Probing the Biology of Emotion

Neuroscientists using an array of new methods to explore the anatomy and chemistry of emotion are finding that intense emotions can leave a long-lasting physical imprint in the brain

After he cracked the origin of species, Charles Darwin turned to another of life's mysteries: the nature of emotions. In his 1872 book *The Expression of the Emotions in Man and Animals*, Darwin took an outside-in approach, scrutinizing sulky monkeys, snarling dogs, faces of the insane, even his own wailing infant. He found that different species have common ways of expressing certain emotions, reinforcing his belief in the shared ancestry of animals.

A century later, researchers have picked up on Darwin's cross-species approach, but they've turned the study of emotions inside out. In rats, monkeys, and people, neuroscientists are looking beyond the surface expression of emotion into the pockets of brain from which they arise. By recording the activity of single neurons and analyzing brain chemistry in rats and other animals, and scanning brain activity in humans, they are beginning to map the neural circuits that send emotional messages. And although their field is in its infancy, they are poised to integrate these studies into an understanding of the biological basis of emotion. "Emotion is now tractable at a mechanistic level," says neuroscientist Richard J. Davidson of the University of Wisconsin, Madison. "It's been a huge advance, just enormous."

Increasingly, researchers are finding that intense emotions, particularly at key times in early life, can trigger not only behavioral changes but long-lasting physical changes in the brain. These persist long after the emotions themselves have passed and shape emotional responses later in life. This inside-out approach is also lending new insight into another favored Victorian notion—that of emotional temperaments. Individuals who are fearful or resilient not only have characteristic behaviors, they have distinct patterns of brain activity, too.

The new findings have sparked excitement—and more research. In the past month, scientists have gathered at three major meetings on the science of emotions.* And many young clinicians are eager to enter the field, hoping for better ways to diagnose and treat emotional disorders, which afflict an estimated 15 million adults in the United States. Meanwhile, spending by the National Institute of Mental Health (NIMH) on the neurobiological basis of emotion has been relatively modest, but it's growing, reaching $6.3 million in fiscal year 1997. "We think the funding future is very bright," says psychiatrist Ned H. Kalin, who directs the 2-year-old Health Emotions Research Institute at the University of Wisconsin, Madison. Scientifically, "emotion is way behind in many respects," admits Antonio R. Damasio of the University of Iowa College of Medicine in Iowa City. "But it's catching up."

NED H. KALIN / UNIV. OF WISCONSIN SCHOOL OF MEDICINE

Frightful state. Fearful monkeys show high cortisol levels and right brain activity.

The anatomy of emotion

Emotions were long the province of behavioral scientists, while neuroscientists typically focused on cognitive or sensory functions such as vision. Emotions were considered "too vague and difficult to quantify," says Damasio. "It's not as bad as being a sex researcher," adds Stanford University psychiatrist David Speigel, who pioneered studies of stress and cancer survival, "but it comes close."

When researchers did begin to probe the neurobiology of feelings, they first focused on anatomy. They have traced emotional messages to such areas as the prefrontal cortex, just behind the forehead, and the ventral striatum, deep in the brain. But one of the most important emotional sites, as shown over the last 15 years by New York University neuroscientist Joseph LeDoux and others, is the amygdala—an almond-shaped structure in the center of the brain that is a key station in the processing of fear. Over the last several years, work in rats has identified finer and finer areas within the amygdala that are part of the neural fear circuits, says LeDoux. Researchers have shown, for example, that a cluster of neurons called the lateral nucleus brings the fear message in from the senses, and another cluster, the central nucleus, sends it out to other brain structures. Researchers are now pinpointing the neural fear connections at even finer scales.

Meanwhile, less detailed imaging studies show that when humans feel fear, the amygdala becomes active. "It's the hot area," says Yale University psychologist Elizabeth Phelps. She, LeDoux, and others report in a study in press in *Neuron* that when human subjects who have been conditioned to associate a visual cue with a shock see the telltale cue, blood flow to the amygdala increases. In another new study from Damasio's lab, patients with damaged amygdalas rated faces with negative expression to be as trustworthy as faces with positive expression. Without the amygdala to issue a warning, these patients apparently don't feel the usual wariness sparked by a stranger, Damasio said at the NIMH meeting.

