Functional Imaging Has Identified Neural Correlates of Feelings

Conscious experiences of an emotion are generally referred to as feelings. Evidence for the neural correlates of feelings comes primarily from functional imaging studies of humans and from neuropsychological testing of patients with specific brain lesions. A main challenge for these studies is in dissociating the conscious experience of the emotion from other aspects of the emotion, such as the elicitation of physiological responses, since these tend to occur contemporaneously. Another challenge is how to connect such studies with studies of emotion in animals, where we have no agreed-upon dependent measures to assay what they consciously experience.

One early functional imaging study used positron emission tomography to test the idea that feelings are correlated with activity in those cortical and subcortical somatosensory regions that specifically receive inputs related to the internal environment—the viscera, endocrine glands, and musculoskeletal system. Healthy subjects were asked to recall personal episodes and to attempt to reexperience as closely as possible the emotions that accompanied those events. Activity changed in many regions known to represent and regulate body states, such as the insular cortex, secondary somatosensory cortex (S-II), cingulate cortex, hypothalamus, and upper brain stem. These results support the idea that at least a part of the neural substrate for feelings involves brain regions that regulate and represent bodily states, a finding that bears some resemblance to the hypothesis of William James mentioned earlier, that feelings are based on an awareness of bodily reactions.

The importance of both cortical and subcortical structures in processing feelings is also borne out by more recent fMRI studies. One such study examined the feeling of fear induced by anticipation of electrical shock (Figure 42–8). In this study, subjects lay in the scanner while they saw a game on a video screen in which a virtual predator (a red dot) gets closer to the subject. Once the predator caught them, they could receive a painful electric shock to the hand. The anxiety produced when the predator was some distance away was associated with activation of the medial prefrontal cortex; as the predator closed in, the periaqueductal gray became activated, and this was correlated with reports by the subjects of a feeling of dread. This finding supports a role for the medial prefrontal cortex in planning and anticipation related to a distant threat and a role for the periaqueductal gray in mounting the defensive responses required for coping with an immediate threat.

Another brain region of interest in relation to feelings is the subgenual sector of the anterior cingulate cortex (Brodmann's area 25), which has been found in neuroimaging studies to be activated when subjects are experiencing sadness. This region is of special interest because it is also differentially activated in patients with bipolar depression, and it appears thinned in structural MRI scans of patients with chronic depression. Direct electrical stimulation of this brain region (deep brain stimulation) can dramatically improve the mood of some patients with severe depression.

Emotion Is Related to Homeostasis

While it seems clear that no brain region is specialized for any specific emotion, it is even doubtful that there are any brain regions specialized for emotions in general. It may be that all brain regions involved in emotions also carry out other functions. In fact, those nonemotional functions may give us clues about how emotions evolved and, indeed, may be the basic building blocks through which emotion states are assembled.

For example, sectors of the human insular cortex that are activated during recall of feelings are also activated during the conscious sensation of pain and temperature. The insular cortex receives homeostatic information (about temperature and pain, changes in blood pH, carbon dioxide, and oxygen) through pathways that originate in peripheral nerve fibers. These afferent fibers include, for example, the C and Aδ fibers that form synapses with neurons in lamina I of the posterior horn of the spinal cord or the pars caudalis of the trigeminal nerve nucleus in the brain stem. The pathways from lamina I and the trigeminal nucleus project to brain stem nuclei (nucleus of the solitary tract and parabrachial nucleus) and from there to the thalamus and on to the insular cortex. The identification of this functional system is further support for the idea that signals in the afferent somatosensory pathways play a role in the processing of feelings.

Moreover, in patients with pure autonomic failure, a disease in which visceral afferent information is severely compromised, functional imaging studies reveal a blunting of emotional processes *and* attenuation of activity in the somatosensory areas that contribute to feelings. Like other feelings, social feelings engage the insular cortices and the primary and secondary somatosensory cortices (S-I and S-II), as has been found in functional neuroimaging experiments evaluating empathy for pain and, separately, admiration and compassion.

