

# Pain Management and End-of-Life Care CME Program

## Module 9

**Registration:** The registration page and test questions are at the end of this article. The 10 questions must be answered and submitted to the CSA in order to receive the CME credit. The full text of each module of this CME program, along with references, will be accessible through the CSA Web Site, [www.csahq.org](http://www.csahq.org), in the *Bulletin/Online CME* section and as part of the online *CSA Bulletin*.

**Fee:** This is a free service for CSA members. Non-members will be charged \$25 per CME credit hour. Your CME certificate will be mailed from the CSA office.

**Availability:** This module is available from March 31, 2006, until March 31, 2009.

**Target Audience:** California law now requires that every licensed physician complete 12 credit hours in pain management and end-of-life care by the end of 2006. This module fulfills one credit hour of CME toward that requirement. This program is intended for all licensed physicians, including anesthesiologists, residents, and physicians with an interest in pain management.

### Faculty and Disclosures for Module 9:

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All faculty participating in continuing medical education activities sponsored by the California Society of Anesthesiologists are required to disclose any real or apparent conflict(s) of interest related to the content of their presentation(s) or any of the industry sponsors of the meeting. In addition, speakers must disclose when a product is not labeled for the use under discussion or when a product is still investigational.

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For this program, Dr. Mackey has received speaker fees and honoraria from Pfizer and honoraria from Eli Lilly as a consultant.

## Pain and the Brain (cont'd)

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**CME Sponsor/Accreditation:** The California Society of Anesthesiologists is accredited by the Accreditation Council for Continuing Medical Education to sponsor continuing medical education for physicians.

The California Society of Anesthesiologists Educational Programs Division designates this educational activity for a maximum of 1 AMA PRA Category 1 Credit.™

**Evaluation:** An evaluation of Module 9 of this series is offered after the test questions. Please fill in your responses and return them to the CSA office.

**Objectives:** At the conclusion of this course, participants should be able to:

- Understand the role of the brain in the processing and perception of pain.
- Recognize the cognitive and emotional factors that modulate our experience of pain
- Discuss the role of neuroimaging in elucidating the mechanisms involved in pain processing and perception.

**Resources:** These materials, including questions, are offered online at the CSA Web Site at [www.csaHQ.org](http://www.csaHQ.org). Instructions for the *Bulletin* version are on the registration page.

# Pain and the Brain

## What We Have Learned from Functional Neuroimaging

*By Sean Mackey, M.D., Ph.D., Assistant Professor of Anesthesiology and Pain Medicine, Associate Director – Pain Management Division, Stanford University School of Medicine*

Dr. Mackey completed his BSE and MSE in Bioengineering at the University of Pennsylvania and received a Ph.D. in Electrical Engineering at the University of Arizona where he subsequently earned his medical degree. He completed his anesthesiology residency and pain management fellowship at Stanford and then joined the faculty. He is the Associate Director of the Pain Management Division and Co-Director of the Stanford Pain Research and Clinical Center—an interdisciplinary initiative to bring together researchers, clinicians, engineers, patients and their advocacy groups, and industry to work toward solving the problem of chronic pain. He directs an NIH-funded lab (Stanford Neuroimaging and Pain Lab) focusing on the neural processing of pain and neuronal plasticity in patients with chronic pain. Dr. Mackey's state-of-the-art work integrates multiple scientific disciplines to demonstrate the impact of

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*pain on the central nervous system. His work has generated significant interest in the media and the scientific community because of the insight it provides which was barely imaginable a decade ago.*

*Joshua P. Prager, M.D., M.S.  
Editor, CSA Pain Management and  
End-of-Life Care Program*

**P**ain hugely impacts the individual patient, their family, and society as a whole. It is a highly personal and subjective experience modulated by cognitive, emotional, and environmental factors. During the 1990s, designated the Decade of the Brain, investigators significantly advanced our understanding of the function of the brain through imaging techniques such as functional magnetic resonance imaging, magnetoencephalography, single-photon computed tomography, and positron emission tomography. These investigations revealed a complex neural matrix—termed the pain matrix<sup>1</sup>—involved in pain processing and perception, and laid to rest a previously controversial concept, confirming through neuroimaging that the brain/cerebral cortex is involved in pain processing. Recently, functional neuroimaging has provided us with useful information regarding: 1) brain regions involved in cognitive, affective, and physiological manipulation of pain; 2) neural plasticity associated with neuropathic pain conditions as well as other chronic pain disorders; and 3) the effects of therapeutic agents on central neural systems.

