

The Biopsychosocial Approach to Chronic Pain: Scientific Advances and Future Directions

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The prevalence and cost of chronic pain is a major physical and mental health care problem in the United States today. As a result, there has been a recent explosion of research on chronic pain, with significant advances in better understanding its etiology, assessment, and treatment. The purpose of the present article is to provide a review of the most noteworthy developments in the field. The biopsychosocial model is now widely accepted as the most heuristic approach to chronic pain. With this model in mind, a review of the basic neuroscience processes of pain (the *bio* part of biopsychosocial), as well as the psychosocial factors, is presented. This spans research on how psychological and social factors can interact with brain processes to influence health and illness as well as on the development of new technologies, such as brain imaging, that provide new insights into brain-pain mechanisms.

Keywords: biopsychosocial, chronic pain, neuroscience of pain, pain and cognition, pain and emotion

During the past decade, there has been an explosion of research on chronic pain, with significant advances in understanding its etiology, assessment, and treatment (Gatchel, 2004a, 2004b, 2005; Turk & Monarch, 2002). This research has important health care implications. Epidemiological research has shown that chronic pain (loosely defined as prolonged and persistent pain of at least 3 months in duration) and chronic recurrent pain (recurrent episodes of pain interspersed with pain-free periods extending over months or years) affects 10%–20% of adults in the general population (Blyth et al., 2001; Gureje, Von Korff, Simon, & Gater, 1998; Verhaak, Kerssens, Dekker, Sorbi, & Bensing, 1998). For example, in a large-scale epidemiological study, Von Korff et al. (2005) estimated a 19% prevalence for chronic spinal pain (neck and back) in the United States in the previous year and a 29% lifetime rate. The American Academy of Pain Management (2003) asserted that approximately 57% of all adult Americans reported experiencing recurrent or chronic pain in the past year. About 62% of those individuals reported being in pain for more than 1 year, and

40% noted that they were constantly in pain. Indeed, as Gatchel (2004a, 2004b) has summarized, pain is a pervasive medical problem: It affects over 50 million Americans and costs more than \$70 billion annually in health care costs and lost productivity; it accounts for more than 80% of all physician visits. Moreover, chronic pain is often associated with major comorbid psychiatric disorders and emotional suffering.

As the above factors attest, the prevalence and cost of chronic pain is a major physical and mental health care problem in the United States. Moreover, individuals 50 years of age and older are twice as likely to have been diagnosed with chronic pain (Gatchel, 2004, 2005). Currently, there are approximately 35 million Americans aged 65 years or older, accounting for 12.4% of the total population. The proportion of the population aged 65 and over is expected to increase by 57% by the year 2030, with Americans now having an average life expectancy of 77 years (Social Security Administration, n.d.). Awareness of these population trends has contributed to an increased concern about health care issues of older Americans, including chronic pain problems. With these estimates in mind, it is not surprising that the U.S. Congress designated 2001–2010 as the Decade of Pain Control and Research and that the Joint Commission on Accreditation of Healthcare Organizations now requires physicians to consider pain as the fifth vital sign (added to the other vital signs of pulse, blood pressure, core temperature, and respiration).

The statistics cited above and population trends have fueled a great deal of research on chronic pain. The purpose of the present article is to provide a review of some of the most noteworthy scientific advances in this area. As is initially discussed, the biopsychosocial model has proved to be the most widely accepted and most heuristic perspective to the understanding and treatment of chronic pain. Subsequently, reviews

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of important biobehavioral mechanisms and psychosocial factors are provided.

The Biopsychosocial Model of Chronic Pain

The traditional approach embraced a dualistic viewpoint that conceptualized the mind and body as functioning separately and independently. The inadequacy of the dualistic model contributed to a growing recognition that psychosocial factors, such as emotional stress, could impact the reporting of symptoms, medical disorders, and response to treatment. George Engel (1977) is credited as one of the first to call for the need of a new approach to the traditional biomedical reductionistic philosophy that dominated the field of medicine since the Renaissance. This subsequently led to the growth of the field of behavioral medicine and health psychology (Gatchel & Baum, 1983). A major outgrowth, in turn, was the development and evolution of the biopsychosocial model. This model has been especially influential in the area of chronic pain.

The biopsychosocial model focuses on both disease and illness, with illness being viewed as the complex interaction of biological, psychological, and social factors (Gatchel, 2005). As succinctly summarized by several authors (e.g., Gatchel, 2004a, 2004b; Turk & Monarch, 2002), *disease* is defined as an objective biological event involving the disruption of specific body structures or organ systems caused by either anatomical, pathological, or physiological changes. In contrast, *illness* refers to a subjective experience or self-attribution that a disease is present. Thus, illness refers to how a sick person and members of his or her family live with, and respond to, symptoms of disability.

The distinction between disease and illness is analogous to the distinction that can be made between *nociception* and *pain*. Nociception involves the stimulation of nerves that convey information about potential tissue damage to the brain. In contrast, pain is the subjective perception that results from the transduction, transmission, and modulation of sensory information. This input may be filtered through an individual's genetic composition, prior learning history, current psychological status, and sociocultural influences. For pain to be registered, the organism must be conscious. To the best of our knowledge, completely anesthetized patients do not perceive pain; however, nociception can be detected following a surgical incision even in the absence of any subjective report.

Loeser (1982) originally formulated a general model that delineated four dimensions associated with the concept of pain: the dimensions of nociception and pain reviewed above, *suffering* (the emotional responses that are triggered by nociception or some other aversive event associated with it, such as fear or depression), and *pain behavior* (those things that people say or do when they are suffering or in pain, such as avoiding activities or exercise for fear of reinjury). Pain behaviors are overt communications of pain, distress, and suffering.

Waddell (1987) has emphasized that pain cannot be comprehensively evaluated without an understanding of the individual who is exposed to the nociception. Waddell also made a comparison between Loeser's (1982) model of pain and the biopsychosocial model put forth by Engel (1977). In particular, Engel proposed the important dimensions of the physical problem, distress, illness behavior, and the sick role, which corresponded to Loeser's dimensions of nociception, pain, suffering, and pain behavior, re-

spectively. In order to fully understand a person's perception and response to pain and illness, the interrelationships among biological changes, psychological status, and the sociocultural context all need to be considered (see Figure 1). Any model that focuses on only one of these dimensions will be incomplete and inadequate.

Many of the individual dimensions depicted in Figure 1, and the complexities involved with their interactions, are discussed in subsequent sections of this article, particularly the neurobiology of the nociception process and other basic neuroscience processes of pain (the *bio* part of biopsychosocial), as well as psychological and social factors. The psychosocial factors involve both emotion and cognition. Emotion is the more immediate reaction to nociception and is more midbrain based. Cognitions then attach meaning to the emotional experience and can then trigger additional emotional reactions and thereby amplify the experience of pain, thus perpetuating a vicious circle of nociception, pain, distress, and disability. We then review the implications of the new insights for better understanding the etiology, assessment, treatment, and prevention of chronic disability.

The Nociceptive Process

Early Biomedical Models

Historically, 19th and 20th century models of nociceptive processing followed the traditional biomedical model of disease. The ideas followed a Cartesian view that there was an isomorphic relationship between pain and tissue injury. The early biomedical models can, in general, be divided into two general perspectives. One perspective, "specificity theory," generally stated that there were unique receptor mechanisms and pathways that transduced and transmitted specific painful information from the periphery to the spinal cord and then to the brain. This direct transmission line model can be traced back to views expressed by the ancient Greeks. One of the earliest and best known of the modern specificity theorists was von Frey (see Finger, 1994). His work revolved around the identification and description of mechanical and thermal receptive fields on the skin. On the basis of his work, it was suggested that specialized nerve endings were involved in the transduction and transmission of painful information.

Another general theoretical perspective has been referred to as the "pattern response" (Nafe, 1934; Sinclair, 1955; Weddell, 1955). According to this perspective, nociceptive information was not primarily due to activation of specific receptors and pathways but rather was due to the pattern of responses in afferent systems. It was the stimulus intensity and the processing of the pattern of responses that determined the perceptual response to the nociceptive input, namely, pain. Although these two general perspectives explained much of the literature and prompted a wealth of scientific literature, both perspectives had limitations, and many issues and potential explanations related to pain and suffering remained elusive.

Another perspective, harkening back to Aristotle and challenging the pure sensory models described, conceptualized pain as a "quality of the soul"—an emotion in contrast to a pure sensory event. This competing viewpoint was carried forward to more recent times. For instance, Livingston (1943, 1998) was one of the first to expose the weaknesses of specificity theory and argue for pain as a subjective state that arises from activation of aversive

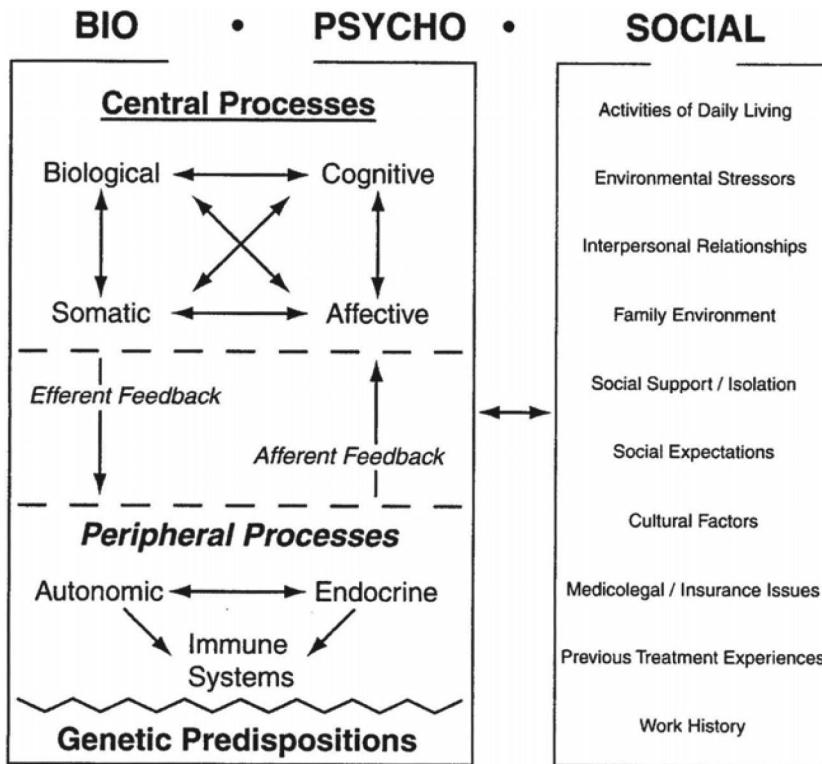


Figure 1. A conceptual model of the biopsychosocial interactive processes involved in health and illness. From “Comorbidity of Chronic Mental and Physical Health Conditions: The Biopsychosocial Perspective,” by R. J. Gatchel, *American Psychologist*, 59, 792–805. Copyright 2004 by the American Psychological Association.

networks in the brain. His concept of “appetites,” with pleasure and pain as the motivating attributes, was a dramatic shift in thought and reflected Hebb’s (1949) belief that pain was a factor motivating behavior. The failure of these unidimensional sensory and affective models to explain much of what was observed experimentally and clinically (Beecher, 1959) and the inadequacy of treatments based on these models served as the impetus for a more complex, integrative model. In particular, the seminal gate control theory of pain postulated by Melzack and colleagues (Melzack & Casey, 1968; Melzack & Wall, 1996).