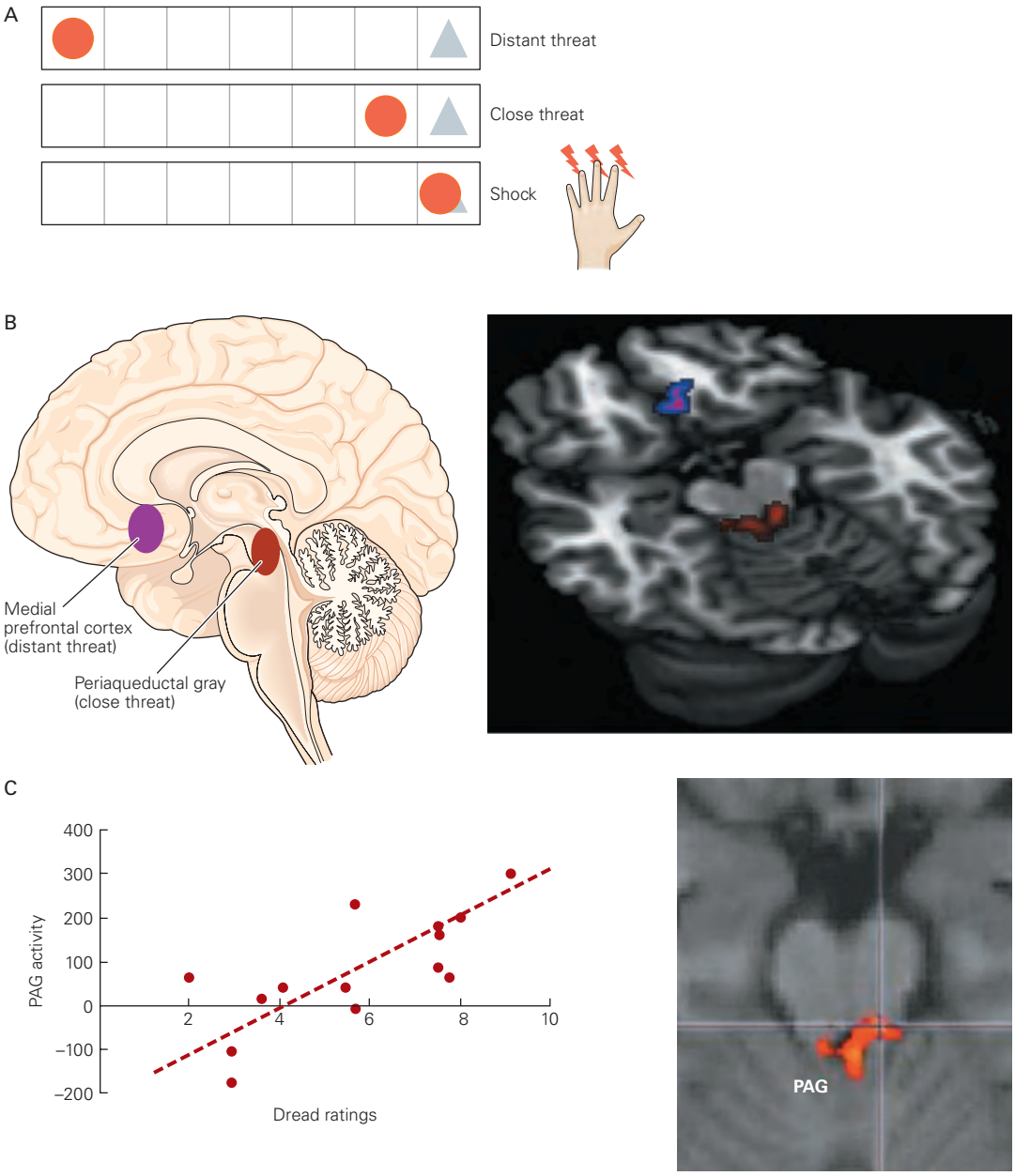

Figure 42–8 Both cortical and subcortical regions come into play during emotion states. Results are from a functional magnetic resonance imaging study in which a subject lies in the scanner while watching a virtual predator (**red dot**) move around on the screen and get closer to a subject (**blue triangle**, representing the actual research participant). (Reproduced, with permission, from Mobbs et al. 2007. Copyright © 2007 AAAS.)

