

The Biology of

Scientists know plenty about depression. Now they are starting to understand the roots of positive emotion

JOY

By MICHAEL D. LEMONICK

RICHARD DAVIDSON WAS IN A LAB OBSERVING A BUDDHIST MONK SINK deep into serene meditation when he noticed something that sent his own pulse racing. Davidson, a professor of psychology and psychiatry at the University of Wisconsin, hurriedly double-checked the data streaming to his computer from electrodes attached to the monk's skull, but there was no mistake. Electrical activity in the left prefrontal lobe of the monk's brain was shooting up at a tremendous rate. "It was exciting," Davidson recalls. "We didn't expect to see anything quite that dramatic."

Davidson's excitement is all the more significant because he's known by colleagues as the king of happiness research. When he made the discovery five years ago, he had been studying the link between prefrontal-lobe activity and the sort of bliss deep meditators experience. But even for someone with his experience, watching the brain crackle with activity as a person entered a trancelike state was unprecedented. It made clear, says Davidson, who published the research study in the *Proceedings of the National Academy of Sciences* late last year, that happiness isn't just a vague, ineffable feeling; it's a physical state of the brain—one that you can induce deliberately.

That's not all. As researchers have gained an understanding of the physical characteristics of a happy brain, they have come to see that those traits

have a powerful influence on the rest of the body. People who rate in the upper reaches of happiness on psychological tests develop about 50% more antibodies than average in response to flu vaccines, and that, says Davidson, "is a very large difference." Others have discovered that happiness or related mental states like hopefulness, optimism and contentment appear to reduce the risk or limit the severity of cardiovascular disease, pulmonary disease, diabetes, hypertension, colds and upper-respiratory infections as well. According to a Dutch study of elderly patients published in

November, those upbeat mental states reduced an individual's risk of death 50% over the study's nine-year duration. Says Laura Kubzansky, a health psychologist at Harvard's School of Public Health, in a masterpiece of understatement: "There's clearly some kind of effect."

It makes sense that there should be. Doctors have known for years that clinical depression—the extreme opposite of happiness—can worsen heart disease, diabetes and a host of other illnesses. But the neurochemistry of depression is much better known than that of happiness, mostly



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NIRVANA CHECK
Davidson, right,
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record the brain
activity of a
Buddhist monk
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—DACHER KELTNER,
University of California, Berkeley

because the former has been studied more intensively and for much longer. Until about a decade ago, says Dacher Keltner, a psychologist at the University of California, Berkeley, “90% of emotion research focused on the negative, so there still are all of these interesting questions about the positive state.”

A growing number of researchers exploring the physiology and neurology of happiness are starting to answer those questions. Perhaps most fundamental of all is what happiness is, in a clinical sense. At this point, nobody can really say with precision. The word happiness, Davidson observes, “is kind of a placeholder for a constellation of positive emotional states. It’s a state of well-being where individuals are typically not motivated to change their state. They’re motivated to preserve it. It’s associated with an active embracing of the world, but the precise characteristics and boundaries have really yet to be seriously characterized in scientific research.”

Still, subjects can reliably tell researchers when they’re feeling good, and two brain-imaging technologies—functional magnetic resonance imaging (fMRI), which maps blood flow to active parts of the brain, and electroencephalograms, which sense the electrical activity of neuronal circuits—consistently point to the left prefrontal cortex as a prime locus of happiness.

That raises the chicken-and-egg question of whether the prefrontal cortex creates the sensation of happiness or whether it merely reflects one’s more general emotional state. Davidson thinks the answer is both: “We’re confident that this part of the brain is a proximal cause of at least certain kinds of happiness.” That suggests some people are genetically predisposed to be happy by virtue of their busy prefrontal cortexes, and research in infants confirms it. Davidson measured left prefrontal activity in babies less than a year old and then subjected them to a test in which their mothers left the room briefly. “Some babies will just cry hysterically the instant the mom leaves,” he says. “Others are more resilient.” It turns out that the babies with the higher left prefrontal activity are the ones who don’t cry. “We were actually able to predict which infants would cry in response to that brief but significant stress.”

In short, as parents know instinctively, some babies are just born happy. But neuroscientists have also learned over the past decade that the brain is highly plastic. It rewires itself in response to experience, and

that's especially true before the age of puberty. One might naively assume, therefore, that negative experiences might destroy a happy personality—and if they're extreme and frequent enough, that might be true. Davidson has learned, however, that mild to moderate doses of negative experience are beneficial. (In animal studies, he compared groups that had been moderately stressed when young to those that never were and found the former better able to recover from stress as adults. In human studies, in which deliberately inducing stress on kids would be unethical, he based his conclusions on self-reported stories of stressful childhoods.) The reason, he believes, is that stressful events give us practice at bouncing back from unpleasant emotions. They're like an exercise to strengthen our happiness muscles or a vaccination against melancholy.

