465e Biology of Psychiatric Disorders

Robert O. Messing, Eric J. Nestler

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. 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 neuropathology 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* (DSM) of the American Psychiatric Association, which is in its fifth edition as of 2013.

There is increasing agreement that the classification of psychiatric illnesses in DSM does not accurately reflect the underlying biology of these disorders. Uncertainties in diagnosis make it extremely difficult to study the neurobiologic and genetic basis of mental illness. This has led to the development of an alternative diagnostic scheme, termed Research Domain Criteria (RDoCs), which classifies mental illness on the basis of core abnormalities—e.g., psychosis (loss of reality) or anhedonia (decreased ability to experience pleasure), which are common symptoms of several illnesses—with the idea that such classifications will assist in defining the biologic basis of at least 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 the inherent limitations of animal models for disorders defined largely by behavioral abnormalities (e.g., hallucinations, delusions, guilt, suicidality) that are inaccessible in animals.

Despite these limitations, the past decade has seen significant advances. Neuroimaging methods are beginning to provide evidence of brain pathology, genome-wide association studies and high-throughput sequencing are at last revealing genes that confer risk for severe forms of mental illness, and investigations using better validated animal models are offering new insight into the molecular, cellular, and circuit mechanisms of disease pathogenesis. There is also excitement in the potential utility of neuron-like cells induced in vitro from a patient's peripheral tissues (e.g., fibroblasts) providing novel ways of studying disease pathophysiology and screening for new treatments. There is consequently justified optimism that the field of psychiatry will transition from behaviorally defined syndromes to true biologic disease entities and that such advances will drive the development of improved treatments and eventually cures and preventive measures. This chapter describes several examples of recent discoveries in basic neuroscience 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 molecular clues about the pathogenesis of psychiatric disorders. A wealth of new information has been made possible by recent technological developments that have permitted affordable, large-scale genome-wide association studies and fine-scale sequencing. As an example, significant progress has been made in the genetics of autism spectrum disorders (ASDs), which are a heterogeneous group of neurodevelopmental diseases that share clinical features of impaired reciprocal social communication and interaction and restricted, repetitive patterns of behavior. ASDs are highly heritable; concordance rates in monozygotic twins (~60–90%) are roughly 10-fold higher than in dizygotic twins and siblings, whereas first-degree relatives show about 50-fold increased risk compared with the general population. ASDs are also genetically heterogeneous. More than 100 known mutations account for up to 20% of cases, although none individually accounts for more than 1% (Table 465e-1). It appears that most cases result from complex genetic mechanisms, including inheritance of multiple genetic risk variants and epigenetic modifications. For example, up to 10% of patients with autism have large (>500 kb) de novo copy number variations scattered across the genome, suggesting that hundreds of different genes can influence autism risk.

Amid this genetic heterogeneity, however, some common themes have emerged that inform pathogenesis of ASDs. For instance, many identified mutations are in genes that encode proteins involved in synaptic function and early transcriptional regulation (Table 465e-1) and have a clear relationship to activity-dependent neural responses that can affect the development of neural systems underlying cognition and social behaviors. Mutations in these genes may be detrimental by altering the balance of excitatory versus inhibitory synaptic signaling in local and extended circuits and by altering mechanisms that control brain growth. Some mutations affect genes (e.g., *PTEN*, *TSC1,* and *TSC2*) that negatively regulate signaling from several types of extracellular stimuli, including those transduced by receptor tyrosine kinases. Their dysregulation can alter neuronal growth as well as synaptic development and function.

With further understanding of pathogenesis and the definition of specific ASD subtypes, there is reason to believe that effective therapies will be identified. Work in mouse models has already demonstrated that some autism-like behaviors can be reversed, even in fully developed adult animals, by modifying the underlying pathology; these results encourage hope for many affected individuals. Treatments that target excitation-inhibition imbalance or altered mRNA translation appear to offer early promise. For example, the genes *TSC1*, *TSC2*, and *PTEN* are negative regulators of signaling through the target of rapamycin complex 1 (TORC1), which regulates protein synthesis. Rapamycin, a selective inhibitor of TORC1, can reverse several behavioral and synaptic defects in mice carrying null mutations in these genes. Another example is fragile X syndrome, which is the leading cause of inherited autism and mental disability and is due to mutations in *FMR1* that result in loss of the encoded fragile X mental retardation protein (FMRP). FMRP is a polyribosome-associated mRNA-binding protein that represses the translation of a subset (~5%) of all mRNAs, several of which encode proteins that comprise the postsynaptic density, including the metabotropic glutamate receptor 5 (mGluR5). Treatment of *Fmr1* knockout mice with mGluR5 antagonists reduces several behavioral and morphologic abnormalities in these mice; these promising preclinical results have led to ongoing trials of mGluR5 antagonists in humans with fragile X syndrome.

The ability to catalog common genetic variants and assay them on array-based platforms and, more recently, to carry out whole-exome sequencing has allowed investigators to collect sample sizes sufficient to detect genetic risk loci for schizophrenia with genome-wide significance. Several of the 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. As in ASDs, copy number variants, single-nucleotide polymorphisms, and small insertions and deletions are common in schizophrenia. Genes that promote risk for drug addiction have also begun to emerge from large family and population studies. The best-established susceptibility loci are regions on chromosomes 4 and 5 containing $GABA_A$ receptor gene clusters linked to alcoholism and the *CHRNA5-A3-B4* nicotinic acetylcholine receptor gene cluster on chromosome 15 associated with nicotine and alcohol addiction.

A recurrent theme that has emerged from genetic studies of psychiatric disorders is pleiotropy, namely, that many genes are associated