Getting the Brain's Attention

Rather than signaling pleasure as previously thought, the neurotransmitter dopamine may be released by brain neurons to highlight significant stimuli

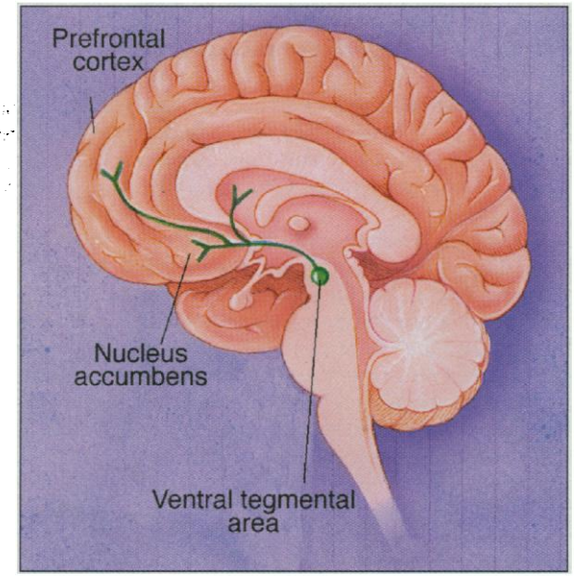
While drug abuse continues to blight society, science is getting a clearer view of the causes and effects of addiction, as this special issue of *Science* shows. The following News stories describe a new view of how the neurotransmitter dopamine may contribute to addiction and how fetal cocaine exposure may affect brain development. And a series of Articles beginning on page 45 covers areas ranging from basic mechanisms of addiction to policies aimed at dealing with addictive drugs.

A bite of moist chocolate cake, a romantic kiss, or a puff of the day's first cigarette will send the hedonist in many of us coming back for more. For 20 years, neuroscientists thought that they understood why people succumb to these cravings, as well as to the more dangerous ones for addictive drugs such as heroin and cocaine. Their satisfaction triggers the release from cells deep inside the brain of the chemical dopamine—a neurotransmitter supposed to act on the brain's reward system to produce feelings of pleasure. But recent evidence suggests a different role for dopamine in producing these behaviors—one much broader and more subtle than previously envisioned.

Dopamine is still thought to play a critical role in motivation and reward, but many researchers no longer believe it acts by directly producing feelings of pleasure or euphoria. Instead, new data indicate that dopamine release within the brain highlights, or draws attention to, certain significant or surprising events. These include not only those the organism finds rewarding, such as consuming a tasty morsel of food or engaging in sexual activity, but also events that predict rewards, and stimuli, like loud noises and flashing lights, that are simply startling. By underscoring such events, say these researchers, the dopamine signal helps the animal learn to recognize them—and in some cases, to repeat them.

Although not everyone agrees with this idea, it is winning some prominent supporters. "These are very exciting years, because the notion of what dopamine is doing is rapidly changing," says Kent Berridge, a psychologist at the University of Michigan, Ann Arbor, whose work in rats suggests dopamine is not a pleasure juice. Indeed, even psychologist Roy Wise of Concordia University in Montreal, the primary architect of the pleasure theory, has altered his position. "I no longer believe that the amount of pleasure felt is proportional to the amount of dopamine floating around in the brain," he says. Facilitating learning may be one of its functions, he agrees.

This new view of dopamine as an aid to learning rather than a pleasure mediator may help explain why many addictive drugs, which unleash massive surges of the neurotransmitter in the brain, can drive continued use without producing pleasure—as when cocaine addicts continue to take hits long after the euphoric effects of the drug have worn off or when smokers smoke after cigarettes become distasteful. It may also provide a better understanding of schizophrenia and attention-deficit disorder (ADD), both of which have been linked to abnormal dopamine transmission. People with ADD and some schizophrenics become so distracted by sensory events that most people's brains filter out—a passing car, say, or a bouncing ball—that they can't work or study. The pleasure hypothesis can't explain these symptoms, but the idea that dopamine works to heighten attention to external events might.