Exactly what is the physical difference, though, between a left prefrontal cortex that is predisposed to happiness and one that isn't? It almost certainly has in part

to do with neurotransmitters, the chemicals that ferry signals from one neuron to the next. And while the prefrontal cortex is awash in many neurotransmitters, including dopamine, serotonin, glutamate, GABA and more, Davidson believes dopamine may be especially important. Animal studies have shown that dopamine mediates the transfer of signals associated with positive emotions between the left prefrontal area and the emotional centers in the limbic area of the brain, such as the nucleus accumbens, situated within the ventral striatum. In humans, people with a sensitive version of the receptor that accepts dopamine tend to have better moods, and researchers are actively studying the relationship of dopamine levels to feelings of euphoria and depression.

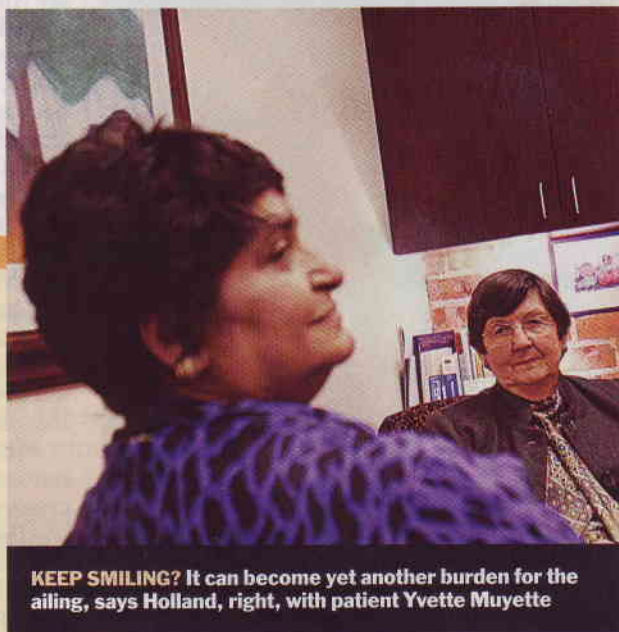
Dopamine pathways may be especially important in aspects of happiness associated with moving toward some sort of goal (monks achieving a meditative state as well as cigarette smokers allowed to light up after 24 hours of deprivation). But other neurochemicals may be more central to other kinds of happiness, including physical pleasure. "People have made progress differentiating the positive feeling you get when you approach a goal, which maps onto dopamine, and the sensory pleasure of enjoying something, which maps onto the opioid system," says Berkeley psychologist Keltner. "We're just beginning to apply a lens to all those parts of the nervous system in which the positive emotions are embodied. This is really neat territory."

Among those exploring that territory is Brian Knutson, an assistant professor of psychology and neuroscience at Stanford, who, like Davidson, uses MRI to monitor the brains of test subjects. The mental mode he studies is anticipation. "When people

HEALING

Can Sunny Thoughts Halt Cancer?

It's almost an article of faith: your best ally in the fight against cancer is a doggedly optimistic outlook. And it would seem that mounting evidence of the links between emotional and physical well-being would bolster that view. The only problem, says Dr. Jimmie Holland, a psychiatrist at Memorial Sloan-Kettering Cancer Center in New York City, is that there is no good evidence to support that belief when it comes to cancer. Moreover, the "tyranny of positive thinking," as she calls it, often becomes just one more burden for the afflicted. Cancer patients shouldn't feel obliged to smile through their suffering. More critically, she says, "they shouldn't have to feel guilty if their treatment fails."



KEEP SMILING? It can become yet another burden for the ailing, says Holland, right, with patient Yvette Muyette

It was research in the 1970s and '80s that first popularized the idea that attitude might affect cancer outcomes. Such research led doctors to encourage patients to think happy thoughts and visualize their immune system blasting away tumor cells. But most of those studies have been dismissed as either flawed or inconclusive. A review of 37 studies that was published in the *British Medical Journal* in 2002 found that although a positive outlook does correlate with the perception of less pain by patients—a real benefit—there is "little consistent evidence that coping styles play an important part in survival

from or recurrence of cancer."

Still, the optimism theory remains seductive. One reason is that Westerners live in a culture that covets control. We want to believe that we can beat cancer by imposing our will on the disease. A better reason is that mental states like depression and chronic anxiety have been shown to have physical consequences that affect the progression of such illnesses as heart disease and diabetes. While a similar connection is biologically plausible for cancer, it is far from proven.

