REVIEW: NEUROSCIENCE

# Psychological and Neural Mechanisms of the Affective Dimension of Pain

Donald D. Price

**The affective dimension of pain is made up of feelings of unpleasantness and emotions associated with future implications, termed secondary affect. Experimental and clinical studies show serial interactions between pain sensation intensity, pain unpleasantness, and secondary affect. These pain dimensions and their interactions relate to a central network of brain structures that processes nociceptive information both in parallel and in series. Spinal pathways to limbic structures and medial thalamic nuclei provide direct inputs to brain areas involved in affect. Another source is from spinal pathways to somatosensory thalamic and cortical areas and then through a corticolimbic pathway. The latter integrates nociceptive input with contextual information and memory to provide cognitive mediation of pain affect. Both direct and corticolimbic pathways converge on the same anterior cingulate cortical and subcortical structures whose function may be to establish emotional valence and response priorities.**

Unpleasant emotional feelings are integral components of pain because of unique sensory qualities and because these qualities often occur within a context that is threatening, such as during disease or physical trauma. Thus, pain contains both sensory and affective dimensions and is often accompanied by desires to terminate, reduce, or escape its presence (*1*, *2*). Part of the affective dimension of pain is the moment-by-moment unpleasantness of pain, made up of emotional feelings that pertain to the present or short-term future, such as distress or fear. Pain unpleasantness is often, although not always, closely linked to the intensity of the painful sensation. Another component of pain affect, "secondary pain affect," includes emotional feelings directed toward long-term implications of having pain (e.g., "suffering"). This review provides evidence for serial interactions between sensory, unpleasantness, and secondary affective dimensions of pain and their underlying neural mechanisms.

## Psychological Mechanisms of Pain Affect

Multiple factors contribute to pain unpleasantness. Several sensory attributes of pain dispose unpleasant emotional feelings. The foremost among these is that sensations of pain are often more intense than other types of somatic sensations. In addition, pain presents characteristics of slow adaptation (i.e., persistence), temporal summation (for some types of pain), spatial spread of sensation at suprathreshold levels, spatial summation, and unique sensory qualities, as implied by words such as stinging, burning, and aching (*1*, *2*). Sensory attributes dispose us to perceive pain as invasive and intrusive for both the body and consciousness (*2*). Both neural and psychological processes related to pain-related sensation can be conceived as important causal links in the production of pain-related emotional disturbance. The persistence of pain enhances unpleasantness over time.

Nociceptive, exteroceptive (e.g., sight and sound), and interoceptive sensory processes (e.g., startle and increased autonomic responses) may provide parallel contributions to pain affect (*2*). Consistent with Damasio's (*3*) neurological view of emotion mechanisms, pain unpleasantness reflects the contribution of several sources, including pain sensation, arousal, autonomic, and somatomotor responses, all in relation to meanings of the pain and to the context in which pain presents itself.

Psychophysical studies demonstrate that pain sensation and pain unpleasantness represent two distinct dimensions of pain that demonstrate reliably different relations to nociceptive stimulus intensity and are separately influenced by various psychological factors. Psychophysical relations of both pain sensation intensity and pain unpleasantness ratings to 45° to 51°C 5-s skin temperature stimuli are power functions, yet the ratio of pain unpleasantness judgments to pain sensory judgments is less than 1.0 for temperatures within this range (*4*). The lower ratings of unpleasantness in comparison with sensation intensity are likely the result of assurances of safety or the brevity of the 5-s stimuli. Ratios of affective to sensory ratings of brief experimental pain stimuli (5-s heat and electric shock) are systematically less than 1.0, whereas those of long-duration pain stimuli (ischemia and cold pressor) are 1.0 or greater (*5*). Thus, systematic differences in ratios of affective to sensory ratings of nociceptive stimulus intensity occur as a predicted consequence of simple factors, such as stimulus duration and presence or absence of assurances. These differences provide evidence for separate dimensions of pain.

