FUNCTIONAL MAGNETIC RESONANCE IMAGING STUDY OF PAIN AND EMOTION

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FUNCTIONAL MAGNETIC RESONANCE IMAGING STUDY OF PAIN AND EMOTION

ABSTRACT OF DISSERTATION

A dissertation submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy in the College of Arts and Sciences at the University of Kentucky

By
Claude Ervin Davis
Lexington, Kentucky

Co-Directors: Dr. Charles R. Carlson, Professor of Psychology and Dr. Lee X. Blonder, Associate Professor of Behavioral Science
Lexington, Kentucky
2003

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Neuroscience research has followed two fairly distinct paths in investigating central neural mechanisms of pain and emotion. Rarely have studies been conducted which intentionally combined painful and emotional stimulation while observing brain function. Theories of emotion and pain processing predict an interaction between pain and emotion such that emotional states may serve to both increase or decrease pain. This increase or decrease may also correspond to different effects on different dimensions of the overall pain experience as defined in pain neuromatrix theory. Theories of emotion begin with emotions as interpretations of bodily states, to more contemporary theories focusing on the functions of emotions. These emotion theories predict neuroanotomic relations between emotion and pain in the brain. Similarly neuromatrix theory predicts an affective dimension of pain experience, which has been defined in terms of pain unpleasantness and secondary affect, emphasizing the role of emotion in pain experience. To further explore the relationship between pain and emotion, in the present study, painful heat stimulation is applied to the face while simultaneously conducting whole
brain imaging using functional magnetic resonance imaging (fMRI). Also personal episodes involving anger, fear, and neutral emotion are recalled during fMRI both with, and without, painful heat stimulation. Similar brain regions are involved in processing pain, anger, and fear, and these responses compare favorably with those in the literature. The results also demonstrate that simultaneous emotional episode recall modulates the patterns of brain activity involved in pain. Anger recall especially seems to increase pain-related activity. The study allows greater understanding about the way that the brain's emotional processing networks for fear and anger affect pain experience and how pain affects the emotional processing network to produce affective experience, such as fear and anger, related to pain. Further application of these procedures to patients with chronic pain can aid understanding of central pathological mechanisms involved.

KEYWORDS: Functional Magnetic Resonance Imaging, Pain, Emotion, Anger, Fear

Claude Ervin Davis

October 25, 2003
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DISSEYATION

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Integration of Pain and Emotion Theory

In light of recent evidence from neuroscience research demonstrating activity in common brain regions, pain and emotion may share common brain networks. Recently, pain research has shifted from a focus on peripheral, spinal, and brainstem processes to focus on supraspinal or central processes. The current neuromatrix formulation of the gate control theory of pain predicts that central factors will play a principal role in pain modulation (Melzack, 1999; Melzack & Wall, 1965). The neuromatrix theory of pain states that the brain integrates inputs from the peripheral senses (touch, taste, smell, vision, hearing) and from internal states into an overall pain experience (Melzack, 1999). This integration yields three dimensions of pain experience: a sensory-discriminative dimension, an affective-motivational dimension, and a cognitive-evaluative dimension (Melzack, 1999).

The sensory-discriminative dimension of pain is subserved by those brain circuits or networks that define the specific location, intensity, quality, and duration of pain. The second dimension of the neuromatrix, the affective-motivational dimension, corresponds to the affective or emotional reaction to pain. This affective dimension encompasses the suffering aspect of pain, captured in typical adjective descriptions such as agonizing, fearful, frightful, terrifying, annoying, vicious, nagging, torturing, and dreadful typically reported by patients in pain, as on instruments such as the McGill Pain Questionnaire (Melzack, 1975). The affective dimension involves both emotion states, based on prior experience and learning, and emotion states related to the present experience of pain. The affective dimension could involve two parts: the feelings of unpleasantness related to pain, and other emotions associated with future implications of pain, termed secondary affect (Price, 2000). It is this affective-motivational dimension of pain that may be of most interest when considering relationships between pain and emotion function in the brain.

The third dimension of the neuromatrix is the cognitive-evaluative dimension that is related to the meaning of pain. For example, whether the pain results from a life threatening injury or minor cut, whether the pain represents a fundamental loss of ability
or limitation, a threat to survival, or simply a minor irritation and inconvenience, these are all judgments on the cognitive-evaluative domain (Melzack, 1971; Melzack, 1989, Melzack, 1990, Melzack, 1991, Melzack, 1995, Melzack, 1999). Emotions may influence the cognitive-evaluative dimension by changing meaning as it relates to pain. Emotions themselves are said to have a conscious cognitive, feeling component that has specific implications for the individual, as opposed to the automatic and unconscious processes thought to occur in emotional states (Le Doux, 1996).

Theories of emotion parallel pain theories, and may predict how the brain processes pain and emotion together. Because the pain neuromatrix contains an affective dimension, some of these pain processing brain regions, in theory, must also relate to emotional experience. Classical emotion theories relate physiological and sensory input to the experience of emotion (James 1884, Cannon 1932). Similarly, pain experience in neuromatrix theory is related to physiological and sensory experience. Initially it was hypothesized that the cognitive experience of emotion was secondary to physiological arousal and behavioral response (James, 1884). Subsequently, it may be hypothesized that emotional experience, as with pain experience, depends on multiple inputs from both within, and outside the body, and involves a network of brain regions. Higher-level processing, integration, and elaboration of incoming information from the senses, gives overall meaning to the emotion (James, 1884; Cannon, 1927; Cannon, 1932; Arnold, 1960; Schlacter, 1964; Lang, 1995; Lang, Bradley, & Cuthbert, 1998).

Schlacter (1964) proposed that ambiguous signals from the periphery arrive at the cortex along with information from other senses. The cortex uses this peripheral information, along with individual expectations and social context, to actively construct an emotional state. Arnold (1960) stated that emotion is a product of unconscious evaluation of situations as potentially harmful or threatening. Feeling, in contrast, is the conscious or cognitive evaluation of the unconscious appraisal.

Paralleling these emotion theories, current pain theory suggests that the brain assembles nociceptive and sensory information originating from the periphery to construct pain experience and emotional reactions to pain. Pain can also activate the stress response and the brain's emotional systems. Emotional states, such as anger and
Fear, can further modify the experience of pain, and frequently these negative emotions occur in conjunction with pain.

Brain research on emotions has focused on the brain regions that subserve the various emotional functions such as happiness, joy, fear, anger, sadness, and disgust (Le Doux, 1996). Similarly the proposed cognitive-evaluative dimension of pain is the conscious evaluation of information from other parts of the brain and nervous system. In summary, both emotion theory and neuromatrix pain theory have construed emotions and pain experience as resulting from a higher-level interpretation of bodily states and thus, it seems likely that emotion and pain processing should share common brain mechanisms.

Negative or aversive emotions (fear, anger, sadness, disgust) and positive or appetitive emotions (joy, happiness, love), and approach (happiness, love, anger) or avoidance (fear, sadness, disgust) emotions (Shaver, Schwartz, Kirson, & O'Connor, 1987; Izard, 1991) may be related to pain differently. Negative, aversive emotions such as fear and anger can provide strong motivations for action. Fear involves the tendency to avoid, and anger involves the tendency to approach. The present investigation is concerned specifically with how fear may relate to the tendency to avoid pain, and how anger, as an approach tendency, could interfere with effective treatment or modulate pain perception. Positive emotion such as joy, happiness, or love may tend to diminish or counteract pain and emotional suffering due to pain. Positive states may relieve or reduce pain, and have potential therapeutic effects in the treatment of chronic pain conditions. Little research, however, has explored the potential pain-reducing benefits of positive emotion (Bruehl, Carlson, & McCubbin, 1993; Waltz, Kriegel, & van't pad Bosch, 1998). The present study focuses on the negative emotions of fear and anger and pain, leaving positive emotion and pain for future study. Now, further details of the relationship between fear and pain, and anger and pain will be reviewed.

Relationship of Fear and Pain

Fear and anger have been studied frequently in relation to pain. Pain-related fears and avoidance have been shown to be related to disability in back pain patients (Crombez, Vlaeyen, Heuts, & Lysens, 1999). Anxiety and fear, however, are said to have divergent effects on the experience of pain, with fear decreasing pain, and anxiety.
increasing it (Rhudy & Meagher, 2000). Also, exposure to fear-producing electrical shocks reduced pain sensitivity, while anxiety produced by the threat of these shocks increased pain sensitivity (Buchel, Dolan, Armony, & Friston, 1999). Further understanding how fear and anger may relate to pain would help in predicting how these negative emotions may influence pain processing in different brain networks.

Relationship of Anger and Pain

Anger is a negative emotion that motivates an approach-oriented response to a perceived threat or harm. Anger involves retaliation or seeking of redress against the offending or blameworthy object or other person (Fernandez & Turk, 1995). Anger intensity, in chronic pain patients, was a significant contributor to reports of perceived pain interference and activity level (Kerns, Rosenberg, & Jacob, 1994) and inhibition, or non-expression of angry feelings, has been shown to be the strongest predictor of pain intensity and pain behavior. Anger may compound the effects of pain and depression, adversely affect psychosocial functioning, and have negative consequences for physical health and health habits (Fernandez & Turk, 1995). Several studies considering the relationship between anger and chronic pain showed that a high proportion of pain patients reported angry feelings with this anger being related to pain and life interference (Fernandez & Turk, 1995; Burns, Johnson, Mahoney et al., 1996; Burns, 1997; Okifuji, Turk, & Curran, 1999).

Brain Circuits for Pain and Emotion

Papez (1937) first proposed a neural circuit for emotion (the limbic system), which was later elaborated (MacLean, 1955). It is known that the brain processes emotional information and cognitive information in widely distributed regions, but research and theory of emotional processing in the brain are still developing (Le Doux, 2000). This emotion neural circuit involves connections from the hippocampal formation and amygdala (AM) to the hypothalamus, and from the hypothalamus to anterior thalamus and pre-frontal cortex. The anterior thalamus also connects to the cingulate gyrus. Other areas of association cortex are also connected to cingulate gyrus and
h Hippocampal formation (with reciprocal connections). The brain circuit for pain and emotion relies upon the reciprocal connections between the cingulate gyrus and hippocampus with prefrontal cortex, motor cortex, insula, and posterior parietal cortex (Price, 2000). In particular, the cingulate gyrus has principal connections with dorsolateral prefrontal cortex, hippocampus, and the amygdale complex, while the hippocampal formation connects with medial orbitofrontal cortex and parietal/occipital association areas (Miller & Cummings, 1999).

Pain Neuroscience Research

A recent review of neuroimaging research concluded that widely distributed multiple cortical areas process painful stimuli (Treede, Kenshalo, Gracely, & Jones, 1999). The areas shown to be involved in pain processing are the primary somatosensory cortex (SI) and secondary somatosensory cortex (SII), parietal operculum, insula, anterior cingulate cortex (ACC), and prefrontal cortex (PFC) (Treede et al., 1999). More than half of imaging studies of pain, reviewed in meta-analysis, have found activations in the insula, mid-ACC, and in the dorsolateral pre-frontal cortex (DLPFC) (Peyron, Laurent, & Garcia-Larrea, 2000). Fewer studies have found activity in the medial prefrontal cortex (MPFC) (18% of studies), and in the ACC (13% of studies).

