Scientists Find Connections in the Brain Between Physical and Emotional Pain

Brian Vastag

POETS MUSE ABOUT THE AGONY OF a broken heart. Losing a friend hurts, and rejection can feel like a kick in the gut.

It turns out that these expressions are more than metaphorical. When Wake Forest University psychologist Mark Leary, PhD, investigated the linguistics of pain, he discovered that the overlap is not a coincidence of English. Each of the 15 languages he analyzed likened emotional pain to physical harm.

Scientists are beginning to understand why. It turns out that the brain processes both experiences in much the same way. While a large part of how the brain responds to physical pain remains mysterious, a series of recent discoveries has unveiled an evolutionary efficiency: the brain circuits and structures that respond to a twisted ankle also recognize a stinging rebuke.

DEPRESSION CONNECTION

For decades, physicians have known that physical pain and depression are intertwined. Chronic pain can cause depression, while depression can heighten pain. In fact, up to 80% of patients with depression present with mainly physical symptoms (*Am J Psychiatry*. 1993; 150:734-741).

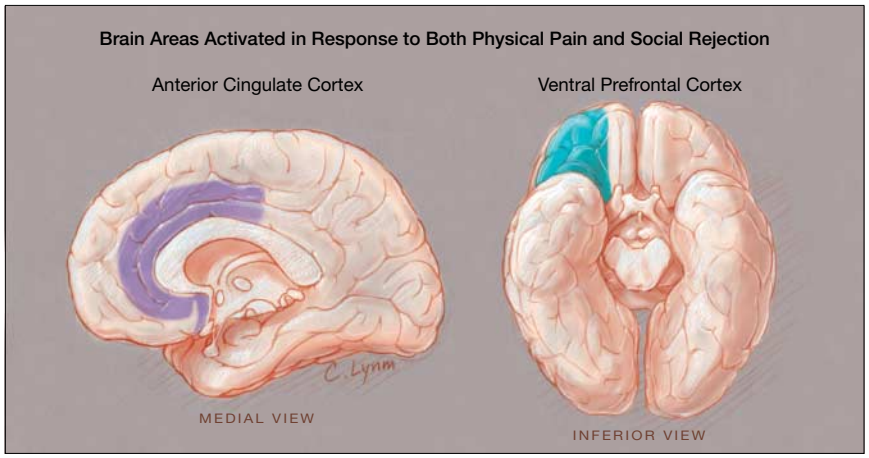
Thirty years ago, the first empirical evidence of a neurochemical overlap between pain and depression appeared when physicians discovered that small doses of tricyclic antidepressants can ease chronic pain. The phenomenon is so well-known that tricyclics are considered a first-line therapy for fibromyalgia and other poorly understood pain syndromes (*Curr Opin Investig Drugs*. 2002;3:454-458). The latest research continues to bear out the benefit of these older antidepressants. One recent study found that in patients with chronic tension headaches, tricyclics work better than relaxation strategies; combined, the two approaches proved synergistic (*JAMA*. 2001;285:2208-2215).

Newer antidepressants show promise, too. A few clinical studies have found that drugs that work on serotonin and norepinephrine—two neurotransmitters that help regulate mood—can relieve some chronic pain, including migraine headaches. One review found that venlafaxine, the best studied of the newer antidepressants, is just as efficacious against neuropathic pain as the tricyclic antidepressants, with fewer adverse effects (*Minerva Anestesiol*. 2002;68:105-114). However, a paucity of data led those authors and others to call for randomized clinical trials of newer antidepressants for chronic pain.

One connection between mood and chronic pain, then, lies with the so-called monoamine neurotransmitters, serotonin and norepinephrine. Cells heavy with these signaling molecules sow axons into essential mood-regulating areas of the brain. But these cells also send fibers down the spinal cord, where they help regulate external and internal sensation, according to research from Stephan Stahl, MD, PhD, a psychopharmacologist at the University of California, San Diego.

SENSORY GATEKEEPING

When the body is functioning normally, serotonin and norepinephrine circuits suppress routine autonomic input, like that from the stomach during digestion, and somatic input, like that from the musculoskeletal system. This prevents the brain from wasting en-



Imaging studies have revealed that the emotional pain of social rejection activates two brain regions that are also important in the response to physical pain. Pain activates the anterior cingulate cortex, which signals higher brain regions that impel an individual to act to stop the pain; social rejection similarly triggers activity in this region. Activation of the right ventral prefrontal cortex appears to help dampen the distress of both physical pain and social exclusion.

ergy on irrelevant details. But in depressed people, these routinely ignored sensations may reach the brain.