Two related experiments provide further support for the uniqueness of the two pain dimensions and help establish the direction of causation between them (*6*). For both, the left hands of subjects were immersed in a moderately painful 47°C water bath. Hypnotic suggestions were alternately given for enhancing and then decreasing only pain unpleasantness in the first experiment and for enhancing and then decreasing pain sensation intensity in the second. Only pain unpleasantness ratings were changed in the directions suggested in the first experiment, whereas both pain intensity and unpleasantness ratings changed in parallel in the second. These results establish the direction of causation—pain sensation is in series with and is a cause of pain unpleasantness and not vice versa (Fig. 1). These results are consistent with studies showing that some psychological factors selectively influence pain unpleasantness and others alter pain unpleasantness in response to changes in pain sensation (*2*, *4*).

Unlike pain unpleasantness, secondary pain affect is based on more elaborate reflection related to that which one remembers or imagines. This involves meanings such as perceived interference with one's life, difficulties of enduring pain over time, and the implications for the future (*2*, *4*). Pain is often experienced not only as a threat to the present state of one's body, comfort, or activity but also to one's future well-being and life in general. The perceived implications that present distress holds for future well-being and functioning support the link between pain unpleasantness and secondary pain affect.

Studies of pain patients show the distinction between immediate pain unpleasantness

Departments of Oral and Maxillofacial Surgery and Neuroscience, University of Florida, Health Science Center, Post Office Box 100416, Gainesville, FL 32610–0416, USA. E-mail: dprice@dental.ufl.edu

and secondary pain affect and their sequential interactions. Harkins *et al.* (*7*) assessed the influence of two personality traits, neuroticism and extraversion, on pain sensation intensity, pain unpleasantness, and secondary pain affect, using Eysenck and Eysenck's (*8*) personality inventory. A group of 105 myofascial pain dysfunction (MPD) patients were given validated scales to rate sensory and affective dimensions of pain. First, the personality trait of neuroticism had no influence on sensory ratings of experimental heat pain or clinical pain. Second, neuroticism was associated with a small but statistically significant enhancement of patients' unpleasantness ratings of both experimental and clinical pain. Third, high neurotic score patients rated emotions of secondary pain affect (i.e., depression and anxiety) as much more negative in comparison with low neurotic score patients. Extraverts and introverts did not differ in their ratings of any pain dimensions. The same overall pattern of results was obtained in a study of 205 chronic pain patients (*9*). Both studies demonstrated that neuroticism exerted its largest influences not on early stages of pain sensory processing and pain unpleasantness, but on secondary pain affect.

The sequential model of intensity-unpleasantness-secondary affect also was supported by multivariate (linear structural relations) analyses of ratings of these pain dimensions by 1008 chronic pain patients. The sequential model scored high on several indices of goodness of fit (*10*).

## Neural Mechanisms of Pain Unpleasantness and Secondary Pain Affect

Relations between these dimensions of pain can be at least partly related to present understanding of their underlying neural mechanisms. Multiple ascending pathways project to several brainstem and cortical regions, as shown in Fig. 2. Some of these pathways project from the spinal cord dorsal horn directly to brainstem and limbic system areas. These pathways include a spinohypothalamic pathway (*11*), a spinopontoamygdaloid pathway (*12*), and a component of the spinothalamic pathway that projects to specific midline thalamic nuclei (*13*). The latter projects to limbic cortical areas such as anterior cingulate (ACC) and insular cortex (IC) (*13*). Individual neurons often project in more than one of these pathways. Another component of the spinothalamic pathway projects to somatosensory relay nuclei of the thalamus [ventroposterior lateral nucleus (VPL) and ventroposterior inferior nucleus (VPI)] that relay nociceptive information to somatosensory (S-1 and S-2) cortices (*1*, *2*, *13*). S-1 and S-2 are anatomically interconnected with a ventrally directed cortico-limbic somatosensory pathway that integrates somatosensory input with other sensory modalities such as vision and audition and with learning and memory (*14*). This pathway proceeds from S-1/S-2 to posterior parietal cortical areas and to IC and from IC to amygdala, perirhinal cortex, and hippocampus (*14*). Importantly, this system ultimately converges on the same limbic and subcortical structures that are directly accessed by ascending spinal pathways (Fig. 2). This dual convergence may be related to a mechanism whereby multiple neural sources contribute to pain affect.