In the PFC, activity of these regions with pain, perhaps represents the use of attention and memory networks in pain processing (Peyron et al., 2000). The frontal cortex is hypothesized to subserve the function of “second-order appraisals,” which involve secondary pain affect, and more elaborate reflection on experience related to that which one remembers or imagines (Price, 2000). These elaborations may include considerations of life interference, difficulty enduring pain, implications of pain for the future, threats to well-being, and other long-term implications of pain. This network of interconnected brain regions processes nociceptive input in series and parallel (Price, 2000). This proposed network of pain processing demonstrates how areas related to sensory information processing, such as the SI and SII, receive peripheral information from the spino-latero-thalamic pathway and relate to the sensory-discriminative dimension of pain processing. In parallel, the brainstem and medial nuclei of the thalamus relay peripheral
information to the amygdala, insula, and ACC, proposed as being involved in affective pain processing. In addition, the sensory areas (SI and SII) relay information to the insula and ACC through parietal pathways, while the ACC also has connections to prefrontal cortex possibly related to second-order appraisals and secondary pain affect (Price, 2000). Price characterized the affective dimension of pain as being comprised of feelings of unpleasantness due to pain, along with secondary affect related to long-term emotional feelings about having pain. Also lesion studies have revealed information about the role of the ACC in pain processing. In a study of 23 pain patients, 72 percent of patients who underwent bilateral anterior cingulotomies for chronic, intractable pain experienced long-term pain relief (Wilkinson, Davidson, & Davidson, 1999). Some patients experienced transient pain for several months after surgery before attaining more sustained relief. The patients, after surgery, were said to be less fixated and less aware of pain and more easily distracted from it (Wilkinson et al., 1999). It has also been suggested that cingulotomy decreases the affective responses to pain, but preserves the ability to localize painful stimuli (Peyron et al., 2000). For instance, a patient who had neurosurgical lesions of the fibre tracts connecting frontal lobes to subcortical structures (anterior internal capsule) for obsessive-compulsive disorder, experienced reductions in intensity and unpleasantness of acute heat pain stimuli and pain in the cold-pressor task, although tolerance times in the cold-pressor task were reduced (Talbot, Villemure, Bushnell, & Duncan, 1995).

Specific cortical areas, SI and SII, parietal operculum, insula, ACC, and PFC probably process pain in parallel because they activate simultaneously in response to painful stimuli (Treede et al., 1999; Price, 2000; Peyron et al., 2000). The SI and SII, insula, ACC, and PFC have also been shown to be active in processing fear and anger in neuroimaging studies and have been proposed as part of the emotion processing system (Beck & Fibiger, 1995; Morris, Friston, & Dolan, 1997; Morris, Friston, Buchel et al., 1998; Sprengelmeyer, Rausch, Eysel, & Przuntek, 1998; Baker, Shaw, Frith et al., 1999; Buchel, Dolan, Armony, & Friston, 1999; Hariri, Bookheimer, & Mazziotta, 1999; Shi & Davis, 1999; Adolphs, Damasio, Tranel, & Damasio, 1996; Adolphs, Damasio, Tranel, Cooper, & Damasio, 2000).
A variety of neuroimaging research studies have been carried out investigating either emotional or pain processing (for reviews see Le Doux, 1996; Iversen, Kupfermann & Kandel., 1999; Treede et al., 1999; Peyron et al., 2000; Price, 2000; Treede, Apkarian, Bromm et al., 2000). In a typical study, an emotional stimulus or pain stimulus, alternated with a neutral or baseline stimulus, is presented to subjects while undergoing functional neuroimaging. Brain activation maps using statistical parametric mapping may be constructed for individual subjects and averaged across groups of subjects using standardized anatomical transformations (Talaraich & Tournoux, 1988). The procedures are extremely useful in identifying key regions of brain activity in different emotion and pain states (Peyron et al., 2000; Price, 2000; Treede et al., 2000).

Table 1. lists brain regions that previous research has demonstrated to be involved in pain processing.

**Fear Neuroscience Research**

Recent animal research has investigated the neural circuitry in the brain associated with the processing of fear and pain (Bellgowan & Helmstetter, 1996; Shi & Davis, 1999) by using lesioning, drugs, and behavioral techniques. An aversive learning paradigm using painful shocks has been used to study the effect of induced lesions in specific regions of the rat brain amygdale (AM) upon learning and behavior (Parkinson, Robbins & Everitt, 2000). This research showed specific areas of the AM to be involved in classical conditioning of fear responses. Other studies using drugs which block anxiety and fear, showed which neural structures become less active in the presence of the drug, and thus which regions may have been important in a fear response. Hypoalgesia, or lowered pain sensitivity, occurs when an organism experiences intense fear, such as during a life-threatening attack. Fear-produced hypoalgesia was blocked in rats by lesions to a neurocircuit involving the medial geniculate nucleus (of the thalamus) which projects to the AM, the lateral and central AM, and periaqueductal gray (Bellgowan & Helmstetter, 1996).

The administration of fluoxetine (Prozac), which may lessen the neurobiological activity of the fear system, was shown to produce slower escape from foot shock and slower learning in shock-terminating shuttle tasks than controls while showing no actual
difference in sensory thresholds for shock or heat (Nelson, Jordan, & Bohan, 1997). In a study using early gene c-fos expression as a marker for neural activation, classically conditioned fear of footshock in rats activated c-fos expression in a large number of widely dispersed cortical and subcortical structures (including cingulate cortex, AM, and hypothalamus). Diazepam administration then reduced this expression in a dose-dependent manner, owing to diazepam's role in reducing the fear response by reducing the actions of the associated neural circuits (Beck & Fibiger, 1995). From these data it is speculated that the AM itself modulates nociceptive signals entering the spinal cord dorsal horn, probably through connections with the periaqueductal gray (Manning, 1998). Thus, the central and basolateral nuclei of the AM play a substantial role in fear conditioning and pain modulation. In rats, lesions in the caudal granular/dysgranular insular cortex, but not lesions in the intralaminar nuclei of the thalamus, blocked the conditioned acquisition of fear-potentiated startle. However post-training lesions of both areas did not prevent expression of conditioned fear. The authors concluded that two parallel pathways, a cortical (insula to AM) and a subcortical (thalamus to AM) pathway, are involved in relaying information to the AM during conditioning (Shi & Davis, 1999).

In humans, neuroimaging studies using positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) used exposure to emotionally expressive fearful faces or emotional words, and analyzed differences between these and neutral faces or words. These types of procedures provide a basis for studying the effects of fear on pain processing in humans using neuroimaging, and highlight brain regions of importance. Three studies used emotionally expressive faces to study fear-processing networks (Morris et al., 1998; Whalen, Rauch, Etcoff, et al., 1998; Kesler/West, Andersen, Smith, Avison, Davis, Kryscio, & Blonder, 2001). The results in one study showed the importance of AM processing by demonstrating enhanced activity in the left AM, left thalamic pulvinar, left anterior insula, and bilateral ACC during the processing of fearful faces. Specific AM responses were shown to predict facial-expression-specific responses in the extrastriate cortex, known to be associated with visual processing (Morris et al., 1998). Fearful faces selectively activated the left inferior frontal gyrus, while AM and fusiform gyri were activated in a neutral face versus scrambled (baseline) condition (Kesler/West et al., 2001). The third study demonstrated significantly increased
AM activation to covertly presented fearful facial expressions and decreased AM activation to happy faces in conjunction with increased activation (with both fear and happy) in the sublenticular substantia inominata (Whalen et al., 1998). Other studies using aversive fear conditioning have provided evidence that specific cortical regions are involved in this type of learning (Morris et al., 1997; Buchel et al., 1999). Because they use conditioning, these studies may highlight the processes occurring when a fearful emotional response is actually evoked in subjects. Classically conditioned aversive responses (fear conditioning) produced event-related fMRI activations in the ACC, the anterior insula and the hippocampus (Buchel et al., 1999). The ACC and insula are areas of cortex involved in fear and threat processing, while the hippocampus is associated with long-term memory and retrieval of explicit memories.

Emotional faces have also been used to study fear conditioning (Morris et al., 1997). Aversively conditioned, emotionally expressive faces produced PET activations of the pulvinar nucleus of the right thalamus with increases in salience and conflicts between the innate and acquired value of the stimuli. These activations correlated positively with increases in the right AM and basal forebrain (Morris et al., 1997). The results of these studies emphasize the existence of a network of brain regions subserving fear processing, and it is therefore expected that pain-related activity in areas of overlap (especially the insula, ACC, and PFC) may be modulated by fear-related stimuli. A recent meta-analysis of emotion studies showed that, in studies of fear, 64% found activity in the AM. A third of studies with fear found activity in the insula, and 27% found activity in medial and lateral PFC. Fewer than 20% of studies found ACC activations, and fewer than 10% observed activations in orbitofrontal cortex, posterior cingulate cortex, and mid-cingulate cortex (Phan, Wager, Taylor, & Liberzon, 2002). Brain regions, frequently observed during the processing of fear, are listed in Table 1.

**Anger Neuroscience Research**

Typical neuroimaging studies of anger in humans involve having participants recall autobiographical events that were associated with anger and view faces with angry expressions. A variety of brain regions activate under these conditions. In one study using fMRI, participants viewed photographs of faces showing angry, happy, sad, fearful, and
neutral expressions (Kesler/West et al., 2001). Viewing angry faces produced the most widespread activation of the four emotions presented. In a study by Baker et al. (1999), recollection of prior autobiographical, adverse life events associated with anger also activated the insula, ACC, inferior frontal, premotor cortex, and caudate nucleus. Work involving emotionally arousing films that induced actual emotion has demonstrated AM responses (Reiman, Lane, Ahern, Schwartz, Davidson, Friston, Yun, & Chen, 1997). The insula, ACC, and inferior frontal cortex have also been shown to be active in fear processing, implying that these regions could function as part of a general emotion processing system that subserves both fear and anger (Beck & Fibiger, 1995; Morris et al., 1997; Morris et al., 1998; Buchel et al., 1999; Shi & Davis, 1999). Right somatosensory cortex was shown to be involved in recognizing emotional facial expression, perhaps in generating a somatosensory awareness of the emotional state (Adolphs et al., 2000). This result demonstrates another parallel between emotion processing and pain processing, as the somatosensory cortex is involved in processing the awareness of the sensory-discriminative aspect of pain.

Both fear and anger were investigated using PET imaging using recall of personal episodes involving fear and anger to induce emotional states (Damasio, Grabowski, Bechara et al., 2000). The researchers also measured skin conductance changes and heart rate changes in response to emotional recall, to better confirm emotion states, in addition to having participants rate the emotional intensity of the particular emotion. The measured physiological parameters and emotion ratings were all significantly different from the measures during neutral states. With anger, brain-imaging data revealed activation of midbrain and pons, anterior and posterior cingulate, and insula, and deactivation of SII, and orbitofrontal cortex. The AM was not activated. With fear the midbrain was activated, the insula showed mixed activation, and left SII, hypothalamus, and orbitofrontal cortex deactivated. Again the AM showed no activation with fear, and this finding is consistent with other neuroimaging results using fear recall, rather than visual or auditory stimuli (Damasio, et al., 2000; Paun, Wager, Taylor et al., 2002).

Narrative scripts developed from autobiographical information were used to induce anger and neutral states in males, while brain activity was observed using PET imaging. Anger was shown to be associated with activation of the left orbitofrontal
cortex, right ACC (affective division) as seen in angry face processing, and bilateral anterior temporal poles (Dougherty, Shin, Alpert, Pitman, Orr, Lasko, Macklin, Fischman, & Rauch, 1999). Results did not show activation in the AM or insula as expected, although lesions to the AM have been shown to decrease aggression (Lee, Bechara, Adolphs et al., 1998). Anxiety and anger were studied using PET imaging by having subjects recall prior life events that involved anxiety or anger while viewing faces showing corresponding expressions. The anxiety and anger conditions produced increased regional cerebral blood flow (rCBF) in left inferior frontal and left temporal poles and decreased rCBF in the right posterior temporal/parietal and right superior frontal cortex compared to the neutral condition (Kimbrell, George, Parekh et al., 1999). A recent meta-analysis of emotion studies showed that, in studies of anger, 40% found activations of the ACC, thalamus, orbitofrontal cortex, MPFC, posterior cingulate cortex, and lateral PFC (Phan et al., 2002). Some studies (20%) found activity in the mid-cingulate cortex and insula.

