

# MRI Captures Differences in Pain Perception

*Statistically significant differences in brain activity found beyond the thalamus but not within it.*

BY JOHN R. BELL  
Associate Editor

BETHESDA, MD. — Pain perception, far from being the simple one-directional process first proposed by Descartes in 1664, appears to be modulated by several psychological, genetic, and other factors specific to the individual experiencing it, several presenters said at a meeting sponsored by the National Institutes of Health's Pain Consortium.

Robert C. Coghill, Ph.D., of Wake Forest University, Winston-Salem, N.C., noted that subjective factors influencing pain perception include the environment in which the pain is experienced, as well as the person's memories of past experiences with the particular stimulus and future implications associated with it.

"It's a complex combination of afferent information with who the person really is—what they're thinking about, what that stimulus means to them," Dr. Coghill said.

As evidence of this subjectivity, he noted a "tremendous" variability among 17 normal, healthy individuals' perceived intensity of a pain stimulus in a functional MRI study that he and his colleagues conducted.

He noted that brain activity in the highly sensitive participants was greater than in the less-sensitive subjects as assessed on fMRI; the highly sensitive subjects also had activity in brain areas different from those in the less-sensitive subjects. These findings show that the subjects had a physical difference in the way they experienced pain, correlating with their self-reported sensitivity to the stimulus.

However, the investigators were surprised to note no such differences in activity within the thalamus. The fact that there were statistically significant differences in activity beyond the thalamus but not within it led his team to theorize that many differences in pain are not attributable to a bottom-up process but to a top-down process.

"Maybe these individuals are getting a generally similar input from their peripheral nerves through their spinal cord up into their thalamus," he said. "Then, once it gets to the thalamus, and gets beyond and starts to get integrated into who that person really is—maybe that's where the individual differences are emerging."

This idea led Dr. Coghill and his colleagues to investigate expectations as the source of such differences, by using a previously devised expectation model he called the "the stew-in-your-own-juices paradigm."

Expectations, along with desire, he noted, "are a fundamental component of the placebo response" and are easy to manipulate and control. Moreover, they result from a person's experience with a particular stimulus to form an expectation for future experiences.

The investigators played an audio tone for the participants before subjecting them to a thermal pain stimulus; the longer the interval between the tone and the stimulus, the hotter the stimulus was. Thus participants were trained to expect pain based on the length of the interval. The investigators then gave subjects a tone/stimulus interval leading them to expect less pain—but instead gave them the most severe stimulus. All 10 subjects, true to their training, reported less pain, and their pain-related brain activation also declined.

"The experience of pain is really unique from one individual to the next," Dr. Coghill said. "Our sensory

reality is highly subjective; it's shaped very much by what we think it's going to be."

When asked what physicians should say to patients before administering a potentially painful procedure, he responded, "Certainly, the nurse with the big, huge needle full of tetanus immunization or whatever, saying, 'This won't hurt a bit' is a problem, because ... expectations are created, and immediately you realize that they're not valid."

Dr. Coghill suggested telling patients honestly that pain might be forthcoming—but also giving them a projected duration of the pain.

The differences in pain perception may also be a function of attention and emotion, M. Catherine Bushnell, Ph.D., of McGill University, Montreal, said in her presentation. She noted clinical and anecdotal evidence showing the effect of attention on pain perception—including human and animal studies that, like Dr. Coghill's, presented subjects with a pair of painful heat stimuli and a pair of sounds.

Subjects were asked to detect subtle differences in one stimulus or the other. By making the task more difficult, the researchers increased the subjects' level of attention on the task. They found that when subjects were more focused on the painful stimuli, there was more activity in corresponding regions of the brain, she said.

Dr. Bushnell also explained that some experiments can arouse a sympathetic reaction, which involves the cardiovascular system as well as emotions, as manipulation

of subjects by tension tasks often does, she noted.

To separately examine the effects of mood and attention on pain perception, she and her colleagues performed an experiment that, instead of an auditory stimulus, used an olfactory stimulus, because smells "have strong emotional impact on people," she said.

The investigators determined odors each patient did not like and then performed essentially the same comparison test as before, but using two odors with the two painful heat stimuli.

They found that regardless of where the subjects' attention was focused, if the odor was pleasant, they were in a good mood, but a bad odor always put them in a bad mood.

Attention significantly affected subjects' ratings of pain intensity but not of pain unpleasantness, whereas odor, the more emotionally fraught stimulus, had a strong and significant effect on unpleasantness and thus mood but no such effect on intensity.

She concluded that psychological factors might contribute to many pain states—for example, allodynia, in which a light touch can elicit severe pain. In such cases—including in experiments conducted by her pain clinic—the patient's perception is borne out by what is happening in the brain.

When asked in a panel discussion whether the ability to divert attention from one's pain could be affected by cognitive factors, she alluded to research findings that chronic-pain patients with more solicitous spouses reported more pain and had more activation of the pain region in the brain than did those with less solicitous spouses.

"By constantly asking a patient about their pain, you're focusing their attention on their pain," Dr. Bushnell said.