SOCIETY FOR NEUROSCIENCE/LYDIA KIBIUK

Not just a pleasure path? The dopamine-releasing neurons (green) of the ventral tegmental area extend to the nucleus accumbens and the prefrontal cortex, an area involved in learning.

The new work on dopamine may thus eventually lead to better drug treatments that fix the attentional filter in ADD patients and certain schizophrenics. It may also help experts develop new therapies for drug addiction that work, for example, by blocking the cravings addicts get when they see objects that remind them of a drug—and that commonly cause relapse.

Producing pleasure

Before 1990, almost all of the data on dopamine's role in addiction or reward suggested that the transmitter signaled something akin to emotional value or pleasure. In 1975, for example, Wise and Robert Yokel, also at Concordia, found that rats given high doses of a dopamine-blocking chemical called pimozide eventually stopped pressing a lever that caused amphetamine to be delivered into their veins. Because the rats first tried pressing the lever faster, ruling out the possibility that their movements were impaired, the result indicates that amphetamine was no longer rewarding to the animals.

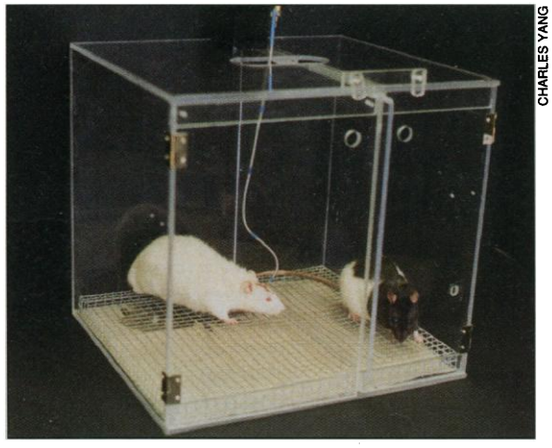
Similarly, David Roberts and Hans Fibiger at the University of British Columbia (UBC) in Vancouver and their colleagues showed in the late 1970s that selectively destroying dopamine-producing cells in a midbrain region called the ventral tegmental area (VTA) shut down cocaine-seeking behavior by rats. Such experiments, says their British Columbia colleague Anthony Phillips, "convincingly implicated dopamine as a reward transmitter." Since then, other researchers have produced a flood of data showing that a variety of addictive drugs, from alcohol to heroin, unleash a surge of dopamine from cells in the VTA. The dopamine is released into a part of the brain, called the nucleus accumbens, that is known to be activated by pleasurable behaviors.

Indeed, further work by Wise's team suggested that the dopamine reward system plays a fundamental role in encouraging behaviors, such as feeding, needed for life. They found, for example, that dopamine-blocking agents blunt the reinforcing impact of food in hungry rats, eventually making them stop running toward food. Researchers logically concluded that the transmitter, when released, causes the animals to feel good, and by setting off

these positive emotions, also teaches them to repeat pleasure-producing actions.

Skeptics noted, however, that the hypothesis that dopamine produces pleasure was hard to reconcile with what's known about schizophrenia, in which too much of the neurotransmitter seems in many cases to cause a heightened state of arousal—not pleasure. When Wise proposed the pleasure hypothesis, psychologist Richard Katz, then of Johns Hopkins University in Baltimore, commented that if Wise was right, then schizophrenics should be "inextinguishably fat and happy. They are just the opposite ... as anyone who has worked with them knows."

Beginning in the early 1990s, researchers began picking up hints that even in pleasurable behaviors, dopamine may have a more subtle role than the pleasure hypothesis suggests. Some of these hints came from experiments in which they measured dopamine levels in the nucleus accumbens and found that they surge not just in response to food and sexual rewards, but also in response to events that predict those rewards.



CHARLES YANG

Anticipation. Dopamine levels go up in the male rat (left) even before he's allowed to mate with the female at right.