Further work to induce anger, to directly compare emotions to one another, to enable ratings of subjective experience, and to measure arousal during target emotions can further enhance understanding of brain regions processing anger. The conclusions from presently available data emphasize the existence of a network of brain regions subserving anger processing, and it is expected that pain-related activity in areas of overlap (especially the insula, ACC, and frontal cortex) may be modulated by anger-related stimuli, and these regions are the focus of the present investigation. Brain regions, which have been frequently found to be active in anger processing, are summarized in Table 1.
Table 1. Brain Regions Frequently Activated in Pain, Anger, and Fear in Previous Neuroimaging Work.

<table>
<thead>
<tr>
<th>Pain</th>
<th>Anger</th>
<th>Fear</th>
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<tbody>
<tr>
<td>Somatosensory</td>
<td>Anterior Cingulate</td>
<td>Amygdala</td>
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<td>Insula</td>
<td>Thalamus</td>
<td>Insula</td>
</tr>
<tr>
<td>Mid-Anterior Cingulate</td>
<td>Orbitofrontal</td>
<td>Medial Prefrontal</td>
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<td>Dorsolateral Prefrontal</td>
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</tr>
<tr>
<td>Medial Prefrontal</td>
<td>Posterior Cingulate</td>
<td>Anterior Cingulate</td>
</tr>
<tr>
<td>Anterior Cingulate</td>
<td>Lateral Prefrontal</td>
<td>Orbitofrontal</td>
</tr>
<tr>
<td></td>
<td>Mid-Cingulate</td>
<td>Posterior Cingulate</td>
</tr>
<tr>
<td></td>
<td>Insula</td>
<td>Mid-Cingulate</td>
</tr>
</tbody>
</table>

Present Investigation Hypotheses

The present study examined the effects of fear and anger on pain processing in brain networks. The specific hypotheses were that:

1) Unique patterns of activity for each condition (pain, fear, and anger) will be observed as changes in the fMRI signal.

**Rationale:** It was expected that unique patterns of activity related to emotion recall alone, and to painful stimulation alone, would be observed in the regions of interest. Specifically, their proximity and/or overlay and possible functional relationship, could be described. Activations have been previously observed using neuroimaging with painful stimulation and with procedures involving fear and anger processing (Treede et al., 1999; Price, 2000; Morris et al., 1997; Baker et al., 1999).

2) Fear and anger will produce changes in the extent and magnitude of pain-related activity in the cognitive-evaluative and affective-motivational brain areas (ACC, insula, and PFC) for pain processing, but not in the sensory discriminative areas (thalamus, SI and SII).

**Rationale:** Activity with pain has been previously been seen in these brain regions. These regions are thought to be involved in the affective-motivational and the cognitive-evaluative dimensions of pain. These brain regions are common to the pain neural circuit and the emotion neural circuit (Papez, 1937; MacLean, 1955; Le Doux, 2000; Treede et
In pain neuromatrix theory, emotion should have an effect in the affective and cognitive dimensions, but not in the sensory dimension (Melzack, 1999). These predictions for the thalamus and somatosensory cortex reflect previous findings demonstrating changes in activity in the thalamus and somatosensory cortex with painful stimulation as reflecting the stimulus-related, sensory-discriminative aspect of pain processing, that is, the location, intensity, and stimulus-quality of pain. These activations are not expected to change dramatically, if at all, with the emotional stimuli because this sensory-discriminative dimension does not involve emotion, but more directly relates to the painful stimuli alone. For the brain regions involved in the affective-motivational and cognitive-evaluative dimensions of pain, it was expected that pain processing would be modulated by emotion. The brain areas thought to be responsible for affective and cognitive dimensions (the ACC, insula, and PFC) would show changes with emotion, whereas the brain areas related primarily to sensory processing (thalamus, somatosensory cortex) would not (Treede et al., 1999; Price, 2000; Peyron et al., 2000).

3) With anger specifically, pain activity will be modulated upwards in the insula, cingulate cortex, and PFC, while with fear, only the insula will be modulated upwards. The cingulate and PFC will have less activity in response to pain with fear.

Rationale: In the insula, the processing of pain information is said to be taking place in order to evaluate the threat of the pain stimulus (Price, 2000). For the negative emotion states (fear and anger with pain), the insula is expected to become more activated, because the emotion states could make the pain seem more threatening. The cingulate cortex and PFC are said to be involved in the affective-motivational dimension of pain experience. Pain-related activations in the cingulate cortex may be related to pain unpleasantness (Treede et al., 1999; Price, 2000; Treede et al., 2000). The emotion stimuli may be expected to modify the pain unpleasantness consistently with observed emotional effects of negative emotion in exacerbating chronic pain (Crombez et al., 1999; Pauli, Wiedemann, & Nickola, 1999). Consistent with the idea that pain would be more unpleasant in the presence of the negative emotions, the activity in the cingulate cortex would increase with anger. The literature shows that anger exacerbates the pain...
experience leading to more pain intensity, suffering, and greater disability (Fernandez & Turk, 1995; Okifuji et al., 1999; Burns et al., 1996; Burns, 1997). Fear has been specifically contrasted with anxiety as leading to a less-intense experience of pain, and somehow may block the emotional awareness of pain (Rhudy & Meager, 2000). Thus, activations in the cingulate cortex may be expected to decrease with fear. The decrease with fear would be presumably due to a hypothetical pain-blocking mechanism of fear. The assumption used in this study is that the function of the PFC occurs in conjunction with the cingulate cortex, highly interconnected with the prefrontal cortex, and which produces conscious awareness of emotional states, including pain-related emotions, and determines the long-term consequences, emotion feeling states, secondary affect, and meaning (the cognitive-evaluative dimension) of pain. Therefore, the PFC is expected to mirror the effects in the cingulate cortex in response to the emotion states during pain.

The regions of interest corresponding to the above hypotheses are summarized in Table 2 below.

Table 2. Brain Regions of Interest in the Interaction of Pain, Anger, and Fear.

1. Superior Frontal
2. Middle Frontal
3. Inferior Frontal
4. Medial Frontal
5. Anterior Cingulate
6. Cingulate
7. Posterior Cingulate
8. Insula
Chapter Two
Methods

Participants

Participants were twelve healthy, Caucasian female volunteers ages ranging from 18 to 41 (\( \bar{x} = 25.8 \) years, \( \text{sd} = 7.1 \)). They were right handed, with no first-degree biological relative who was left handed. The average years of education was \( \bar{x} = 16.5 , \text{sd} = 3.3 \). All participants were non-smoking, not on medication that could affect results, and were pain-free at the time of the evaluation. Participants were excluded if they had any of a variety of neurological, psychological, and other medical disorders that could affect the central nervous system. Participants had visual acuity of at least 20/25 based on a brief vision screening. The participants reported no history of chronic pain including face pain, headache, and back pain. They gave informed consent under an approved protocol of the University of Kentucky Medical Institutional Review Board and were paid $100 for their participation.

Visual Stimuli

The visual stimuli for the fear, anger, and neutral episode recall, consisted of visual cues (text was presented on a screen—the word “fear,” “anger,” or “neutral”) to recall fear and anger episodes, along with four keywords, which each individual participant had generated. The key words were used to help them in quickly recalling the specific episode. The keywords were specific for each individual and emotion, and derived from descriptions of the personal fear and anger experiences each participant recalled prior to the scanning session.

Presentation Apparatus

The images were presented using an NEC Multisync VT-440 high intensity liquid crystal display (LCD) projector that provided an image on a rear-projection screen placed at the foot of the scanner bed. Participants viewed the screen from within the bore of the magnet by means of a mirror placed on the head coil approximately 4 inches from the
participant’s face. The images subtended a visual angle of 5 degrees horizontal and 6 degrees vertical.

Pre-fMRI Assessments

Participants completed the SCL-90-R and the State-Trait anxiety inventory immediately prior to the scanning session. Individual differences in levels of psychological distress or anxiety were not used to eliminate participants, but were considered in the post-hoc analysis. They were then given a description of what to expect in the scanning session (e.g. as far as length of time, positioning, scanner sounds, being still, getting instructions, and viewing images) and were exposed to the visual and pain stimuli and asked to perform ratings of the painful stimuli.

For the emotion recall task, the participants were asked to name a specific event in their lives that involved feeling very angry or very fearful. For the neutral control task, they were asked to recall a specific time in the recent past when they were not experiencing any particular emotion (i.e. emotionally neutral). The memories were then reviewed by the experimenter to determine if the memory was appropriate (i.e. the correct emotion and not mixed emotions) and other specific stimuli (location, environmental sights, sounds, smells, clothing, weather etc.) could be elicited. One specific memory for each state (fear, anger, and neutral) was selected by the experimenter to have the subject recall during the scanning session. This emotion-induction procedure follows previously performed work involving personal recall (George, Ketter, Parekh et al., 1995; George, Ketter, Parekh et al, 1996; Dougherty et al., 1999; Kimbrell et al., 1999; Damasio et al., 2000), except that no passive viewing of emotional faces was used in the present study as in some of the earlier work.

Subjects were pre-exposed to the type of stimuli (a short sequence of warm and painful stimuli, and a 30 second trial period of recall of anger, fear, and neutral episodes) used in the fMRI session using the thermal stimulator and visual prompts. Instructions identical to those used in the scanning session were given to the participants in this pre-exposure before the scanning session. For the fear, anger, and neutral recall, participants practiced recalling the appropriate emotional event (corresponding to the on-screen cues). They were instructed to recall the specific anger, fear, or neutral episode as practiced, but
were given no specific instructions to experience a particular emotion, although they were told they would be rating their emotional experience after the scanning session.

A pain threshold session and a pain-level rating session were also performed prior to the scanning session using the MEDOC TSA-2001 thermal stimulator with 1” x 0.5” thermode applied to the left facial/trigeminal nerve region. Warm thresholds and pain thresholds were measured using COVAS software and by having the participant press a button when the stimuli became painful.

In addition, a 30 second period of warm stimuli (39° C) and two 30 second periods of painful hot stimuli (48° C) were presented to each participant prior to the scanning sessions and each participant subsequently made pain intensity and unpleasantness ratings of the painful stimuli on a 100 mm visual analog scale (VAS) (“0” = little or no pain, “100” = worst possible pain). Instructions identical to those used in the scanning session were given: the subjects were asked to notice and remember the warm and painful sensations so they could report these ratings on a VAS after the scanning session.

**Imaging Parameters**

Functional magnetic resonance images were collected on a Siemens Magnetom VISION 1.5 Tesla imaging system using a circularly polarized transmit/receive head coil. Foam padding was used to stabilize head position and to fix the location of the thermal stimulation probe on the left facial/trigeminal field region. Blood oxygen level-dependent (BOLD) signal intensity data were collected from 44 axial/obliqued at 30°, 3 mm thick slices, covering the entire cerebellum and upper cortex. A T2* weighted gradient echo echoplanar imaging (EPI) sequence with minimal inflow weighting was used with these acquisition parameters: TR/TE= 4000/45 ms, F. A. = 90 degrees, matrix= 64x64, FOV=228x228 mm, 44 axial-oblique slices (30° oblique), 3 mm slice thickness. The collected images were motion corrected using SPM’99 software (Friston, Williams, Howard et al., 1996). A 3D MPRAGE sequence (TR/TE/TI == 11.4 ms/4.4 ms / 300 ms, FA = 8 degrees, 1 x 1 mm in-plane resolution, sagittal slice thickness = 2 mm) was used to collect anatomical images for the localization of the functional activity and for the
registration of the fMRI data to the stereotactic space of Talairach and Tournoux (1988). An anatomical reference image consisting of the mean of the intensity-normalized MPRAGE images from all 12 subjects was used to display group mean activation maps.

fMRI Session Protocol

Instructions were given to the participants before the experiment began and again before the start of each fMRI run (the three runs in the study are the emotion recall fMRI series, the painful stimulation series, and the combined emotion and pain series). At the start of each run a “sham” cycle consisting of (baseline) neutral recall or warm sensation was presented for 24 seconds. The “sham” cycle simply refers to collecting fMRIs with a baseline task (in this case, 6 images) and later discarding these images or not using them in the analysis. The sham cycle was used to allow sufficient time for the participants to adapt to the task and for the BOLD effect to stabilize.

