

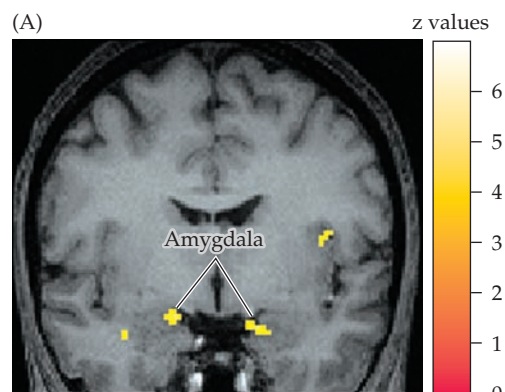
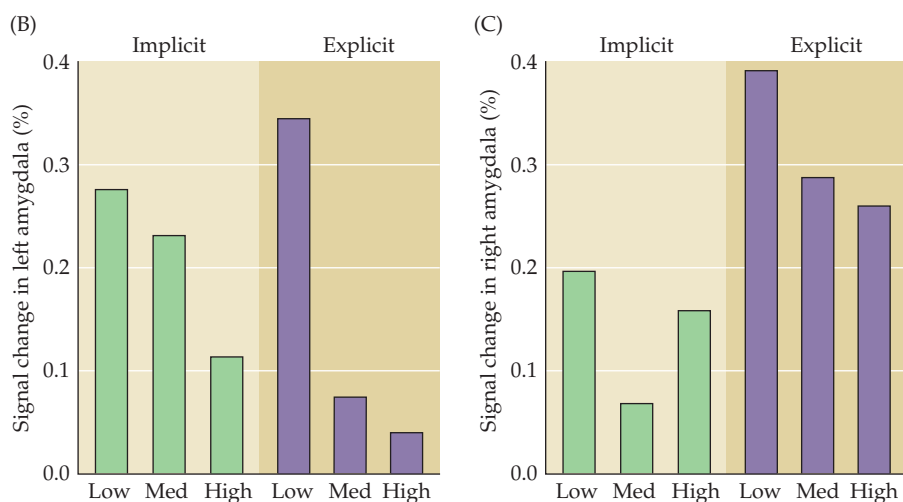


FIGURE 31.9 Activation of the amygdala during judgments of trustworthiness. (A) Functional MRI shows increased neural activation bilaterally in the amygdala when normal individuals appraise the trustworthiness of human faces; activity is also increased in the right insular cortex. (B,C) The degree of activation is greatest when individuals evaluate faces that are considered untrustworthy (low, med, and high indicate ratings of trustworthiness; low = untrustworthy). The same effect was observed when individuals were instructed to evaluate the trustworthiness of the faces (explicit condition) or whether the faces were those of high school or university students (implicit condition). (After Winston et al., 2002.)



responsible for rational thinking. These same neural networks are engaged by sensory stimuli (e.g., facial expressions) that convey important cues pertinent to appraising social circumstances and conventions. Thus, when judging the trustworthiness of human faces—a task of considerable importance for successful interpersonal relations—neural activity in the amygdala is specifically increased, especially when the face in question is deemed untrustworthy (Figure 31.9). It is not surprising, then, that individuals with bilateral damage to the amygdala differ from controls in their appraisals of trustworthiness; indeed, individuals with such impairments often show inappropriately friendly behavior toward strangers in real-life social situations. Such evidence adds further weight to the idea that emotional processing is crucial for competent performance in a wide variety of complex brain functions.

Emotion and Addiction

Understanding the neurobiological basis of emotion and the contributions of affective neural processing to higher brain functions remains an important goal of neuroscience. The urgency of achieving this goal is highlighted by the

pervasiveness and impact of drug abuse and addiction, behaviors that reflect the vulnerability of emotional neural circuits when exposed to drugs that alter their normally adaptive operations in goal-directed behavior. Under physiological conditions, emotional processing in the limbic system can signal the presence of or prospect for reward and punishment, as well as promote the activation of motor programs aimed at procuring beneficial rewards and avoiding punishment. With this in mind, it is not surprising that most known drugs of abuse—including heroin and other opiates, cocaine, alcohol, marijuana, nicotine, amphetamines, and their synthetic analogs—act on elements of limbic circuitry (see Figure 31.11). What may be surprising is that such diverse

natural and synthetic compounds do so by altering the neuromodulatory influence of **dopamine** on the processing of reinforcement signals in the ventral divisions of the basal ganglia, which in turn leads to the consolidation of addictive behavior in limbic circuitry.

