The Joyful Mind

A new understanding of how the brain generates pleasure could lead to better treatment of addiction and depression—and even to a new science of happiness

By Morten L. Kringelbach and Kent C. Berridge

In the 1950s psychiatrist Robert Heath of Tulane University launched a controversial program to surgically implant electrodes into the brains of patients institutionalized with epilepsy, schizophrenia, depression and other severe neurological conditions. His initial objective: to locate the biological seat of these disorders and, by artificially stimulating those regions, perhaps cure individuals of their disease.

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According to Heath, the results were dramatic. Patients who were nearly catatonic with despair could be made to smile, converse, even giggle. But the relief was short-lived. When the stimulation ceased, the symptoms returned.

To extend the potential therapeutic benefit, Heath fitted a handful of patients with buttons they could press themselves whenever they felt the urge. Some felt the urge quite frequently. One patient—a 24-year-old homosexual whom Heath was attempting to cure of depression (and of his desire for other men)—was compelled to stimulate his electrodes some 1,500 times over the course of a single, three-hour session. According to Heath, this obsessive self-stimulation gave the subject, patient B-19, "feelings of pleasure, alertness, and warmth (goodwill)." The end of his session was met with vigorous protest.

The experiments helped to define a set of structures that would come to be known as the "pleasure center" of the brain. They also spawned a movement—both in science and in popular culture—to better understand the biological basis of pleasure. Over the next 30 years neurobiologists identified the chemicals that the brain regions delineated by Heath and others send and receive to spread their tidings of joy. And people began to imagine brave new worlds in which activation of these centers could produce instant bliss.

Yet the discovery of the brain's alleged pleasure center has not led to any breakthroughs in the treatment of mental illness. It may have even misled scientists into thinking they understood how pleasure is encoded and generated within the brain. Studies in rodents and humans now suggest that activating these structures with electrodes or chemicals does not actually produce pleasure at all. It may merely precipitate craving and hence the manic drive to self-stimulate.

With the help of modern molecular biological techniques, combined with improved methods for deep-brain stimulation, our laboratories and others are redefining the brain's pleasure circuitry. We are finding that the pleasure-generating systems in the brain are much more restricted—and much more complex—than previously thought. By pinpointing the true neurological underpinnings of pleasure, we hope to pave the way to more targeted and effective treatments for depression, addiction and other disorders—and perhaps to offer new insights into the roots of human happiness.

MISLEADING ELECTRODES

WHETHER EXPERIENCED as shivers of delight or the warm thrum of contentment, pleasure is more than an ephemeral extra—that is, something to be sought only after one's more basic needs have been met. The sensation is actually central to life. Pleasure nourishes and sustains animals' interest in the things they need to survive. Food, sex and, in some cases, social communion generate positive feelings and serve as natural rewards for all animals, including ourselves.

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The first apparent insights into the biological basis of these feelings came nearly 60 years ago from the original discoverers of the so-called pleasure electrodes. James Olds and Peter Milner of McGill University were searching for brain regions that could influence animal behavior. Earlier studies from Yale University—in which electrodes had been inserted into rats' brains—had identified an area that, when stimulated, would cause an animal to avoid whatever action had coincided with the stimulation. While trying to replicate these findings, Olds and Milner came across a brain region that the rodents would take active steps to stimulate—in the same way that animals will repeat any task or behavior that yields a suitable reward.

Placing the electrodes in different regions—and sometimes not where they intended—the pair were surprised to find a part of the brain that animals seemed to enjoy having zapped with a mild electric current. Rats placed in a large box returned repeatedly to the corner in which the researchers would give them a small electric jolt. Using this approach, Olds and Milner found they could steer the rodents to almost any location. In some instances, the animals even chose stimulation over food. If the researchers pressed the button when the rats were halfway through a maze that promised a tasty mash at the end, the creatures simply stayed put, never bothering to proceed to the treat.