Even researchers who believe that studies will ultimately establish links

between stress and the progression of cancer, like Stanford's Dr. David Spiegel, know the picture is complex. "It isn't a matter of 'Fix it in your mind, and you fix it in your body,'" he says, "but it would be strange if what goes on in our minds didn't affect how our bodies deal with illness."

So where does that leave cancer patients? Doctors know that individuals will always bring their own disposition—sunny, sour or sarcastic—to bear on their illness and treatment. Pressuring them to be paragons of positive thinking is futile. Worse, it could cause them to hide their fears and shun support. But clinicians must remain alert for signs of depression, which can affect the outcome of any disease if it interferes with treatment. And many patients will also need—and welcome—help to improve poor coping skills. Spiegel says, "Having worked with people with life-threatening illnesses for 30 years, it's clear that there are better and worse ways to deal with these things." False optimism isn't helpful, but neither is despair. —By David Bjerklie

think of happiness," says Knutson, "they think of feeling good, but a big part of happiness is also looking forward to something." Knutson's research was inspired by the classic work of Ivan Pavlov, who trained dogs to salivate at the sound of a bell, which they associated with mealtime.

Instead of food, Knutson used money: a small cash payoff if subjects won a video game. "When we looked at their brains just before they got the reward," he says, "we saw this spark that clearly had to do with how positive the idea of making money was." The spark showed up not in the left prefrontal cortex but in what Knutson terms an old section, the nucleus accumbens, located in the subcortex, at the bottom of the brain. The bigger the prize, Knutson found, "the more activation." Knutson believes he is looking at the kind of happy feelings we experience as excitement. The primary focus of his work is to understand the neurophysiology of motivation and decision making—how emotion and reason work together as people make choices. But it could also be a key to mapping out the brain's broader happiness circuitry.

Understanding the neurophysiology of feeling good is one aspect of happiness research; another is understanding how positive emotion affects the rest of the body. As with the brain studies, the term happiness is too broad for a rigorous approach, so researchers tend to focus on specific aspects. Harvard psychologist Kubzansky has chosen to study optimism. In a large study she tracked 1,300 men for 10 years and found that heart-disease rates among men who called themselves optimistic were half the rates for men who didn't.

"It was a much bigger effect than we expected," she says—as big as the difference between smokers and nonsmokers. "We also looked at pulmonary function, since poor pulmonary function is predictive of a whole range of bad outcomes, including premature mortality, cardiovascular disease and chronic obstructive pulmonary disease." Again, optimists did much better. "I'm an optimist," she says, "but I didn't expect results like this."

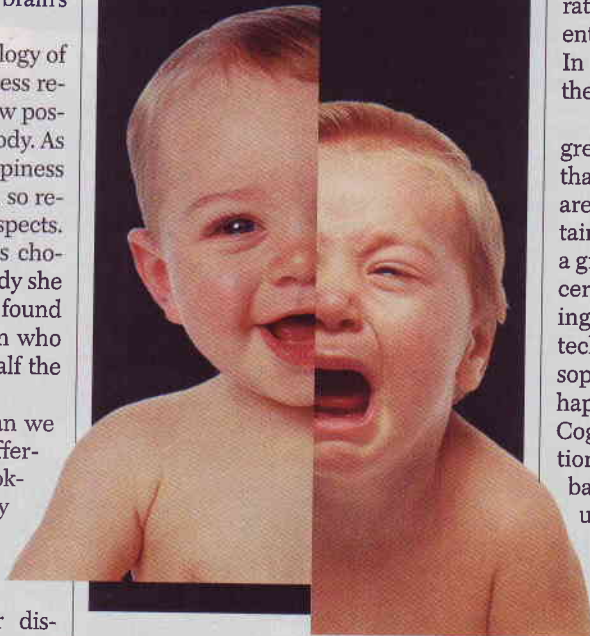
In a separate study, meanwhile, which has been accepted by the journal *Health Psychology*, Kubzansky, working with Duke psychologist and lead researcher Laura Richman, looked at hopefulness and curiosity—mental states that overlap with optimism in some ways. "We found them to be protective against hypertension, diabetes and upper-respiratory infection," she says. Such protective effects

may explain the longevity advantage found in that Dutch study of the elderly—an advantage for happy optimists that persisted even when researchers corrected for diet, education and other factors.