"It's entirely possible that a malfunctioning of these descending serotonergic and noradrenergic pathways allows routine sensory input to be felt as uncomfortable or even painful," said Stahl. "When depressed patients complain of headache, abdominal pain, or musculoskeletal pain in the lower back, joints, and neck . . . these sensations have escaped up the spinal cord and into the brain where they are interpreted as pain." Stahl recommends antidepressants with serotonin and norepinephrine action for depressed patients with pain.

INHERITED DIFFERENCES

Researchers at the National Institute of Alcoholism and Alcohol Abuse (NIAAA) recently published a genetic finding that also implicates norepinephrine (*Science*. 2003;299:1240-1246). In a search for individual differences in response to pain, the team came across an enzyme, catechol-O-methyltransferase (COMT), that metabolizes both norepinephrine and dopamine. Individuals carry one of three versions of the *COMT* gene that produces enzymes with low, medium, or high efficiency.

During their most recent work, the researchers, led by NIAAA's David Goldman, MD, subjected 29 people to painful saline solution injections. Those with the high-efficiency COMT experienced less subjective pain than those with the low-efficiency enzyme. Positron emission tomography scans confirmed the phenomenon: subjects with high-efficiency COMT displayed more activation of pain-relieving opioid receptors in certain brain structures than those with low-efficiency COMT. These differences were largest in the thalamus, a key sensory relay station, and the amygdala, which sends out fear and distress signals to other parts of the brain. Recent animal research also supports the idea that soothing the amygdala will inhibit pain (*Nature*. 2003;424:316-320).

Perhaps the most striking example of the brain's parallel processing of emotional and physical pain comes from a group at the University of California at Los Angeles (UCLA). Using functional magnetic resonance imaging (MRI) scans, which produce real-time maps of blood flow, the researchers found that social rejection lights up two brain regions key in the response to physical pain (*Science*. 2003;302:290-292).

KEY BRAIN REGIONS

The first area, the anterior cingulate cortex, acts as a neural alarm system, said Matthew Lieberman, PhD, assistant professor of psychology at UCLA. Pain, as the most primitive "something is wrong" signal, strongly activates this area, which then sends signals to higher brain regions that prompt the individual to act to stop the pain.

The second area, the right ventral prefrontal cortex, helps dampen the emotional distress caused by pain. Activation of this area lessens pain response in rats, and also appears to improve pain symptoms in humans given placebo, said Lieberman, citing his team's own unpublished work.

It turns out that these two regions also activate during social rejection. To test this idea, the UCLA team recruited subjects to play a game of "cyberball" while inside a functional MRI scanner. Participants were told that they would be throwing a virtual ball to two other study subjects. They were then scanned as the other players—computer simulations, really—stopped throwing the ball to them.

The results were dramatic. As a participant felt more excluded, the anterior cingulate cortex became more active.

"This was a powerful response," said Lieberman. "Anything that looked like exclusion triggered it."

Conversely, as the person felt less excluded when the ball was thrown to them, the right ventral prefrontal cortex displayed more activity. In other words, said Lieberman, the prefrontal cortex area dampens the distress signal sent from the anterior cingulate cortex.

He said that the study provides compelling evidence of the evolutionary piggybacking of social attachment to pain response. Because young mammals need to be near their caregivers to survive, it makes sense that their brains register painlike alarm in response to rejection or exclusion. The area of the anterior cingulate cortex most activated by rejection, said Lieberman, overlaps with the area activated by internal, rather than external pain. That means rejection "feels more like a punch in the stomach than a broken arm," he said.

Jaak Panksepp, PhD, a neuroscientist at Bowling Green University in Bowling Green, Ohio, said that the study by Lieberman and colleagues marks the first attempt to map emotions onto pain centers in the human brain. Since the 1970s, Panksepp has studied the neurochemistry of emotion in rats and other laboratory animals. His most robust finding is that small doses of opioids diminish the cry response in young animals separated from their parents. Again and again, "trickle doses" of opioids soothe the frightened animals. "The animals are not simply being drugged," he said, because the animals do not act sedated.

Panksepp would like to see the UCLA group explore similar research; he thinks that opioids may well dampen the anterior cingulate cortex during the cyberball challenge.

"For thousands of years, sensitive physicians have known that opioids ease social pain," said Panksepp, who wrote a commentary that accompanied the UCLA report (*Science*. 2003; 302:237-238).

Individuals who abuse opioids may simply be searching for an ersatz social balm, a replacement for human warmth. In the same vein, those suffering from depression and other emotional pain could conceivably benefit from small doses of opioids. Although the idea is controversial, Panksepp is among a group of researchers who believe this line of research could bear fruit.

"We might just discover a whole new type of antidepressant," he said. □