## Nociception vs. Pain

Pain has been defined by the International Association for the Study of Pain as “an unpleasant sensory or emotional experience associated with actual or potential tissue damage, or described in terms of such damage.”<sup>2</sup> This defines pain as a subjective experience; therefore, unlike many diseases such as hypertension or diabetes, there is no objective measurement for a patient’s pain. We must do our best to correlate objective data (physical exam findings, imaging results, lab tests) with the patient’s subjective reporting. Further complicating the problem is the fact that pain is often confused with the

Abbreviations Key	
<b>ACC</b>	anterior cingulate cortex
<b>DLPFC</b>	dorsolateral prefrontal cortex
<b>fMRI</b>	functional magnetic resonance imaging
<b>LBP</b>	low back pain
<b>MEG</b>	magnetoencephalography
<b>MRS</b>	magnetic resonance spectroscopy
<b>OFC</b>	orbitofrontal cortex
<b>PAG</b>	periaqueductal gray
<b>PET</b>	positron emission tomography
<b>PFC</b>	prefrontal cortex
<b>rCBF</b>	regional cerebral blood flow
<b>S1</b>	primary somatosensory cortex
<b>S2</b>	secondary somatosensory cortex
<b>SMA</b>	supplementary motor area
<b>SPECT</b>	single-photon computed tomography

## **Pain and the Brain (cont'd)**

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concept of nociception—the neural signals generated and transmitted to the spinal cord and brain in the face of stimuli that are potentially or actually tissue-damaging. Pain, in contrast, requires a functioning brain to process these nociceptive signals and translate them into a subjective experience.

This contrast is particularly important in chronic pain conditions where there is a lack of objective tissue damage but pain is still present. These neuropathic or non-nociceptive conditions are often the result of dysfunction or damage within the spinal cord, brainstem, or brain. It is this damage to the peripheral and central nervous system that warns us of actual or potential tissue damage. However, with neuropathic pain, these signals have become maladaptive in that they impart no beneficial survival value. Chronic neuropathic pain becomes insidious in that it is often associated with depression, anxiety, decreased libido, altered appetite, and sleep disturbances.<sup>3</sup>

### **Functional Neuroimaging and the Brain Regions Involved in Pain**

Investigators using functional neuroimaging techniques have identified a variety of human brain regions—both cortical and subcortical—involved with the cerebral response to noxious stimuli. These regions include the primary and secondary somatosensory cortices, thalamus, the anterior cingulate cortex, prefrontal cortex, and the insular cortex.<sup>4-6</sup> Additional regions less frequently identified and still somewhat controversial are areas such as the premotor cortex, supplementary motor area, parietal cortex, amygdala, basal ganglia, cerebellum, and striatum.<sup>7</sup> Researchers have confirmed that specific brain regions encode both the intensity and/or unpleasantness of the pain experience. The regions correlated with pain perception are the ACC, posterior cingulate cortex, contralateral primary and secondary somatosensory cortices, medial PFC, insular cortex, parietal, SMA, motor cortex, premotor areas, cerebellum, putamen, thalamus, and PAG.<sup>8</sup> Recently, a study found that in highly sensitive vs. low sensitive individuals, the highly sensitive group showed greater activity in S1, ACC, and PFC.<sup>9</sup> This study helped us to better understand the neural physiology of what we intuitively already know—that there is a wide variation in people's perception to the same nociceptive stimulus.

### **Emotional and Cognitive Influences on Pain**

The intensity and unpleasantness components of pain correlate well with the level of noxious stimulation. We know, however, that the pain experience can be significantly modulated by our own thoughts and feelings. Factors that modulate our perception of pain include attention, fear, anxiety/anticipation, depression, and placebo. Each have been shown to impact the way we perceive

## **Pain and the Brain (cont'd)**

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pain, and there is an increasing number of functional neuroimaging studies investigating how these factors affect pain perception and activity in the brain.

### **Attentional Effects on Pain**

There have been anecdotal reports for centuries of people who suffer traumatic injuries and yet experience little or no pain. Furthermore, it is well established that distraction from a noxious stimulus results in a decreased perception of pain.<sup>10</sup> Distraction is a technique utilized by chronic pain patients in their management and takes many forms. Walking the dog, listening to music, reading a book, and working are just some examples. Attention to a different task or cognitive distraction have been shown to attenuate activity in the ACC, insular cortex, thalamus, somatosensory regions, and the PAG.<sup>11</sup>

Attention to pain, however, has produced varied results, sometimes enhancing pain perception and sometimes reducing it. The variability may be gender-related and potentially due to differences between normal subject populations and pain patients.