Even more surprising, when the electrodes were wired so that the rats could stimulate their own brain by pressing a lever, Olds and Milner discovered that they did so almost obsessively—some more than 1,000 times an hour [see "Pleasure Centers in the Brain," by James Olds; SCIENTIFIC AMERICAN, October 1956]. When the current was turned off, the animals would press the bar a few more times—and then go to sleep.

The results prompted Olds and Milner to declare, "We have perhaps located a system within the brain whose peculiar function is to produce a rewarding effect on behavior." The regions the researchers identified—including the nucleus accumbens, which reclines at the base of the forebrain, and the cingulate cortex, which forms a collar around the fibrous bundle that bridges the brain's left and right halves—thus became enshrined as the operational base of the brain's reward circuit.

Almost immediately other scientists reproduced these ef-

IN BRIEF

New research has uncovered hotspots in the brain that, when stimulated, enhance sensations of pleasure.

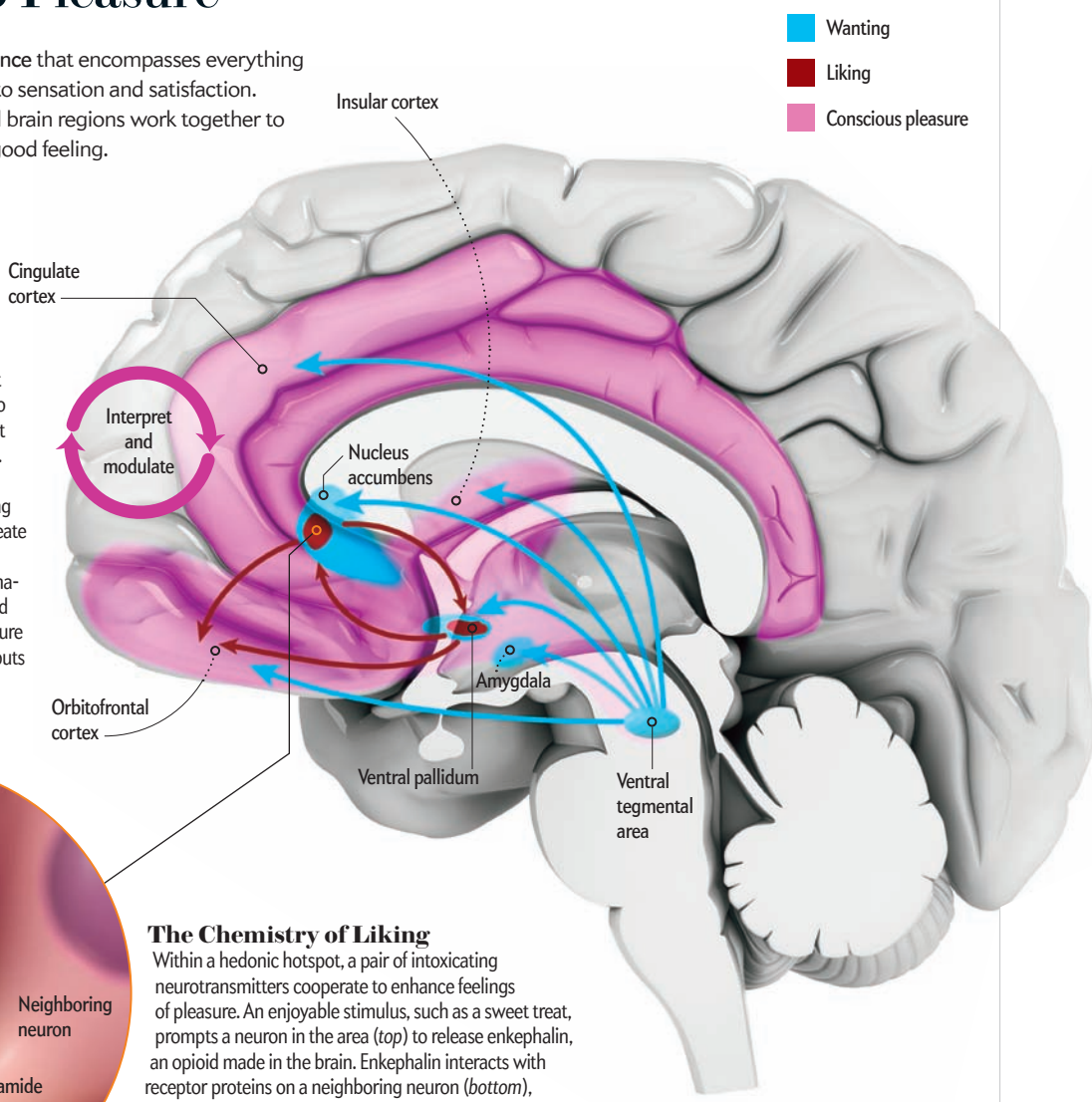
These hedonic hotspots differ from the "reward circuit" previously thought to be the basis of good feelings—a pathway now believed to mediate desire more than enjoyment.