The scheme for the presentation of the painful stimulation and emotion recall set is shown in Figure 1. For the painful stimulation, a baseline of warm sensation (39°C) was alternated with painful stimulation (48°C). Each period of stimulation lasted 24 seconds and warm sensation and painful stimulation were varied, with one or two of each in alternating blocks. This stimulation scheme was unpredictable for participants and also matched warm stimulation and pain equally with each emotion state in the combined emotion and pain run. At the beginning of the emotion run, the neutral recall was done first, followed by the angry and fearful sets. Each block of 24-second neutral, fear, and anger recall alternated the presentation of anger or fear recall. Each warm sensation, pain, fear, anger, and neutral state lasted 24 seconds and involved acquisition of 6 images, for a total of 36 images in each emotion state, and 54 in each warm sensation or painful stimulation state. The total runtime for each run was 464 seconds (7.7 minutes). The number of images collected during that time was 116. The emotion recall run (neutral, fear, and anger) and the painful heat stimulation run (warm and painful stimulation) were both done separately (order counterbalanced) and then combined in a third run, also of 116 images. In the combined run, presented last, participants experienced painful heat stimuli and recalled neutral, fear, and anger episodes simultaneously. This resulted in 18
images in the painful state simultaneously with each emotion state (18 images with neutral, 18 images with fear, and 18 images with anger), and 18 images in the warm state with each emotion state in the combined run (again see Figure 1.) so that half of each of these emotion sets were presented simultaneously with warm (39°) sensation and half (the other 3) were presented simultaneously with hot painful (48°) sensation.

The presentation of stimuli was counterbalanced. Half of the participants randomly received one block ordering first, such as neutral-fear-anger first, and the other half of participants received the other block ordering, neutral-anger-fear first.

Figure 1. Procedure for Fear, Anger, and Neutral Recall and Painful Stimulation Sequence

Post fMRI Assessments

After the scanning session, the participants completed VAS ratings of pain intensity and unpleasantness experienced while in the scanner by recalling their experience during the different periods of the scanning session. They made a mark on a 100 mm VAS scale corresponding to the level of pain intensity and unpleasantness during each period. Again the VAS scale was anchored at “0” corresponding to “no pain” and “100” corresponding to the “worst possible pain.” A separate rating for pain during each emotion state was recorded. Also, after the scanning session, the participants
completed the state portion of the STAI to rate their anxiety levels retrospectively during the scanning session. Participants also rated the intensity and experienced emotion in the emotion runs retrospectively using 100 VAS with “0” corresponding to “no emotion” and 100 corresponding to the “most intense emotion.” The neutral periods were rated for any emotion experienced other than neutral.

Data Analysis

The fMRI data were analyzed with Analysis of Functional Neuroimaging (AFNI) software using the cross-correlation method (Cox, 1996). The activations were analyzed in the following search areas: lateral and medial thalamus, SI and SII, insula, cingulate gyrus, ACC, and PFC in the regions where pain-related activations have been previously observed (Treede et al., 1999; Price, 2000; Peyron et al., 2000). Activity in the AM was also examined in the emotion, and combined pain and emotion conditions.

Correlation coefficients were generated voxel by voxel using a box-car reference waveform with no time lag using the AFNI 3dfim program (Ward & Cox, 1999). The parametric maps contain a fractional signal change and associated correlation coefficient for each voxel. The correlation coefficient can then be related to a t-statistic and a threshold established for display of voxels with a magnitude above a specific threshold. A threshold of $t=2.22, p=.05$ was chosen as the cutoff for display for the pain, fear, and anger conditions. A threshold $t$ value of $t=2.1, p=.05$ was used for the pain with anger and the pain with fear maps. The maps were transformed to a Talairach coordinate frame (Talairach & Tournoux, 1988), referenced to each participant’s own anatomical images, and were resampled at 2x2x2 mm using a cubic spline interpolation and averaged across subjects. A Gaussian spatial smoothing at FWHM=7 mm was used to take advantage of the spatial coherence between voxels. The anatomical reference image consisting of the mean of the intensity-normalized MPRAGE images from all 12 subjects was used as a background to display group mean activation maps.

A cluster analysis was conducted using the AFNI auxiliary program 3dclust (Ward & Cox, 1999) to identify clusters in the following Talaraich regions bilaterally: superior frontal cortex, middle frontal cortex, inferior frontal cortex, medial frontal cortex, anterior cingulate cortex, cingulate cortex, posterior cingulate cortex, and insula.
Clusters greater than 400 mm$^3$, with a connectivity radius of 5.3 mm, were retained as significant, corresponding to the minimum resolvable voxel size with spatial smoothing, and voxels that may be connected in adjacent slices on a diagonal.

A subsequent region of interest (ROI) analysis was carried-out on the mean activation maps for each task condition, in each Talaraich region, and by hemisphere. The ROI analysis was further restricted to the union of above-threshold cluster activity across task conditions to increase statistical power and reduce the type I error rate. The use of specific ROIs based on voxels above a certain threshold in a Talaraich, stereotaxic system followed by an ANOVA, is a standard technique used in functional neuroimaging that can provide robust and excellent data (Constable, Skudlarski, Mencl et al., 1998).
Chapter Three
Results

Psychological Data

The Symptom Checklist-90 (SCL-90) (Derogatis, 1996) was administered to screen for psychological distress, and the State-Trait Anxiety Inventory (STAI) (Spielberger, Gorsuch, & Lushene, 1970) was given as a measure of anxiety. State anxiety was assessed before and during the scan. The SCL-90 t-scores, using the Nonpatient Adult Female Norms, for General Symptom Index (GSI ) were $T_{ave}=52$, $T_{min}=43$, $T_{max}=63$. Other subscale scores ranged from $T_{min}=34$ to $T_{max}=67$, $T_{ave}=53$. Thus, these scores indicate that the participants at baseline showed no significant psychological distress. Scores for trait anxiety ($x=31$, $sd=4.7$) indicated no significant distress. Scores for state anxiety before the scan ($x=26.9$, $sd=5.2$) and state anxiety levels during the scan ($x=38$, $sd=13.8$) indicated a significant increase in anxiety during the scan, $t=2.9$, $p=.013$.

Heat-Pain Stimulus Thresholds and Ratings

Heat pain temperature thresholds were collected for each subject before the scanning session. Heat pain temperature thresholds had a of mean 45.6 °C, ranging from 40.5 °C to 49.2 °C, $sd=2.3$. All of the subjects rated the 48 °C stimulus as painful on the VAS. The 0-100 Visual Analog Scale (VAS) pain ratings for each participant, of the 48 °C heat pain stimuli, were given separately for each of the fMRI runs, and during a baseline period before the fMRI session. Ratings were made for the fMRI with no emotion recall (thermal stimulation only), and separately for the painful stimulation during each emotion recall of neutral, anger, and fear. The VAS pain ratings indicated significant pair-wise differences between the pre-fMRI baseline and the painful stimulation with fear recall $t=2.99$, $p=.012$ and between the pre-fMRI baseline and the painful stimulation with neutral recall $t=2.72$, $p=.052$. All other pairwise comparisons
were non-significant. Pain ratings tended to be higher in the fMRI condition as opposed to baseline, and there were no significant differences across emotion category.

**Emotion Ratings**

Participants rated the intensity of the specific emotion (on a 0-100 VAS) experienced on average across all recall trials during the fMRI session, while recalling personal episodes involving anger, fear, and neutral. On this scale “0” represents “no emotion,” and “100” represents the “most intense emotion.” Figure 2. shows the mean VAS ratings for each category of recall. Participant’s mean ratings of anger experienced during anger recall as $x= 63.5$, $sd=21.5$ on the 0-100 VAS, and mean ratings of fear during fear recall were $x= 58.7$, $sd=17.3$, on the 0-100 VAS scale. In the neutral category, participants rated the intensity of any emotion (other than just neutral) experienced while recalling the neutral episode ($x=27.4$, $sd=22.4$). The emotion ratings differed across category $F(2,11)=14.9$, $p=.003$. Mean rated emotional intensity was different in pairwise comparisons between Anger and Neutral $t=3.86$, $p=.003$, and between Fear and Neutral $t= 3.70$ $p=.003$. The rated emotional intensity includes trials both with, and without thermal stimulation, that is, for the emotion-alone run, and in the combined emotion and pain run.
Figure 2. VAS Scale Ratings of Emotional Intensity During the fMRI Sessions Emotional Recall Task. The emotional intensity was rated on a 0 to 100 Visual Analog Scale with “0”=”No Emotion” and “100”=”Very Intense Emotion”. The Neutral ratings were based on rated intensity of any emotion experienced during recall of the neutral episode.

Correlations Between Pain, Emotion, and Anxiety Ratings

Pearson product moment correlations were calculated between VAS pain ratings and VAS emotion ratings during simultaneous painful stimulation and emotion recall. Also correlations were calculated for pain ratings and overall state anxiety during the entire fMRI session. All correlations were of moderate size (.47 - .56). Correlations between pain ratings during anger recall and anger ratings were significant (one-tailed) $r = .515$, $p = .043$. Correlations between pain ratings during fear recall and fear ratings approached significance $r = .475$, $p = .06$. Correlations between state anxiety on the STAI during the scan and pain ratings during no emotion recall were significant $r = .564$, $p = .028$.  

24
fMRI Results—General

The fMRI results are reported for each experimental task condition in comparison with the baseline condition. Data for painful stimulation, anger, fear, pain with anger, and pain with fear are reported in statistical parametric maps (SPMs) and in tables. The patterns of activity for each state (pain, fear, and anger) are displayed as a basis for comparison with the activation maps that show pain modulation with emotion (pain with anger and pain with fear). These patterns were examined in the brain regions of interest where changes, and no changes, were hypothesized. These brain regions are thalamus, SI and SII, insula, cingulate cortex, and PFC. Positive signal changes, above a \( p = .05, t = 2.22 \) (or \( t = 2.1 \) for the pain with anger or fear maps) threshold, are displayed in the SPMs and listed in the accompanying tables. The maps are color-coded corresponding to \( t \)-statistic on the fractional signal change ranging from 1.0 to 4.0.