Predictive power

In 1993, for example, Phillips's team in British Columbia found that after hungry rats learned to associate the sound of a buzzer with food delivery, the buzzer produced the same dopamine surge in the nucleus accumbens as the food did. And in experiments reported just this year, Phillips's team showed that dopamine levels in the accumbens surge in rats during periods of sexual anticipation before mating. In this experiment, dopamine levels rose 44% when male rats were exposed to a female, who was kept out of reach behind a screen. When they were then allowed to copulate with her, the levels went even higher, but dropped off again as the males became sexually satiated. However, the presence of a second female prompted another small dopamine surge, which increased further, to 34% above baseline, as the male copulated with her.

At about the same time, another line of work in which researchers directly measured the activity of dopamine-producing nerve cells, rather than brain concentrations of the neurotransmitter, added support to the idea that the neurons' true role is to draw attention to events that predict rewards rather than to trigger pleasure. Wolfram Schultz, a neurophysiologist at the University of Fribourg in Switzerland, and his colleagues were investigating the actions of dopamine-producing nerve cells in a brain region called the substantia nigra, which are thought to be important for controlling movements. Such information would be helpful in understanding Parkinson's disease, which is caused by a loss of those neurons, but Schultz found the results of his experiments taking him in an unexpected direction.

He and his colleagues began by recording the activities of individual dopamine cells in the substantia nigra of monkeys who were supposed to perform a series of learned movements. They expected to see the neurons fire whenever the monkeys moved or prepared to move. Instead, all the neurons remained silent. Then, one day, the researchers gave the monkeys a piece of apple as a reward during one of the experiments. This time, Schultz recalls, "the neurons started going crazy. We couldn't believe it."

At first, the researchers assumed that the firing simply prepared an animal to approach the apple morsel. But further work ruled out that idea. For one thing, dopamine neurons fired just as much in response to rewarding stimuli when the monkeys were not required to move as when they were. Indeed, the Schultz team's results began to point to a more interesting function for the dopamine-producing neurons: providing incentives to act when something important is going on. The researchers found, for example, that the cells would respond only to "behaviorally significant" stimuli, such as rewards. A piece of apple worked, but a bare wire that normally held the food did not.

The cells might then simply signal the presence of a reward. But in 1992 and 1993, Schultz's team showed that the neurons would fire in response to stimuli that were not in themselves rewarding, such as a light, if they predicted a food reward. Indeed, after monkeys learned that a light predicted food, the neurons would stop firing to the food itself. Because the food presumably remained more pleasurable than the light, these data cast doubt on the idea that dopamine is a pleasure transmitter, indicating instead that dopamine teaches an animal to predict an upcoming reward correctly.

At the 1996 Society for Neuroscience meeting, Schultz and former postdoc Jeffrey Hollerman presented perhaps the best evidence for that idea: recordings of single dopamine neurons during an entire learning episode. They first taught a monkey that touching one of a pair of pictures would produce a reward. Then, while recording from a dopamine cell, they switched to two novel pictures, so the monkey no longer knew which to choose. When the monkey picked the correct one by chance, the dopamine cell would fire as the monkey got the reward, but after the monkey knew which one was correct, the cell greeted the reward with silence. The researchers found the same pattern in 45 neurons tested with separate picture pairs. The results, says Schultz, "show that dopamine cells respond to reward only when it occurs unpredictably—for example, during learning—and this response, which reveals the difference between what is predicted and what occurs, looks like a perfect teaching signal."

If dopamine does mark reward-predicting stimuli, that function should be reflected in the responses of the neurons receiving its signals in the brain's ventral striatum, a structure that includes the nucleus accumbens. In 1996, a team led by neuropsychologist Barry Richmond of the National Institutes of Health in Bethesda, Maryland, garnered evidence that, indeed, striatal cells seem to help an animal keep close tabs on its progress toward a reward.