Now that this wave of research has marked off some of the brain territory crucial to emotions, other researchers are studying the biochemical events that take place there. They are detailing how intense or even mundane emotional experiences leave their marks on the chemistry of the developing mammalian brain. For example, Trevor W. Robbins's group at the University of Cambridge has been comparing adult rats subjected to two different kinds of early life stress. One set of rats is stressed by being raised in solitary cages after weaning. The other group is stressed early by repeated separations from their mothers but then grow up among other rats.

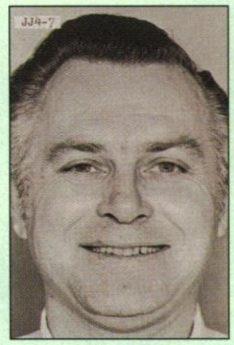
The two different stressors produced almost opposite behavioral syndromes, Robbins said at the Madison meeting. Isolation-reared rats appear frenzied, becoming overexcited in response to food cues and a new environment, and they are unusually sensitive to amphetamines—similar in some ways to the attention dysfunction seen in schizophrenia and other diseases. In contrast, maternally de-

* Wisconsin Symposium on Emotion, Madison, 17–18 April; Society for Neuroscience 1998 Brain Awareness Symposium, Chicago, 24 April; National Institute of Mental Health and Library of Congress, "Discovering Our Selves: The Science of Emotion," Washington, D.C., 5–6 May.

Unmasking the Emotional Unconscious

What—or where—is the unconscious mind? That question has long been the province of psychotherapists, but now neuroscientists are exploring the nature of awareness (*Science*, 3 April, pp. 59 and 77), and emotion researchers are joining in. A handful of clever—if controversial—imaging studies offer what may be a glimpse of the elusive unconscious mind at work by revealing different patterns of brain activity when people react to conscious and unconscious emotional stimuli.

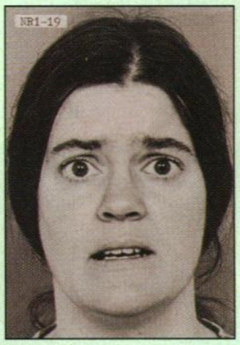
Most such emotion studies are based on a method perfected by neuropsychologist Arne Öhman of the Karolinska Institute in Stockholm. Researchers flash a fearful or angry face before subjects for several milliseconds, then flash a neutral face for a longer period. They also measure subjects' skin conductance—a reflection of sweat gland activity and a sign of nervousness. The neutral face apparently masks subjects' awareness of the negative face, as they report seeing only the second image.

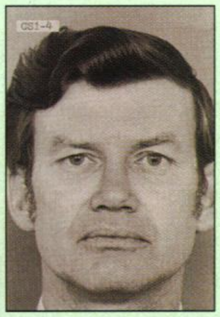


But the split-second glimpse of the negative face doesn't go completely unnoticed, as a team led by neuroscientists Paul Whalen and Scott L. Raush of Harvard Medical School and Massachusetts General Hospital in Boston reported in January in the *Journal of Neuroscience*. They used Öhman's "masking" method while scanning subjects' brains with functional magnetic resonance imaging, which reveals areas of high oxygen uptake. When the fearful face was flashed, the brain showed activity almost exclusively in the amygdala—a structure known to store emotional memory, especially fear. When a positive, happy image was flashed, the signal from the amygdala was reduced, showing that it was less involved.

A new study by Öhman and neuroscientists John Morris and Ray Dolan of University College London adds another twist. Researchers first conditioned subjects by repeatedly showing them the angry face followed by an obnoxious noise, training them, in classic Pavlovian fashion, to have a stronger reaction to the face. Then they did the masking experiment, using positron emission tomography (PET) scans.

Emotions on display. Happy, fearful, and angry faces are used in tests of emotional response.





PHOTOS: PAUL EKMAN/HIL/UCSF

The difference in brain activity when the subjects were aware and unaware of the face, Dolan told the 4th annual Wisconsin Symposium on Emotion last month in Madison, was "dramatic." When subjects did not report seeing the angry faces, they still registered an increase in skin conductance—and the right amygdala lit up in the PET scan. When subjects were aware of the threatening cues, the left amygdala showed activity, suggesting that the left side is involved with conscious response and the right with the unconscious mind.

"What these data are suggesting is that conscious awareness of a target stimulus . . . can modulate the associated neural response," Dolan said in his talk. Noting that language is mostly a left-hemisphere function, he speculated that it may help define consciousness.