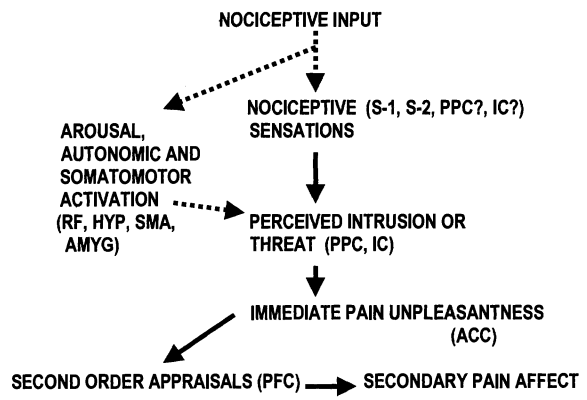


**Fig. 1.** A schematic used to illustrate interactions between pain sensation, pain unpleasantness, and secondary pain affect (solid arrows). Neural structures likely to have a role in these dimensions are shown by abbreviations in adjacent parentheses, and their full names are given in the legend of Fig. 2. Dashed arrows indicate nociceptive or endogenous physiological factors that influence pain sensation and unpleasantness.

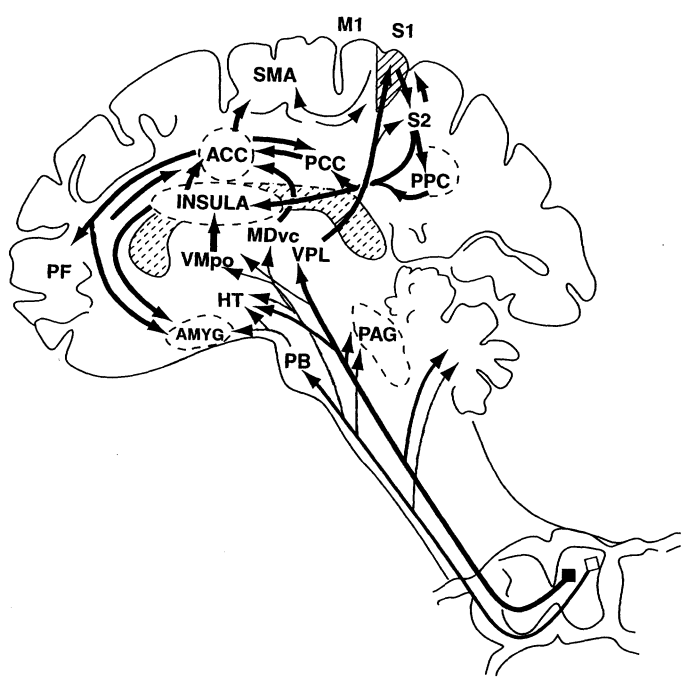


**Fig. 2.** Schematic of ascending pathways, subcortical structures, and cerebral cortical structures involved in processing pain. PAG, periaqueductal gray; PB, parabrachial nucleus of the dorsolateral pons; VMpo, ventromedial part of the posterior nuclear complex; MDvc, ventrocaudal part of the medial dorsal nucleus; VPL, ventroposterior lateral nucleus; ACC, anterior cingulate cortex; PCC, posterior cingulate cortex; HT, hypothalamus; S-1 and S-2, first and second somatosensory cortical areas; PPC, posterior parietal complex; SMA, supplementary motor area; AMYG, amygdala; PF, prefrontal cortex.

Thus, several ascending pathways and brain regions are activated by nociceptive input and participate in pain processing. The number and extent of activation of all of these regions are variable and controversial across neural imaging studies [see (*15*) for review]. A likely major source of this variability is that the number of activated structures is a function of pain intensity itself. Graded nociceptive (46°, 48°, and 50°C) and control (35°C) skin temperature stimuli were used to determine stimulus-neural response relations for several brain areas just described (*16*). Increases in magnitude and spatial distribution of neural activation and additional recruitment of more brain structures in response to ascending temperatures rated as increasingly painful were observed. These stimulus-response relations were obtained for several functionally diverse brain areas, including those likely involved in pain sensation (S-1, S-2, and IC?), motor control (supplementary motor area), affect, and/or attention (ACC) (*16*). These results underscore the idea that precise coding of the intensity of nociceptive stimulation is common to all functions associated with pain.