fMRI Results--Painful Versus Warm

The fMRI data for 48°C painful stimulation were averaged across all trials and participants without emotion recall and compared to 39°C warm stimulation across all trials without emotion recall. The correlation coefficient between the time-course of signal change for each brain voxel and a boxcar reference waveform corresponding to the stimuli was computed for each participant. These fMRI data were used to produce SPMs of the difference for each subject displayed as a \( t \)-statistic. These SPMs were then combined and averaged across all subjects in Talarach coordinates, and overlayed on the averaged MRI anatomy scans for the 12 study participants. The threshold for display (significance-level) for all SPMs was set at \( t = 2.22, p = .05 \). A mask, using the Talarach regions previously specified, was used in selecting functional data for display. The SPM of these functional data, overlayed on the averaged anatomical scans (from all 12 participants) in Talarach coordinates, is shown in Figure 3. These maps are shown in axial sections for the entire brain. Areas of positive signal change in the functional data are represented in shades of orange and yellow. Negative signal change has been removed from this display for clarity. The views follow the standard radiology
convention (i.e. left is right, right is left). A cluster analysis using AFNI 3dclust was performed using a minimum cluster size of 400 mm$^3$. A listing of areas of fMRI positive signal change above the size and significance thresholds, their cluster center in Talaraich coordinates, name of brain region, cluster volume, Brodman’s area (BA), and mean t-value, is given in Table 3. (NOTE: The Talaraich coordinates in the Tables are reported using the AFNI convention, such that a minus sign should be used before the x (lateral-medial) and y (anterior-posterior) values, to be completely consistent with the standard Talaraich atlas). Six clusters of activity are seen in the right middle frontal gyrus (2 clusters), right superior frontal, left insula, right ACC, and left middle frontal gyrus. The thalamus and SI, SII were also examined for activity for the pain versus warm comparison; however no voxels were observed having values above the threshold in these areas. Also, Brodman area 6 (middle frontal, pre-motor area) is active bilaterally.
Figure 3. SPM of Painful 48°C Thermal Stimulation Versus Warm 39°C Stimulation (Threshold for display is set at \( t = 2.22, p = .05 \)).
Table 3. Table of Positive Signal Change Locations for Painful 48°C Thermal Stimulation Versus Warm 39°C Stimulation. (Locations above threshold at $t=2.22$, $p=.05$)

<table>
<thead>
<tr>
<th>Site</th>
<th>Talarach Coordinate x, y, z</th>
<th>Brain Region</th>
<th>Cluster Volume (mm$^3$)</th>
<th>Brodman Area</th>
<th>t</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>-36 -31 38</td>
<td>R Middle Frontal</td>
<td>4152</td>
<td>8/9</td>
<td>2.78</td>
</tr>
<tr>
<td>2</td>
<td>-26 -59 22</td>
<td>R Superior Frontal</td>
<td>1880</td>
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</tr>
<tr>
<td>3</td>
<td>-4 1 56</td>
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<td>560</td>
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</tr>
<tr>
<td>4</td>
<td>36 -16 11</td>
<td>L Insula</td>
<td>544</td>
<td>13</td>
<td>2.89</td>
</tr>
<tr>
<td>5</td>
<td>0 -34 16</td>
<td>R Anterior Cingulate</td>
<td>520</td>
<td>32/24</td>
<td>2.67</td>
</tr>
<tr>
<td>6</td>
<td>14 -3 56</td>
<td>L Middle Frontal</td>
<td>416</td>
<td>6</td>
<td>2.60</td>
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</table>


fMRI Results–Anger Versus Neutral

The fMRI data for recall of anger compared to neutral were averaged across all trials and participants (without thermal stimulation). The anger without painful stimulation was compared to the neutral recall without painful stimulation. The data for each voxel were cross correlated with a reference boxcar waveform for each participant. These data were averaged across all 12 participants in Talaraich coordinates to produce statistical parametric maps (SPMs) of the difference as a t-statistic, and overlaid on the averaged anatomical scans of all participants. The threshold for display for all SPMs was set at $t=2.22$, $p=.05$. A mask, using the Talaraich regions in the ROIs previously specified, was used in selecting activity for display. The SPM of these data, overlayed on the averaged anatomical scans from the 12 subjects in Talaraich coordinates, is shown in Figure 4. These maps are shown in axial sections for the entire brain. Areas of positive signal change in the functional data are represented in orange and yellow, while negative signal change is not displayed. The views follow the standard radiology convention (i.e. left is right, right is left). A cluster analysis using AFNI 3dclust was performed using a minimum cluster size of 400 mm$^3$ and connectivity radius of 5.3 mm. A listing of areas of fMRI signal change above the size and significance thresholds, their cluster center in Talaraich coordinates, name of brain region, cluster volume, Brodman area, and mean t-value is given in Table 4. Ten clusters of activity are seen in the bilateral middle frontal gyrus (BA 6/8), the right superior frontal, the left medial frontal, left inferior frontal, bilaterally in the insula (BA 13), in the left posterior cingulate, and in the right cingulate (2 clusters). The AM were examined for activity in the anger versus neutral recall task; however no above threshold voxels were observed.
Figure 4. SPM of Anger Recall Versus Neutral Recall. (Positive Signal Change)
(Threshold for display is set at $t=2.22$, $p=.05$.)
Table 4. Table of Positive Signal Change Locations for Anger Recall Versus Neutral Recall. (Locations above threshold at $t=2.22$, $p=.05$)

<table>
<thead>
<tr>
<th>Site</th>
<th>Talarach Coordinate x, y, z</th>
<th>Brain Region</th>
<th>Cluster Volume (mm$^3$)</th>
<th>Brodman Area</th>
<th>t</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
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</tr>
<tr>
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<td>3.03</td>
</tr>
<tr>
<td>3</td>
<td>-47 -8 41</td>
<td>R Middle Frontal</td>
<td>1448</td>
<td>8/6</td>
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<tr>
<td>4</td>
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<td>2.67</td>
</tr>
<tr>
<td>5</td>
<td>36 -8 3</td>
<td>L Insula</td>
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<td>13</td>
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</tr>
<tr>
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<td>648</td>
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</tr>
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<td>7</td>
<td>0 35 24</td>
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<td>8</td>
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<td>L Inferior Frontal</td>
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<td>2.49</td>
</tr>
<tr>
<td>9</td>
<td>-7 26 38</td>
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<tr>
<td>10</td>
<td>-9 -6 35</td>
<td>R Cingulate</td>
<td>448</td>
<td>24</td>
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</table>
fMRI Results–Fear Versus Neutral

The fMRI data for recall of fear episodes were averaged across all participants and trials. The fear recall trials without painful stimulation were compared to neutral episode recall without painful stimulation. The data for each voxel were cross-correlated with a reference boxcar waveform for each participant. These data were averaged across all 12 participants in Talaraich coordinates to produce statistical parametric maps (SPM) of the difference displayed as a t-statistic. The threshold for significance for all SPM was set at $t=2.22$, $p=.05$. A mask, using the Talaraich regions previously specified, was used in selecting functional data for display. The SPM of these data, overlaid on the averaged anatomical scans from the 12 subjects in Talaraich coordinates, is shown in Figure 5. These maps are shown in axial sections for the entire brain. Areas of positive signal change in the functional data are represented in orange and yellow. Negative signal change is not displayed. The views follow the standard radiology convention (i.e. left is right, right is left). A listing of areas of fMRI signal change above the size and significance threshold, their cluster center in Talaraich coordinates, name of brain region, cluster volume, Brodman area, and mean t-value is given in Table 5. Four clusters of activity are seen in the right superior frontal gyrus, bilaterally in the inferior frontal gyrus (BA 9), and in the left medial frontal cortex (BA 9). The AM were examined for the fear versus neutral recall task; however no above threshold voxels were observed.
Figure 5. SPM of Fear Recall Versus Neutral Recall. (Threshold for display is set at $t=2.22$, $p=.05$.)
Table 5. Table of Positive Signal Change Locations for Fear Recall Versus Neutral Recall. (Locations above threshold at \( t=2.22, p=.05 \))

<table>
<thead>
<tr>
<th>Site</th>
<th>Talarach Coordinate x, y, z</th>
<th>Brain Region</th>
<th>Cluster Volume (mm(^3))</th>
<th>Brodman Area</th>
<th>t</th>
</tr>
</thead>
<tbody>
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<td>1</td>
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</tr>
<tr>
<td>2</td>
<td>50 -9 24</td>
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</tr>
<tr>
<td>3</td>
<td>-53 -10 26</td>
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<td>4.26</td>
</tr>
<tr>
<td>4</td>
<td>8 -44 21</td>
<td>L Medial Frontal</td>
<td>600</td>
<td>9</td>
<td>3.27</td>
</tr>
</tbody>
</table>
fMRI Results—Pain With Anger

To evaluate the hypothesis that anger would increase activity related to pain processing in frontal and cingulate cortex, a comparison of the pain with anger versus no pain with anger states was calculated. The data for combined emotion recall and painful stimulation were reported for episodes of painful versus non-painful stimulation during the recall of either anger or fear emotion. In other words, the participants were recalling the particular emotion episode during all trials (either anger or fear) and experienced heat pain on half, and warm sensation on half of the trials. The fMRI data for painful 49°C stimulation versus non-painful 39°C stimulation during the recall of anger was compared across all trials using a cross-correlation with a box-car waveform for each participant. These data were averaged across 11 of the 12 participants in Talaraich coordinates to produce statistical parametric maps (SPMs), as a t-statistic, of the difference. (One participant was excluded due to equipment malfunction and the absence of fMRI data during the combined pain and emotion trials.) The threshold for display for all SPMs was set at $t=2.1$, $p=.05$. The SPM of these data overlaid on the averaged anatomical scans from the 11 participants in Talaraich coordinates is shown in Figure 6. These maps are shown in axial sections for the entire brain. Areas of positive signal change in the functional data are represented in orange and yellow. The views follow the standard radiology convention (i.e. left is right, right is left). A cluster analysis using AFNI 3dclust was performed using a minimum cluster size of 400 mm$^3$ and connectivity radius of 5.3 mm. A listing of areas of fMRI signal change above this threshold, their cluster center in Talaraich coordinates, name of brain region, cluster volume, Brodman area, and mean t-value is given in Table 6. Nine clusters of activity are seen in left middle frontal cortex, bilaterally in the superior frontal cortex, the right medial frontal, right inferior frontal, right posterior cingulate, right cingulate (2), and right ACC. Activation is observed in common Brodman areas (BA 9) in the left middle frontal and right superior frontal gyrii, and in BA 11 in the left superior and right medial frontal gyrii. These data may be compared with the pain-only baseline in Figure 3. to observe the specific effects of simultaneous anger on pain processing. These comparisons between pain only, and pain with anger, are further addressed in the subsequent ROI analysis.
Figure 6. SPM of Painful Versus Non-Painful Thermal Stimulation During Anger Recall. (Threshold for display is set at $t=2.1$, $p=.05$.)
Table 6. Table of Positive Signal Change Locations for Painful 48°C Stimulation Versus Non-Painful 39°C Stimulation With Anger. (Locations above threshold at $t=2.1$, $p=.05$)

<table>
<thead>
<tr>
<th>Site</th>
<th>Talarach Coordinate x, y, z</th>
<th>Brain Region</th>
<th>Cluster Volume (mm$^3$)</th>
<th>Brodman Area</th>
<th>$t$</th>
</tr>
</thead>
<tbody>
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<td>1</td>
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<tr>
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</tr>
<tr>
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<tr>
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<td>11</td>
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</tr>
<tr>
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<td>-59 -21 17</td>
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</tr>
<tr>
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<td>-10 -31 22</td>
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</tr>
</tbody>
</table>
fMRI Results–Pain With Fear

To evaluate the hypothesis that fear would decrease pain related activity in the ACC and prefrontal cortex, and increase activity in the insula, a comparison of the pain with fear versus no-pain with fear was calculated. The fMRI data for painful 49°C stimulation versus non-painful 39°C stimulation during the recall of fear were averaged across all trials. These data were averaged across 11 of the 12 participants in Talaraich coordinates to produce statistical parametric maps (SPMs), as a t-statistic, of the difference. (One participant was excluded due to equipment malfunction and absence of fMRI data during the combined pain and emotion trials.) The threshold for significance for all SPM was set at $t=2.1$, $p=.05$. The SPM of these data overlaid on the averaged anatomical scans from the 11 participants in Talaraich coordinates is shown in Figure 7. These maps are shown in axial sections for the whole brain. Areas of positive signal change in the functional data are represented in orange and yellow. The views follow the standard radiology convention (i.e. left is right, right is left). A cluster analysis using AFNI using AFNI 3dclust was performed using a minimum cluster size of 400 mm$^3$. A listing of areas of fMRI signal change above this threshold, their cluster center in Talaraich coordinates, name of brain region, cluster volume, Brodman area, and mean t-value is given in Table 7. Six clusters of activity are seen in the left middle frontal cortex, the right inferior frontal, the right cingulate (2 sites, BA 24 and BA 32), and left cingulate (2 sites, BA 31 and BA 24) cortex. These data may be compared with the pain-only baseline shown in Figure 3 to observe the effect of simultaneous fear processing on pain. These comparisons between pain only and pain with fear are further addressed in the subsequent ROI analysis.
Figure 7. SPM of Painful Versus Non-Painful Thermal Stimulation During Fear Recall. (Threshold for display is set at $t=2.1$, $p=.05$.)
Table 7. Table of Positive Signal Change Locations for Painful 48°C Stimulation Versus Non-Painful 39°C Stimulation With Fear. (Locations above threshold at $t=2.1$, $p=.05$)

<table>
<thead>
<tr>
<th>Site</th>
<th>Talarach Coordinate x, y, z</th>
<th>Brain Region</th>
<th>Cluster Volume (mm$^3$)</th>
<th>Brodman Area</th>
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Table 8. Summary Table of Positive Signal Change Locations for Pain, Anger, Fear, and Pain with Anger, Pain with Fear, by Brodman Area (t values given are average for the particular cluster).