Recall from Chapter 18 that the dorsal divisions of the basal ganglia (dorsal caudate, putamen, and globus pallidus) are instrumental in gating the activation of thalamocortical circuits that initiate volitional movement. Also mentioned briefly in Chapter 18 is the existence of other, parallel processing streams that similarly gate the activation of non-motor programs, including those that pertain to cognition and affective processing in limbic circuits (see Clinical Applications). The organization of these non-motor processing streams is fundamentally comparable to the “direct pathway” for volitional movement: There are major excitatory inputs from cortex to striatum, neuromodulatory projections from midbrain dopaminergic neurons to striatum, internuclear connections from striatum to pallidum, and output projections from pallidum to thalamus. What distinguishes the “limbic loop” from the “motor loop” discussed in Chapter 18 is the source and nature of the cortical input, the relevant divisions of striatum and pallidum that

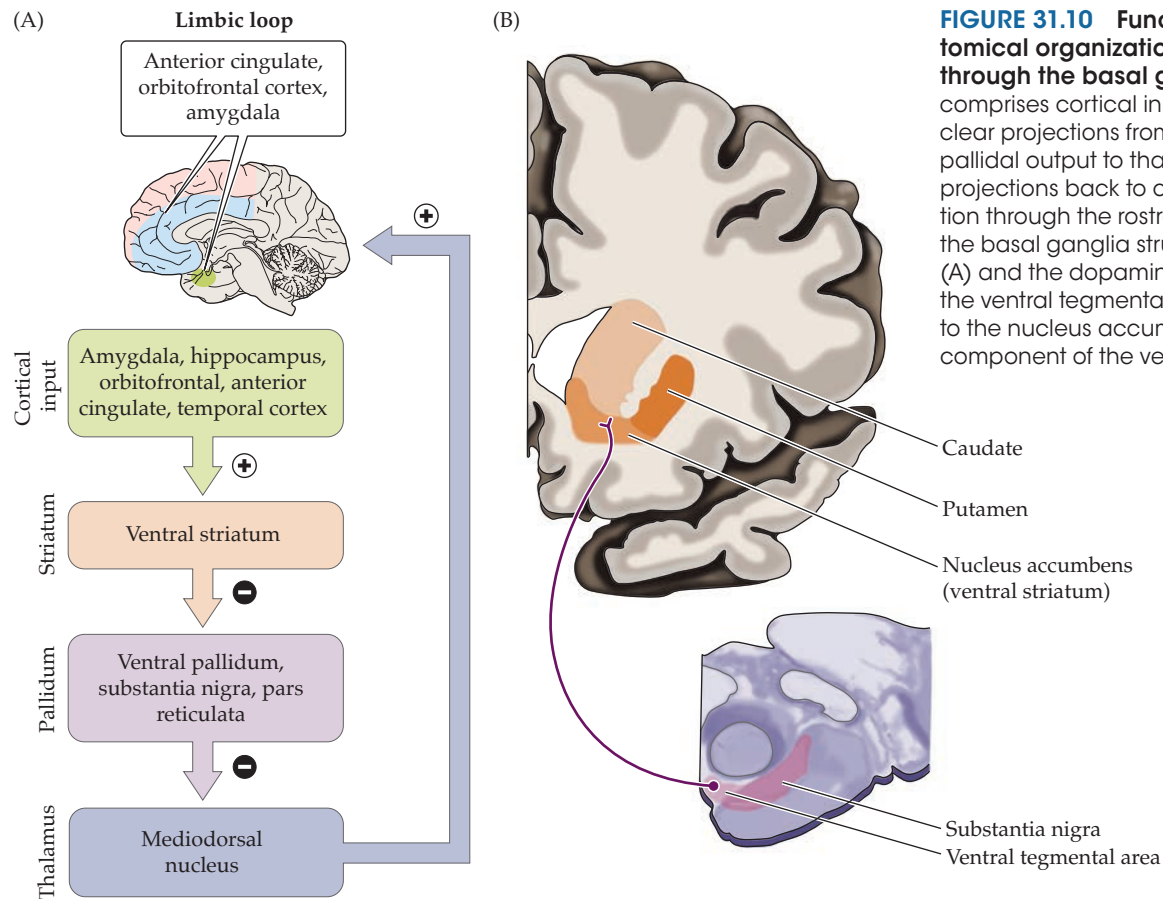


FIGURE 31.10 Functional and anatomical organization of the limbic loop through the basal ganglia. (A) This circuit comprises cortical inputs to striatum, internuclear projections from striatum to pallidum, pallidal output to thalamus, and thalamic projections back to cortex. (B) Coronal section through the rostral forebrain, showing the basal ganglia structures represented in (A) and the dopaminergic projection from the ventral tegmental area of the midbrain to the nucleus accumbens, the principal component of the ventral striatum.

process this input, the source of dopaminergic projections from the midbrain, and the thalamic target of the pallidal output (Figure 31.10).