The neural correlates responsible for attentional modulation of pain are not known. Data suggest multiple levels of the central nervous system are involved. One such system is the opiate-sensitive descending and ascending pathways: a pathway from the frontal cortex to the amygdala, PAG matter, rostral ventral medulla, and finally the dorsal horn of the spinal cord, as well as ascending pathways through the medial thalamus to the ACC.<sup>12</sup>

Although data is limited, studies have demonstrated that patients with chronic pain have an impaired ability to distract from their chronic pain independent of their pain intensity. These studies strongly suggest cortical and/or subcortical dysfunction as a cause for this impairment with probable areas including the orbitofrontal cortex and ACC. Another method of neuroimaging—volumetric brain morphometry—has characterized changes in anatomical gray and white matter in patients with chronic back pain and found that chronic pain patients showed 5 percent to 11 percent less gray matter, particularly in the PFC regions, an area strongly associated with attentional modulation.<sup>13</sup> This loss was equivalent to 10 to 20 years of normal aging.

### **Anticipation, Fear, and Anxiety Effects on Pain**

Expectation and anticipation of pain are known to influence the immediate unpleasantness of pain. Uncertain pain has been demonstrated to increase unpleasantness and to result in less pain tolerance compared with certain pain. There also is evidence in humans that acute stress can activate the pain modulating circuit that contributes to analgesia. This may be achieved by the stress

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regulatory systems including endocrine, autonomic, immune, and opioid systems. A small number of studies have examined the neural mechanism underlying the anticipation of pain<sup>14</sup> and showed that the expectation of pain activated the medial frontal lobe, insular cortex, and cerebellum that were neighboring, but did not activate locations that mediated pain experience itself.<sup>15</sup> Recently, it has been shown that most of the brain systems associated with pain processing can be activated by anticipation of a painful stimulus; however, the anticipatory responses are smaller than the pain intensity-related responses.<sup>16</sup>

### **Effects of Mood on Pain**

Mood and emotion have also been shown to alter pain perception, although dissociation of mood and attention has been difficult and may have confounded previous reports. Manipulations positively affecting mood or emotion—such as soothing music, pleasant pictures and humorous films—generally reduce pain perception. However, manipulations negatively affecting mood or emotion have not always been consistent.

People who are fearful of pain tend to report more negative pain experiences. Those with a high fear of pain exhibited a selective attentional bias towards pain-related information, compared to those classified as low for the fear of pain. We recently investigated the effects of fear and anxiety related to painful sensations as a means of explaining individual differences in pain perception,<sup>16</sup> and we identified that fear of pain correlated strongly with lateral orbitofrontal brain activation—a region associated with response regulation. Anxiety related to pain correlated with medial prefrontal activation—a region associated with self-focused attention.<sup>17</sup> We believe that these psychological factors may play a significant role in explaining the differences in pain perception related to emotion.

Studies on the attentional, anticipatory, and other cognitive modulations of pain, together with the biochemical and anatomical understandings of analgesia, provide us with insights into the top-down and bottom-up plastic changes that occur in the central nervous system. Functional neuroimaging research in this area has just begun, concentrating on the interplay between affect and pain perception. Future research using functional neuroimaging in this area is warranted and is likely to have a significant impact on cognitive and other therapeutic interventions.

### **Neuroimaging Chronic Pain States**

Evidence suggests that generation and maintenance of chronic pain, as opposed to acute pain, involves changes in central pain processing mediated through mechanisms of neural plasticity and ultimately leading to hyper-

excitability of central structures.<sup>17</sup> It has been thought for many years that acute and chronic pain are very distinct processes involving different pain systems (i.e., the medial system with chronic pain and lateral system with acute pain). So far, there is very little evidence from functional neuroimaging studies that acute and chronic pain are processed within different parts of the pain matrix. Neuroimaging studies in patients with peripheral or central nerve lesions have also implicated similar brain structures activated during experimental acute pain. Peripheral nerve lesions (compression, nerve section, or amputation) often lead to spontaneous neuropathic pain in the involved area. Imaging studies have demonstrated a decrease in rCBF in the contralateral thalamus in patients with neuropathic pain. Interestingly, deep brain stimulation of the contralateral thalamus in patients with neuropathic pain has been shown to provide symptomatic relief with accompanying increase in rCBF in this area as well as in S1 and insular cortex. Additionally, changes in the somatotopy of primary sensory cortex have been shown to occur in amputees and have correlated with their experience of phantom pain; similar findings have been found in low back pain patients.<sup>18</sup>