How then is it possible to determine brain structures that are differentially involved in sensory and affective dimensions of pain? In a recent positron emission tomography (PET) study, hypnotic suggestions were used to selectively increase or decrease unpleasantness ratings of experimental pain (*17*). Significant pain-related activation occurred in the so-

matosensory area I (S-1), ACC area 24, and IC during control conditions. Hypnotic suggestions resulted in much larger unpleasantness ratings during the "high unpleasantness" condition as compared with the "low unpleasantness" condition with no differences in pain sensation ratings. Consistent with these changes, activity in the posterior sector of ACC area 24 was much greater in the high as compared with the low unpleasantness condition, yet no differences occurred for S-1. A separate regression analysis, controlling for factors such as pain sensation intensity ratings, showed that pain unpleasantness ratings were significantly associated with activity in the posterior sector of ACC area 24 ($R$ = 0.55, $P < 0.001$). A subsequent study that used hypnosis to modify pain sensation intensity showed corresponding changes in S-1 cortex (*18*).

A PET study confirmed results of Rainville *et al.* (*17*) by using a different experimental approach to induce selective variation in pain unpleasantness (*19*). With the use of noxious heat and four successive experimental pain trials, lower ratios of pain unpleasantness to pain sensation intensity were evoked on the first two trials and higher ratios were evoked on the second. Regression analysis showed that although several brain structures were activated during pain, only pain unpleasantness was encoded in ACC area 24 (*19*). Both studies suggest that ACC may be more proximate to the production of pain affect than somatosensory cortical areas (*17*, *19*). However, the latter also contributes to pain affect.

The functional role of ACC and related limbic structures could be further clarified by consideration of how they fit into the general circuitry associated with pain processing. The general ways in which multiple ascending pathways and brain regions could participate in the various components of pain affect are evident in Fig. 2. Nociceptive pathways originating from the spinal cord dorsal horn directly activate brain structures involved in rudimentary aspects of autonomic system activation, escape, motoric orientation, arousal, and fear (*2*, *11–13*). These structures include medullary and midbrain reticular formation nuclei, deep layers of the superior colliculus, central gray, amygdala, hypothalamus, and specific medial thalamic nuclei. Activation of these structures likely occurs during the early phase of pain, wherein fear, defensive behavior, and autonomic responses would take place. These responses would occur somewhat automatically and involve a minimum amount of cognition.

A second general mechanism could result from activation of somatosensory cortices and subsequent activation of brain structures involved in perceptual and cognitive aspects of pain processing, the most rudimentary of which would be that related to appreciation of the intensive and qualitative aspects of pain sensation. S-1 and S-2 somatosensory cortical areas would be involved at this level. However, higher levels of processing also occur within posterior parietal and insular regions that integrate somatosensory nociceptive input with other contextual inputs to provide an overall sense of intrusion and threat to the physical body and self (*2*, *3*, *14*, *20–22*). Studies showing that sensory and unpleasantness dimensions of pain are in series are consistent with this mechanism (*4*, *6*).

Evidence for this mechanism derives from a study that found that some neurons of the infraparietal cortical area 7b in the monkey responded to nociceptive stimuli (44°C to 47°C) and yet were enhanced by antecedent or concurrent visual stimuli (*23*). However, this enhancement only occurred if the target location or direction of motion within the visual receptive field was spatially aligned with the cutaneous receptive field. The enhancement was much greater for mild nociceptive stimuli (44° to 45°C) than for stronger stimuli (47°C) (*23*). The neural organization of this region of the posterior parietal cortex appears to be that of integrating nociceptive inputs with other sensory inputs in a manner that conveys information about the overall degree of threat presented to an organism. This integration is especially critical at the low end of the nociceptive stimulus range, wherein an organism must make a behaviorally relevant decision about the extent of threat presented by an object. Processing of pain requires an evaluation of sensation in relation to its overall context, an evaluation that may help link sensation with affect. This function would require integration of somatosensory input with other sensory modalities and with memory.

