pituitaryadrenal (HPA) axis characterized by increased secretion of cortico tropin-releasing factor (CRF) and glucocorticoids. One hypothesis posits that in these patients excessive glucocorticoids cause atrophy of hippocampal neurons, which is associated with reduced hippocampal volumes seen clinically. Chronic antidepressant administration might reverse this atrophy by increasing brain-derived neurotrophic factor (BDNF) or a host of other neurotrophic factors in the hippocampus. A role for stress-induced decreases in the generation of newly born hippocampal granule cell neurons, and its reversal by antidepressants through BDNF or other growth factors, has also been suggested.

PART 13 Neurologic Disorders A major advance in recent years has been the identification of several rapidly acting antidepressants with non–monoamine-based mechanisms of action. The best established is ketamine, a noncompeti tive antagonist of N-methyl-d-aspartate (NMDA) glutamate receptors among other actions, which exerts rapid (hours) and robust antidepres sant effects in severely depressed patients who have not responded to other treatments. Ketamine, which at higher doses is psychotomimetic and anesthetic, exerts these antidepressant effects at lower doses with minimal side effects. However, the response to ketamine is transient, which has led to several approaches to maintain treatment response, such as repeated ketamine delivery. The mechanism underlying ket amine’s antidepressant action is not known, and its action as an NMDA receptor antagonist has recently been called into question. Neverthe less, ketamine’s striking clinical efficacy has stimulated animal research on the role of glutamate neurotransmission and synaptic plasticity in key limbic regions. Recent evidence supports a role for TORC1 or BDNF activation, as blockade of either blocks the antidepressant-like effects of ketamine in animal models. Mechanisms by which ketamine activates these signaling cascades are currently an active area of investigation. Another area of great interest is the potential clinical utility of psy chedelic drugs and 3,4-methylenedioxy-methamphetamine (MDMA or ecstasy). Psychedelic drugs are thought to act as partial agonists of serotonin 5-HT2A receptors, whereas MDMA promotes serotonin release from nerve terminals. Both are being studied for treatment of depression and posttraumatic stress disorder, although much addi tional clinical research is needed to establish their efficacy, safety, and mechanism of action. A major goal in the field of substance use disorders has been to identify neuroadaptive mechanisms that lead from recreational use to addiction. Such research has determined that repeated intake of abused drugs induces specific changes in cellular signal transduction, leading to changes in synaptic strength (long-term potentiation or depression) and neuronal structure (altered dendritic branching or cell soma size) within the brain’s reward

circuitry. These drug-induced modifications are mediated in part by changes in gene expression, achieved by regu lation of transcription factors (e.g., CREB [cAMP response elementbinding protein] and ΔFOSB [a FOS family protein]) and their target genes. Such alterations in gene expression are associated with lasting alterations in epigenetic modifications, including histone acetylation and methylation and DNA methylation. These adaptations provide opportunities for developing treatments targeted to drug-addicted individuals. The fact that the spectrum of these adaptations differs in part depending on the particular addictive substance used raises hope that treatments could be developed that are specific for different classes of addictive drugs and less likely to disturb basic mechanisms that gov ern normal motivation and reward. Increasingly, causal relationships are being established between individual molecular and cellular adaptations and specific behavioral abnormalities that characterize the addicted state. For example, acute activation of μ-opioid receptors by morphine or other opioids activates

