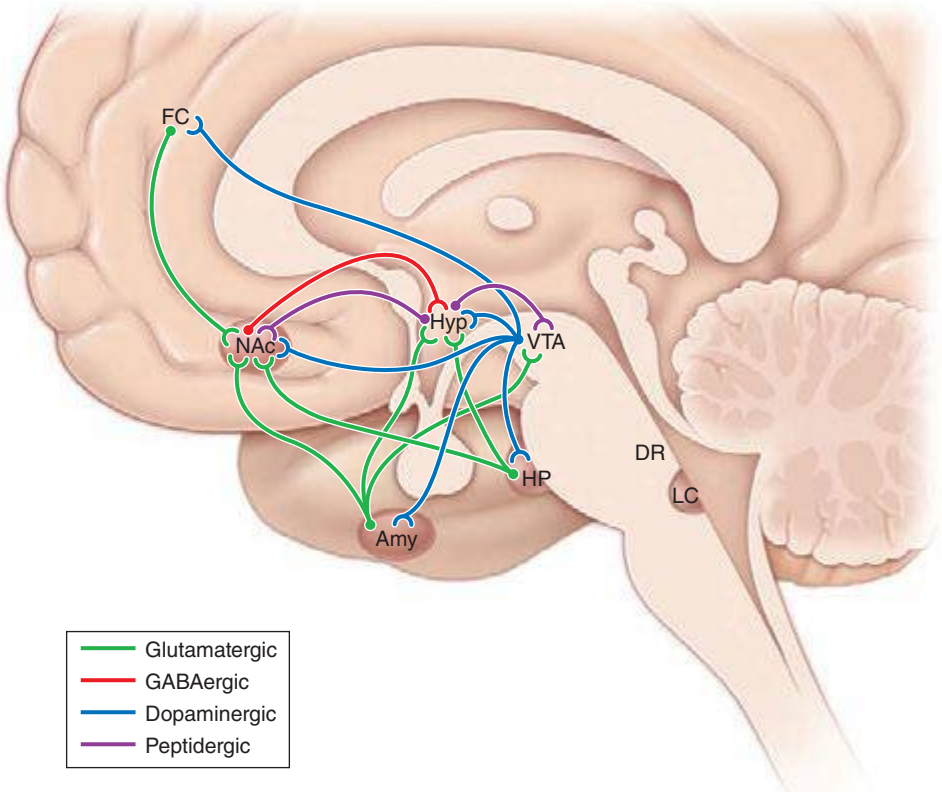


**FIGURE 465e-2 Neural circuitry of depression and addiction.** The figure shows a simplified summary of a series of limbic circuits in brain that regulate mood and motivation and are implicated in depression and addiction. Shown in the figure are the hippocampus (HP) and amygdala (Amy) in the temporal 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.

system and reduction of cortical and subcortical gray matter in frontal and temporal lobes and in the limbic system. The reduction in cortical thickness 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 consistently show reduced expression of the gene encoding the enzyme glutamic acid decarboxylase 1 (*GAD1*), which synthesizes γ-aminobutyric acid (GABA), the principal inhibitory neurotransmitter in the brain. Neuregulin 1 (*NRG1*), a member of the epidermal growth factor (EGF) family of growth factors, and its receptor *ERBB4*, have been implicated in schizophrenia, and they serve important roles in the maturation of GABAergic interneurons in cerebral cortex; loss of *NRG1-ERBB4* in mice leads to a reduced neuropil, thus phenocopying a pathologic finding in schizophrenia. These findings are consistent with one working hypothesis of schizophrenia as a developmental neurodegenerative disorder due in part to loss of cortical interneurons in frontal and temporal lobes.

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 by repeated drug administration (Fig. 465e-2). Midbrain 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 stimuli. These neurons thereby transmit crucial survival signals to the rest of the limbic brain to promote reward-related behavior, including motor responses to seek and obtain the rewards (nucleus accumbens), memories of reward-related cues (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 neurotransmitter transporters (Table 465e-2). 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 nucleus accumbens 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 pathologic adaptations have been described. First, drugs produce tolerance and dependence in reward 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 prolonged 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 anterior 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 inflammatory mechanisms in a subset of depressed patients. These individuals display elevated blood levels of interleukin 6 (IL-6), tumor necrosis factor α (TNF-α), and other cytokines. Moreover, rodents exposed to chronic stress exhibit similar increases in peripheral cytokines, and peripheral or central delivery of those cytokines 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 cytokine action.

Recent evidence has also linked proinflammatory signaling in the brain to addiction, particularly to alcohol. Human alcoholism is associated with impaired innate immunity, increases in circulating proinflammatory cytokines, and an increase in brain levels of the cytokine monocyte chemotactic protein-1 (MCP-1, also referred to as CCL2). Many of these cytokines are produced by astrocytes and microglia, and by neurons under certain pathologic conditions, where they play important roles in modifying neuronal function and plasticity. For example MCP-1 modulates the release of certain neurotransmitters and, when administered into the VTA, increases neuronal excitability, promotes dopamine release, and increases locomotor activity. Recent gene expression array studies of alcohol drinking in mice have