A. Once the predator catches up to the subject, there is a chance that a real and painful electric shock will be delivered to the hand.

B. When the predator gets closer to the subject, activity in the prefrontal cortex and periaqueductal gray matter increases. Notably, this pattern of neural activation shifts such that a distant predator elicits greater activity in the medial prefrontal cortex, whereas a predator close by elicits more activity in the periaqueductal gray.

C. Activation of the periaqueductal gray (**PAG**) is correlated with the subjective sense of dread measured by ratings that subjects gave while in the scanner.

Using these data as support, some influential modern theories build on William James's original hypothesis and propose that the feeling of all emotions is grounded in the brain's representation of bodily homeostasis. As in the case of the amygdala's role in both positive and negative emotions, the insula's role in processing both interoceptive and emotional information is still compatible with the possibility that these processes are distinct. That is, different populations of neurons within these structures may be involved in processing different emotions. Therefore, fMRI may not provide the level of resolution needed to elucidate distinct yet anatomically intermingled neuronal populations, and cellular techniques in animal models may be required.

Although most neuroscience research thus far has focused on negatively valenced emotions, the neural circuitry for positively valenced emotions is being elucidated in studies in both humans and animals. These studies consistently implicate the medial prefrontal cortex in computing the subjective value of rewards, as well as the nucleus accumbens and other nuclei of the basal ganglia in processing the hedonic component (or pleasure) of positive emotions. A growing number of functional imaging studies in humans—especially in the fields of neuroeconomics and social neuroscience—links the role of these structures in emotion processing to their role in value-based decision making and social behavior.

Highlights

1. In the overall physiology of regulating the body and behavior of organisms, emotion states carry out functions intermediate to those of the simpler processes of reflexes and homeostatic regulation, on the one hand, and those of cognitive processes and deliberate behavior on the other. Emotions are more flexible, context-dependent, and controlled than are simple reflexes, but less flexible, context-dependent, and controlled than deliberate behavior. Emotions evolved to produce behavior in response to recurring environmental and internal challenges that are too varied for reflexes, but sufficiently stereotyped that they do not require the full flexibility of cognition.
2. Emotion states need to be carefully distinguished from the conscious experience of emotion (feelings) and also from the concepts and words that we have in everyday language to describe emotions. For example, a hissing cat's behavior is caused by an emotion state, but whether the cat consciously feels afraid is unclear. The cat probably has no concept, and certainly no words, with which to think about the emotion. Human subjects who recognize fear while observing a facial expression are attributing fear to another person and are thinking about a particular emotion, but are not themselves necessarily in a state of fear or experiencing fear. It is a major challenge in designing experiments, especially in humans, to independently control and manipulate these different components of emotion.
3. Emotions coordinate integrated changes in many organismal parameters, including effects on somatic behavior, autonomic and endocrine responses, and cognition. We do not yet understand how this coordination arises, although it is probably achieved through a combination of hierarchical control (through brain regions that function as "command centers" of sorts) and distributed dynamics. Understanding how this is accomplished in biological organisms will also inform how we might engineer robots that exhibit emotional behaviors in the future.
4. Different specific emotions can be thought of categorically (eg, happiness, fear, anger) or dimensionally (in terms of arousal and valence or other dimensional frameworks). It is likely that many of the categories for which we have words in a particular language (like the examples just given) will need to be revised once we have a more scientific understanding. New analytic methods applied to data acquired using fMRI, including methods that take into account the spatial and temporal patterns of brain activity and utilize powerful machine-learning algorithms, may provide new insights into how the brain mediates a broad range of emotions.
5. In humans, emotions can be regulated by several mechanisms. Thus, we have some control over how we feel and some control over how we express emotional behaviors, for instance, through facial expressions. Nonhuman animals do not have this same level of control, and so their emotional behaviors will generally be honest signals of their emotion state, whereas humans often engage in strategic deception.
6. Fear is probably the emotion whose neurobiology is best understood. It depends on the amygdala, in both animals and humans. However, some data suggest that certain types of fear, such as the panic of suffocating induced by inhaling carbon dioxide, are independent of the amygdala. Indeed, we now know that the amygdala is part of a distributed

brain system, and therefore, many other brain regions also participate in processing fear. Increasingly, modern studies use sophisticated genetic and cellular techniques to image and to causally manipulate brain function, allowing us to understand the necessary and sufficient roles of multiple brain structures in mediating different emotional behaviors.