The Gate Control Theory of Pain

The initial framework for the gate control theory of pain, which built on the ideas of the Dutch surgeon Nordenbrass (1959), was developed to ensure that the known properties of clinical pain conditions at the time were explained. Melzack and Wall (1965) sought to combine the properties of the specificity theories with the best features of the pattern response theories and the affective-motivational view in order to generate the more inclusive gate control theory of pain. They recognized that there was a certain degree of specificity for peripheral nerve function. They also realized that there was a certain degree of pattern recognition that was responsible for the underlying peripheral and central processing of noxious information. Moreover, they acknowledged that a comprehensive model must take into consideration the amplifying effects of emotion and the interpretive role of cognitive evaluation.

As outlined by Melzack and Wall (1996), the gate control theory of pain had to account for a number of facts such as the following:

- (1) the variable relationship between injury and pain;
- (2) non-noxious stimuli can sometimes produce pain;
- (3) the location of pain and tissue damage is sometimes different;
- (4) pain can persist long after tissue healing;
- (5) the nature of the pain and sometimes the location can change over time;
- (6) pain is a multi-dimensional experience; and
- (7) there is a lack of adequate pain treatments. (p. 165)

It is precisely these facts that no theory at the time could explain.

The initial formulation proposed that there are five stages that compose the mechanism by which noxious signals enter the spinal cord from the periphery and then proceed to higher level brain areas. The first stage consisted of the small diameter peripheral nerve fiber transmission of signals to cells in the spinal cord. The second stage included facilitatory interneurons in the region of the spinal cord to account for the fact that cells in the spinal cord can show prolonged afterdischarge following the arrival of a signal from the peripheral nerve (Wall, 1960). The afterdischarge was accounted for by an excitatory interneuron. The third stage incorporated a large-fiber, low-threshold input. This third stage focused attention on a group of additional peripheral fiber inputs to the spinal cord that could be involved in pain processing. As they indicated, most research prior to the gate control theory focused on nociceptive specific neurons, or those cells that responded only to high-threshold peripheral stimulation. The fourth stage included inhibitory interneurons to account for the fact that postsynaptic

inhibition was likely to occur in the spinal cord. The fifth stage was the inclusion of a descending modulatory system to account for the finding that there was an inhibitory influence from the brainstem to the spinal cord (Wall, 1967). The final stage was the inclusion of a loop system, with the assumption that ascending signals to the brain engage and influence descending modulatory systems. Therefore, Figure 2 illustrates the final diagram of the gate control theory. There is little doubt that the gate control theory, with a focus on the multidimensional and variable relationship between pain and tissue damage, was a major advancement in the field of pain research and management, prompting much research and ultimately increasing researchers' understanding of pain mechanisms. As the field of pain research and management evolves, the adequacy of the gate control theory of pain to explain different factors has also continued to be examined.

The Neuromatrix Theory of Pain

The neuromatrix theory of pain proposes that pain is a multi-faceted experience that is produced by a characteristic neurosignature of a widely distributed brain neural network, called the *body-self neuromatrix* (Melzack, 2001, 2005; see Figure 3). The body-self neuromatrix integrates cognitive-evaluative, sensory-discriminative, and motivational-affective components proposed by Melzack and Casey (1968). The theory proposes that the output patterns of the neuromatrix engage perceptual, behavioral, and homeostatic systems in response to injury and chronic stress. A critical component of the neuromatrix theory of pain is the recognition that pain is the consequence of the output of the widely distributed brain neural network rather than a direct response to sensory input following tissue injury, inflammation, and other pathologies (Melzack, 2001).

The development of such a hypothetical system stems primarily from reports and research in patients with spinal cord injuries and in patients that experience phantom limb and phantom limb pain. In a large number of cases, paraplegics will continue to experience body sensations and pain below the level of the spinal section. A significant proportion of individuals who lose a limb or sensation

in other body regions will continue to experience the presence of the limb or the otherwise anesthetic area (e.g., below a spinal lesion). Although the experience of the phantom limb might be in some cases maintained by altered peripheral nerve activity in the region of the stump (Hunter, Katz, & Davis, 2005), there is sufficient evidence indicating that peripheral mechanisms do not fully account for such phenomena (Katz & Melzack, 1990; Ramachandran, 1998; Ramachandran & Hirstein, 1998; Wu et al., 2002). Traditional specificity and pattern theories of pain, in particular, have difficulty accounting for these phenomena. The body-self neuromatrix, however, requires no actual sensory input to produce experiences of the body.

Homeostasis, Allostatic Load, and Hypothalamic-Pituitary-Adrenal (HPA) Axis Dysregulation

It is becoming clear that the pain experience is determined by a multitude of factors. Although the focus has historically been directed at sensory mechanisms, more attention is being placed on factors related to cognitive, affective, behavioral, and homeostatic factors. The primary basis for including discussions of homeostatic factors is that chronic pain threatens the organism and produces a cascade of events that eventually contributes to the maintenance of such conditions even after the original tissue damage has been resolved or in the absence of any objectively determined pathology. If one views pain as a primary threat to the organism, similar to the stress of extreme hunger and thirst, then mechanisms should be present to engage and motivate the organism to restore basic homeostatic function (LaGraize, Borzan, Rinker, Kopp, & Fuchs, 2004). The major consequence of homeostatic imbalance is stress. Regardless of the source, stressors activate numerous systems such as the autonomic nervous system and the HPA axis. Prolonged activation of the stress system has disastrous effects on the body (cf. Selye, 1950; Korte, Koolhaas, Wingfield, & McEwen, 2005) and sets up a condition of a feedback loop between pain and stress reactivity.

During periods of short-term stress and homeostatic imbalance, the hypothalamus activates the pituitary gland to secrete adrenocorticotropic hormone, which acts on the adrenal cortex to secrete cortisol. Secretion of cortisol elevates blood sugar levels and enhances metabolism, an adaptive response that allows the organism to mobilize energy resources to deal with the threat and restore homeostatic balance (i.e., fight or flight response). The situation is much more serious during prolonged periods of stress and homeostatic imbalance that is associated with long-term psychological stress, including chronic pain and other pathological conditions. Prolonged, elevated levels of cortisol are related to the exhaustion phase of Selye's (1950) General Adaptation Syndrome. The negative effects of this stage of the adaptation syndrome include atrophy of muscle tissue, impairment of growth and tissue repair, immune system suppression, and morphological alterations of brain structures, which together might set up conditions for the development and maintenance of a variety of chronic pain conditions (Chrousos & Gold, 1992; McBeth et al., 2005; McEwen, 2001; McLean et al., 2005). The concept of allostatic load, and the factors that contribute to physiological burden, is becoming increasingly recognized as an important component of disease and disabilities (Seng, Graham-Bermann, Clark, McCarthy, & Ronis,

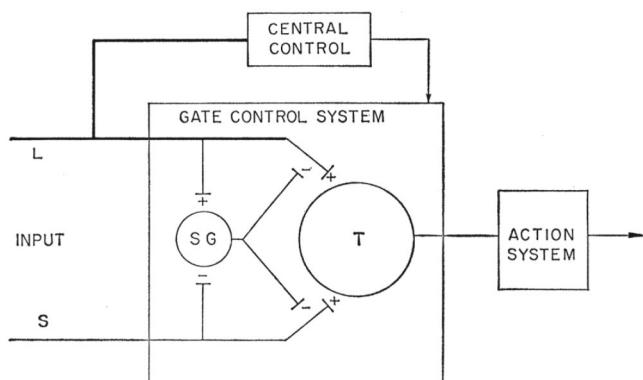


Figure 2. L = large diameter fibers; S = small diameter fibers; SG = substantia gelatinosa; T = first central transmission cells; + = excitation; - = inhibition. Melzack and Wall's gate control theory of pain. From "Pain Mechanisms: A New Theory," by R. Melzack and P. D. Wall, 1965, *Science*, 150, p. 975. Copyright 1965 by the American Association for the Advancement of Science. Reprinted with permission.

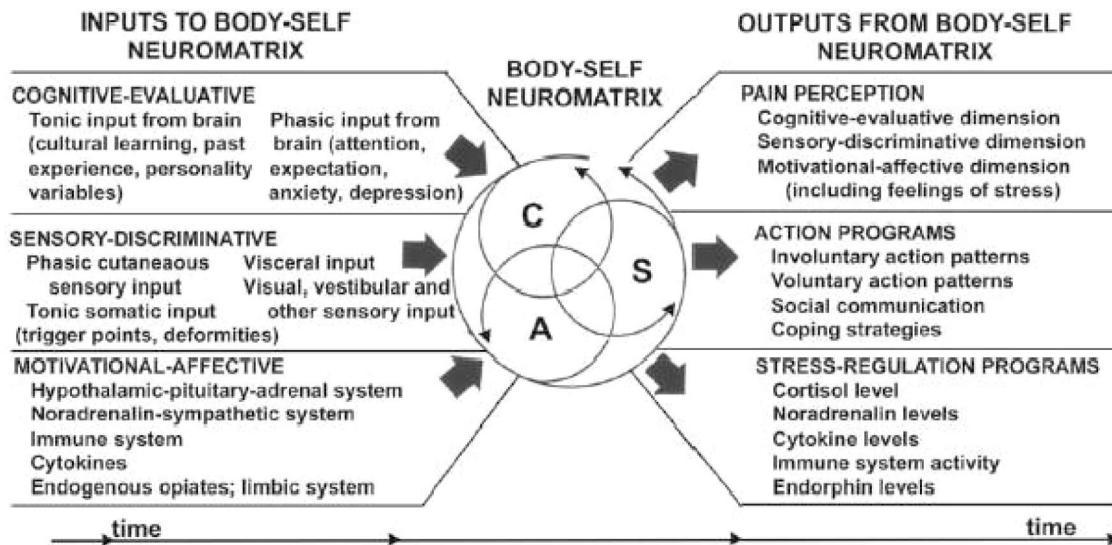


Figure 3. **Melzack's body-self neuromatrix model of pain.** From "Pain and the Neuromatrix in the Brain," by R. Melzack, 2001, *Journal of Dental Education*, 65, p. 1382. Copyright 2001 by the American Dental Education Association. Reprinted with permission.

2005; Singer, Friedman, Seeman, Fava, & Ryff, 2005; Tucker, 2005).