Central to the organization and function of the limbic loop are inputs from the amygdala, the subiculum (a ventral division of the hippocampal formation), and orbital-medial prefrontal cortex that convey signals relevant to emotional reinforcement to ventral divisions of the anterior striatum, the largest component of which is called the *nucleus accumbens*. Like the caudate and putamen, the nucleus accumbens contains medium spiny neurons that integrate excitatory telencephalic inputs under the modulatory influence of dopamine. However, unlike the larger dorsal division of the striatum, the nucleus accumbens receives its dopaminergic projections from a collection of neurons that lies just dorsal and medial to the substantia nigra, in a region of the midbrain called the **ventral tegmental area (VTA)**. The nucleus accumbens and the ventral tegmental area are primary sites where drugs of abuse interact with the processing of neural signals related to emotional reinforcement; they do so by prolonging the action of dopamine in the nucleus accumbens or by potentiating the activation of neurons in the ventral tegmental area and nucleus accumbens (Figure 31.11).

Under normal conditions, these dopaminergic neurons are only phasically active; when they do fire a barrage of action potentials, however, dopamine is released in the nucleus accumbens, and medium spiny neurons are much more responsive to coincident excitatory input from telencephalic structures such as the amygdala and orbital-medial prefrontal cortex. These activated striatal neurons in turn project to and inhibit pallidal neurons in a region just below the globus pallidus called the **ventral pallidum**, as well as in the pallidal division of the substantia nigra (pars reticulata). The suppression of tonic activity in the pallidum then disinhibits the thalamic target of the limbic loop, which is the mediodorsal nucleus, the thalamic nucleus that innervates cortical divisions of the limbic forebrain (see Figure 31.5). Activation of these cortical regions via the mediodorsal nucleus is reinforced by direct cortical projections of dopaminergic neurons in the ventral tegmental area and glutamatergic projections from the basolateral group of nuclei in the amygdala that target these same regions (see Box 31B).

Activation of these complex limbic circuits is believed to cause the rewarding effects of natural agents and experiences such as food, water, sex, and more complex social rewards. However, the phasic release of dopamine is also

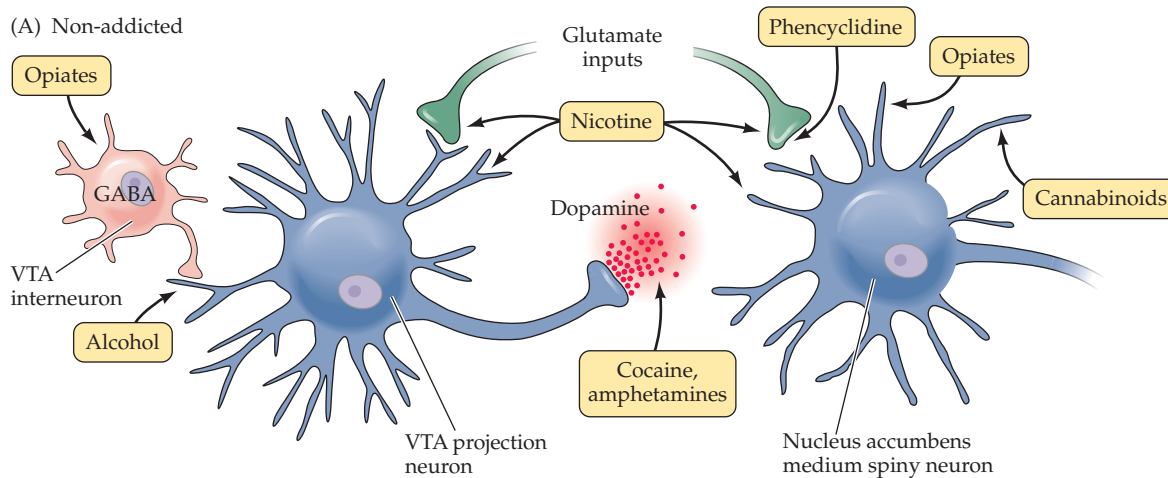
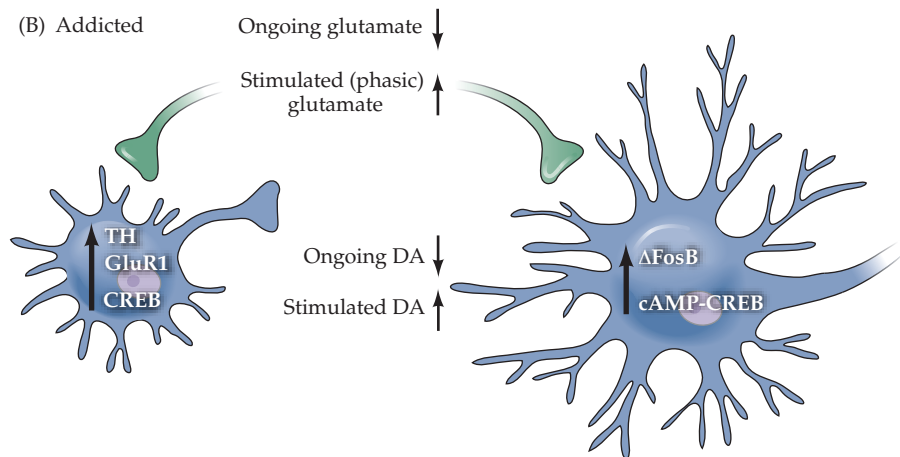