7. The ventral and medial prefrontal cortex is intimately involved in emotion and connected with the amygdala. Social emotions, reward representations, and emotion regulation and extinction all involve specific sectors of prefrontal cortex. This region of the brain, together with the insula, may also be the most important for our conscious experience of emotions, an aspect of emotion that remains the most challenging to study.

C. Daniel Salzman
Ralph Adolphs

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43

Motivation, Reward, and Addictive States

Motivational States Influence Goal-Directed Behavior

One day a cheetah, taking refuge from the mid-day sun in the shade of a tree, views a distant antelope with apparent indifference. Later in the afternoon, the sighting of the antelope provokes immediate orienting and stalking behavior. The stimulus is the same, but the behavioral responses are very different. What has changed is the motivational state of the animal.

Motivational states influence attentiveness, goal selection, investment of effort in the pursuit of goals, and responsiveness to stimuli. They thus drive approach, avoidance, and action selection. This chapter focuses on the neurobiological basis of motivational states related to rewards and the manner in which reward-related brain circuits are implicated in mechanisms underlying drug addiction.

Both Internal and External Stimuli Contribute to Motivational States

Motivational states reflect one's desires, and desires can be influenced by physiological status as well as by stimuli that predict future rewarding and aversive events. Motivational states thus depend on both internal and external variables. Internal variables include physiological signals concerning hunger or thirst, as well as variables related to the circadian clock. For example, the frequency and duration of foraging vary with the time of day, the time since an animal has last eaten, and whether, if female, she is lactating.

Other internal variables are related to cognitive processes. In the game of blackjack, for instance, being dealt the same card in different hands can cause a player to go bust or make 21, leading to very different emotional responses and adjustments in subsequent decision making and action selection. The differential meaning of the same stimulus (a particular card) is made possible by the cognitive understanding of the rules of the game of blackjack. The cognitive understanding of

a rule is an internal variable. Similarly, different social situations often elicit distinct behavioral responses to the same stimulus, such as whether one chugs wine at a college party or sips it at a formal dinner.

External variables also influence motivational states. These variables include *rewarding incentive stimuli.* For example, when a dehydrated cheetah comes across a watering hole during a search for antelopes, the sight of the water may serve as an incentive stimulus, tipping the balance between hunger and thirst and driving the animal to interrupt its quest for food to drink. However, an internal variable—the state of the cheetah's hydration—can also lead to a different reward value being assigned to the same sensory stimulus, the watering hole. Even innately rewarding stimuli, such as a sweet tastant that normally elicits pleasure, can in some circumstances become unpleasurable. Chocolate cake may be innately rewarding to chocolate lovers, but satiation to the chocolate—which involves modulation of an internal variable—can decrease the reward value of this stimulus and thereby affect motivational state.

Rewards Can Meet Both Regulatory and Nonregulatory Needs on Short and Long Timescales

Feeding, drinking, and thermoregulatory behaviors and their underlying motivational states typically arise in response to (or anticipation of) a physiological imbalance. In these cases, actions acquire rewards in a relatively short timescale. In contrast, some motivational states serve biological imperatives other than short-term physiological homeostasis. More complex long-term goals, such as finding and sustaining a love partner or achieving an educational or professional goal, require goal-oriented actions on longer timescales. Nonregulatory motivational states may resemble those arising from physiological signals, but motivated behaviors often involve sequences of actions in which not every action is immediately rewarded (except in the sense of making progress toward a longer-term goal).