But others, such as neuroscientist Richard Davidson of the University of Wisconsin, Madison, aren't quite convinced. "I would regard [the finding] as preliminary," he says. "We don't [know] at this point what the neural substrates are of emotional consciousness." Still, he and others are intrigued. What the masking experiments show, says Whalen, is that "some part of your body knows that something's out there even when you don't. That's interesting." –C.M.

prived rats seem to be less responsive to their environment and exhibit dull reactions, similar to human mood disorders, he says.

These behavioral syndromes correspond to different changes in the rats' brain chemistry. By inserting microprobes into rat brains and sampling neurotransmitters, Robbins's group found that the isolation-reared rats had higher levels of dopamine—a neurotransmitter thought to go awry in schizophrenia—in certain areas of the brain known to be involved in addiction and motor control. The maternally deprived rats, in contrast, were found in post-mortem tissue analyses to have reduced levels of the mood-mediating neurotransmitter serotonin—malregulated in depressed humans—in parts of the brain that process emotions and memory, Robbins reported at the Madison meeting.

In contrast, researchers have shown that intense mothering—presumably an emotionally positive experience for the infant rat—also has a powerful effect on brain development. Graduate students have long noticed that when rat pups are handled often by people, they grow up to be relatively less anxious and more resilient. The key, Michael Meaney of McGill University in Montreal, Paul Plotsky of Emory University in Atlanta, and their colleagues found last year, is the intense attention—licking, grooming, and nursing—that the rat mothers lavish on the pups each time they are returned to the nest (*Science*, 12 September 1997, pp. 1620 and 1659). The team found that a certain subset of "good mothers" gave even nonhandled pups this extra attention, and these pups showed similar beneficial effects.

And in the 28 April *Proceedings of the National Academy of Sciences*, researchers report neurochemical changes that correspond to these behavioral differences. Rats with especially attentive mothers have more receptors for neurotransmitters that inhibit the activity of the amygdala and fewer for corticotropin-releasing hormone, a stress hormone. Those changes in receptor numbers could explain why the adult animals display more equanimity in novel environments, says Plotsky.

Even subtle factors in a young animal's environment can color the emotional life of the adult. For example, in a study of 28 lab rhesus monkeys, Kalin and his colleagues identified a birth-order effect. Later born monkeys had lower levels of cortisol—a neurally controlled stress hormone—than first- or early-borns, the researchers report in the February *Behavioral Neuroscience*. Noting that experienced mothers have different mothering styles, Kalin suspects that the emotional state of the mother, who might be calmer with later borns, somehow affects the offspring's hormone levels.

Although no one is ready to make a direct leap from rats or monkeys to humans, the point is clear: Emotional events in young mammals can have major, long-lasting effects on the neurochemistry of the developing brain—and therefore on mood and behavior. "We're talking about the effects of very early experience on the adult brain, when most of the very early [hormonal] stressor effects have waned," says Robbins. "They are lasting effects." Adds Plotsky, "you can do something fairly mundane in the first days of the animal's life, and somehow this changes how that animal responds to its environment for the rest of its life."

Tracing temperament

But it's not only environmental effects—both extreme and subtle—that color emotional responses. Studies in both animals and humans support the idea that individuals carry certain dispositions throughout their lives. For example, Kalin has found that some infant monkeys are abnormally fearful, exhibiting a startled "freeze" behavior with very little provocation and having high baseline cortisol levels. And in humans, decades of study by Harvard University psychologist Jerome Kagan and his colleagues are revealing what look like innate, lifelong temperaments. Kagan's group examined 450 baby boys and girls, first at 16 weeks, then again at 14 months, 21 months, 4 years, and 7 years, by testing their response to cues they could see, hear, and smell, such as a cotton swab dipped in alcohol.

They found that 20% of the 16-week-old infants fell into a test category Kagan calls "high reactive": The tests made them fretful and agitated. Another 35% responded with little distress and low motor activity. Over time, some of the high reactives began to respond normally, while others began to show extreme shyness. None became a bold, fearless child, says Kagan. By age 7, about one-third of the high reactives had developed extreme fears compared with 10% of the others, Kagan said at the NIMH meeting.

Brain imaging complements these behavioral studies by showing a consistent package of brain activation that dovetails with temperamental differences. In Kalin's study, the abnormally fearful rhesus monkeys also had relatively more right frontal brain activity, as recorded by electroencephalograms.