FIGURE 31.11 Schematic representation of how drugs of abuse affect dopamine projections from the ventral tegmental area to the nucleus accumbens. (A) Most drugs of abuse potentiate the activity of dopamine by interacting directly with dopamine synapses in the nucleus accumbens, or indirectly by modulating the activity of neurons in the ventral tegmental area (VTA). Other drugs may act directly on accumbens neurons to increase their responsiveness to telencephalic input. (B) Drug addiction is associated with cellular and molecular adaptations of this circuit (see text for details). The net effect of addiction is a chronic decrease in basal activity and an increase in the intensity of phasic activity in the presence of abusive drugs. (After Nestler, 2005.)

subject to experience-dependent plasticity. During associative learning, for example, the activity of ventral tegmental neurons comes to signal the presence of the reward-predicting stimulus with diminished responsiveness to the presence of the primary reward itself (Figure 31.12A,B). Interestingly, if a stimulus is not followed by delivery of the predicted reward (e.g., because of an inappropriate behavioral response in an instrumental learning paradigm), ventral tegmental neurons are suppressed at precisely the same time that the neuronal response would have signaled the presence of a reward (Figure 31.12C). These observations suggest that the phasic release of dopamine signals the presence of reward relative to its prediction, rather than the unconditional presence of reward. The integration of such signals in the nucleus accumbens, orbital-medial prefrontal cortex, and amygdala leads to the activation of behaviors directed at obtaining and consolidating the benefits of the rewarding event.

Unfortunately, the plastic potential of these limbic circuits can be co-opted by chronic exposure to drugs of abuse, leading to cellular and molecular changes that



promote abnormal regulation (see Figure 31.11B). In the ventral tegmental area of addicted individuals, the activity of the dopamine-synthesizing enzyme tyrosine hydroxylase increases, as does the ability of VTA neurons to respond to excitatory inputs. The latter effect is secondary to increases in the activity of the transcription factor CREB (see Chapter 7) and the upregulation of GluR1, an important subunit of AMPA receptors for glutamate (see Chapter 6). In the nucleus accumbens, addiction is characterized by increases in another transcription factor, Δ FosB, in addition to induction of CREB with chronic exposure to at least some classes of addictive drugs. Activation of these molecular signaling pathways leads to a generalized reduction in the responsiveness of accumbens neurons to glutamate released by telencephalic inputs by regulation of different AMPA receptor subunits and/or changes in postsynaptic density proteins that alter the dynamics of receptor trafficking. However, during the phasic release of dopamine, the responsiveness of these striatal neurons is intensified, mediated in part by a shift in the expression of D1 and D2 classes of dopamine receptors and a coordinated upregulation of cAMP-PKA signaling pathways.

FIGURE 31.12 Changes in the activity of ventral tegmental area dopamine neurons in an awake monkey during stimulus–reward learning. In each panel, poststimulus time histograms (blue, above) and data plots (below) report summed activity across trials and individual spikes within trials, respectively. (A) Before learning, the presentation of an unexpected juice reward evokes a burst of activity (darker-shaded zone). (B) After learning trials, the neurons respond to the presentation of visual or auditory cues (conditioned stimuli), but not to the reward itself. (C) In trials when a reward was predicted but never delivered, dopaminergic neurons become suppressed (light-shaded zone) at the time when the reward would have been available. These results show that the ventral tegmental area signals the occurrence of reward relative to its prediction. (After Schultz et al., 1997.)