According to Melzack (2005), psychological stress, as well as sensory and cognitive events, modulates the neurosignature of the body-self neuromatrix which, as a consequence of altered neuromatrix output, is associated with chronic pain conditions. The concept of the neuromatrix has potentially important explanatory implications for brain function in general and, together with the concepts of allostasis and homeostasis, provides a theoretical framework for the biopsychosocial perspective of chronic pain. As is discussed later, there is a growing literature demonstrating the importance of psychosocial factors (emotion and cognition) in this neuromatrix conceptualization.

The Neuroscience of Pain

The field of neuroscience has contributed to a better delineation of basic mechanisms in pain processing by conducting carefully controlled experimental studies. In doing so, several experimental pain models have been proposed involving inflammatory pain, neuropathic pain, and cancer pain. These models, in turn, have led to important clinical applications, such as the development of analgesic agents for improved management of chronic pain. A summary of research related to these three models is presented in Table 1. The purpose of this section is to simply provide a general overview of the wide breadth of neuroscience research of chronic pain that is ongoing. Research on inflammatory, neuropathic, and cancer pain models is reviewed.

Inflammatory mediators and their action on pain pathways have a direct effect on pain states through stimulation or potentiation of nociceptive transduction at peripheral terminals and central changes contributing to hypersensitivity (Levine & Reichling, 1999; Raja, Meyer, Ringkamp, & Campbell, 1999). As noted in Table 1, inflammatory pain models have been tested with a number of different techniques, such as experimental arthritis by intra-

articular injections of certain substances, cutaneous inflammation by application of certain extracts, and so forth. In addition to the somatic pain models, several visceral pain models have been developed, including writhing test by intraperitoneal injection of phenylquinone or acetic acid or injection of formalin into the colon wall. Other methods used have been intracolonic application of mustard oil or capsaicin, colorectal distention, and intrabladder injection of xylene, to mention some of the more commonly used ones.

Neuropathic pain results from damage to the nervous system, including peripheral nerves, spinal cord, and certain central nervous system (CNS) regions. As seen with many other clinical pain conditions, the clinical symptoms of neuropathic pain include spontaneous pain, allodynia (i.e., pain due to a stimulus that does not normally produce pain, such as soft touch), and hyperalgesia (i.e., an exaggerated response to a stimulus that is normally somewhat painful). It may spread to the neighboring cutaneous distribution of the injured nerve or develop bilaterally in mirror image sites with the quality of burning, shooting, stabbing, piercing, and electric shock.

Following trauma, inflammation or infection causes almost half of human neuropathies. Sciatic inflammatory neuritis models have been developed to address this issue by injection of zymosan around the sciatic nerve. As a further model for two of the major human diseases that cause peripheral neuropathy, there has been the development of the postherpetic neuralgia model, involving reactivation of a primary infection with varicella-zoster virus, and the diabetic neuropathic pain model, involving injection of streptozocin or use of animal strains (such as insulin-deficient rats and mice, insulin resistant mice, and Mongolian gerbil).

Cancer pain is an increasingly devastating problem affecting the quality of life for patients undergoing active treatment and advanced cancer stages. Cancer-related pain can be caused directly by tumor infiltration or compression of peripheral nerve, plexus, or

Table 1
Summary of Experimental Pain Models

Category	Models	Procedures	References
Inflammatory pain	Experimental arthritis	Intra-articular injection of kaolin and carrageenan	Schaible & Schmidt (1985); Schaible & Schmidt (1988a, 1988b); Neugebauer & Schaible (1990); Schaible & Grubb (1993)
		Intra-articular injection of Freund's adjuvant	Butler et al. (1992); Grubb et al. (1993); L. F. Donaldson et al. (1993)
	Cutaneous inflammation	Topical application of mustard oil	Woolf & King (1990); Koltzenburg et al. (1992); Koltzenburg & Handwerker (1994)
		Injection of carrageenan	Traub (1996); Ren, Williams, et al. (1992); Meller et al. (1994)
		Injection of complete Freund's adjuvant	Ren, Hylden, et al. (1992); Ren & Dubner (1993); Ren et al. (1994); Ren & Dubner (1996); Ruda et al. (2000)
		Injection of formalin	Dubuisson & Dennis (1977); Dickenson & Sullivan (1987); Coderre et al. (1990); Coderre & Melzack (1992a, 1992b); Coderre et al. (1993); Abbott et al. (1995)
		Injection of bee venom	Lariviere & Melzack (1996); J. Chen et al. (1998); J. Chen et al. (1999); Lariviere & Melzack (2000)
		Injection or topical application of capsaicin	Bodnar et al. (1983); Simone et al. (1989); LaMotte et al. (1991, 1992); Torebjörk et al. (1992); Sluka et al. (1997)
	Myofascial pain	Injection of acidic saline	Sluka et al. (2001); Hoeger-Bement & Sluka (2003); Radhakrishnan et al. (2003); Skyba, et al. (2005)
		Injection of carrageenan	Radhakrishnan et al. (2003); Skyba et al. (2005)
Visceral pain	Visceral pain	Intraperitoneal injection of phenylquinone	Hendershot & Forsaith (1959); Taber et al. (1964)
		Intraperitoneal injection of acetic acid	Taber et al. (1969)
		Injection of formalin into the colon wall	Miampamba et al. (1994)
		Intracolonic application of mustard oil or capsaicin	Laird, Martinez-Caro, et al. (2001)
		Colorectal distention	Ness et al. (1991); Al-Chaer et al. (1996)
	Neuropathic pain	Intrabladder injection of xylene	Abelli et al. (1988, 1989)
		Intrauterine injection of mustard oil	Wesselmann et al. (1998)
		Vaginal hyperalgesia through endometriosis	Berkley et al. (2001)
		Artificial ureter stone	Giamberardino et al. (1995)
		Spared root paradigm	Liu & Chambers (1958); Loeser & Ward (1967); Goldberger & Murray (1974); Basbaum & Wall (1976); Wall et al. (1979); Pubols & Goldberger (1980); Brinkhus & Zimmerman (1983)
Neuropathic pain	Deafferentation pain	Nerve transaction	Devor & Wall (1981a, 1981b); Woolf & Wall (1982); Hylden et al. (1987)
		Bennett model	Mosconi & Kruger (1996); Bennett & Xie (1988); Maves et al. (1993)
		Seltzer model	Seltzer et al. (1990)
	Peripheral neuropathic pain (Kim et al., 1997)	Chung model	S. H. Kim & Chung (1992); Palecek et al. (1992); Carlton et al. (1994); Yoon et al. (1996); Ali et al. (1999)
		Sciatic cryoneurolysis	DeLeo et al. (1994); Imamura & Bennett (1995); Willenbring et al. (1995)
		Freezing of the sciatic nerve	Wallace et al. (2003)
		Sciatic demyelination	White et al. (1950); Levitt & Levitt (1981); Lenz et al. (1987, 1989); Vierck et al. (1990); Ovelmen-Levitt et al. (1995); Vierck & Light (1999); Weng et al. (2000)
		Central neuropathic pain (Boivie et al., 1989; Leijon et al., 1989; Boivie, 1990; Willis, 2002)	Siddall et al. (1995); Basso et al. (1995); Hulsebosch et al. (2000); Christensen et al. (1996); Christensen & Hulsebosch (1997a, 1997b); Yezierski & Park (1993); Yezierski et al. (1993, 1998)
		Contusion	LaBuda et al. (2000)
		Spinal cord hemisection	Hao, Xu, Yu, et al. (1991); Hao, Xu, Aldskogius, et al. (1991); Hao, Xu, Yu, et al. (1992); Xu et al. (1992); Hao, Xu, Aldskogius, et al. (1992)
Sciatic inflammatory neuritis	Injection of quisqualic acid	Injection of quisqualic acid	Gazda et al. (2001); Chacur et al. (2001)
		Injection of kainate	Maves et al. (1993)
	Ischemia	Ischemia	Eliav et al. (1999)
		Injection of zymosan around the sciatic nerve	Sadzot-Delvaux et al. (1990, 1995); Fleetwood-Walker et al. (1999)
Postherpetic neuralgia model	Placing proinflammatory gut suture		
	Placing dead bacteria or carrageenan		
	Infection with varicella-zoster virus		

Table 1 (continued)

Category	Models	Procedures	References
Cancer pain	Diabetic neuropathic pain model	Injection of streptozocin	Wuarin-Bierman et al. (1987); Courteix et al. (1993, 1994)
		Insulin deficient BB rat NOD mice	Sima (1980)
		Insulin resistant ob/ob and db/db mice	Mosseri et al. (2000); Pieper et al. (2000)
	Chemotherapy-induced peripheral neuropathy model	Mongolian gerbil	Meyerovitch et al. (1991); Takeshita & Yamaguchi (1998)
		Injection of vincristine	Vincent et al. (1979); Shafrir et al. (2001)
		Injection of taxol	Aley et al. (1996); Nozaki-Taguchi et al. (2001); Tanner et al. (1998)
		Injection of cisplatin	Apfel et al. (1991); Cavaletti et al. (1995); Cliffer et al. (1998); Boyle et al. (1999); Authier et al. (2000); Dina et al. (2001); Polomano et al. (2001)
	Cancer invasion pain model	Implantation of Meth A sarcoma cells around the sciatic nerve in BALB/c mice	de Koning et al. (1987a, 1987b); Verdu et al. (1999); ter Laak et al. (2000)
		Injection of osteolytic mouse sarcoma NCTC2472 cells into the femur bone marrow	Shimoyama et al. (2002, 2005)
	Bone cancer pain model	Injection of MRMT-1 rat mammary gland carcinoma cells into the tibia bone marrow of Sprague-Dawley rats	Schwei et al. (1999); Honore et al. (2000); Mantyh et al. (2002); Luger et al. (2005)
			Medhurst et al. (2002); Walker et al. (2002)

roots; indirectly by immunoreactive and pronociceptive substances released from tumors; or by treatment (chemotherapy, radiation, or surgery). In order to model human cancer pain, several cancer-related pain models have been developed, including the chemotherapy-induced peripheral neuropathy model by injection of vincristine, taxol, and cisplatin; the cancer invasion pain model by implantation of Meth A sarcoma cells around the sciatic nerve; and the bone cancer pain model by injection of osteolytic mouse sarcoma NCTC2472 cells into the femur bone marrow or by injection of MRMT-1 rat mammary gland carcinoma cells into the tibia bone marrow of rats.

With the establishment of these pain models, the biological mechanisms of pain can be further studied by application of various techniques. For example, following the L5 spinal nerve ligation, in combination with behavioral observation, electrophysiological techniques can be applied to study the peripheral single fiber response properties and change of excitability of central dorsal horn neurons; genetic expression of target proteins (such as different voltage sensitive sodium channels, opioid receptors, early response genes) can be evaluated during the acute phase and chronic phase of the neuropathic pain. In addition to anatomical, behavioral, psychophysical, and computational neural modeling tools, genetic, electrophysiological, and imaging techniques can be widely used in the investigation of these three models of pain. They are discussed next.