In general, incentive stimuli, even stimuli that only signal progress toward a longer-term goal, can influence motivational states so that complex behavioral sequences are completed. A simple example of this concept is when a cheetah must stalk, chase, run down, and kill an antelope, and then drag the carcass to a refuge before beginning to feed. Of course, even the complexity of the actions involved in foraging and feeding is far simpler than the steps required of a student motivated to achieve a graduate degree and develop an academic career. Motivational states must be sustained across challenging circumstances in order to achieve such goals.

The Brain's Reward Circuitry Provides a Biological Substrate for Goal Selection

Rewards are objects, stimuli, or activities that have positive value. Rewards can incite an animal to switch from one behavior to another or to resist interruption of ongoing action. For example, a rat that encounters a seed while scouting the environment may cease exploring in order to eat the seed or carry it to a safer place; while nibbling the seed, the rat will resist the efforts of another rat to steal the food from its paws. If seeds are made available only at a particular location and time, the rat will go to that location as the expected moment of reward delivery approaches.

Much contemporary work in neuroscience is directed at elucidating the neural systems that process different types of rewards. These systems must link the initial sensory representation of a reward to different behaviors that respond to physiological needs and environmental challenges and opportunities. Pathologies such as addiction can highjack these reward systems, resulting in maladaptive behavior (discussed in the latter part of this chapter).

Goal-directed behaviors entail the assessment of risks, costs, and benefits. Straying from the herd may offer an antelope better opportunities for foraging but only at the risk of becoming an easier target for a lurking cheetah. Attacking the venturesome antelope offers the cheetah an easier promise of a meal but at the risk that energetic and hydromineral resources will be depleted needlessly if the antelope gets away. Thus, the neural mechanisms responsible for goal selection must weigh the costs and benefits of different behaviors that might attain a specific goal.

In 1954, James Olds and Peter Milner reported their work on the neural pathways responsible for reward-related behaviors. These classic studies employed electrical brain stimulation as a goal. Rats and other vertebrates ranging from goldfish to humans will work for electrical stimulation of certain brain regions. The avidity and persistence of this self-stimulation are remarkable. Rats will cross electrified grids, run uphill while leaping over hurdles, or press a lever for hours on end in order to trigger the electrical stimulation. The phenomenon that leads the animal to work for self-stimulation is called *brain stimulation reward* (Figure 43–1A). Brain stimulation, therefore, elicits a motivational state, a strong drive to perform an action (eg, lever pressing) that will deliver further stimulation.

Although brain stimulation reward is an artificial goal, it mimics some of the properties of natural goal objects. For example, brain stimulation can compete with, summate with, or substitute for other reward-predictive stimuli to induce motivational states that