Exactly how states of mind affect the body's biochemistry is still far from clear. "We can do some good speculation," says Kubzansky, "based on what we know about anxiety and depression, so there are a couple of places to look in terms of neuroendocrine function and immune-inflammatory pathways." One clue: in addition to reporting

Is happiness wired in from the beginning?

A cheerful outlook may be inborn. Babies with less activity in the left prefrontal cortex tend to cry when their mothers leave the room; those with more activity stay placid. By looking at brain scans, researchers could predict which infants would cry



a positive mood when their left prefrontal cortexes are active, subjects in Davidson's experiments have lower levels of cortisol, a hormone produced by the adrenal gland in response to stress—and cortisol is known to depress immune function. Optimists may simply feel less stress than pessimists and thereby avoid the noxious biochemical cascades that stress is known to trigger. Another likely factor: optimistic, happy types seem to take better care of themselves than sad sacks do. Numerous studies—as well as common sense—suggest that to be the case.

In a series of studies begun in 1998, psychologist Robert Emmons of the University of California at Davis has found further evidence that happy people are better at health maintenance. Emmons randomly assigned 1,000 adults to one of three groups. The first group kept daily journals of their moods and rated them on a scale of 1 to 6. The second group did that and listed the things that annoyed or hassled them throughout their day. The third group kept a journal but added an activity that has repeatedly been shown to improve one's sense of satisfaction with life: they were asked to write down every day all the things for which they were grateful.

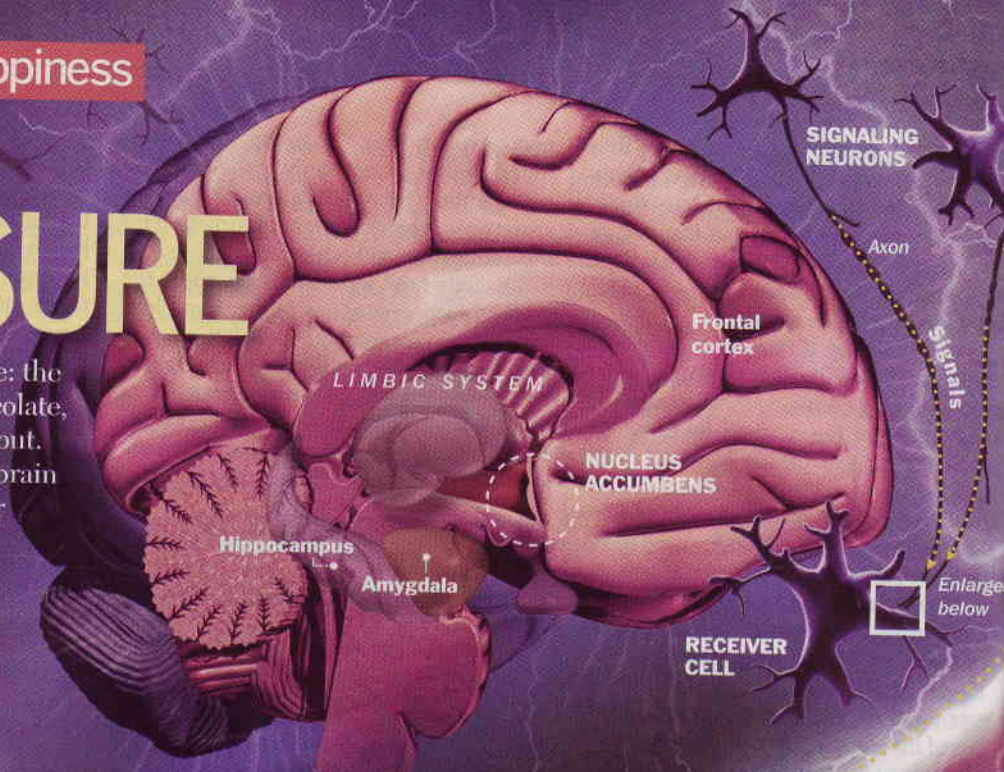
Despite being assigned randomly, the last group not only had the predicted jump in their overall feelings of happiness, says Emmons, but were also found to spend more time exercising, be more likely to have regular medical checkups and routinely take preventive health actions like wearing sunscreen. Overall, the "gratitude" group were promoting better health. "They rate themselves as more energetic, more enthusiastic, more alert," Emmons reports. In short, keeping the diaries contributed to their physical and emotional well-being.

Not surprisingly, the advantages were greatest when compared with the group that focused on life's hassles. "People who are grateful tend to view their body a certain way," says Emmons. "They see life as a gift, health as a gift. So they want to take certain measures to preserve it." Reminding yourself of what you're grateful for is a technique open to anyone, but more sophisticated methods of manipulating happiness are showing promise as well. Cognitive-behavior therapy and medication, for example, are used mostly to combat depression, but they may also be useful in enhancing happiness.