Genetics

With the rapid advances in molecular biology and genetics, the human genome was mapped out in 2001 (Jasny & Kennedy, 2001). Biological functions of every system, organ, and each individual cell depend on genetic expression to produce peptides or proteins, which either contribute to the structure of the cell or participate in

metabolism through various enzymes. Overexpression or elimination of a gene results in functional changes. The neuronal activities involved in pain transmission can be influenced by activities of immediate, early genes as well as transcriptional factors, all of which may result in changes in gene expression. With the understanding of the gene expression in response to noxious stimuli, genetic engineering can be applied in experimental or potential clinical conditions. Examples of this are "knock-out" mice or antisense oligonucleotides and viral transfection of neurons locally at various levels along the ascending or descending pathways of noxious signal transmission (Mogil, Yu, & Basbaum, 2000).

A recent new technique, ribonucleic acid interference (RNAi), has been introduced in studying the effect of delta opioid receptor in the spinal cord and dorsal root ganglion (Luo et al., 2005). Double-stranded, short-interfering RNAs (siRNAs) of 21–22 nucleotides in length initiate a sequence-specific, post-transcriptional gene silencing in animals and plants known as RNAi. siRNA has been found to selectively silence the delta opioid receptor, but not mu opioid receptors. The antinociceptive effects of the corresponding agonists are dose-dependently and reversibly blocked (Luo et al., 2005). A brief summary of genetic manipulation is listed in Table 2.

In contrast to an increased sensitivity along the somatosensory system to nociceptive signal transmission, a rare opposite condition, congenital insensitivity to pain (usually associated with anhidrosis), has been reported in the literature (see Table 2). As opposed to increased pain sensitivity, it is characterized by recurrent episodic fevers, anhidrosis (inability to sweat), absence of reaction to noxious (or painful) stimuli, self-mutilating behavior and mental retardation. It is explained by several genetic mechanisms:

1. Developmentally, a combined defect in sensory and au-

Table 2
Brief Summary of Genetic Modulation of Pain

Category	Causes	Symptoms and Signs	References
Congenital insensitivity to pain	A combined defect in sensory and autonomic neurons derived from the neural crest Overexpression of endogenous opioids Reduced number of primary afferent nociceptors Loss of neurons in sympathetic ganglia Loss of trkA function (receptor for nerve growth factor) as the result of mutations of the trkA receptor gene	A reduced evoked potential Lack of pain experience following electrical shock; Self-mutilation and fractures Lack of flare response to histamine injection Lack of temperature regulation	Chatrian et al. (1975); Shorey & Lobo (1990) Manfredi et al. (1981) Itoh et al. (1986); Chatrian et al. (1975); Matsuo et al. (1981); Sweet (1981); Derwin et al. (1994); Nolano et al. (2000); Schulman et al. (2001) Manfredi et al. (1981); Nolano et al. (2000)
Rat strain differences	Carrageenan to induce inflammatory pain	Inbred Lewis (LEW), Fischer 344 (F344), and outbred Sprague-Dawley (SD) rat strains differ in their pain sensitivity to mechanical and thermal stimuli	Itoh et al. (1986); Matsuo et al. (1981); Vital et al. (1998); Sztriha et al. (2001) Dehen et al. (1977, 1978)
Modulation at sensory receptor	Mechanoreceptor	BNC1 (a non-voltage-dependent sodium channel) DRASIC	Larner et al. (1994)
	TRPV1-deficient mice	DRASIC Essential for selective modalities of pain sensation and for thermal hyperalgesia	Dyck et al. (1983); Derwin et al. (1994); Shorey et al. (2001); Sztriha et al. (2001)
Modulation at membrane receptor	Null mutants for nerve growth factor Deletion of neurokinin-1 receptors	Loss of primary afferent and sympathetic neurons Reduction in response to intradermal injection of capsaicin Reduction in response to second phase of formalin test	Indo et al. (1996); Mandy et al. (1999); Yotsumoto et al. (1999); Shatzky et al. (2000); Toscano et al. (2000); Greco et al. (2000); Miura, Hiura, et al. (2000); Miura, Mandy, et al. (2000); Indo (2001); Toscano & Andria (2001); Bodzioch et al. (2001); Miranda et al. (2002); Barone et al. (2005)
	Deletion of the CGRP gene	Fail to develop secondary heat hyperalgesia by kaolin and carrageenan	Fecho et al. (2005)
	Deletion of mu opioid receptor gene	Oprm1 gene	
Genetic modulation at intracellular molecules	Deletion of the R1β subunit of protein kinase A (PKA)	Reduction of allodynia by tissue damage, a reduction of the responses to the second phase of formalin test, and central sensitization caused by intrathecal injection of PGE2	M. P. Price et al. (1996); Drummond et al. (2000); M. P. Price et al. (2000); Drummond et al. (2001); Welsh et al. (2002)
	Deletion of the gamma isoform of protein kinase C (PKCγ)	Fail to develop neuropathic pain after partial sciatic nerve injury, but show normal responses to acute noxious stimuli	Crowley et al. (1994)
	Mitogen-activated protein kinase (MAPK)	Regulation of central sensitization	Laird, Roza et al. (2001)
RNA interference (RNAi)	Short interfering RNAs (siRNA) of 21–22 nucleotide	Selectively silence the delta opioid receptor, but not mu opioid receptors	De Felipe et al. (1998)
			Zhang et al. (2001)
			Matthes et al. (1996); Sora et al. (1997); Lotsch & Geisslinger (2005)
			Malmberg, Brandon, et al. (1997)
			Malmberg, Chen, et al. (1997)
			Ji & Woolf (2001)
			Luo et al. (2005)

tonomic neurons derived from the neural crest. This has been supported by the following findings: (a) a reduced evoked potential and lack of pain experience following electrical shock, (b) self-mutilation and fractures, (c) lack of flare response to histamine injection, and (d) lack of temperature regulation.

2. Overexpression of endogenous opioids leads to suppression of nociceptive transmission either peripherally or centrally.
3. Reduced number of primary afferent nociceptors eliminates the ability to initiate a nociceptive signal in the periphery, whereas loss of neurons in sympathetic ganglia contributes to anhidrosis.
4. Loss of trkA function (receptor tyrosine kinase type A for nerve growth factor [NGF]) results from mutations of the trkA receptor gene, which is located on chromosome 1. It has also been demonstrated that the presence of a trkA mutation in B lymphocytes results in a lymphocyte signaling defect, which could contribute to recurrent episodes of fever.

Other genes involved in various sensory transmissions have been identified. Mechanoreceptor plays a role in transduction of mechanical force by opening ion channels that link to extracellular matrix and the cytoskeleton. Opening of these channels leads to excitation of mechanoreceptors. Subunits of these ion channels have been demonstrated in cutaneous mechanoreceptors, which are known as BNC1 (brain type Na channel), a nonvoltage-dependent sodium channel, and DRASIC (dorsal root acid sensitive ion channel), both belonging to the DEG/ENaC (epithelial Na⁺ channel/nematode degenerins) family. In DRASIC-knock-out mice, the sensitivity to light touch is increased, but the sensitivity to noxious pinch is reduced.

NGF has been playing critical roles in developing and maintaining the survival of the nerves (especially sympathetic nerves) and contributing to increased nociception. A loss of primary afferent and sympathetic neurons has also been found in null mutants for NGF. These mice also show depletion of immunoreactivity for trkA receptors and calcitonin gene-related peptide (CGRP) and substance P (SP). Both CGRP and SP are important neuropeptides found in A-delta and C fibers, the ones responsible for transmission of nociceptive and thermal signals. Most of the animals die within a week. Those who survive show almost no response to noxious mechanical and thermal stimuli. On the other hand, there is an increased sympathetic innervation of dorsal root ganglion cells in mice with an overexpressed NGF. They show exaggerated responses to noxious mechanical and thermal stimuli. In addition, deletion of neurokinin-1 receptors (receptors for SP) in mice shows normal response to brief noxious mechanical stimuli, but a reduction in response to intradermal injection of capsaicin and the second phase of a formalin test. Mice with deletion of the CGRP gene have normal responses to noxious stimuli but fail to develop secondary heat hyperalgesia by kaolin and carrageenan. When carrageenan is used to induce inflammatory pain, inbred and outbred rat strains differ in their pain sensitivity, as tested by mechanical stimulation (the von Frey monofilament test) and

noxious heat pain (the Hargreaves radiant heat test), also suggesting a genetic basis for differential sensitivity to pain.

A specific block of the morphine effect in mice with deletion of the mu-opioid receptor gene has also been found. Recent studies with inbred and knockout mice have revealed that the mu-opioid peptide receptor encoded by the Oprm1 gene has a crucial role in the analgesic and addictive properties of opiate drugs. Differences in Oprm1 gene sequences affect the amount of Oprm1 messenger RNA and sensitivity to opiates, and more than 100 polymorphisms have been identified in the human OPRM1 gene, some of which are related to vulnerability to drug dependence in some populations.

Genetic modulation of intracellular signal transduction molecules has played a significant role in pain transmission. Deletion of the R1β subunit of protein kinase A in mice shows a reduction of allodynia by tissue damage, a reduction of the responses to the second phase of formalin test, and central sensitization caused by intrathecal injection of PGE2. In contrast, mice with deletion of the gamma isoform of protein kinase C show normal responses to acute noxious stimuli but fail to develop neuropathic pain after partial sciatic nerve injury. Tissue injury-induced inflammatory and nerve injury-induced neuropathic pain (expressed as neuronal plasticity) is generated by injury and intense noxious stimuli to trigger an increased excitability of nociceptive neurons in the spinal cord. This central sensitization is an activity-dependent functional plasticity that results from activation of different intracellular kinase cascades, leading to the phosphorylation of key membrane receptors and channels and increasing synaptic efficacy. Several different intracellular signal transduction cascades converge on mitogen-activated protein kinase (MAPK). The activation of MAPK appears to be a master switch or gate for the regulation of central sensitization. In addition to posttranslational regulation, the MAPK pathway may also regulate long-term pain hypersensitivity via transcriptional regulation of key gene products. Furthermore, activated microglia is a key cellular intermediate step in the pathogenesis of nerve injury-induced pain hypersensitivity. This is supported by the observation that p38 MAPK, together with P2X₄ purinoceptors, are present in activated microglia and are required molecular mediators.

Similar to other neural transmission, transmission of pain signals requires a variety of molecules, including neurotransmitters, neuromodulators, neurotransmitter receptors, signal transduction molecules, and enzymes involved in protein synthesis. To ensure a normal synaptic transmission, it is crucial to have a normal process of protein synthesis (transcription and translation from the genetic code), neurotransmitter transportation, storage, release, receptor binding, and breakdown or reuptake. To accomplish these complicated processes, various proteins or peptides are playing either vital or supporting roles. Any malfunction of each individual step will cause either elevated or reduced transmission of pain signals. Some important molecules for pain processing include substances that act on (a) neurotransmitters and neuromodulators (e.g., bradykinin, capsaicin, CGRP, glutamate, histamine, serotonin, norepinephrine, neuropeptide Y, prostaglandin E₂, and SP); (b) membrane receptors (mu and delta opiate receptors, purinergic receptor P2X3, tyrosine kinase receptor A, and vanilloid receptor 1); (c) ion channels (e.g., Na⁺, K⁺, and Ca⁺⁺ channels, tetrodotoxin-resistance Na⁺ channels); (d) intracellular signal transduction molecules (e.g., R1β subunit of protein kinase A and

gamma isoform of protein kinase C); and (e) enzymes (e.g., fluoride-resistant acid phosphatase).