This interpretation is consistent with effects of lesions to this area or to IC that receives input from S-2/7b. Focal damage to S-2/7b in the monkey results in an absence of escape responses to painful temperatures despite preservation of the ability to detect the offset of noxious thermal stimuli (*24*). An area that receives input from areas S-2/7b is IC (*14*). When the latter is damaged in humans, a resultant syndrome of pain asymbolia results wherein patients no longer appreciate the destructive significance of pain and do not withdraw from nociceptive stimuli or threatening gestures (*25*, *26*). This deficit occurs despite their capacity to detect sensory features of pain.

Posterior parietal cortical areas that integrate somatosensory input with other sensory modalities and with learning and memory are at the origin of a ventrally directed corticolimbic pathway (*14*). This pathway converges on the same cortical and subcortical limbic structures (ACC, IC, and amygdala) that receive direct input from spinal pain pathways. As shown in Fig. 2, somatosensory input related to pain proceeds from S-1 and S-2 through posterior parietal cortex to IC and finally to ACC (*22*). Convergence at the level of ACC would be consistent with a mechanism in which somatic perceptual and cognitive features of pain would be integrated with attentional and rudimentary emotion mechanisms. On the basis of neurological evidence (*27*), the ACC may have a complex pivotal role in interrelating attentional and evaluative functions with that of establishing emotional valence and response priorities. Response priorities would be closely related to premotor functions that are integrally related to motivation and emotions and may be associated with immediate efforts to cope with, escape, or avoid the pain and pain-evoking situation. In this view, cortical areas controlling sensory, attentional, premotor, and affective functions of pain are largely in series, an interpretation supported by both psychological (*4*, *6*) and brain imaging studies (*17–19*) described above.

Response priorities change over an extended period of time. Pain unpleasantness endured over time engages prefrontal cortical areas involved in reflection and rumination over the future implications of a persistent pain condition. The ACC may serve this function by coordinating somatosensory features of pain with prefrontal cerebral mechanisms involved in attaching significance and long-term implications to pain, a function associated with secondary pain affect. Thus, ACC may be a region that coordinates inputs from parietal areas involved in perception of bodily threat with frontal cortical areas involved in plans and response priorities for pain-related behavior. Both functions would help explain observations on patients with prefrontal lobotomy and patients with pain asymbolia as described above. The former have deficits in spontaneous concern or rumination about their pain but can experience the immediate threat of pain once it is brought to their attention (*28*). In contrast, asymbolia patients appear incapable of perceiving the threat of nociceptive stimuli under any circumstances (*25*, *26*).

### A Parallel-Serial Model of Pain Affect

This view of pain affect mechanisms is that of a central network of brain structures and pathways that contains both serial and parallel connections (Fig. 2). Direct spinal inputs to lower brainstem and limbic structures may contribute to rudimentary aspects of pain affect, such as arousal, autonomic, and somatomotor activation. Spinothalamic pathways to medial thalamic nuclei provide direct input regions involved in monitoring the overall

state of the body (IC), directing attention (ACC), and assigning response priorities (ACC). However, ACC receives a major serial input from a ventrally directed somatosensory-limbic pathway that contributes varying degrees of cognitive evaluation to pain affect (Fig. 2). This pathway is consistent with evidence that pain unpleasantness is in series with sensory aspects of pain and is cognitively mediated (Fig. 1). Additional parallel contributions to pain affect could include arousal and consequences of autonomic/somatomotor activation and would be consistent with both psychological (Fig. 1) and neuroanatomical (Fig. 2) evidence. The ACC is a pivotal area that receives multiple inputs and is more closely associated with pain unpleasantness than are cortical structures and ascending pathways that project there. Secondary pain affect is sustained by pain unpleasantness and may depend on ACC-prefrontal cortical interactions that add further cognitive evaluation to emotions associated with pain.

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29. This work was supported by NIH grant R01 295527912.