μ-opioid receptor K+ Ca2+ AC Gi/o + – – Increased excitability cAMP + R R Regulation of proteins by PKA phosphorylation C C C C PKA Nucleus + P CREB Altered gene expression FIGURE 462-2 Opioid action in the locus coeruleus (LC). Binding of opioid agonists to μ-opioid receptors on LC neurons catalyzes nucleotide exchange on Gi and Go proteins, leading to inhibition of adenylyl cyclase (AC), neuronal hyperpolarization via activation of K+ channels, and perhaps inhibition of Ca2+ channels. Inhibition of AC reduces protein kinase A (PKA) activity and phosphorylation of several PKA substrate proteins, thereby altering their function. For example, opioids reduce phosphorylation of the cAMP response element-binding protein (CREB), which initiates longer term changes in neuronal function. Chronic administration of opioids increases levels of AC isoforms, PKA catalytic (C) and regulatory (R) subunits, and the phosphorylation of several proteins, including CREB (indicated by red arrows). These changes contribute to the altered phenotype of the drug-addicted state. For example, the excitability of LC neurons is increased by enhanced cAMP signaling. Activation of CREB causes upregulation of AC isoforms and tyrosine hydroxylase, the rate-limiting enzyme in catecholamine biosynthesis. Gi/o proteins, leading to inhibition of adenylyl cyclase (AC), resulting in reduced cyclic AMP (cAMP) production, protein kinase A (PKA) activation, and activation of the transcription factor CREB. Repeated administration of these drugs (Fig. 462-2) evokes a homeostatic response involving upregulation of ACs and PKA and increased acti vation of CREB. Such upregulation of cAMP-CREB signaling has been identified in the locus coeruleus (LC), periaqueductal gray, ventral tegmental area (VTA), nucleus accumbens (NAc), and several other central nervous system (CNS) regions and contributes to opioid crav ing and signs of opioid withdrawal. The fact that endogenous opioid peptides do not produce tolerance and dependence, while morphine and related drugs do, may relate to the observation that, unlike endog enous opioids, morphine and like drugs are weak inducers of μ-opioid receptor desensitization and endocytosis. Therefore, these drugs cause prolonged receptor activation and inhibition of ACs, which provides a powerful stimulus for the upregulation of cAMP-CREB signaling that characterizes the opioid-dependent state. ■ ■SYSTEMS NEUROSCIENCE The study of interconnected brain circuits that drive behavior has been greatly advanced through newer methods in brain imaging that have documented abnormalities in neural function and connectivity in psy chiatric disorders. Electroceutical devices, which use electrical or mag netic stimulation to control neuronal activity, have had some success in depression, obsessive-compulsive disorder, pain, and addiction. The past decade has also witnessed the development of revolutionary new

FC VTA Hyp NAc HP LC Amy Glutamatergic GABAergic Dopaminergic Peptidergic FIGURE 462-3 Neural circuitry of depression and addiction. The figure shows a simplified summary of a series of limbic circuits in the brain that regulate mood and motivation and are implicated in depression and addiction. Shown in the figure are the hippocampus (HP) and amygdala (Amy) in the temporal lobe, regions of prefrontal cortex, nucleus accumbens (NAc), and hypothalamus (Hyp). Only a subset of the known interconnections among these brain regions is shown. Also shown is the innervation of several of these brain regions by monoaminergic neurons. The ventral tegmental area (VTA) provides dopaminergic input to each of the limbic structures. Norepinephrine (from the locus coeruleus [LC]) and serotonin (from the dorsal raphe [DR] and other raphe nuclei) innervate all of the regions shown. In addition, there are strong connections between the hypothalamus and the VTA-NAc pathway. Important peptidergic projections from the hypothalamus include those from the arcuate nucleus that release β-endorphin and melanocortin and from the lateral hypothalamus that release orexin. techniques—optogenetics, designer receptors, and ligands—that pro vide unprecedented temporal and spatial control of neural circuits. The development of genetically encoded calcium detectors and of high-density electrode arrays has allowed in vivo monitoring of thou sands of neurons in multiple brain regions simultaneously. Advances in histology and microscopy now permit three-dimensional imaging of specific proteins in the intact brain, while advances in endoscopic microscopy allow imaging of hundreds of neurons within deep brain structures in awake, freely moving animals. Together with recent advances in machine learning and artificial intelligence for analysis of large complex datasets, these new methods are revolutionizing our ability to understand the circuit basis of brain function. Positron emission tomography (PET), diffusion tensor imaging (DTI), and functional magnetic resonance imaging (fMRI) have identified neural circuits that contribute to psychiatric disorders, for example, defining the neural circuitry of mood within the brain’s lim bic system (Fig. 462-3). Integral to this system are the NAc (impor tant also for brain reward—see below), amygdala, hippocampus, and regions of prefrontal cortex. Recent optogenetic research in animals, where the activity of specific types of neurons in defined circuits can be controlled with light, has confirmed the importance of this limbic circuitry in controlling depression-related behavioral abnormalities. Given that many symptoms of depression (so-called neurovegetative symptoms) involve physiologic functions, a key role for the hypothal amus is presumed as well. A subset of depressed individuals shows a small reduction in hippocampal size, as noted above. In addition, brain imaging investigations have revealed increased activation of the amygdala by negative stimuli and reduced activation of the NAc by rewarding stimuli. There is also evidence for altered activity in

prefrontal cortex, such as hyperactivity of subgenual area 25 in anterior cingu late cortex. Such findings have led to trials of deep brain stimulation (DBS) of either the NAc or subgenual area 25 (see Fig. 32-1), which appears to be therapeutic in some severely depressed individuals.