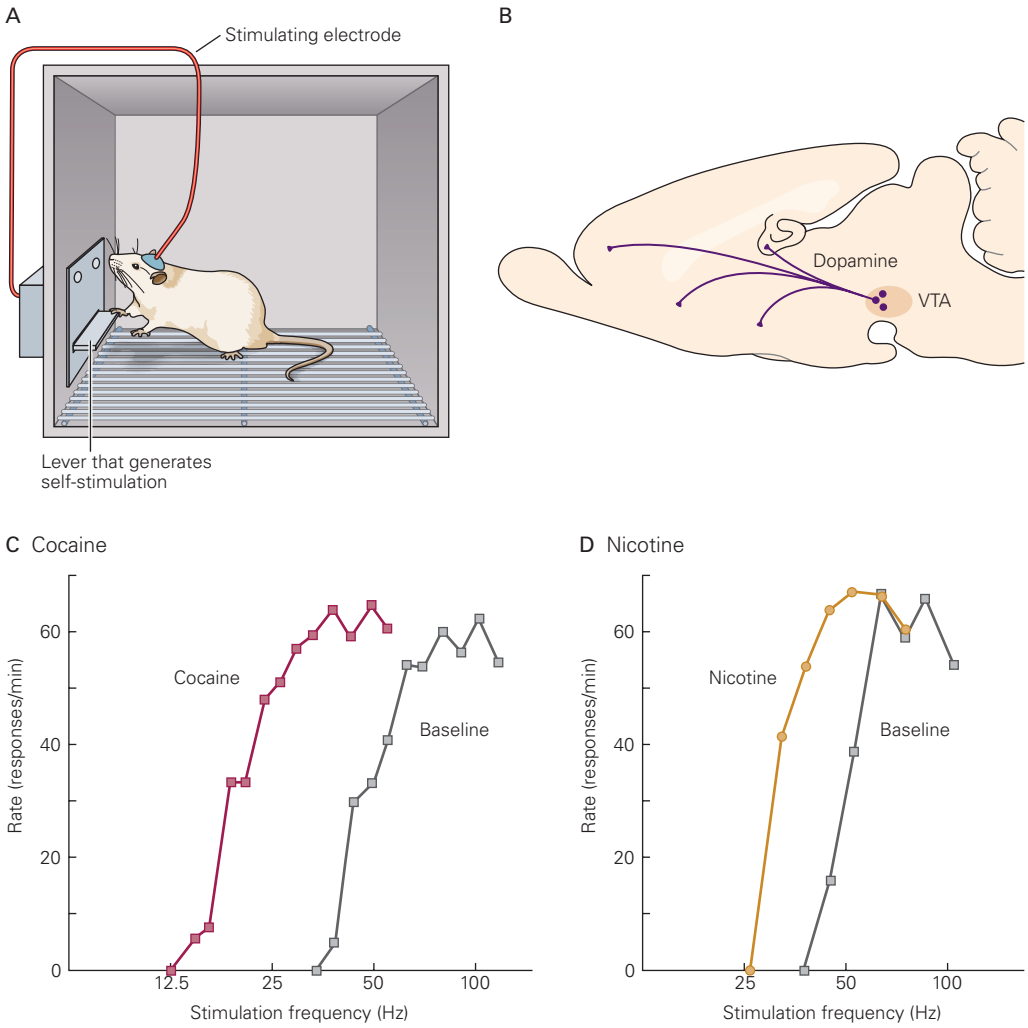

Figure 43–1 Intracranial self-stimulation recruits reward circuitry and dopaminergic neural pathways.

A. Classic testing apparatus for self-stimulation experiments. In this example, an electrode is implanted in a brain region of a rodent. Lever pressing by the rodent triggers electrical stimulation of that brain area.

B. Brain structures that produce self-stimulation behavior typically activate dopaminergic pathways emanating from the ventral tegmental area (**VTA**), among other pathways.

C–D. Cocaine and nicotine affect the rate of electrical self-stimulation. The rate at which the animal presses the stimulation lever increases with increases in the frequency of the self-stimulation current. In the presence of the drugs, animals press the lever at lower stimulation frequencies, indicating that the drugs augment the effects of the electrical stimulation.

drive goal-directed behaviors. The circuitry that mediates brain stimulation reward is broadly distributed. Rewarding effects can be produced by electrical stimulation of sites at all levels of the brain, from the olfactory bulb to the nucleus of the solitary tract.

Particularly effective sites lie along the course of the medial forebrain bundle and along longitudinally oriented fiber bundles coursing near the midline of the brain stem. Stimulation of either of these pathways results in activation of dopaminergic neurons in the ventral tegmental area of the midbrain. These neurons project to several areas of the brain, including the nucleus accumbens (the major component of the ventral striatum), the ventromedial portion of the head of the caudate nucleus (in the dorsal striatum), the basal forebrain, and regions of the prefrontal cortex (Figure 43–1B).

Activation of dopaminergic neurons in the ventral tegmental area plays a crucial role in brain stimulation reward. The effects of this activation are strengthened

by increases in dopaminergic synaptic transmission and weakened by decreases. These dopaminergic neurons are excited by glutamatergic cells in the prefrontal cortex and amygdala as well as from cholinergic cells in the laterodorsal tegmental and pedunculopontine nuclei of the hindbrain, and are inhibited by local GABAergic cells within or just caudal to the ventral tegmental area. Brain stimulation is thought to activate dopaminergic neurons in the ventral tegmental area in part through the activation of these hindbrain cholinergic neurons. Blockade of this cholinergic input reduces the rewarding effects of the electrical stimulation. While most attention has focused on dopamine pathways in mediating brain stimulation reward, it is important to emphasize the involvement of non-dopaminergic pathways as well.