The researchers trained monkeys in a task in which they received a dollop of juice if they correctly performed a simple action—letting go of a bar when a spot on a computer screen changed from red to green—from one to three times. The animals could track their progress by a second light, which brightened as the juice reward neared. The monkeys acted as if they understood this light cue: The closer they were to receiving a reward, the faster they released the bar and the more accurate they were. Striatal neurons reflected this knowledge. For example, many of the 138 cells sampled in two monkeys fired more rapidly when a monkey knew a trial would produce a reward. "You can figure out where you are in the sequence of trials by listening to these neurons," Richmond says.

Now, a study in the September issue of *Neuron* suggests an anticipatory role for the nucleus accumbens in drug abuse. A team led by Hans Breiter and Bruce Rosen of Harvard Medical School in Boston and Steven Hyman, who recently became director of the National Institute of Mental Health, used functional magnetic resonance imaging to scan the brains of cocaine addicts under the drug's influence. This revealed the areas active when the subjects felt a brief, euphoric

"rush," and then those that remained active after the euphoria wore off and the subjects were craving, or anticipating, another hit. Despite its previous association with pleasure, the nucleus accumbens remained active during the craving stage, suggesting a tie between craving and the dopamine neurons located there.

An attention-getting device?

Meanwhile, very recent neurophysiological evidence suggests that the dopamine system may have an even broader role in learning: It may highlight novel or startling sensory events that attract an animal's attention but are not related to reward. A team led by Jon Horvitz of Columbia University in New York City and Princeton University's Barry Jacobs exposed cats, at unpredictable times, to either loud clicks or flashes of a bright light, and found that the neurons in the animals' VTAs responded to both the clicks and the light flashes, most commonly with a burst of activity of the type that unleashes a surge of dopamine. The results suggest, Horvitz says, "that dopamine neurons respond to salient events regardless of whether the salience derives from conditioned reward properties or from physical characteristics of the stimulus," such as a sudden onset.

Still, not all recent experiments have supported dopamine's proposed role as an attention-getter. In 1995, for instance, a team led by UBC's Fibiger repeatedly exposed a group of hungry rats to a delicious liquid behind a wire mesh screen before lifting the screen and allowing them to eat. They discovered a significant rise in dopamine in the nucleus accumbens when the rats consumed the food, but not while they eyed the food behind the screen. "My belief is that changes in dopamine release are more reliably associated with consumption of reward than anticipation of reward," Fibiger says.

Neurobiologists aren't sure why the results obtained by direct recording from dopamine neurons don't always jibe with data—like Fibiger's—that are based on dopamine levels. But the different time scales of these two data types may offer an explanation. Because dopamine levels are measured over minutes, they may miss the tiny, momentary increases produced by dopamine-cell firing. "When the smoke clears, I think dopamine will be playing a role in learning the value of stimuli that are important in an animal's environment," Phillips predicts.

The smoke hasn't cleared quite yet, however. Other researchers are still racking up correlations between dopamine and pleasure. Earlier this year, an imaging study by Nora Volkow's team at Brookhaven National Laboratory in Upton, New York, linked the euphoria produced by cocaine to dopamine levels in a part of the striatum next to the nucleus accumbens. The researchers gave different doses of the drug to 17 people who were already cocaine users. Then, to get an indication of dopamine levels in the subjects' striata, they used positron emission tomography and radioactive cocaine to detect cocaine binding to dopamine transporter proteins. These proteins pick up dopamine released by neurons and carry it back into the cells so it can be used again. When cocaine binds to the transporters, it blocks them and results in increased brain dopamine levels.

Volkow and her colleagues found that the intensity of the subjects' highs increased in proportion to the percentage of dopamine transporters blocked by the drug in the striatum—which, they believe, reflect what's happening with the transporters in the nucleus accumbens. "The ensuing rise in dopamine triggers the high," Volkow concludes.