Higher brain regions receive information from these pleasure and reward circuits to consciously represent the warm glow we associate with joy.

A decoupling of the brain systems that generate "wanting" and "liking" may underlie addictive behavior—a clue that may lead to new treatments.

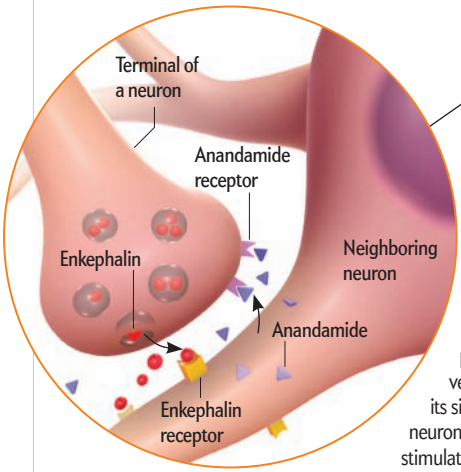
Paths to Pleasure

Pleasure is a complex experience that encompasses everything from anticipation and desire to sensation and satisfaction. So it's no surprise that several brain regions work together to generate this warm glow of good feeling.



Wanting and Liking

A neural circuit (*blue*) that begins near the brain stem and reaches out to the forebrain was once thought to be the sole mediator of pleasure. But it is actually more focused on desire. In addition to this pathway, several so-called hedonic hotspots, including two shown here (*red*), interact to create a sense of liking. A quilt of cortical regions (*pink*) then translates information received from the "wanting" and "liking" circuits into conscious pleasure and adjusts this feeling based on inputs from other brain regions.



The Chemistry of Liking

Within a hedonic hotspot, a pair of intoxicating neurotransmitters cooperate to enhance feelings of pleasure. An enjoyable stimulus, such as a sweet treat, prompts a neuron in the area (*top*) to release enkephalin, an opioid made in the brain. Enkephalin interacts with receptor proteins on a neighboring neuron (*bottom*), potentially triggering production of anandamide, the brain's version of marijuana. As anandamide diffuses away from its site of synthesis, it can interact with receptors on the first neuron, intensifying the sensation of pleasure and perhaps even stimulating the production of more enkephalin. Together these chemicals form a pleasure-boosting loop of liking.

fects, making similar findings in higher primates and humans. Heath, in particular, pushed the interpretation of his results to the limit, insisting that stimulating these regions not only reinforces a behavior but produces sensations of euphoria. In the minds of many scientists and the general public, these structures became known as the brain's chief pleasure center.

About 10 years ago, though, the two of us began wondering whether the act of electrical self-stimulation was really the best measure of pleasure. How do we know that subjects stimulate those regions because they like the way it feels and not for some other reason? To probe the pleasure circuitry more precisely, we felt we needed to devise a different way of assessing what subjects—including animals—actually enjoy.