In schizophrenia, structural and func tional imaging studies have confirmed earlier pathologic studies that show enlargement of the ventricular system and reduction of cortical and subcortical gray matter in frontal and temporal lobes and in the limbic system. Functional imaging studies show reduced metabolic (presumably neural) activity in the dorso lateral prefrontal cortex at rest and when performing tests of executive function, including working memory. There is also evidence for impaired structural and taskrelated functional connectivity, mainly in frontal and temporal lobes. The reduc tion in cortical thickness seen in schizo phrenia is associated with increased cell packing density and reduced neuropil (defined as axons, dendrites, and glial cell

processes) without an apparent change in neuronal cell number. Specific classes of interneurons in prefrontal cortex con sistently show reduced expression of the gene encoding the enzyme glutamic acid decarboxylase 1 (GAD1), which syn thesizes γ-aminobutyric acid (GABA), the principal inhibitory neurotransmit ter in the brain. Recently, results from well-powered genome-wide association studies point to synaptic pruning, includ ing the involvement of microglia, as a potential contributing mechanism. In the region of the genome most strongly associated with schizophrenia risk, variations in the relative expression of two isotypes of comple ment component 4, C4A and C4B, have been found to account for a significant proportion of this genetic signal. Studies of loss of C4 in mice show deficient synaptic pruning, leading to the hypothesis that increased expression of C4A in humans may result in excessive syn aptic pruning. Such results point to the potential for a gene-driven understanding of pathophysiology; however, the findings also leave some important questions unanswered. The strongest effect haplo type in humans still only accounts for a very small increase in risk, with an odds ratio of <1.3. In contrast, having a sibling with schizo phrenia increases risk approximately tenfold. In short, whether this allele reflects a driving pathophysiologic mechanism remains to be determined. Moreover, humans have diverged at the C4 locus com pared with rodents such that only a single C4 isotype is present in the mouse, preventing any analysis of the putative effects of changing the ratio of C4A to C4B—the phenomenon associated with disease risk in humans. Nonetheless, all the aforementioned findings support the notion that schizophrenia is a developmental neurodegenerative disorder with some evidence pointing to loss of cortical interneurons in frontal and temporal lobes. CHAPTER 462 DR Biology of Psychiatric Disorders Work in rodent and nonhuman primate models of addiction has established the brain’s reward regions as key neural substrates for the acute actions of drugs of abuse and for addiction induced in vulner able individuals by repeated drug administration (Fig. 462-3). Mid brain dopamine neurons in the VTA function normally as rheostats of reward: they are activated by natural rewards (food, sex, social interaction) or even by the expectation of such rewards, and many are suppressed by the absence of an expected reward or by aversive

TABLE 462-1 Initial Actions of Drugs of Abuse NEUROTRANSMITTER AFFECTED DRUG TARGET (ACTION) DRUG Opioids Endorphins, enkephalins μ- and δ-opioid receptors (agonist) Psychostimulants (cocaine, amphetamine, methamphetamine) Dopamine Dopamine transporter (antagonist—cocaine; reverse transport—amphetamine, methamphetamine) Nicotine Acetylcholine Nicotinic cholinergic receptors (agonist) Ethanol GABA GABAA receptors (positive allosteric modulator)  Glutamate NMDA glutamate receptors (antagonist)  Acetylcholine Nicotinic cholinergic receptors (allosteric modulator) PART 13 Neurologic Disorders  Serotonin 5-HT3 receptor (positive allosteric modulator)  Others Calcium-activated K+ channel (activator) Marijuana Endocannabinoids (anandamide, 2-arachidonoylglycerol) CB1 receptor (agonist) Phencyclidine Glutamate NMDA glutamate receptor (antagonist) Abbreviations: GABA, γ-aminobutyric acid; NMDA, N-methyl-d-aspartate. stimuli. These neurons thereby transmit crucial survival signals to the rest of the limbic brain to promote reward-related behavior, includ ing motor responses to seek and obtain the rewards (NAc), memories of reward-related cues and contexts (amygdala, hippocampus), and executive control of obtaining rewards (prefrontal cortex). Drugs of abuse alter neurotransmission through initial actions at different classes of ion channels, neurotransmitter receptors, or neu rotransmitter transporters (Table 462-1). Studies in animal models have demonstrated that although the initial targets differ, the actions of these drugs converge on the brain’s reward circuitry by promoting dopamine neurotransmission in the NAc and other limbic targets of the VTA. In addition, some drugs promote activation of opioid and cannabinoid receptors,