Such positive results gratify America's happiness researchers, who haven't been very successful in attracting federal dollars. "I could easily see being spoofed on the Senate floor for whatever award they give for esoteric, needless research," says Keltner. "But as the findings trickle in showing that positive emotions and happiness make your immune system function better, or help you battle disease, or help you live longer, then you're into fundable territory." Thanks to Keltner, Davidson and others, those findings have gained the field a degree of respectability that's long overdue—and that ultimately could make the world a whole lot happier. —Reported by Dan Cray/
Los Angeles

The Paths to PLEASURE

We all know what it feels like: the delight in a mouthful of chocolate, the afterglow of a good workout. A look at two systems in the brain that, with the right natural or artificial stimulus, conjure these sensations

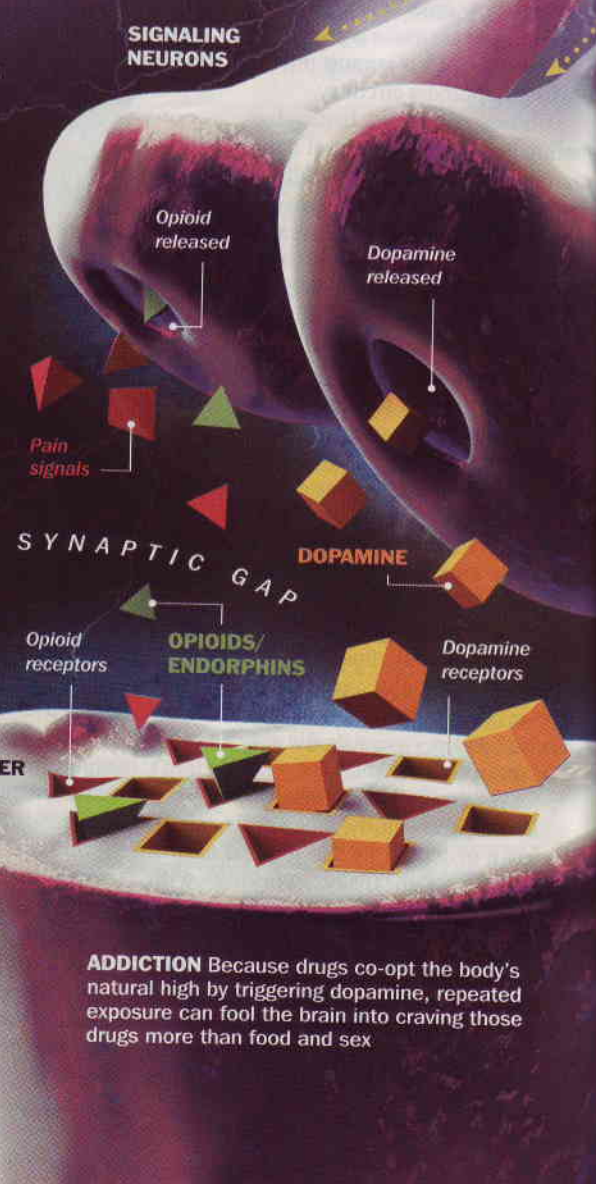


The Natural High

Two key brain chemicals regulate how happy the body feels. **Dopamine**, which is released in the **nucleus accumbens** and the **frontal cortex**, bathes neurons involved in memory and emotion, rewarding activities like eating and sex with pleasurable feelings. **Endorphins**, which are chemically similar to morphine, promote pleasure by dampening pain and producing a high

DOPAMINE Once released, it floods the **synaptic gap** between nerve endings and binds to **receptors** on adjacent cells. With more dopamine, more neurons involved in memory and emotion are activated, reinforcing feelings of joy

OPIOIDS/ENDORPHINS Physical stress, such as a long run, stimulates **pain signals**. In response, neurons release **opioids**, such as endorphins, preventing the signals from reaching nearby cells and producing pleasure elsewhere in the brain



The Artificial Buzz

Drugs can alter the brain's normal reward circuit, making it harder to feel pleasure without help

NARCOTICS mimic opioids by binding to the same receptors, numbing pain and producing a feeling of euphoria

COCAINE triggers the release of dopamine in the nucleus accumbens to produce a very powerful high

ALCOHOL AND NICOTINE affect both endorphin and dopamine circuits in more roundabout ways

ADDICTION Because drugs co-opt the body's natural high by triggering dopamine, repeated exposure can fool the brain into craving those drugs more than food and sex