Davidson finds a similar asymmetry in people. People who are negative or depressed according to standardized psychological tests tend to show more baseline prefrontal activity on the right, he says. And the happy-go-lucky folks who are more likely to bounce back when life throws a curve ball tend to show more activity in the left prefrontal cortex.

He speculates that the prefrontal cortex modulates the emotional activity of the amygdala. People with more left prefrontal cortex activity can shut off the response to negative stimuli more quickly, he says. "Being able to shut off negative emotion once it's turned on is a skill that goes with left activation." He adds that it's not yet known whether such temperaments are inborn or a product of very early life experiences.

Indeed, Davidson and others caution that they have far to go in explaining the full biological basis of our passions. LeDoux calls the state of the science of emotions "infantile," as the only emotion for which the neural hardware and software is well understood is fear, and even that has mostly been parsed in the rat. "Things have not entirely coalesced into a coherent picture," agrees NIMH director Steve Hyman. He hopes to help it develop, by pushing neuroimagers to test hypotheses about the neural circuits, and by "goosing cognitive neuroscience to start considering emotion." Darwin would no doubt approve and sympathize. Understanding the origin of emotional expressions remains a great difficulty, he wrote, and "it deserves still further attention."

–Christine Mlot

Christine Mlot is a science writer in Madison, Wisconsin.

PALEONTOLOGY

Biggest Extinction Looks Catastrophic

The most profound ecological disaster in the history of the planet struck at the end of the Permian period 250 million years ago, snuffing out about 85% of the species living in the ocean and 70% of the vertebrate genera on land. But devastating as this event was, until recently most paleontologists believed that the dying was long and slow, lasting 8 million years or more. And most looked to such causes as gradual sea level fall and climate change. Then last year new dates from Chinese rocks shrank the final pulse of marine extinctions to less than 1 million years (*Science*, 7 November 1997, p. 1017). Now more dating of the same rocks squeezes the disaster even further—and suggests a catastrophic cause, perhaps even a comet or asteroid impact.


D. ERWIN / NMNH / SMITHSONIAN INSTITUTION

End of an era. Late Permian rock (light band) records an isotopic shift.

The new results, reported on page 1039, show that a shift in the ratio of carbon isotopes recorded in marine rocks—an event intimately tied to the extinctions—lasted perhaps as little as 10,000 years. "It's the final nail in the coffin of those who say the extinction was prolonged," says paleontologist Paul Wignall of the University of Leeds in the United Kingdom.

The telltale rocks, near the village of Meishan in southern China, are beds of ancient marine sediments that record the disappearance of marine animals and, at the same time, a huge spike in the ratio of carbon-13 to carbon-12. The isotopes, taken from the rock itself, offer a more continuous record than fossils, which are subject to the vagaries of preservation. So geochronologist Samuel Bowring of the Massachusetts Institute of Technology, paleontologist Douglas Erwin of the National Museum of Natural History in Washington, D.C., paleontologist Jin Yugan of the Nanjing Institute of Geology and Paleontology in China, and their colleagues applied a well-established dating technique—based on the clocklike radioactive decay of uranium to lead—to volcanic ash layers scattered through the rock beds. The team's dates showed that the isotopic drop and a partial recovery took 165,000 years at most, and possibly as few as 10,000 years.

Such a dramatic, rapid shift in oceanic carbon isotopes requires an equally dramatic explanation—perhaps that the microscopic plants that maintain a normal carbon isotopic ratio in the ocean were suddenly nearly wiped out, say Bowring and colleagues. That makes falling sea level, for example, an unlikely driving force, notes Erwin.

The researchers speculate that the ultimate culprit was volcanism—the massive eruption of the Siberian Traps, which began at or within a few hundred thousand years of the boundary and ended in less than a million years. The global haze of sulfur particles from the eruption—the largest ever on land—may have caused a sudden chill by reflecting sunlight, or massive carbon dioxide emissions might have led to prolonged greenhouse warming, the team speculates. Or perhaps these direct volcanic effects induced indirect effects, such as a sudden overturning of the ocean, that both killed off species and triggered the isotopic spike.

It's even possible that a huge impact was the culprit, say Bowring and Erwin. If the impactor was a comet, its considerable load of organic material, which would have contained isotopically light carbon, might have directly produced the spike. For now, the ultimate cause remains a mystery. But "whatever happened," says Erwin, "it happened very quickly."

–Richard A. Kerr