In summary, with all this aforementioned evidence of how gene expression can modulate the sensitivity of pain, with individual variation, a new direction for screening individual patients for genetic susceptibility will provide a potential targeted treatment of pain in the future. Indeed, three genetic haplotypes of the gene encoding catecholamine-*O*-methyltransferase is significantly associated with variation in sensitivity to experimental pain and is also correlated to the risk of developing temporomandibular joint disorder (Diatchenko et al., 2005). The serotonin transporter gene is also a promising candidate locus for the genetic susceptibility of migraine (Szilagyi et al., 2006). Eventually it may become possible to "turn on" or "turn off" a single gene or batch of gene expression to relieve patient suffering from various types of pain.

Electrophysiology

Since the perception of pain is mainly dependent on the neuronal activities along the axis of the somatosensory system through signal reception, transduction, action potential generation, and action potential propagation, it makes electrophysiological recording the most direct measurement to study pain nociceptive processing. It provides the most accurate temporal responses of the nervous system in response to external stimuli (mechanical, thermal, chemical, and electrical). In general, there are five electrophysiological approaches to study the peripheral and central neuronal activities involved in pain processing at various levels: (1) extracellular recording *in vivo* from axon tracts, individual axons, or cell body of neurons; (2) intracellular recording *in vivo*; (3) intracellular recording from neurons in intact ganglia or tissue slices *in vitro*; (4) intracellular recording from dissociated neurons *in vitro*; and (5) patch clamp recording *in vitro* and *in vivo*. A simple illustration is presented in Figure 4.

Extracellular recording in vivo. Extracellular recording *in vivo* has been widely used in the primary afferent neurons, spinal cord dorsal horn neurons, brainstem, thalamus, and the cortex. The advantages of extracellular recording include (a) a complete characterization of receptive fields, response properties, and conduction velocity by primary afferent recording *in vivo*; (b) minimizing the amount of tissue injury to gain the access to the afferents; (c) the ability to study changes in peripheral terminals of sensory neurons; and (d) the ability to activate brain regions to study the central descending modulation of the primary afferent inputs.

Population responses can be recorded by cord dorsum potential and intraspinal field potentials extracellularly, which are the distributions of activity that are evoked in large populations of spinal cord neurons by stimulation of primary afferent fibers. The potentials reflect, in large part, the depolarization of interneurons or of primary afferent fibers in the dorsal horn. The cord dorsum potentials can be recorded from the dorsal surface of the spinal cord in response to electrical stimulation of myelinated cutaneous afferent fibers in a peripheral nerve, which include an afferent volley, one or more negative (N) waves, and a positive wave (Beall, Applebaum, Foreman, & Willis, 1977; Gasser & Graham, 1933; Hughes & Gasser, 1934a, 1934b; Lindblom & Ottosson, 1953a, 1953b; Willis, Weir, Skinner, & Bryan, 1973). The negative potentials can be subsequently named N1 (evoked by A α β fibers), N2 (evoked by A α β and A δ fibers), and N3 (evoked by

A δ fibers). The maximal response of these negative potentials can be recorded within the spinal cord (Beall et al., 1977). The negative potential recorded in the extracellular space is due to the moving of positively charged ions into dorsal horn neurons that occurs during excitatory postsynaptic potentials and action potentials. The positive wave that follows the N waves, evoked by stimulation of cutaneous nerve, reflects a long-lasting depolarization of primary afferent fibers. This part of the cord dorsum potential corresponds to the negative dorsal root potential, which can be recorded from a disconnected filament of dorsal root (Barron & Matthews, 1938; Eccles & Krnjevic, 1959; Eccles, Magni, & Willis, 1963; Eccles, Schmidt, & Willis, 1963; Lloyd, 1952; Lloyd & McIntyre, 1949). Primary afferent fibers are considered to be one of the mechanisms responsible for the inhibitory process known as presynaptic inhibition (Eccles, 1964; Rudomin & Schmidt, 1999; R. F. Schmidt, 1971; Willis, 1999).

In the spinal cord, ascending tract neurons or motor neurons can be distinguished from interneurons by antidromic activation following stimulation of their axons near projection targets in the brain or of motor axons in a ventral root or peripheral nerve. Criteria for antidromic activation include (a) the action potential follows the stimulus at a constant latency, (b) collision between orthodromic and antidromic action potentials, and (c) the antidromic action potential can follow high frequencies of stimulation (Trevino, Coulter, & Willis, 1973).

Some of the most important discoveries about the nature of pain and nociception were determined with extracellular recordings. The finding of the superficial laminae of the spinal cord for nociception demonstrated that these neurons responded to mechanical and thermal nociceptive inputs in lamina I (B. N. Christensen & Perl, 1970) and II (Kumazawa & Perl, 1978). Another important finding was that the plasticity of neuronal responses is located deeper in the dorsal horn. An enhanced response ("windup") was demonstrated when peripheral nerves were stimulated at C-fiber intensities (Mendell & Wall, 1965; Woolf, 1996). Clinically, windup has been reported in fibromyalgia patients compared to normal controls, suggesting that central sensitization contributes to processes underlying hyperalgesia and persistent pain states (Price et al., 2002; Staud, Price, Robinson, Mauderli, & Vierck, 2004).

One type of extracellular recordings is the compound action potential recording from nerves and fiber tracts, which is a record of the various peaks related to the conduction velocity of various axon population in the peripheral nerve (Clark, Hughes, & Gasser, 1935; Gasser, 1941). Recording of compound action potentials in humans is crucial to determine the impulse conduction in the slowest fibers, which is correlated to the sensation of pain (Collins, Nulsen, & Randt, 1960; Heinbecker, Bishop, & O'Leary, 1933). Field potential in the CNS tracts is also a valuable approach in determining the rostrocaudal distribution of nociceptive primary afferent axons and their terminal arborizations (Traub & Mendell, 1988; Traub, Sedivec, & Mendell, 1986).

Microneurography (Hagbarth & Vallbo, 1967) in humans is another extracellular recording technique, which led to many human studies that clearly defined the involvement of unmyelinated C-fibers in pain sensation and some pathological conditions (Hagbarth, 1979; Hallin & Wu, 1998; Ochoa & Torebjörk, 1980; Ochoa, Torebjörk, Culp, & Schady, 1982; Torebjörk & Hallin, 1970; Torebjörk, Ochoa, & McCann, 1979; Vallbo, Hagbarth, Torebjörk, & Wallin, 1979; Van Hees & Gybels, 1972). The

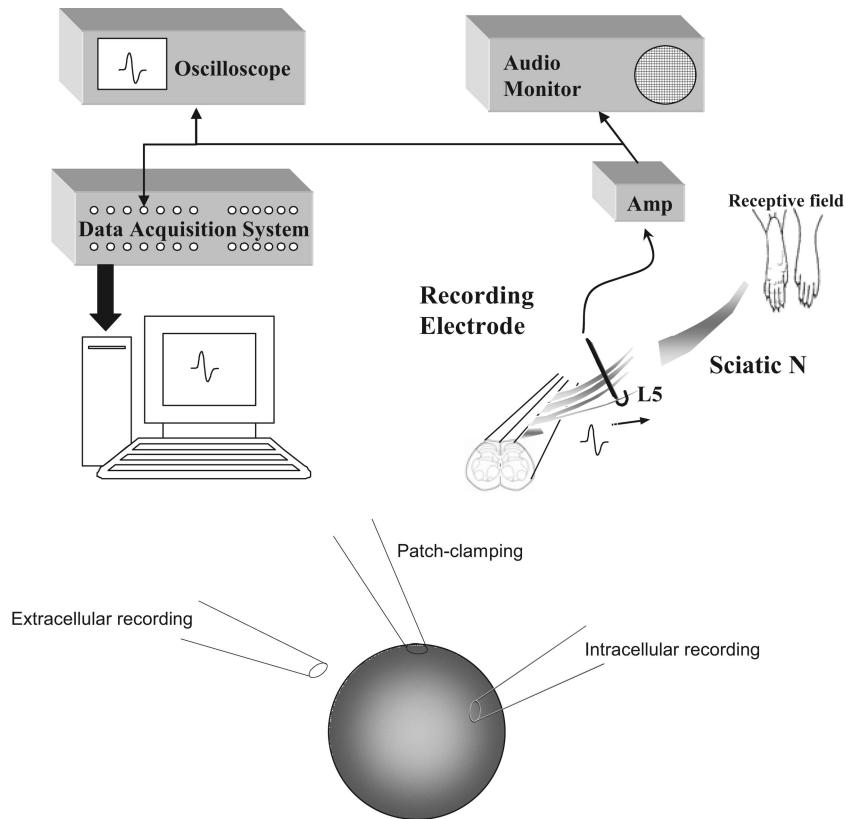


Figure 4. An illustration of an electrophysiological setup for extracellular, intracellular, and patch-clamp recording in either *in vivo* or *in vitro* preparations.

advantage of microneurography is that recorded axons can be stimulated relatively selectively following isolation of a single unit (Simone, Marchettini, Caputi, & Ochoa, 1994; Torebjörk, Vallbo, & Ochoa, 1987), while allowing the human subject to describe accurately the quality and intensity of pain (Marchettini, Simone, Caputi, & Ochoa, 1996; Ochoa & Torebjörk, 1989; Torebjörk et al., 1987) as well as of an itch (Schmelz et al., 2003; Schmelz, Schmidt, Bickel, Handwerker, & Torebjörk, 1997).

Single unit recording from axon fibers of the peripheral nerve has also been tested on their own peripheral nerves by some neuroscientists (Hensel & Boman, 1960) and later were mostly used in animals studies (LaMotte & Campbell, 1978). It is a relatively simple technique, but it is crucial for determining the spontaneous discharge in sensory fibers after peripheral nerve injury, especially when ectopic spikes are generated from the ganglion (Kajander, Wakisaka, & Bennett, 1992; Xie, Zhang, Petersen, & LaMotte, 1995).

Intracellular recording. Intracellular recording can directly measure the membrane potential change, and one can inject a dye into the recording neuron for labeling purposes. Technically, it is more difficult than extracellular recording and may not be accessible to small diameter fibers. In addition, it may cause damage of the neuron because of the nature of the technique (puncture of the cell membrane by a sharp electrode). By directly monitoring the membrane potential, intracellular recording *in vivo* contributes important information of the classification of sensory neurons in

response to peripheral receptive properties (Djouhri, Bleazard, & Lawson, 1998; Giesler, Gerhart, Yezierski, Wilcox, & Willis, 1981; Koerber, Druzinsky, & Mendell, 1988; Lawson, Crepps, & Perl, 1997; Ritter & Mendell, 1992; Willis, Trevino, Coulter, & Maunz, 1974), such as inflammation or nerve injury (Czech, Kudo, & Kuno, 1977; Djouhri & Lawson, 1999). Intracellular recording of substantia gelatinosa neurons has demonstrated direct modulation of their activity through stimulation of brainstem structures (NRM and PAG; Bennett, Hayashi, Abdelmoumene, & Dubner, 1979; Light, Casale, & Menetrey, 1986; Steedman, Molony, & Iggo, 1985).