<table>
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<th>Site</th>
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<th>Pain with Fear t</th>
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<td>2.49</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Indicates areas overlapping or in close proximity in the same brain region.
Region of Interest Analysis

An ROI analysis was carried out for the areas previously defined in the data analysis methods section (1. superior frontal, 2. middle frontal, 3. inferior frontal, 4. medial frontal, 5. anterior cingulate, 6. cingulate, 7. posterior cingulate, and 8. insula). As there was no above threshold activation observed in the thalamus and somatosensory cortex, these areas were not included in the ROI analysis. Furthermore, the areas of consideration were limited to the union of those brain regions identified as clusters in analysis of the individual tasks. Separate analyses were conducted for the pain, anger, and pain with anger conditions, and for the pain, fear, and pain with fear conditions. The ROI analyses allow direct comparisons of brain activity in the pain alone condition to the pain with anger, or pain with fear conditions, for each brain region of interest. Also, the ROI analysis, having used a repeated measures ANOVA, yields the significance of each of the within-subjects factors: task, hemisphere, and region (i.e., task: pain, anger, pain with anger, pain, fear, pain with fear; hemisphere: right or left; region: superior frontal, middle frontal, inferior frontal, medial frontal, ACC, cingulate, posterior cingulate, insula).

Overall ANOVA results from the ROI analysis yield, for pain, anger, and pain with anger, a pattern of main effects ($T = \text{task}$, $H = \text{hemisphere}$, $R = \text{region}$) and interactions using a cutoff value of $p = .05$. For the pain with anger analysis, the main effect of task $T$: $F(2,20)=6.26$, $p = .008$ and hemisphere $H$: $F(1,10)=19.47$, $p = .001$ were significant, the effect of region $R$: $F(7,70)=.66$, $p = .708$ was non significant. All two-way interactions were significant $T \times H$: $F(2,20)= 4.89$, $p = .019$, $T \times R$: $F(14,140)=7.853$, $p < .001$, $H \times R$: $F(7,70)=2.772$, $p = .013$. The three-way interaction of all factors was significant $T \times H \times R$: $F(14,140)=6.684$, $p < .001$. Pairwise comparisons between pain alone and pain with anger, are plotted in the bar chart of Figure 8. The Figure shows separate plots for each brain hemisphere, and separate bars for each task by brain region. The cutoff value used for interpreting pairwise significance was $0.05/3 = 0.02$ (Bonferroni correction) to correct for multiple comparisons across task conditions. In examining the pairwise comparisons for pain to pain with anger we see bilateral increases in activity in the middle and inferior frontal cortex and an increase in left cingulate. The posterior cingulate shows increases in the right hemisphere and decreases in the left, whereas the medial frontal and anterior cingulate show an increase in the left hemisphere and a
decrease on the right. Table 8 gives a summary of the brain regions active in each condition and the cluster size for each ROI used in the analysis. The actual brain regions used in the ROI analysis of pain and anger are the union of the clusters in the pain, anger, and pain with anger conditions (tan shaded areas) in Table 9. The table also lists the table number and row number for each site and the corresponding Brodman area.

For the pain with fear analysis, the main effect of hemisphere $H$: $F(1,10)=39.08, p<.001$ was significant and the main effects of task $T$: $F(2,20)=.38$, $p=.689$, and region $R$: $F(7,70)=.89$, $p=.522$ nonsignificant. The two-way interactions between task and region $T \times R$ $(14,140)$: $F=2.17$, $p=.012$, and hemisphere and region $H \times R$: $F(7,70)=3.35$, $p=.004$ were significant, while the two-way interaction between task and hemisphere $T \times H$: $F(2,20)=1.13$, $p=.343$ was nonsignificant. The three-way interaction of all factors was significant $T \times H \times R$: $F(14,140)=2.56$, $p=.003$. Pairwise comparisons between pain alone and pain with fear are plotted in the bar chart of Figure 9. The Figure shows separate plots for each brain hemisphere and separate bars for each task by brain region. The cutoff value used for interpreting pairwise significance was $.05/3=.02$ (Bonferroni correction) to correct for multiple comparisons across task conditions. The pairwise comparisons for pain and pain with fear demonstrate bilateral increases in activity in the middle and inferior frontal cortex (as with anger), and an increase in the left cingulate and right insula. All other right hemisphere areas (superior frontal, medial frontal, anterior cingulate cingulate, and posterior cingulate) show decreased activity from pain to pain with fear. In the left hemisphere, posterior cingulate and insula also show decreases. The left hemisphere superior frontal, medial frontal, and anterior cingulate did not show significant change.

Table 9 gives a summary of the brain regions active in each condition and the cluster size for each ROI used in the analysis. The actual brain regions used in the ROI analysis of pain and fear are the union of the clusters in the pain, fear, and pain with fear conditions (blue shaded areas) in Table 9. The table also lists the table number and row number for each site and the corresponding Brodman area. Table 10 shows a comparison of the changes from the pain condition to the pain with anger and pain with fear conditions. The pattern of changes from pain to pain with anger and from pain to pain with fear is consistent for all but one brain region. Only a single brain region (right
posterior cingulate) demonstrated changes in the opposite direction for pain with anger and pain with fear. The following are the numbered regions of interest (ROIs) as labeled in Figures 8 and 9 and Tables 9 and 10: (1. superior frontal, 2. middle frontal, 3. inferior frontal, 4. medial frontal, 5. anterior cingulate, 6. cingulate, 7. posterior cingulate, and 8. insula).
Figure 8. ROI Analysis Barchart of Mean Intensity for the Pain with Anger Analysis for Each Task Condition and Brain Region.

Right Hemisphere -- Pain, Anger, Pain w. Anger

pairwise comparisons between pain alone and pain with anger are significant at p<.001 except where indicated

Left Hemisphere -- Pain, Anger, Pain w. Anger

pairwise comparisons between pain alone and pain with anger are significant at p<.001 except where indicated

n.s. = non significant, p>.02
Figure 9. ROI Analysis Bar chart of Mean Intensity for the Pain with Fear Analysis for Each Task Condition and Brain Region.

Right Hemisphere -- Pain, Fear, Pain w. Fear

pairwise comparisons between pain alone and pain with fear are significant at p<.001 except where indicated

Left Hemisphere -- Pain, Fear, Pain w. Fear

pairwise comparisons between pain alone and pain with fear are significant at p<.001 except where indicated
Table 9. Summary of Activated Clusters (p<.05) for ROI Brain Regions and Task Conditions. (Cluster Size in mm$^3$, Numbers in parentheses refer to Table Number.Row Number and Brodman Area.)

<table>
<thead>
<tr>
<th>Condition</th>
<th>Region</th>
<th>Hemis.</th>
<th>Pain</th>
<th>Anger</th>
<th>Fear</th>
<th>Pain with Anger</th>
<th>Pain with Fear</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain</td>
<td>Superior Frontal</td>
<td>R</td>
<td>1880(3.2)(10)</td>
<td>2880(4.2)(10)</td>
<td>1446(5.1)(11)</td>
<td>1256(6.5)(9)</td>
<td>ns</td>
</tr>
<tr>
<td></td>
<td></td>
<td>L</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
<td>1488(6.3)(11)</td>
<td>ns</td>
</tr>
<tr>
<td>Anger</td>
<td>Middle Frontal</td>
<td>R</td>
<td>4152(3.1)(8/9), 560(3.3)(6)</td>
<td>1446(4.9)(6/8)</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
</tr>
<tr>
<td></td>
<td></td>
<td>L</td>
<td>416(3.6)(6)</td>
<td>9256(4.1)(8)</td>
<td>ns</td>
<td>1920(6.2)(9/8)</td>
<td>1696(7.1)(10)</td>
</tr>
<tr>
<td>Fear</td>
<td>Inferior Frontal</td>
<td>R</td>
<td>ns</td>
<td>ns</td>
<td>888(5.3)(9)</td>
<td>464(6.3)(44/45)</td>
<td>512(7.5)(9)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>L</td>
<td>ns</td>
<td>528(4.8)(47)</td>
<td>1046(5.2)(9)</td>
<td>ns</td>
<td>ns</td>
</tr>
<tr>
<td>Pain with Anger</td>
<td>Medial Frontal</td>
<td>R</td>
<td>ns</td>
<td>ns</td>
<td>888(5.7)(11)</td>
<td>ns</td>
<td>ns</td>
</tr>
<tr>
<td></td>
<td></td>
<td>L</td>
<td>ns</td>
<td>1360(4.9)(9)</td>
<td>609(5.4)(9)</td>
<td>ns</td>
<td>ns</td>
</tr>
<tr>
<td>Pain with Fear</td>
<td>Anterior Cingulate</td>
<td>R</td>
<td>520(3.9)(23)</td>
<td>ns</td>
<td>ns</td>
<td>456(6.9)(32)</td>
<td>ns</td>
</tr>
<tr>
<td></td>
<td></td>
<td>L</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
<td>456(7.6)(24)</td>
</tr>
<tr>
<td></td>
<td>Cingulate</td>
<td>R</td>
<td>ns</td>
<td>480(4.9)(31), 446(4.10)(24)</td>
<td>ns</td>
<td>1304(8.6)(31), 1168(6.6)(24)</td>
<td>984(7.2)(20), 830(7.3)(22)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>L</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
<td>646(7.4)(21)</td>
</tr>
<tr>
<td></td>
<td>Posterior Cingulate</td>
<td>R</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
<td>2144(6.1)(23)</td>
<td>ns</td>
</tr>
<tr>
<td></td>
<td></td>
<td>L</td>
<td>ns</td>
<td>600(4.7)(23)</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
</tr>
<tr>
<td>Insula</td>
<td>R</td>
<td>648(4.8)(13)</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
</tr>
<tr>
<td></td>
<td>L</td>
<td>544(4.4)(33)</td>
<td>788(4.6)(33)</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
</tr>
</tbody>
</table>

Key to Shaded Regions Defining the ROI Analysis Clusters:

- Regions Used Only in the Pain, Anger, and Pain with Anger Analysis
- Regions Used Only in the Pain, Fear, and Pain with Fear Analysis
- Regions Used in Both Analyses
Table 10. Summary of Effects of Anger and Fear on Pain in ROI Analysis Showing Consistency of Results With Anger and Fear. (All changes are significant at p<.001 unless otherwise indicated, n.s. = non-significant).