The cellular and molecular maladaptations of ventral tegmental, striatal, and cortical neurons to chronic exposure of abusive drugs remain poorly understood. Nevertheless, the net effect of these and other changes is that addiction dampens the response of this emotional reinforcement circuitry to less potent natural rewards, while intensifying the response to addictive drugs. At a systems level, these changes are likely reflected in the “hypofrontality”—reduced baseline activity in orbital-medial prefrontal cortex—commonly seen in addicts. Taken together, these alterations in neural processing could account for the waning influence of adaptive emotional signals in the operation of decision-making faculties as drug-seeking and drug-taking behaviors become habitual and eventually compulsive.

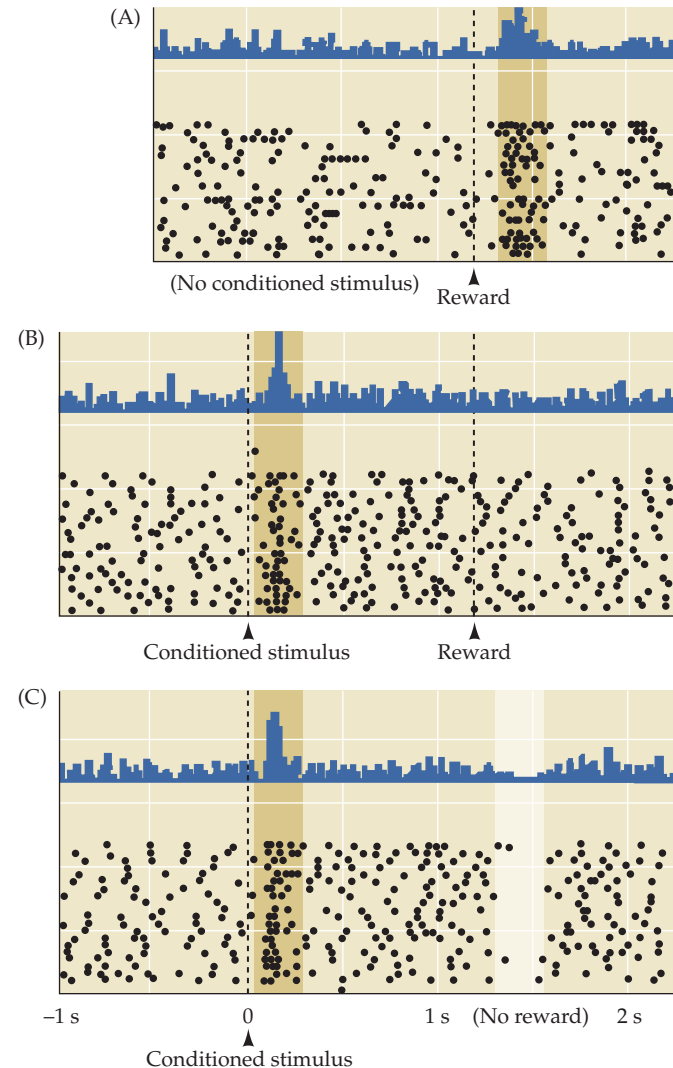
Posttraumatic Stress Disorder

The following description gives some sense of what **post-traumatic stress disorder (PTSD)** entails:

For months after the attack, I couldn't close my eyes without envisioning the face of my attacker. I suffered horrific flashbacks and nightmares. For four years after the attack I was unable to sleep alone in my house. I obsessively checked windows, doors, and locks ... I lost all ability to concentrate or even complete simple tasks. Normally social, I stopped trying to make friends or get involved in my community.

P. K. Philips, www.adaa.org

PTSD typically emerges following exposure to a traumatic stressor, such as rape, robbery, or combat, that elicits feelings of fear, horror, or helplessness to forestall bodily injury or threat of death. Community-based studies in the United States estimate that 50% of people will have a traumatic experience during their lifetime, and an estimated 5% of men and 9% of women will develop PTSD as a result. Symptoms include persistently re-experiencing the traumatic event,



avoiding reminders of the event, numbed responsiveness, and heightened arousal. PTSD is often accompanied by depression and substance abuse, each of which complicates treatment and recovery. While cognitive–behavioral therapies and antianxiety and antidepressant medications often help, there is no cure for this debilitating condition that can persist for decades.

Some of the structural abnormalities associated with PTSD are reductions in hippocampal and amygdala volume and altered dendritic remodeling in these structures (Figure 31.13A). Hippocampal atrophy has been linked to declarative memory deficits in some patients with PTSD, and functional impairments in the amygdala are associated with hyperarousal symptoms and exaggerated responses to threats in others. Problems with fear reduction are further exacerbated by hyporesponsiveness in the rostral anterior cingulate and ventromedial prefrontal cortex, which provide inhibitory control over neurons in the amygdala (Figure 31.13B).