The strength of brain stimulation reward is indicated by the finding that starving rats provided with brief daily access to food will forego eating to press a lever for brain stimulation. The heedless pursuit of an artificial goal to the detriment of a biological need is one of many parallels between self-stimulation and drug abuse. Indeed, drugs of abuse augment the rewarding effects of activation of dopaminergic pathways with brain stimulation (Figure 43–1C,D). Lower frequencies of stimulating currents accompanied by cocaine or nicotine administration—both of which enhance dopaminergic neurotransmission through different mechanisms—produce a rate of lever pressing equivalent to that obtained during self-stimulation at higher stimulating currents in the absence of these drugs. These results indicate that cocaine and nicotine amplify the effects of neuronal activation elicited by microstimulation.

Dopamine May Act as a Learning Signal

An earlier view of the function of dopamine was that it conveyed "hedonic signals" in the brain and that, in humans, it was directly responsible for subjective pleasure. From this point of view, addiction would reflect the habitual choice of short-term pleasure despite a host of long-term life problems that emerge. In fact, however, new research indicates that the hedonic principle cannot easily explain the persistence of drug use by addicted persons as negative consequences mount.

The effects of dopamine have proven to be far more complex than was first thought. Dopamine can be released by aversive as well as by rewarding stimuli, and the short latency component of a dopamine neuron's response may not be related to the rewarding or aversive qualities of a stimulus at all. Moreover, rodents lacking dopamine—rats in which dopamine is depleted by 6-hydroxydopamine and mice genetically engineered so that they cannot produce dopamine—continue to exhibit hedonic responses to sucrose. Dopamine delivery itself is not currently considered to produce hedonic qualities. Instead, the degree to which a particular sensory stimulus is rewarding is thought to be processed by a broad network of brain areas, spanning sensory cortices of different modalities, association cortex, prefrontal cortex (in particular, orbitofrontal regions), and many subcortical areas such as the amygdala, hippocampus, nucleus accumbens, and ventral pallidum.

Many of the brain areas whose activity is modulated by reward anticipation or receipt receive dopaminergic input. What information do dopaminergic neurons transmit to these brain areas? Wolfram Schultz and his colleagues discovered that dopaminergic neurons often have a complex and changing pattern of responses to rewards during learning. In one experiment, Schultz trained monkeys to expect juice at a fixed interval after a visual or auditory cue. Before the monkeys learned the predictive cues, the appearance of the juice was unexpected and produced a transient increase in firing above basal levels by ventral tegmental area dopaminergic neurons. As the monkeys learned that certain cues predict the juice, the timing of the firing changed. The neurons no longer fired in response to presentation of the juice—the reward—but earlier, in response to a predictive visual or auditory cue. If a cue was presented but the reward was withheld, firing paused at the time the reward would have been presented. In contrast, if a reward exceeded expectation or was unexpected, because it appeared without a prior cue, firing was enhanced (Figure 43–2).

These observations suggest that dopamine release in the forebrain serves not as a pleasure signal but as a *prediction error* signal. A burst of dopamine would signify a reward or reward-related stimulus that had not been predicted; pauses would signify that the predicted reward is less than expected or absent. If a reward is just as expected based on environmental cues, dopaminergic neurons would maintain their tonic (baseline) firing rates. Alterations in dopamine release are thus thought to modify future responses to stimuli to maximize the likelihood of obtaining rewards and to minimize fruitless pursuits. For natural rewards, like the sweet juice consumed by the monkeys in Schultz's experiments, once the environmental cues for a reward are learned, dopaminergic neuron firing returns toward baseline levels. Schultz has interpreted this to mean that as long as nothing changes in the environment, there is nothing more to learn and therefore no need to alter behavioral responses.

Experiments using functional magnetic resonance imaging in humans have provided further evidence