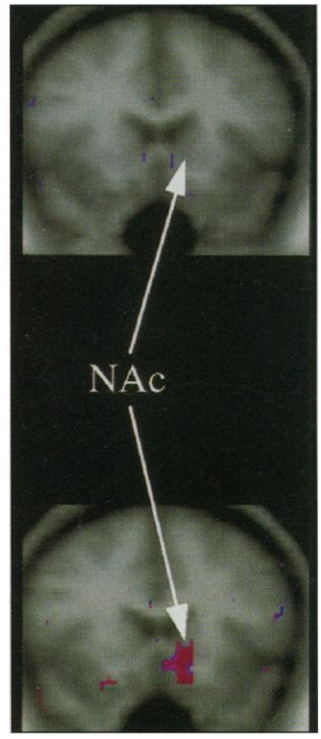
Given the conflicting results so far, more work will be needed to resolve whether dopamine has some role in conscious emotion, such as pleasure, or whether it is mainly a subconscious signal in learning and attention. One line of research that could settle the debate is directed at dopamine's role, if any, in unpleasant events. Some data suggest that dopamine helps animals learn and remember unpleasant stimuli such as electric shocks. The evidence so far is controversial, but if it holds up, it would buttress the idea that dopamine functions primarily as a general purpose attention-getter.

Researchers could also bolster dopamine's proposed role in learning by unraveling the brain mechanism through which the neurotransmitter would exert this effect. One clue to the mechanism may be the connections between dopamine cells in the VTA and the frontal cortex, where short-term memories are held. Some scientists think dopamine may cause frontal neurons to hold onto some temporary memories for longer, increasing the chances that they will stick in the mind. "I see dopamine as a possible modulatory cue that allows short-term memories to hold their state for a while, such that there's a better chance of remembering them the next day," says Donald Woodward, a neurophysiologist who studies cocaine reward at the Bowman Gray School of Medicine in Winston-Salem, North Carolina.

Ultimately, scientists hope their dopamine research will lead to more general insights into how mammalian brains work, and equally important, how they malfunction. If the dopamine signal serves to draw attention to salient events of all sorts as Horvitz's work suggests, then its overactivity in schizophrenia might explain some of the disorder's symptoms. "It is very possible," says Horvitz, "that the bizarre associations schizophrenics make, and the significance they attach to stimuli that we would consider irrelevant, are due to the fact that the stimuli are entering the nervous system under a state of high dopamine activity."

Once scientists unravel the larger neural circuit in which dopamine acts, they may find that as dopamine delivers its message, other parts of the brain may reverberate with a conscious emotion—pleasure, excitement, or even fear—depending on the circumstances. But it is now doubtful that dopamine's cry directly summons such feelings; instead, it may make a person look up in surprise, like a schoolchild just called on by a teacher, to warn that it's time to listen to the lesson.

–Ingrid Wickelgren



BREITER *ET AL.*, *NEURON* **19**, 591 (1997)

All lit up. Nucleus accumbens (NAc) activity indicates a closer link to the "craving" phase (*bottom*) of the brain's response to cocaine than to the "rush" (*top*).

Additional Reading

J. Altman *et al.*, "The biological, social and clinical bases of drug addiction: Commentary and debate," Offprint from *Psychopharmacology* **125**, 285 (1996).

E. M. Bowman *et al.*, "Neural signals in the monkey ventral striatum related to motivation for juice and cocaine rewards," *Journal of Neurophysiology* **75**, 1061 (1996).

F. Fiorino, A. Coury, A. G. Phillips, "Dynamic changes in nucleus accumbens dopamine efflux during the Coolidge effect in male rats," *Journal of Neuroscience* **17**, 4849 (1997).

J. C. Horvitz *et al.*, "Burst activity of ventral tegmental dopamine neurons is elicited by sensory stimuli in the awake cat," *Brain Research* **759**, 251 (1997).

W. Schultz, P. Dayan, P. R. Montague, "A neural substrate of prediction and reward," *Science* **275**, 1593 (1997).

N. D. Volkow *et al.*, "Relationship between subjective effects of cocaine and dopamine transporter occupancy," *Nature* **386**, 827 (1997).

R. A. Wise, "Neurobiology of addiction," *Current Opinion in Neurobiology* **6**, 243 (1996).