A MEASURE OF PLEASURE

FOR EXPERIMENTS IN PEOPLE, assessing pleasure is fairly straightforward: just ask. Of course, the resulting ratings might not fully capture or accurately reflect the underlying sensations. Further, such inquisition is not possible in laboratory animals—the subjects in which biology is most easily explored.

An alternative approach takes its lead from Charles Darwin. In his 1872 book *The Expression of the Emotions in Man and An-*

Illustration by AXS Biomedical Animation Studio

imals, Darwin noted that animals change their affect in response to environmental situations—in other words, they make faces. We now know that the neural mechanisms underlying such expressions work similarly in most mammalian brains. Hence, certain facial gestures have been conserved in animals as distantly related as rodents and humans—including the "yummy faces" we make in response to tasty food.

Food is one of the most universal routes to pleasure—as well as an essential requirement for survival. It is also one of the most accessible experimental tools used by psychologists and neuroscientists studying animal behavior. In our studies, we have found that the response to food provides a window through which we can observe unspoken pleasures.

Anyone who has spent time around babies knows that even the youngest humans have ways of advising their caregivers about the palatability of a meal. Sweet tastes elicit a contented licking of the lips, whereas bitter tastes tend to be met with gaping mouths, shaking heads and a vigorous wiping of the mouth. The same responses seen in human infants also occur in rats, mice and nonhuman primates. The more subjects like the taste, the more often they will lick their lips. By making video recordings of subjects' responses to food and then counting the number of times their tongues dart out—as if to capture every last molecule of flavor—we can measure how much a given gustatory stimulus is liked. And we have used that information to assess where pleasure really resides in the brain.

Pleasure does not arise in the brain quite where—or how—past thinking said it should.

WANTING IS NOT LIKING

ONE OF THE FIRST THINGS we discovered is that pleasure does not arise in the brain quite where—or how—past thinking said it should. The regions first identified by Olds and Milner and others, positioned at the front of the brain, are activated by the neurotransmitter dopamine, released by neurons that originate near the brain stem. If these frontal areas truly regulate pleasure, we reasoned, flooding them with dopamine—or removing dopamine entirely—should alter how an animal responds to an enjoyable stimulus. That is not what we found.

For these experiments, our colleague Xiaoxi Zhuang of the University of Chicago engineered mice lacking a protein that retrieves dopamine once it has been released by an excited neuron, returning the neurotransmitter to the cell's interior. Animals with such a knockout mutation maintain unusually high concentrations of dopamine throughout their brain. Yet we found that the mice do not appear to derive more pleasure from sweets than their unaltered cage mates do. Relative to normal rodents, the dopamine-doped mice do speed more quickly toward sweet rewards; however, they do not lick their lips any more often. On the contrary, they do so even less than mice with average amounts of dopamine.

We see the same thing in rats that have dopamine elevated by other means. For example, injecting amphetamine into the nucleus accumbens causes dopamine in that area to rise. Again, however, sugary treats seem no more pleasant to these rats after their chemically assisted dopamine boost—although the animals are more motivated to obtain them.

Conversely, rats that have been depleted of their dopamine show no desire for sugary treats at all. These animals will actually starve to death unless they are actively nursed. Yet dopamine-free rats that have no interest in food nonetheless find whatever sweets might be placed into their mouth whisker-licking good.

So it seems that dopamine's effects may be subtler than previously understood. The chemical appears to contribute more to motivation than to the actual sensation of pleasure itself. In humans, too, dopamine levels appear to track more closely with how much individuals claim to "want" a delicious tidbit than with how much they say they "like" it.