Magnetic resonance spectroscopy makes it possible to directly investigate tissue metabolism and biochemistry. Recent investigations have demonstrated differences in N-Acetyl aspartate concentration in patients with chronic LBP compared with controls, anxiety levels (high vs. low) and brain regions (dorsolateral PFC, orbitofrontal cortex, thalamus, cingulate), resulting in a three-way interaction.<sup>19</sup> There was a precise relationship between perception and brain chemistry in that sensory vs. affective pain was represented best in the DLPFC and OFC in chronic LBP patients, high vs. low anxiety in OFC in normals, and all four regions in chronic LBP patients, and the affective component of pain in the cingulate. It is expected that as the spatial and temporal resolution and the number of substances increase, this technique will become more prevalent on its own or in combination with other neuroimaging techniques with better spatial and temporal resolution.

The neuroimaging of brain activity in patients with chronic pain is still in its infancy. The preliminary data supports the notion that persistent chronic pain states involve functional abnormalities in the cortical and subcortical areas activated by noxious experimental stimuli in normal subjects.

### **Future Functional Neuroimaging Studies of Pain in Humans**

Advances in functional neuroimaging promise to provide unprecedented opportunities to explore the neural mechanisms underlying pain, linking decades of research in animal models to clinical practice. While the field of functional neuroimaging is coming of age, there are still many obstacles to

overcome. Many key regions that are known to be part of the pain matrix are subcortical regions or lie at the spinal cord level. They may involve small volumes that may be difficult to investigate with current functional neuroimaging technology because of what is being measured (e.g., fMRI measures blood oxygenation and flow, EEG measures extracellular, and MEG measures intracellular current). Furthermore, there are significant limitations in spatial resolution (e.g., PET, MRS) and in source localization (e.g., EEG, MEG). Studies using multi-modal imaging may help overcome this. In addition to spatial and temporal functional information, studies of anatomical and functional connectivity may prove useful in the converging evidence of the neural circuitry involved in pain perception and how cognitive and affective factors modulate pain. For example, diffusion tensor imaging provides microscopic structural information of oriented tissue *in vivo* noninvasively. White matter tract structure as measured by water proton, anisotropic diffusion, is highly sensitive to subtle changes and is being used in studies of cognition and various disorders. While studies of functional connectivity can be studied using fMRI, EEG, and MEG, issues related to signal detection and statistical inference remain. In addition, imaging techniques such as MEG are a valuable tool to measure the temporal relationship between brain regions. PET and MRS are also valuable in identifying the metabolism and specific neurotransmitters involved in pain processing. The advent of real-time fMRI is another exciting tool that may be useful in the studies of pain. Recently, we studied chronic pain patients and healthy individuals by externally applying pain to elucidate whether one can learn to modulate the perception of pain using feedback of fMRI BOLD signals of brain regions related to pain in real time.<sup>20</sup> This technique not only provides causal evidence between certain brain regions and the perception of pain, but also may have therapeutic potential. These directions will further shape our understanding of pain perception and may be useful in assessing or developing new or existing treatments.

### Conclusion

Pain remains a serious health care problem, affecting millions of individuals, costing billions of dollars, and causing an immeasurable amount of human suffering. In designing improved therapies, there is still much to learn about peripheral nociceptors, nerves, spinal cord, and brainstem modulatory systems. However, it is the brain that presents us with an incredible opportunity to finally understand the experience we call pain. Functional neuroimaging is helping unlock the secrets of the sensory and emotional components of pain and its autonomic responses. These techniques are helping us to understand that pain is not a static disease with the pathology localized to the periphery, but instead a highly plastic condition affecting multiple central neural systems. Functional neuroimaging is transforming our understanding of the

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neurobiology of pain and will be instrumental in helping us design more rational treatments ultimately aimed at reducing its impact on our patients.