When neurons in a part of the nervous system are isolated and set in a recording chamber, intracellular recording from a tissue slice *in vitro* has several advantages over *in vivo*. It has the following properties: better control of the extracellular milieu (e.g., absence of blood-brain barrier), some degree of electrical control of the soma membrane, possible identification of primary afferents and their receptive field properties, a possible observation of injury-induced increase in excitability, and a condition without enzymatic or mechanical treatment prior to recording. However, intracellular recording *in vitro* also suffers from several disadvantages. For example, it may not be able to determine the change in response properties due to a direct change in the neuron or an indirect change caused by surrounding cells. In an isolated environment, there is an absence or a low level of the proteins necessary for the transduction of stimuli.

Intracellular recording from dissociated neurons *in vitro* has several advantages as compared with slice preparation. It allows for complete control of the extracellular milieu, as well as the intracellular milieu, when used with patch-clamp techniques. Redistribution of proteins to the plasma membrane that are normally presenting afferent terminals has been observed. For example, a proton receptor/ion channel complex that is usually present in terminals has been demonstrated in the isolated cell body (Bevan & Yeats, 1991; Steen, Issberner, & Reeh, 1995). However, this approach suffers from several disadvantages. It is impossible to identify the primary afferents with respect to conduction velocity or receptive field properties. There is a potential for damage of the membrane properties due to enzymatic treatment. There is also the potential for alteration of neuron properties because of a lack of unknown important factors. The results cannot be applied directly to the conditions in the behaving animals because of lack of supporting cells and other neurons.

Patch-clamp recording in vitro. First described by Neher and Sakmann (1976), patch-clamp recording *in vitro* is now a powerful method for studying electrophysiological properties and chemosensitivity of neurons involved in the transduction and transmission of nociceptive stimuli. It is widely used to study the primary afferent terminals (Brock, McLachlan, & Belmonte, 1998; Reid, Scholz, Bostock, & Vogel, 1999; Scholz, Reid, Vogel, & Bostock, 1993), soma of the sensory ganglion (Huang & Neher, 1996; L. Liu & Simon, 1996; L. Liu, Wang, & Simon, 1996; Todorovic & Anderson, 1990), dissociated central neurons (Reichling, Kyrozis, Wang, & MacDermott, 1994; Rusin, Jiang, Cerne, & Randic, 1993), slice preparations (Baba et al., 1998; Bao, Li, & Perl, 1998; Pan, 1998; Pan & Fields, 1996; Pan, Tershner, & Fields, 1997; Schneider, Eckert, & Light, 1998; Yoshimura & Nishi, 1993), and *in vivo* (Light & Willcockson, 1999). Even though cell-attached recording of an afferent terminal of corneal afferents was reported (Brock et al., 1998), this approach has been used to record ion channel activity from C-fiber axons, as well as the afferent cell body (Reid et al., 1999; Scholz et al., 1993). One of the advantages of this technique is that it can generate the most detailed information of the biophysical properties of the ion channel. It is also possible to record from specific sites on a neuron to obtain information of the relative distribution of ion channels. However, the disadvantage is that it is the most technically difficult and labor intensive electrophysiological approach.

A relative easier target is the cell body of the primary afferent neuron. It has been suggested that the cell body of acutely isolated sensory neurons *in vitro* is a valid model for the afferent terminal *in vivo*. Receptors and ion channels in the peripheral or central terminals of sensory neurons are present and are functional in the plasma membrane of the cell body *in vitro* (Huang & Neher, 1996; L. Liu & Simon, 1996; L. Liu et al., 1996; Todorovic & Anderson, 1990). Pharmacologically, these receptors on the cell body show properties similar to those near the peripheral and central terminals (Carlton & Coggeshall, 1997; Carlton, Zhou, & Coggeshall, 1999; X. Chen, Belmonte, & Rang, 1997; X. Chen, Gallar, & Belmonte, 1997; Coggeshall & Carlton, 1998; H. Liu, Wang, Sheng, Jan, & Basbaum, 1994). It is also possible to induce a similar change in the excitability of the cell body *in vitro* with the same manipulations that induce changes in the peripheral terminals *in vivo*. For example, PGE2 can induce sensitization of the cell body *in vitro* (Baccaglini & Hogan, 1983; Fowler, Wonderlin, & Weinreich,

1985; Gold, Dastmalchi, & Levine, 1996; Nicol & Cui, 1994; Vasko, Campbell, & Waite, 1994; Weinreich & Wonderlin, 1987). Furthermore, the sensory neuron cell body *in vitro* can be induced to release neurotransmitters (Gu, Albuquerque, Lee, & MacDermott, 1996; Gu & MacDermott, 1997; Lee, Engelman, & MacDermott, 1999; MacDermott, Role, & Siegelbaum, 1999), which is a Ca^{2+} -dependent process (Huang & Neher, 1996).

*Patch-clamp recording *in vivo*.* Following the successful application of patch-clamp recording *in vivo* in other systems (Covey, Kauer, & Casseday, 1996; C. I. Moore & Nelson, 1998), use of whole-cell recording techniques in the nociceptive systems of the spinal cord of the rat *in vivo* was reported (Furue, Narikawa, Kumamoto, & Yoshimura, 1999; Graham, Brichta, & Callister, 2004; Light & Willcockson, 1999; Weng & Dougherty, 2002; Yoshimura, Doi, Mizuno, Furue, & Katafuchi, 2005). The obvious advantages of this technique include better control over the electrical properties of the neuron, a more robust technique than sharp electrode intracellular recording, the ability to observe single channel activity in the native milieu, and easier control of both intracellular and extracellular medium for drug application. However, this technique suffers from difficulties in stabilization of animals and obtaining adequate seals due to movement and covering glial cells. It is not the best choice for obtaining large samples in a study.

Imaging

A variety of imaging techniques have been developed and used to study pain and nociception. Functional imaging techniques have played a crucial role because of the advantage of correlating the brain activity with human perception.

Positron emission tomography (PET). Since its development in the 1970s, PET has been used for imaging human brain function. A PET image is created by the detection of positrons emitted from an intravenously injected radionuclide (i.e., the tracer). Through blood circulation, the tracer is distributed to the brain. As the tracer decays, it emits a positron which travels a few millimeters, collides with an electron, and releases two photons (gamma rays) in opposite directions. A series of PET detectors over the head detects the signals, which are used to create a tomographic image. PET images can be overlapped with a subject's own fMRI to fit onto a standardized atlas to be visualized. Depending on the half-life, different radionuclides can be used for different purposes. For example, ^{15}O is used to measure cerebral blood flow in activation studies because of its half-life (2 min); ^{18}F with a half-life of 110 min can be used to measure cerebral glucose metabolism; ^{11}C with a half-life of 20 min can be used to study receptor binding of dopamine, benzodiazepine, and opiates (Kegles & Mann, 1997; Phelps & Mazziotta, 1985; Slifstein & Laruelle, 2001; Tai & Piccini, 2004). PET can be used in three major ways. The receptor density and binding properties of ligands in the brain can be identified by injecting a radioactive receptor antagonist or agonist (Sadzot et al., 1991). It can also be used to measure regional cerebral blood flow (rCBF) in the resting state to detect neurological abnormalities in disease or injury (Hsieh, Belfrage, Stone-Elander, Hansson, & Ingvar, 1995; Iadarola et al., 1995; Peyron et al., 1998). Finally, in activation studies, $[^{15}\text{O}]H_2\text{O}$ is injected to identify task-related changes in blood flow. The advantages of PET include a relatively open, noise-free environment that

can accommodate most experimental or internal devices. The disadvantages include that it is relatively expensive, injection of radioactive tracer is invasive, the time frame is relatively restricted because of the half-life of the tracer, and it has a moderate to poor spatial resolution and poor temporal resolution.

The PET scan was first applied to study acute pain (Talbot et al., 1991), which identified four cortical regions of activation by noxious heat stimuli: primary and secondary somatosensory cortex, anterior insula, and anterior cingulate cortex (ACC). Subsequent studies have confirmed and extended cortical areas in thermal, mechanical, and laser-evoked pain, such as prefrontal cortex, supplemental motor cortex, basal ganglia, cerebellum, and the hypothalamus and periaqueductal gray (Aziz, 1997; Casey, 1999; Casey et al., 1994; Casey, Minoshima, Morrow, & Koepp, 1996; Coghill et al., 1994; Derbyshire et al., 1997; Hsieh et al., 1996; Jones, Brown, Friston, Qi, & Frackowiak, 1991; Svensson, Minoshima, Beydoun, Morrow, & Casey, 1997; Xu et al., 1997). An example is provided in Figure 5. The widespread cortical activations identified in pain studies have been implicated in affective, cognitive, and reflexive responses to a painful stimulus, which demonstrate that there is a distributed network of many brain areas that are recruited by a painful stimulus that contribute to the multidimensional experience (Coghill et al., 1994; Coghill, Sang, Maisog, & Iadarola, 1999). In a study that used hypnosis to manipulate pain unpleasantness independent of pain intensity, a

relationship between unpleasantness and ACC activation was identified (P. Rainville, Duncan, Price, Carrier, & Bushnell, 1997). The ACC was uniquely activated both in real pain and during an illusion of pain evoked by simultaneous warm and cool stimuli (Craig, Reiman, Evans, & Bushnell, 1996). PET scans obtained during motor cortex stimulation for chronic pain revealed activation of the thalamus, ACC, anterior insula, and frontal cortex (Garcia-Larrea et al., 1999; Peyron et al., 1995). Thalamic stimulation also activates the ACC (Davis et al., 2000) and the anterior insula, which is accompanied by thermal sensations (Duncan et al., 1998).

Single-photon emission computerized tomography (SPECT). Similar to PET, the SPECT scanner has a gamma camera that detects emissions from decaying isotopes, which have long half-lives (often in the order of hours). Cerebral blood flow can be measured with the inhalation of Xenon-133 or technetium 99mTc HM-PAO (99m-hexamethylpropyleneamineoxime; Canavero et al., 1993; Di Piero, Pantano, Ricci, & Lenzi, 1993). The long retention of SPECT tracers allows for flexibility in the timing of data acquisition, after injection, of the overall effect of an injury, disease, stimulus, treatment, or other manipulation (Prichard & Brass, 1992). However, the SPECT scanner is more expensive and suffers from poor spatial and temporal resolution.