The same may be true in addiction. Drugs of abuse flood the brain with dopamine—particularly those regions associated with "wanting." This dopamine barrage not only triggers intense craving, it renders cells in these regions more sensitive to future drug exposure. Moreover, work from our colleague Terry Robinson of the University of Michigan suggests that this sensitization can persist for months or years. Thus, even after the drug no longer brings pleasure, Robinson reasons, an addict can still feel a strong urge to use—an unfortunate consequence of dopamine's actions.

Given this new understanding, we believe that the "pleasure" electrodes that stimulate accumulation of this chemical in the brains of rats—and humans—might not have been as enjoyable as was originally assumed. In support of this view, we find that activation of electrodes that elevate dopamine in the nucleus accumbens will motivate a rat to eat and drink, yet the same stimulation does not make that food more pleasing—just the opposite. Rats that are moved to eat sweets by electrical stimulation wipe their mouth and shake their head—signs of active dislike, as if the current had rendered the sweetness bitter or disgusting to them. The fact that the electrodes compel rats to consume large quantities of a food that is not bringing them pleasure is evidence that wanting and liking are controlled by different mechanisms in the brain.

We think the differential control also occurs in humans. The application of current through the classic pleasure electrodes led at least one patient to a strong desire to drink. In others, including B-19, electrical stimulation triggered an urge for sex. At the time, such sexual cravings were considered evidence of pleasure. Yet in our extensive reviews of the literature, we have never come across evidence that a patient implanted with these electrodes found them expressly pleasurable. B-19 never once exclaimed, "Oh, that feels nice!" Instead stimulation of the pleasure electrodes simply made him and the others want more stimulation—probably not because they liked it but because they were made to desire it.

HEDONIC HOTSPOTS

WANTING AND LIKING are both involved in making an experience feel rewarding. So it makes sense that the real pleasure centers in the brain—those directly responsible for generating pleasurable sensations—turn out to lie within some of the structures previously identified as part of the reward circuit. One of these so-called hedonic hotspots lies in a subregion of the nucleus accumbens called the medial shell. A second is found within the ventral

pallidum, a deep-seated structure near the base of the forebrain that receives most of its signals from the nucleus accumbens.

To locate these hotspots, we searched for brain regions that, when stimulated, amplify the sensation of pleasure—for example, making sweet things even more enjoyable. Chemically stimulating these hotspots with enkephalin—a morphinelike substance made in the brain—enhances a rat's liking of sweets. Anandamide, the brain's version of the active ingredient in marijuana, does the same. Another hormone called orexin, which is released by the brain during hunger, may also stimulate hedonic hotspots, helping to enhance the flavor of food.

Each of these spots is just a fraction of the size of the larger structure in which it lies—only about one cubic millimeter in a rat brain and probably no more than a cubic centimeter in a human. Yet like the islands of an archipelago, they link to one another—and to other brain regions that process pleasure signals—to form a powerful, integrated pleasure circuit.

That circuit is fairly resilient. In our experience, disabling individual components within the pleasure circuit does not diminish the typical response to a standard sweet—with one exception. Damaging the ventral pallidum appears to eliminate an animal's ability to enjoy food, turning a nice taste nasty.

On the other hand, intense euphoria is harder to come by than everyday pleasures. The reason may be that strong enhancement of pleasure—like the chemically induced pleasure bump we produced in lab animals—seems to require activation of the entire network at once. Defection of any single component dampens the high.

Whether the pleasure circuit—and in particular, the ventral pallidum—works the same way in humans is unclear. Not many people come to the clinic with discrete damage to these structures without injuries in surrounding areas. Thus, it is difficult to assess whether the ventral pallidum and other components in the circuit are essential to the sensation of pleasure in humans. We know of one patient whose ventral pallidum became damaged during a massive drug overdose. Afterward, he reported that his feelings were dominated by depression, hopelessness, guilt and an inability to feel pleasure—potentially supporting a central role for this heretofore underappreciated structure.