*Portions of this manuscript were paraphrased or taken verbatim from "Mackey S and Maeda F, Functional Imaging and the Neural Systems of Chronic Pain, Neurosurgery Clin North America, July 2004, Vol 15, No 3, 269-288" with permission of the publisher.*

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### **Pain Management and End-of-Life Care CSA Educational Program**

California law now requires that every licensed physician complete 12 credit hours in pain management and end-of-life care by the end of 2006. The CSA Educational Programs Division is providing a 12-module program to satisfy this requirement. Each article is written by a current or former director of a university-based pain management program in California. The full text of each article, along with references, will be accessible through the CSA Web Site. Joshua P. Prager, M.D., M.S., of the David Geffen School of Medicine at UCLA is the Coordinator of this series.

One module worth one CME credit hour is presented in each quarterly issue of the *CSA Bulletin* for Volumes 53-55 and it is also offered online through the end of 2006 at [www.csahq.org](http://www.csahq.org).

In this issue of the *Bulletin*, Module 9 is available. Modules 1 through 9 are available on the CSA Web Site now. You may also contact the CSA office at (800) 345-3691, and we will send you the materials by fax or mail.

Module 10 will be published in the Summer 2006 issue, Module 11 in the Fall 2006, and the final module, Module 12, will be available online by December 2006 to finish the series. It will also appear in the Winter 2007 issue for those who are still interested.

**Watch for Module 10 by Dr. Ann Lofsky, Volume 55, No. 2 issue.**

# Pain and the Brain (cont'd)

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## Registration

To register for the CSA CME Course in Pain Management and End-of-Life Care, Module 9, fill out this form. Then complete the test and the evaluation, and **mail or fax** all three to the CSA office at:

951 Mariner's Island Boulevard #270  
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### Pain Management and End-of-Life Care CME Course, Module 9

Available March 31, 2006, to March 31, 2009


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Mail with check payable to California Society of Anesthesiologists

## Pain and the Brain (cont'd)

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### Questions

1. The Decade of the Brain was in the:
  - a. 1970s
  - b. 1980s
  - c. 1990s
  - d. 2000s
2. Which of the following are associated with chronic neuropathic pain?
  - a. depression
  - b. anxiety
  - c. decreased libido
  - d. sleep disturbances
  - e. all of the above
3. Brain structure(s) associated with the perception of pain include the:
  - a. somatosensory cortex
  - b. anterior cingulate cortex
  - c. thalamus
  - d. insular cortex
  - e. all of the above
4. Patients with chronic back pain have been shown by neuroimaging to have reductions in cortical gray matter equivalent to how many years of aging?
  - a. 1-2
  - b. 4-8
  - c. 10-20
  - d. 30-40
5. The brain systems responsible for pain can be activated by anticipation of pain alone, without a nociceptive stimulus.
  - a. True
  - b. False
6. Patients who are more fearful of pain have greater brain activity in the:
  - a. Lateral orbitofrontal cortex
  - b. Primary somatosensory cortex
  - c. Auditory cortex
  - d. Visual cortex
7. Neuroimaging studies in patients with chronic pain have demonstrated a reduction of blood flow in the:
  - a. Secondary somatosensory cortex bilaterally
  - b. Broca's area
  - c. Contralateral thalamus
  - d. Supplemental motor cortex

# Pain and the Brain (cont'd)

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- 8. Somatotopic reorganization has been demonstrated in which brain region in patient with phantom limb pain?
    - a. Anterior cingulate cortex
    - b. Frontal cortex
    - c. Primary sensory cortex
    - d. Wernicke's area
  
  - 9. Magnetic resonance spectroscopy studies have demonstrated changes in N-Acetyl aspartate in patients with chronic low back pain in all the following brain regions EXCEPT:
    - a. dorsolateral prefrontal cortex
    - b. orbitofrontal cortex
    - c. thalamus
    - d. cingulate cortex
    - e. motor cortex
  
  - 10. Magnetoencephalography (MEG) is useful to image white matter tracts in the brain and spinal cord.
    - a. True
    - b. False
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## Evaluation of Module 9

As part of the CSA Educational Programs Division's ongoing efforts to offer continuing medical education, the following evaluation of this program is requested. This is a useful tool for the EPD in preparing future CME programs.

- 1. How well were the learning objectives of this program met?

Very Well	5	Above Average	4
Average	3	Below Average	2
Not Well at All	1		
  
- 2. How relevant was the information in this program to your clinical practice?

Very Relevant	5	Above Average	4
Average	3	Below Average	2
Not Relevantl	1		
  
- 3. How would you rate this program overall?

Excellent	5	Above Average	4
Average	3	Below Average	2
Poor	1		
  
- 4. Did you detect any commercial bias in this module?

Yes		No	
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