<p>| Consistencies in ROI Analysis Between Pain with Anger and Fear |</p>
<table>
<thead>
<tr>
<th>Hemisphere</th>
<th>Region</th>
<th>Pain with Anger</th>
<th>Pain with Fear</th>
</tr>
</thead>
<tbody>
<tr>
<td>Right</td>
<td>1</td>
<td>decrease</td>
<td>decrease (p&lt;.01)</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>increase</td>
<td>increase</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>increase (p&lt;.01)</td>
<td>increase</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>decrease</td>
<td>decrease</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>decrease</td>
<td>decrease</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>increase</td>
<td>decrease</td>
</tr>
<tr>
<td></td>
<td>7</td>
<td>increase</td>
<td>decrease</td>
</tr>
<tr>
<td></td>
<td>8</td>
<td>increase</td>
<td>increase</td>
</tr>
<tr>
<td>Left</td>
<td>1</td>
<td>n.s.</td>
<td>n.s.</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>increase</td>
<td>increase</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>increase</td>
<td>increase</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>increase</td>
<td>n.s.</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>increase</td>
<td>n.s.</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>increase</td>
<td>increase</td>
</tr>
<tr>
<td></td>
<td>7</td>
<td>decrease</td>
<td>decrease</td>
</tr>
<tr>
<td></td>
<td>8</td>
<td>decrease</td>
<td>decrease</td>
</tr>
</tbody>
</table>
Summary of Findings

The neuroimaging results observed in the present study are consistent with previous work on pain and emotion, although activations were not observed in all areas previously observed with pain, anger, and fear. Signal changes in selected brain regions were in agreement with those observed in previous pain neuroimaging literature, especially in the cingulate gyrus and frontal lobes. The present study focused on activity in frontal areas and in the cingulate gyrus, because these areas have been implicated in the affective and cognitive dimensions of pain experience, and have also been shown to be important in emotion processing. With painful stimulation, activity was not observed in SI and SII, as may be expected, as a majority of pain studies (60%) have observed activity in those areas (Peyron et al., 2000). A possible reason for this could be that the use of warm sensation as a baseline in the present study may have precluded activity in these areas, as the signal differences may not be sufficient to be detectable. Alternatively, this lack of finding may reflect unique brain responses to trigeminal pain. It was observed that all participants rated the 48°C thermal stimulation as painful, and ratings of pain and intensity and unpleasantness correlated positively with ratings of anger and fear experienced during emotion episode recall. Therefore, the participants’ subjective impressions of pain intensity and unpleasantness were modulated upward by the recall of emotion states. Of note, pain intensity and unpleasantness were highly correlated for all ratings, and were functionally indistinguishable in the present study. Although highly correlated, the distinction between intensity and unpleasantness may remain important constructs in their own right, and the ability to distinguish these may depend on the type of stimulus used, and clinical pain state under investigation (Price, 2000).

Additionally, the participants, as would be expected, reported greater state anxiety during the scanning session than at baseline before the scan. Greater anxiety during the scan can be due to claustrophobia and apprehension about the scanning situation, anticipation of painful stimuli, and the possible anxiety associated with recall of anger and fear. While anxiety also likely plays an important role in modulating pain, the anxiety
level may be assumed to be reasonably consistent across different trials of painful stimulation, with and without emotion. In other words, the design of the present experiment averages out the effect of a consistent level of state anxiety across the entire fMRI procedure, so it can be reasonably assumed that changes in fMRI signal were due to the differences in the pain, anger, and fear states. Additional physiological monitoring of arousal and self-reports of anxiety may help further clarify the role of anxiety in neuroimaging of pain and emotion states.

Overall, a comparison of ratings of pain intensity across baseline, before the scan, to pain during fear and neutral recall, were significant in pair-wise tests. The pain-ratings during the scanning session were higher than those made before the scanning session. Presumably, this is the effect of anxiety and arousal on pain levels. While not statistically significant, a comparison of the ratings of pain without emotion recall to the pain ratings with emotion recall, revealed a trend towards pain with emotion to be higher than in the states with neutral recall, or no emotion recall. What may be of greater importance, was that the statistically significant positive correlations between rated emotion (both fear and anger) and pain ratings during these periods occurred in a dose-response manner. This suggests that the pain experience was subjectively intensified by the negative emotion states of fear and anger in the current study for the individual participants. The behavioral ratings, in conjunction with the observed fMRI results showing effects of emotion on pain processing, are considered strong, concurrent evidence of the ability of emotion states to affect pain processing in specific brain areas. While there is no perfect way to induce emotional states, the procedures used in the present study are consistent with other neuroimaging studies, in terms of brain imaging results and validated procedures used from a number of previous studies of emotion (for a meta analysis see Phan et al., 2002).

Painful Stimulation fMRI Results

The patterns of activity seen in the painful versus warm stimulation are, in part, consistent with those changes observed in the literature in PET studies (Derbyshire, Jones, Gyulai et al, 1997; Derbyshire & Jones, 1998) and in fMRI studies (Davis, Kwan,
Crawley, & Mikulis, 1998) (for reviews see Price, 2000; Treede et al., 2000; Peyron et al. 2000). These studies show widespread activity with painful heat stimuli versus warm stimuli. Especially, a number of studies have observed bilateral activity in frontal cortex and activations in the ACC and insula, which were also observed in the present study. Specific differences in exact site of brain activity between studies can be due to methodological differences such as painful stimulation technique and body site. Also, the present study is unique in applying painful heat stimulation with a thermode to the face, and thus brain activation may differ with facial pain stimulation as opposed to painful stimulation at other body sites.

The pain-related signal changes in the insula have been related to the evaluation of stimulus threat and preparation for action (Price, 2000), and also the insula may play a role in integration of somatosensory data (Peyron et al., 2000). In the present study, pain related signal changes were observed in the left anterior insula (BA 13) with pain alone, and bilaterally in the insula (BA 13) with anger. The ROI analysis revealed positive changes in activity of the insula in the right hemisphere with both pain and anger and pain and fear, and decreases in the left hemisphere. Thus, the increase in activation in the insula was contralateral (right) to the side (left) of stimulation. Other research using PET, fMRI and deep cortical electrodes found contralateral activity in the insula and suggested that this may be an early step in cortical pain processing (Peyron, Frot, Schneider et al., 2002).

Activity in the ACC in response to painful stimuli has been related to the affective dimension of pain. This brain area is part of the limbic network (frequently referred to as paralimbic) and has been shown to be related to perceptions of pain unpleasantness (Rainville, Duncan, Price et al., 1997). Studies of patients undergoing bilateral cingulotomy for intractable chronic pain have demonstrated effective pain relief with lesions to the anterior cingulate cortex (Lee, Bechera, Adolphs, et al., 1998). In a case study of a patient treated for obsessive-compulsive disorder with bilateral lesions of the anterior internal capsule (nerve tracts connecting anterior cingulate cortex to subcortical structures) researchers assessed acute pain thresholds before and after surgery (Talbot et al., 1995). Pain intensity and unpleasantness were reduced post-surgically to the same hot
and cold stimuli used in pre-surgical testing, although pain tolerance decreased on a cold-pressor task.

In the current study, ratings of pain intensity and unpleasantness were highly correlated and could not be distinguished from brain region activity related primarily to pain intensity or primarily to unpleasantness; however it was observed that pain stimulus responses were affected as a function of fear and anger recall in the cingulate cortex, as well as in the frontal cortex and insula. In the present study activity related to painful stimulation alone was observed in the right anterior cingulate cortex (BA 32/24) and activations were also observed in right anterior cingulate cortex (BA 31) in the pain with anger condition. In the ROI analysis, an increase from the pain alone to the pain with anger condition was seen in the left anterior cingulate, the bilateral (mid) cingulate, and the right posterior cingulate. However, the level of activity in the mid cingulate did not change significantly from the anger-alone condition and could be unrelated to pain (i.e. just related to anger). In the pain and pain with fear comparison, an increase was observed in the left cingulate, with decreases in activity in right anterior, mid, and posterior cingulate. These results support previous findings that the cingulate gyrus plays a role in the affective dimension of pain as pain responses are modulated by the emotion states.

In the medial frontal cortex, and in bilateral areas of middle frontal cortex, activity during painful stimulation was observed that was consistent with previous studies. In the present study, pain-related activity was observed in right superior (BA 10) and bilaterally in the middle frontal cortex (BA 6/8/9). However, susceptibility artifacts in these anatomic regions, especially in the medial frontal cortex, can give misleading results. Several functional neuroimaging studies have observed pain related activity in frontal areas (Peyron et al., 2000). This activity probably relates to cognitive and emotional aspects of the pain experience and a conscious awareness and cognition about the painful state and memory (Treede et al, 2000). Although, presumably these responses would be somewhat individualized, depending on the cognitive interpretation of the experimental situation, areas of significant overlap were observed in the data because they are averaged across subjects. These areas of inter-subject agreement may be important brain regions in the conscious evaluation of pain. Using these areas as a baseline for the cognitive aspects
of painful experience in the present study, the effect of the recalled emotion states can be evaluated and used as a basis for comparison for future studies examining modulation of pain activity by emotion. In the pain with anger condition we observed 5 clusters of activity in superior, middle, inferior, and medial frontal cortex. The ROI analysis revealed bilateral increases from pain alone to pain with anger in the middle and inferior frontal regions; however the superior frontal cortex showed a decrease in the right hemisphere and no change in the left. Similarly the ROI analysis, in the pain alone to pain with fear condition, demonstrated increases in middle and inferior frontal cortex, decreases in right superior cortex and no change in the left. This specific pattern of change of pain-related activation in these areas suggests that these frontal brain regions each play unique roles in the cognitive-emotional dimension of pain.

**Anger Recall fMRI Results**

Signal changes in the comparison of anger episode recall versus neutral recall produced the most numerous set of sites of activity of any of the individual conditions. Ten clusters above size and intensity thresholds were identified for the anger condition. The next highest number (nine) of clusters was observed in the pain with anger condition. That anger recall would produce more activity than fear, is consistent with previous research showing greater levels of activity when viewing faces with angry expression as compared to facial expressions of other emotions (Kesler/West et al., 2001). In other studies, anger has produced brain activity in insula, cingulate, and frontal areas consistent with the present study (Baker et al., 1999; Blair, Morris, Frith et al., 1999). Because anger is important in chronic pain (Kerns et al., 1994), it was expected that brain activity with anger and pain would be particularly important and salient. The anger-related activations without pain provided a pattern of baselines from the anger recall task in the present study, that such a paradigm could be used as a basis for comparison with future studies in chronic pain patients.

Activity in the anterior and posterior cingulate, and the insula were observed in other neuroimaging research with anger recall. (Damasio et al., 2000). Again the AM
showed no activation and this finding is consistent with the neuroimaging results using anger and fear recall in previous research (Damasio et al., 2000).

A meta-analysis of emotion brain imaging studies was conducted (Phan et al., 2002). Overall 55 studies were reviewed, 5 involving anger and 13 involving fear. Different studies used different techniques of emotion induction and are divided into those using visual, auditory stimuli, or recall (Phan et al., 2002). Fear produced activity in the AM in 60 percent of studies reviewed, especially involving the viewing of emotional faces with fear expressions, but not in any studies involving the recall of fear. The AM was activated in 50% of the visual induction studies, 7% of the auditory stimulus studies, and in none of the recall studies. The medial prefrontal cortex was activated in a variety of conditions and is said to play a general role in emotional processing which could rely on cognitive demand, such as consciously labeling an emotional facial expression. Induction by emotional recall/imagery especially recruited the ACC and insula, as in the present study with anger recall. Also, emotional tasks with cognitive demand particularly involved the ACC and insula (Phan et al., 2002).