Through use of SPECT, different types of pain have been examined. A decrease in cortical rCBF in the SI region associated

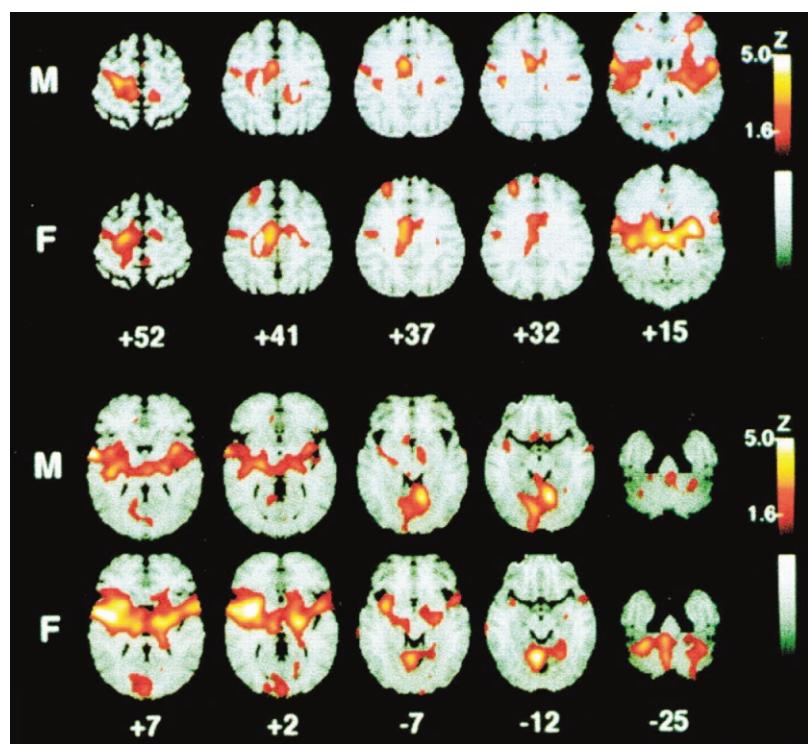


Figure 5. A positron emission tomography scan image of rCBF responses of 10 males (M) and 10 females (F) to repetitive noxious heat stimulation (50°C) of the left volar forearm. Significant activation of the contralateral anterior cingulate cortex, premotor, insular cortex, ipsilateral insula, and bilateral cerebellar vermis has been identified. From "Gender Differences in Pain Perception and Patterns of Cerebral Activation During Noxious Heat Stimulation in Humans," by P. E. Paulson, S. Minoshima, T. J. Morrow, and K. L. Casey, *Pain*, 76, 1998, p. 227. Copyright 1998 by the International Association for the Study of Pain. Reprinted with permission.

with a long (3 min) sustained contralateral heat pain stimulus was found (Apkarian et al., 1992), whereas an increased rCBF in SI contralateral to a tonic cold-pain stimulus was also reported in a cold pressor test (Di Piero et al., 1994) and among cluster headache patients (Di Piero, Fiacco, Tombari, & Pantano, 1997). In a chronic pain state, such as painful restless legs syndrome and spinal cord injury, there is an increase in blood flow in the contralateral SI, ACC, and thalamus (see Figure 6; Ness et al., 1998; San Pedro et al., 1998). However, hypoperfusion was also found in the caudate of a patient with spinal cord injury pain (Ness et al., 1998), in the frontoparietal region (Ogawa, Lee, Nayak, & Glynn, 1990), and in the thalamus of patients with central pain (Pagni & Canavero, 1995; Tanaka et al., 1997).

Functional magnetic resonance imaging (fMRI). fMRI is now widely used in the medical field to obtain normal or pathological anatomical changes. It was first used to study brain function by intravenous injection of gadolinium as a contrast agent to enhance the magnetic resonance signals in the visual cortex evoked by flashing light (Belliveau et al., 1991). It was soon realized that visualization of these signals did not require injection of a contrast agent because the body has its own natural contrast agent, deoxygenated hemoglobin (Ogawa et al., 1992; Ogawa, Lee, Kay, & Tank, 1990; Ogawa, Lee, Nayak, & Glynn, 1990). Most fMRIs now rely on the blood oxygenation level dependent effect, which is based on the increased neuronal firing in response to a stimulus that will induce hemodynamic changes and ultimately modify the magnetic field to increase the fMRI signals (Porro, Lui, Facchini, Maier, & Baraldi, 2004). It is thought that an increased metabolic demand, due to increased neuronal activity, results in an increase in blood flow beyond metabolic needs, such that the final ration of deoxyHb/oxyHb actually is reduced. It is the reduction in deoxyHb that alters the magnetic field properties and produces the increased fMRI signal (DeYoe, Bandettini, Neitz, Miller, & Winans, 1994). The advantages of fMRI include its noninvasiveness, good spatial (down to 1–2 mm), and temporal (hundreds of

ms is possible) resolution. The disadvantages include its expense, limited availability due to time-sharing on a clinical scanner, restriction to metallic devices, and loud noise.

A large body of literature, nevertheless, has been conducted investigating brain mechanisms underlying both chronic and acute pain (see one example in Figure 7). fMRI has been used to study stimulus-related responses, such as noxious electrical stimulation of the skin or peripheral nerve (Davis, Taylor, Crawley, Wood, & Mikulis, 1997; Davis, Wood, Crawley, & Mikulis, 1995; Oshiro et al., 1998); noxious heat or cold (Apkarian, Darbar, Krauss, Gelnar, & Szeverenyi, 1999; Becerra et al., 1999; Davis, Kwan, Crawley, & Mikulis, 1998; Gelnar, Krauss, Sheehe, Szeverenyi, & Apkarian, 1999; Ploghaus et al., 1999; Raji, Forss, Stancak, & Hari, 2005); and mechanical (Disbrow, Buonocore, Antognini, Carstens, & Rowley, 1998), chemical (Maihöfner & Handwerker, 2005; Porro, Cettolo, Francescato, & Baraldi, 1998), or visceral stimuli (Binkofski et al., 1998). Brain areas that can be activated include the primary somatosensory cortex (SI), secondary somatosensory cortex (SII), anterior insula, ACC, thalamus, and cerebellum. With the combination of psychophysical assessment and fMRI, pain-related activations have been obtained in parallel psychophysical sessions (Apkarian et al., 1999) or during the imaging sessions (Davis et al., 1997; Porro et al., 1998; Raji et al., 2005) in order to separate those activations that are due to the mere presence of a stimulus (i.e., due to attention) from those that are related to the subjects' actual sensory experiences. On the other hand, the relationship and interaction of pain, attention, and anticipation has been demonstrated to activate slightly different areas of the brain (Davis et al., 1997; Ploghaus et al., 1999). For example, anticipation of pain activated the anterior ACC, whereas the pain itself activated the posterior ACC. Further dissection on this line demonstrated that the posterior insula/secondary somatosensory cortex, the sensorimotor cortex, and the caudal ACC were specific to receiving pain, whereas the anterior insula and rostral ACC activation correlated with individual empathy scores when the subjects watched their loved ones receiving pain stimuli (Singer et al., 2004). The underlying modulatory effect of expectation on pain transmission might involve activation of descending modulatory systems (Keltner et al., 2006).

Recently, a caution has been raised about fMRI (Nair, 2005; Savoy, 2005), especially when it is used in dissecting the cognitive and emotional mechanisms, because cognitive function is a moving target. It is difficult to design a good fMRI study and to analyze and interpret the data. The notion of whether fMRI is a modern phrenology is under debate (D. I. Donaldson, 2004; Terrazas & McNaughton, 2000; Uttal, 2001). Regardless, fMRI has been used to image allodynia in complex regional pain syndrome (Maihöfner, Handwerker, & Birklein, 2006) and patients suffering from neuropathic pain (Schweinhardt et al., 2006).

Magnetoencephalography (MEG). MEG is a technique that detects weak magnetic fields within the human brain. MEG is the most sensitive for cortical neuronal activity because electrical currents generated by neurons induce a perpendicularly oriented magnetic field, which can be detected directly outside the head by MEG detectors (Hari & Forss, 1999; Naatanen, Ilmoniemi, & Alho, 1994). The major advantage of MEG is that it is noninvasive and has excellent temporal resolution (down to milliseconds) to directly measure neuronal activity. It can also be superimposed onto a high-resolution fMRI to provide good spatial localization.

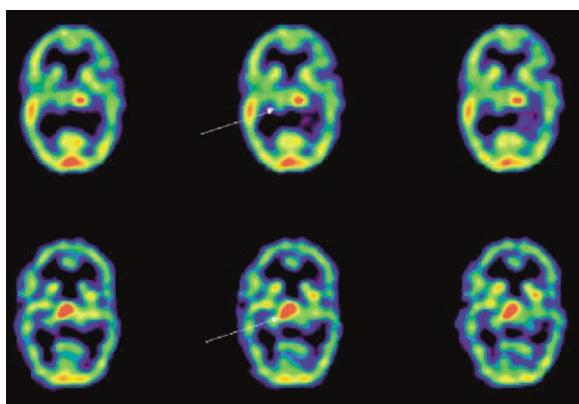


Figure 6. A single-photon emission computerized tomography image showing baseline scan (top row) and postacupuncture scan (bottom row) of the thalamic activity. From "Cerebral Blood Flow Effects of Pain and Acupuncture: A Preliminary Single-Photon Emission Computed Tomography Imaging Study," by A. B. Newberg, P. J. LaRiccia, B. Y. Lee, J. T. Farrar, L. Lee, A. Alavi, 2005, *Journal of Neuroimaging*, 15, p. 45. Copyright 2005 by the American Society of Neuroimaging. Reprinted with permission.