which modulate this reward circuitry. By these mechanisms, drugs of abuse produce powerful rewarding signals, which, after repeated drug administration, corrupt a vulnerable brain’s reward circuitry in ways that promote addiction. Three major patho logic adaptations have been described. First, drugs produce tolerance in reward circuits and increased activity in limbic stress circuits, which promote escalating drug intake and a negative emotional state during drug withdrawal that promotes relapse. Second, sensitization to the rewarding effects of the drugs and associated cues is seen during pro longed abstinence and also triggers relapse. Third, executive function is impaired in such a way as to increase impulsivity and compulsivity, both of which promote relapse. Imaging studies in humans confirm that addictive drugs, as well as craving for them, activate the brain’s reward circuitry. In addition, patients who abuse alcohol or psychostimulants show reduced gray matter in the prefrontal cortex as well as reduced activity in ante rior cingulate and orbitofrontal cortex during tasks of attention and inhibitory control. It is thought that damage to these cortical areas contributes to addiction by impairing decision-making and increasing impulsivity. ■ ■NEUROINFLAMMATION There is increasing evidence for the involvement of nonneuronal cell types and inflammatory mechanisms in a wide range of psychiatric syndromes. For example, a subset of depressed patients displays elevated blood levels of interleukin 6 (IL-6), tumor necrosis factor α

(TNF-α), and other proinflammatory cytokines. Moreover, rodents exposed to chronic stress exhibit similar increases in peripheral levels of these cytokines, and peripheral or central delivery of those cyto kines to normal rodents increases their susceptibility to chronic stress. These findings have led to the novel idea of using peripheral cytokines as biomarkers of a subtype of depression and the potential utility of developing new antidepressants that oppose the actions of specific cytokines. Recent evidence has also linked proinflammatory signaling in the brain to addiction, particularly to alcohol. Alcohol use disorder is associated with impaired innate immunity, increases in circulat ing proinflammatory cytokines, and increases in brain expression of several immune-related genes. Many of these genes are expressed by astrocytes and microglia and by neurons under certain pathologic conditions, where they play important roles in modifying neuronal function and plasticity. For example, cytokine monocyte chemotactic protein-1 (MCP-1) modulates the release of certain neurotransmit ters and, when administered into the VTA, increases neuronal excit ability, promotes dopamine release, and increases locomotor activity. Gene expression studies of alcohol drinking in mice have identified a network of regulated neuroimmune proteins in brain, and a role in regulation of alcohol consumption has been validated for several, including chemokines MCP-1 and chemokine (C-C motif) ligand 3 (CCL3), beta-2 microglobulin, CD14, IL-1 receptor antagonist, tolllike receptors 3 (TLR3) and 7 (TLR7), and cathepsins S and F. This work has led to discovery of anti-inflammatory medications that reduce alcohol intake in animals, such as antagonists of phosphodies terase 4, which regulates cAMP availability, or agonists of peroxisome proliferator-activated receptors (PPARs), which are transcription fac tors that repress key inflammatory signaling molecules such as nuclear factor-κB (NF-κB) and nuclear factor of activated T cells (NFAT). A major focus of current research is to define the sites and mechanisms by which proinflammatory cytokines impair brain function to elicit a depressive episode or promote drug abuse, including a role for astro cytes and microglia. ■ ■CONCLUSIONS This brief narrative illustrates the substantial progress that is being made in understanding the genetic and neurobiological basis of mental illness. It is anticipated that biologic measures will be used increas ingly to more accurately diagnose and subtype psychiatric disorders and that targeted therapeutics will become available for these complex conditions. ■ ■FURTHER READING Fu MJ et al: Rare coding variation provides insight into the genetic architecture and phenotypic context of autism.

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