A study involving induction of anger in healthy men using autobiographical scripts with PET imaging found activity in lateral orbitofrontal cortex (BA 47), rostral anterior cingulate (BA 24/32), anterior temporal poles, precentral gyrus, medial frontal gyrus (BA 9), medial frontal (BA 10), and cerebellum (Dougherty et al., 1999). Psychophysiological parameters (heart rate, skin conductance, and frontalis electromyogram) were also assessed. Participants rated their emotional responses on a 0 – 10 analog scale and also rated imageability, recall, and strength of imagery. Anger recall produced significantly higher ratings than neutral ratings; however psychophysiology ratings did not differ from neutral. The findings and procedures of the present study are consistent with this previous work. Also consistent with previous work using anger recall, the present study observed activity in the left inferior frontal cortex (BA 47) with anger recall (Kimbrell et al., 1999)
Fear Recall fMRI Results

Recall of fear episodes alone produced less widespread activity than anger recall alone; however significant signal change was observed at a distinct number of sites in the frontal lobes. Four clusters above threshold were observed in the fear condition. This pattern can be compared to previous study results where activities with aversive conditioning were observed in the anterior cingulate and anterior insula (Buchel et al. 1999), the left orbitofrontal and right ACC (Dougherty et al., 1999), the left inferior frontal and left temporal cortex (Blair et al., 1999), and right somatosensory cortex (Adolphs at al., 2000). In the present study, activity was not observed in the cingulate cortex, insula, and AM with fear alone, and it may be that the present study lacked sensitivity to observe these changes. Because ratings of pain during fear recall correlated with ratings of fear intensity, it appears that fear may also enhance pain perception. Also, some increases in the magnitude and extent of activity occurred in the pain with fear condition, although there were areas of decreased activity as well. Overall, the modulation of pain activity by fear does not appear to be as great or as extensive, as in the condition of pain with simultaneous anger. Although mean fear ratings were $\bar{x}=58.7$ on a VAS scale with “0” = “no fear” and “100” = the “most intense fear,” and this would seem to suggest that the present study participants experienced at least a moderate level of fear, no absolute determination of the level of fear and real effects on pain perception can be determined relative to previous findings that moderate levels of fear produce hyperalgesia and more intense levels of fear produce analgesia (Rhudy & Meagher, 2000). So, it remains to be determined what level of fear produces more, as opposed to less, perceived pain. From the ROI analysis, increases were observed bilaterally in middle and inferior frontal regions and in the right insula and left cingulate from the pain alone to the pain with fear condition. Decreases were observed in other regions (right superior frontal, right medial frontal, right anterior, mid, and posterior cingulate, and left insula). More mixed effects in brain activity were observed in the present study with pain and fear than with pain and anger, and the fear and pain ratings cover a broad range, so
the effects of fear on pain, overall, appear to be more mixed than those observed with pain and anger. As in the case of anger recall, these results in the present study provide a baseline pattern for the fear recall task that will potentially be a basis for comparison with future studies in chronic pain patients using the same paradigm.

Pain with Anger fMRI Results

The neuroimaging signal changes for pain with simultaneous anger episode recall were increased from the pain-only activity. Nine above-threshold clusters were observed in the pain with anger condition as compared to six clusters in the pain only condition. In the pain versus no pain comparison (pain-only, Figure 3.) clusters of activity were observed bilaterally in the frontal lobes, in the right anterior cingulate gyrus, and insula. The activation differences in the pain with anger condition occur bilaterally in the frontal lobes and in the mid and posterior portions of the cingulate gyrus, so that both the number and size of the clusters in the pain with anger condition (total size 11,088 mm$^3$) relative to pain with no emotion (total size 8042 mm$^3$) were greatly increased. Comparing the activated clusters in the pain with anger condition (Figure 6.) with the pain-only condition (Figure 3.), it was observed that the pain-only areas become significantly enlarged with the addition of anger, and new areas of activity, especially bilaterally in the frontal lobes, appear. Additionally, the signal change magnitudes for pain are significantly greater with addition of anger recall.

In the ROI analysis comparing pain alone to pain with anger increased activity was observed bilaterally in middle and inferior frontal, and in the mid cingulate cortex. Increases were also observed in right posterior cingulate and insula, and in the left medial frontal and left anterior cingulate, although activity decreased in the posterior cingulate and insula in the left hemisphere. Decreases were also seen in the right superior frontal and right medial frontal, and right anterior cingulate. This analysis demonstrates that while the effect of anger on pain processing is predominantly positive (10 regions showed increases and 5 showed decreases) the actual patterns of brain activity are more complex, with some changes being positive changes and some negative. These observations generally support the hypotheses of the study, that anger would increase
pain-related activity in frontal cortex, anterior cingulate cortex, and in the insula. For most of these areas increases were observed; however decreases from pain alone to pain with anger are also evident.

Overall, the anger recall produced a synergistic effect on the pain-related activity. In other words, anger enhanced and elaborated pain processing, because observed activity in the pain with anger condition changed over the pain-only condition. This result seems to be evidence at the neurobiological level of the potential importance and significance of anger, consistent with that which has been observed in the exacerbation of chronic pain states (Fernandez & Turk, 1995; Kerns et al., 1994). The current result appears to be evidence of the ability of anger to modulate pain processing, and to intensify a physically painful experience. Considering this in light of the finding that anger worsens effective treatment of chronic pain patients, because it can adversely affect social relationships, producing more stress and poorer treatment outcomes (Fernandez & Turk, 1995), further underscores the significance of anger as an adverse contributor to chronic pain outcomes.

Further, the implication of the increase in pain-related activity with anger over activity with no emotion, is that in pain-free individuals the anger emotion state can modulate and increase pain perception, especially the affective and cognitive dimensions. These changes are in accordance with hypotheses that were based on data indicating the exacerbation of chronic pain by anger (Fernandez & Turk, 1995; Burns et al., 1996; Burns, 1997; Okifuji et al., 1999). The evidence from the current study suggests that central mechanisms, perhaps in addition to peripheral mechanisms, mediate the relationship between anger and pain. This may also imply that cognitive and behavioral strategies, and medications which act centrally to moderate the pain-intensifying effects of anger, may help with the management of chronic pain.

Pain with Fear

Patterns of activity observed for painful versus warm sensation in the presence of fear were not as widespread, and were of lesser magnitude than with pain and anger. Only six clusters above threshold were observed in the pain with fear condition as opposed to the pain with anger condition. The total cluster volume in the pain with fear
condition was 5128 mm$^3$ as opposed to 11088 mm$^3$ in the pain with anger condition and 8072 mm$^3$ in the pain-alone condition. The literature on fear suggests that fear has the capacity to both increase and reduce pain perception. For example, intense fear-produced hypoalgesia has been related to a thalamic and amygdala circuit in rats (Bellgowan & Helmstetter, 1996). Fear, but not anxiety, also lessened pain sensitivity in a cold-pressor task (Rhudy & Meager, 2000). However, patterns of activity in the present study suggest that the pain experience was modulated by fear, in comparison with pain alone. Sites of activity in the pain with fear condition, not evident in the pain alone condition, may imply increased sensitivity to pain with fear. Activity bilaterally in the mid cingulate, for example, appeared in the pain with fear condition, but not with pain alone. This region may become involved to increase pain when fear interacts with pain perception. It remains somewhat ambiguous as to whether fear increases pain-related activity or reduces it, overall, because some areas of brain activity increased, while some decreased. The results on an average basis are mixed. An individual subjects approach to the analysis of neural responses to pain with fear may be necessary to understand the specific effects.

In the ROI analysis of the pain alone to the pain with fear condition, increased activity was observed from pain alone to the pain with fear condition in middle and inferior frontal cortex bilaterally. In the left mid cingulate and right insula increases were observed, while a decrease was observed in the right mid cingulate. Decreases were also observed in a number of other brain regions: the right superior frontal gyrus, right medial frontal, right anterior and mid cingulate, left insula, and bilaterally in the posterior cingulate. Overall, 6 brain regions showed increases, while activity in 7 regions decreased, and no change was observed in three regions (left superior frontal, left medial frontal, and left anterior cingulate). This analysis provides further evidence of an overall decrease in pain processing with simultaneous fear, and these results are in partly accordance with the hypotheses of the study (decreases in frontal cortex and in anterior cingulate in pain with fear compared to pain alone) except that both an increase and a decrease were observed in frontal cortex, depending on the specific region, an increase observed in the right insula, and decreases observed in the insula in the left hemisphere,
when increases in the insula were predicted because of its possible role in threat evaluation.

In the present study, pain ratings and fear ratings were moderately correlated with marginal significance ($r = .475$, $p = .06$). A closer examination of the pain and fear ratings showed that participants who experienced moderate levels of fear reported the greatest pain levels, and those experiencing the highest and lowest levels experienced less pain. Thus, a somewhat curvilinear relationship was observed. So, participants, who experienced either low or high levels of fear, experienced lower levels of pain. Further work, to explore enhanced production and measurement of human fear states, while imaging neural responses, are necessary to more completely understand the relationships with painful stimulation. Better assessment of fear (especially pain-related fear) seems warranted, both in experimental and clinical settings, because the effects of fear on pain processing are capable of modulating pain. Clinically, it may be that patients with chronic pain who experienced lower levels of fear will experience lower pain levels. It could be quite important to deal with moderate levels of fear, and perhaps also anxiety, in clinical treatment, because they could increase pain, as the data in the current study demonstrate a positive relationship between increasing fear and pain and increases in brain activity at some sites. Anxiety was also significantly correlated with pain intensity in the present study and has generally been shown to increase pain perception in other studies and in the literature on clinical pain, anxiety is positively associated with reported levels of chronic pain (for current review see Dersh, Polatin, & Gatchel, 2002).

**Overall Implications**

The methods developed in the present study may be used to study patients with chronic facial pain or chronic pain at different body sites. The present study, using acute painful stimulation to the face, established a baseline set of brain activations sites for the pain and emotion conditions, which could be compared to brain activity in patients with chronic pain using the same paradigm. Painful thermal stimulation may be more noxious on the face than at other body sites, but the procedure can be applied elsewhere as has been done in previous work (for review see Peyron et al., 2000). The addition of emotion
states to painful stimulation could add meaningful information to the understanding of pain processing. The results of the current study compare well with other painful stimulation neuroimaging work, but could involve some specific effects to stimulation in the face area. The use of emotion recall provides a convenient and meaningful way of studying the effects of emotion states on pain. Distinct patterns of activity were observed for anger and fear and unique effects of each emotion on pain activations were also observed, consistent with self reports of pain, fear, and anger levels. The techniques of the present study have the potential to be used to assess emotion effects on chronic pain, as more data on chronic pain patients is collected, and these effects could be quantified in pain patients (perhaps as fundamentally different from pain-free controls). Especially, these procedures could be used to study patients with chronic face pain. While recall of specific individual emotion episodes differs in content for each individual, and so represents a non-standard stimulus as opposed to standardized emotional pictures or films, the recall is meaningful and potent in producing changes in pain perception and corresponding brain activity as demonstrated in the present findings.

Application to Chronic Pain

The present study involved acute pain stimuli to the face area and healthy participants with no chronic pain. Pain patients may respond to tasks in the present study much differently from the present pain-free, healthy controls. Further, face pain patients may respond differently to painful stimulation (especially to the face area) than patients with other types of chronic pain. Patients may produce emotional episodes that relate more to a chronic pain experience than to emotional experiences without pain content. If neurotransmitter and neuroplastic changes (central sensitization) actually occur in chronic pain patients, as has been suggested (Sessle, 2000), it would be expected that patterns of brain activity would differ in response to pain and emotion recall in these patients. Further work can make use of these techniques to understand chronic pain states and the contribution of altered cerebral pain processing.

The present study demonstrated the importance and significance of anger and fear in modulating pain processing in agreement with previous work and clinical experience.
For future work, the procedures performed with pain, fear, and anger in the present study may be carried out with chronic pain patients to explore differences in pain processing and may be extended to examine the potentially beneficial effects of positive emotion on pain.
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**Publications and Presentations**


Manuscripts in Preparation

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