Roger B. Fillingim, Ph.D., of the University of Florida, Gainesville, presented a discussion of the individual factors affecting pain perception, which can include gender, ethnicity, physiological and psychological states, and genetics. He cited previous research from his laboratory showing that men were able to tolerate ischemic pain longer than women could.

Dr. Fillingim also discussed an analysis showing that for ischemic pain, heat, pressure, and temporal summation of heat pain, the group with the highest pain sensitivity was more heavily populated by women and ethnic minorities. He cautioned, however, that such studies rely on self-reported pain thresholds.

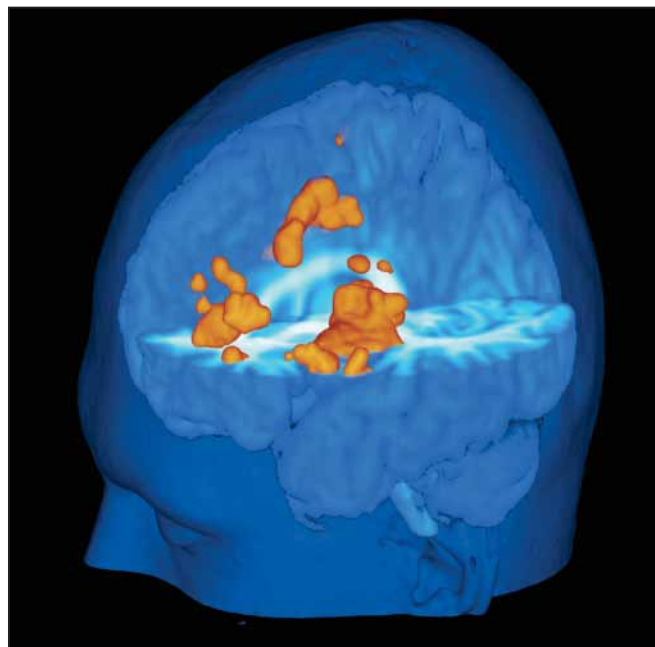
To avoid this limitation, his group performed a study in which they induced a leg-muscle reflex normally correlated with pain. They found that African Americans responded to a lower stimulus intensity than whites did.

In the area of gender differences, Dr. Fillingim's group found that for all pain measures (heat, cold, ischemic, and pressure pain), men had greater-than-average self-reported tolerance, whereas women had less than the mean. This may be influenced by attitudes toward pain, such as catastrophizing, he noted.

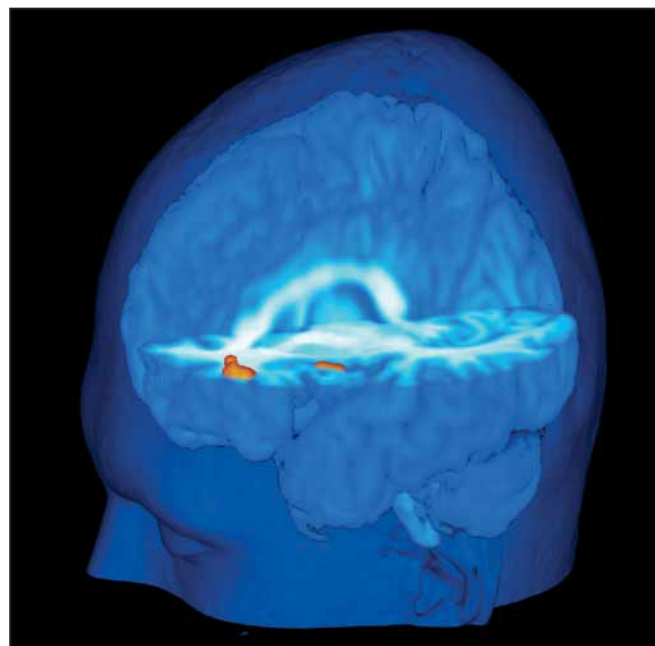
But interestingly, positive affect was correlated with decreased pain sensitivity only in men. Analgesic responses were less consistent; morphine or pentazocine showed only insignificant sex differences in a study by his group. However, negative affect in men predicted less analgesia but had no effect on women's responses to pain medication. The same was true for catastrophizing.

There are also genetic factors that research has shown might influence pain and analgesia, Dr. Fillingim said. In particular, an allele of the *OPRM1* gene predicts lower pressure-pain sensitivity in men. This allele is rare in African Americans but more common in whites and Hispanics, he noted. But only in whites did this allele seem to confer less pain sensitivity; the opposite was true in Hispanic subjects.

It's important to determine which factors predict individual differences in pain response, he emphasized, so that future treatment approaches can be tailored to each patient. ■



**Activation (yellow) is visible during pain stimulation; the subject expected the administered 50° C stimulus.**



**There was less pain-related activation during the same stimulation when the subject expected a reduced stimulus.**

IMAGES COURTESY DR. ROBERT C. COGHILL/WAKE FOREST UNIVERSITY SCHOOL OF MEDICINE