ENOUGH IS ENOUGH

THE CIRCUIT does not act alone in regulating feelings of joy. To add that warm gloss of pleasure to a sensation or experience, additional brain regions come into play. These higher structures help to determine how delightful an experience is, based on current conditions, such as whether one is hungry or full or has simply had enough of one particular pleasure. After eating an entire pan of brownies, for example, even an admitted chocoholic tends to find a candy bar much less appealing.

In the case of food, such selective satiety may have evolved in part because it encourages animals to obtain a wide variety of nutrients rather than fixating on one favorite meal. It seems to be encoded in a part of the brain called the orbitofrontal cortex. This area, located in the underbelly of the prefrontal cortex, which in humans hangs just above the eyes, receives information from the nucleus accumbens and ventral pallidum. It seems to modulate how pleasure is consciously represented—suffusing a sensation with that delicious glow we associate with gratification and toning down the feelings when enough is enough.

With the help of powerful neuroimaging techniques, we have found that the activity of a small region within the orbitofrontal cortex, called the midanterior site, correlates tightly with the subjective pleasantness of a nice sensation, such as the taste of chocolate milk. At the first sip, for example, the site is alight with activity. Yet once subjects have consumed enough of the sweet stuff, the midanterior site shuts down, rendering the experience no longer pleasurable.

Further evidence that the midanterior site is important for human pleasure comes from studies of therapeutic deep-brain stimulation [see "Sparking Recovery with Brain 'Pacemakers,'" by Morten L. Kringelbach and Tipu Z. Aziz; SCIENTIFIC AMERICAN MIND, December 2008/January 2009]. The procedure is being used to treat a few conditions, including to relieve suffering in patients with otherwise untreatable chronic pain. In one patient of ours, an amputee who was feeling pain in his missing limb, stimulation of an area within the brain stem not only relieved the pain but induced deep feelings of pleasure. Simultaneous neuroimaging revealed a burst of activity in the midanterior site as well. Whether such stimulation of specific hotspots in the pleasure system can be used to treat depression or other forms of anhedonia—an inability to experience pleasure—remains an active area of investigation.

Similarly, additional research may reveal how the circuits that govern pleasure and reward are linked. Under normal circumstances, the hedonic hotspots are coupled with the dopamine-driven reward system, such that we desire things that make us feel good and avoid or are indifferent to things that do not. In the case of addiction, these systems somehow become disconnected, causing the individual to continue to crave things that no longer bring pleasure. Such dissociation might also possibly contribute to other types of compulsive behaviors, such as binge eating and gambling. Understanding how and why such uncoupling can occur could reveal better ways to reverse the brain changes that drive addiction, thus restoring the natural alignment between wanting and liking.

Aristotle once observed that happiness consists of two key ingredients: *hedonia,* or pleasure, plus *eudaimonia*—a sense of meaning. Although scientists have made some progress in uncovering the biological basis of *hedonia,* we know very little about how the brain gives rise to a broader sense of a life well lived. We hope, however, that with time this puzzle, too, can be solved and that the discoveries will help people unite pleasure and purpose, elevating everyday experiences to something truly satisfying, perhaps even sublime. SA

MORE TO EXPLORE

A Common Neurobiology for Pain and Pleasure. Siri Leknes and Irene Tracey in *Nature Reviews Neuroscience,* Vol. 9, pages 314–320; April 2008.

The Pleasure Center: Trust Your Animal Instincts. Morten L. Kringelbach. Oxford University Press, 2008.

Pleasures of the Brain. Edited by Morten L. Kringelbach and Kent C. Berridge. Oxford University Press, 2010.

Building a Neuroscience of Pleasure and Well-Being. Kent C. Berridge and Morten L. Kringelbach in *Psychology of Well-Being: Theory, Research, and Practice,* Vol. 1, No. 3; October 2011. www.psywb.com/content/1/1/3

SCIENTIFIC AMERICAN ONLINE

Watch a video of infants, nonhuman primates and rats showing pleasure and displeasure at ScientificAmerican.com/aug2012/pleasure