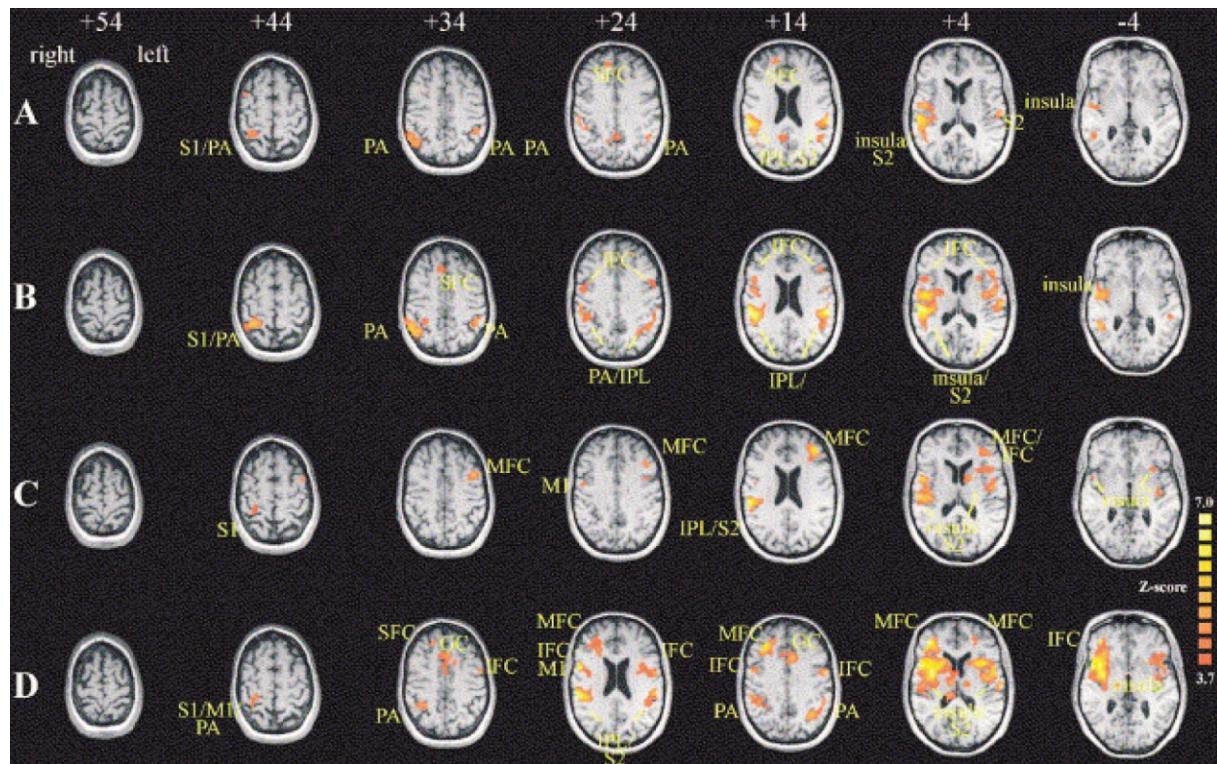


Figure 7. An image from functional magnetic resonance imaging showing key areas of activations in primary somatosensory cortex (S1), primary motor cortex (M1), secondary somatosensory cortex (S2), parietal association cortex (PA), inferior parietal lobule (IPL), superior frontal cortex (SFC), middle frontal cortex (MFC), inferior frontal cortex (IFC), and cingulate cortex (GC) when pin-prick (A, B) or thermal (C, D) stimuli were applied before (A, C) or after (B, D) capsaicin injection. From "Differential Coding of Hyperalgesia in the Human Brain: A Functional MRI Study," by C. Maihöfner and H. O. Handwerker, 2005, *NeuroImage*, p. 1000. Copyright 2005 by Elsevier. Reprinted with permission.

The current major disadvantage is the high cost of the device and the necessity for a magnetically shielded space.

In Figure 8, a sample MEG image indicates activation of the primary motor cortex while stimulation is applied at A-delta and C-fiber intensities (Raij et al., 2005). Use of MEG in the study of pain demonstrated responses to electrical stimulation of the digit at short latencies in the contralateral SI (at 40–60 ms), followed by longer latencies in the ipsilateral and bilateral SII and insula (100–250 ms) (Howland, Wakai, Mjaanes, Balog, & Cleeland, 1995) as well as the ACC (Kitamura et al., 1995, 1997). A study of painful laser-evoked responses reported that both the contralateral SI and SII dipoles occurred at around 130 ms, suggesting a parallel processing of thalamocortical inputs to these two cortical regions (Ploner, Schmitz, Freund, & Schnitzler, 1999). MEG has also been used to follow the extent of cortical plasticity in phantom limb pain in traumatic or congenital amputees (Flor et al., 1995, 1998). It has also been found that focally applied brief painful stimulus generates a global suppression of spontaneous oscillations in somatosensory, motor, and visual areas, indicating that pain induces a widespread change in cortical function and excitability (Ploner, Gross, Timmermann, Pollok, & Schnitzler, 2005; Raij et al., 2005).

Intrinsic optical signals (IOS) and intrinsic optical imaging (IOI). Changes in optical signals of transmitted or reflected light through brain tissue can indicate regional differences in brain

activity. The transmitted or reflected light through brain tissue can be detected or imaged without using dyes or fluorescent markers. Use of IOS and IOI to monitor and understand neural activities and physiological changes in vitro and in vivo becomes more recognized (Asai, Kusudo, Ikeda, & Murase, 2002; Ikeda, Terakawa, Murota, Morita, & Hirakawa, 1996; Johnson, Hanley, & Thakor, 2000; Kristal & Dubinsky, 1997; Lemasters, Nieminen, Qian, Trost, & Herman, 1997; Miller, Petrozzino, Mahanty, & Connor, 1993; Scarfone, McComas, Pape, & Newberry, 1999; Uchino, Elmer, Uchino, Lindvall, & Siesjo, 1995). It is now popularly utilized in the field of neuroscience (Aitken, Fayuk, Somjen, & Turner, 1999; Andrew, Jarvis, & Obeidat, 1999; Haller, Mironov, & Richter, 2001; Nomura, Fujii, Sato, Nemoto, & Tamura, 2000). Subcellular organelles, such as nuclei (Ikeda et al., 1996), and mitochondria (Kristal & Dubinsky, 1997; Lemasters et al., 1997), are known to change size with different levels of tissue activity and injury (Johnson et al., 2000). It is also known that changes of particle size within tissue will result in changes of light scattering. Thus, IOS and IOI of brain tissue have been used to investigate a variety of brain physiology models for more than 25 years (Lipton, 1973), although the causes of changes in light scattering and birefringence (initially studied 30 years ago by L. B. Cohen, Keynes, & Hille, 1968, in giant axons of squid) are still not completely understood (Johnson et al., 2000; Nomura et al., 2000).

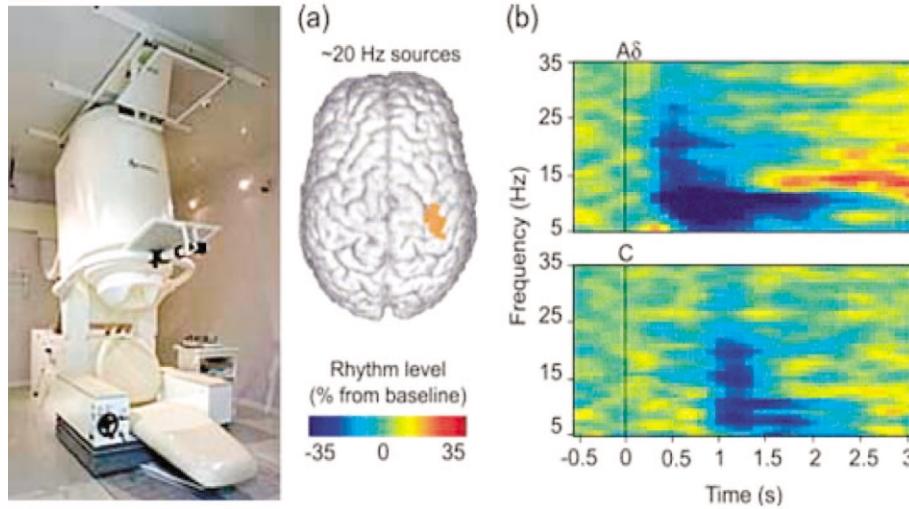


Figure 8. A magnetoencephalography image in the contralateral primary motor cortex (a) while A δ - and C-fiber stimuli were applied (b). From "Modulation of Motor-Cortex Oscillatory Activity by Painful A δ - and C-fiber Stimuli," by T. T. Raij, N. Forss, A. Stancak, and R. Hari, 2004, *NeuroImage*, p. 571. Copyright 2004 by Elsevier. Reprinted with permission.

However, both IOS and IOI are highly affected by light scattering and absorption of the measured neural tissue of the brain, mainly as a result of morphological structures and hemodynamic (such as blood concentrations, blood oxygenation levels, and blood flow) aspects of the brain, respectively. So far, it is difficult to separate light scattering and absorption effects within the measured data of IOS and IOI. One common practice in neuroscience research using optical brain imaging is to define a practical index, such as an intensity index, to associate either the IOS or IOI with the neural activity, without being able to decouple the effects from morphological and hemodynamic aspects of the brain. To date, there is no direct evidence using this technique to address pain problems. However, optical imaging has been used in studying the somatosensory systems (Berwick et al., 2005; Sasaki et al., 2002; Tommerdahl, Simons, Chiu, Favorov, & Whitsel, 2005; see example in Figure 9) and the visual cortex (Blasdel, 1989, 1992). When a sinusoidal mechanical stimulation is applied to the contralateral or bilateral skin in the cat, there is an increase in absorption in the primary and secondary somatosensory cortices (Tommerdahl et al., 2005), whereas ipsilateral stimulation only elicits an increase of absorption in the secondary somatosensory cortex.

Nanotechnology: Quantum dots. Although histological localization has been used extensively through a variety of staining techniques that can be examined under light or an electron microscope, a recent development in nanotechnology, the use of quantum dots, has advanced the field further. In brief, quantum dots are fluorescent semiconductor nanocrystals (i.e., cadmium selenide) that can be conjugated with antibodies of interested targets (i.e., any proteins and peptides), such as variety of ion channels, neurotransmitters and their receptors, enzymes involved in neurotransmitter synthesis and metabolism, and molecules involved in intracellular cascade. The sizes of the quantum dots can be different (2–9.5 nm), which causes emission of different colors (emission wavelength from 400 to 1,350 nm) under microscope. It enables one to label multiple targets in the same tissue to examine cellular

or subcellular structures (see Figure 10; Giepmans, Deerinck, Smarr, Jones, & Ellisman, 2005; Michalet et al., 2005). The major advantages of quantum dots over currently widely used fluorophores include their brightness, distinguishable emission spectra, and resistance to photobleach, which make quantum dots especially valuable for imaging anatomical structure and track physiological events in *in vivo* (Jaiswal, Mattoussi, Mauro, & Simon, 2003; Voura, Jaiswal, Mattoussi, & Simon, 2004) or *in vitro* (Goldman et al., 2004) preparations (Alivisatos, Gu, & Larabell, 2005; Jaiswal & Simon, 2004) without detectable toxicity for weeks to months (Jaiswal et al., 2003) in noninvasive imaging (Ballou, Lagerholm, Ernst, Bruchez, & Waggoner, 2004). Potential applications of quantum dots include bioanalytical assays, fixed cell imaging, biosensors, *in vivo* animal targeting, and *ex vivo* live cell imaging (Michalet et al., 2005). Although there is no report of using quantum dots in the study of pain mechanisms, its use is expected to explode in the near future.

Summary of Neuroscience Research

The overwhelming experimental data generated by basic neuroscience studies will continue to lead to a better understanding of chronic pain. These techniques or tools include molecular biology, anatomy, physiology, behavior, and imaging at cellular, organic, and systemic levels. Although not yet fully developed, the current data have the following implications for dealing with chronic pain.

1. Genetic factors may play a crucial role in the susceptibility, initiation, maintenance, and aggravation of chronic pain.
2. Imbalance of a variety of neurotransmitters, neuromodulators, and their various types and subtypes of receptors, may contribute to the chronic pain state. An overproduction and release of an excitatory neurotransmitter, for example, may increase the membrane excitability, thus leading to an increased sensitivity of neurons that are part of the pain transmission system. On the other

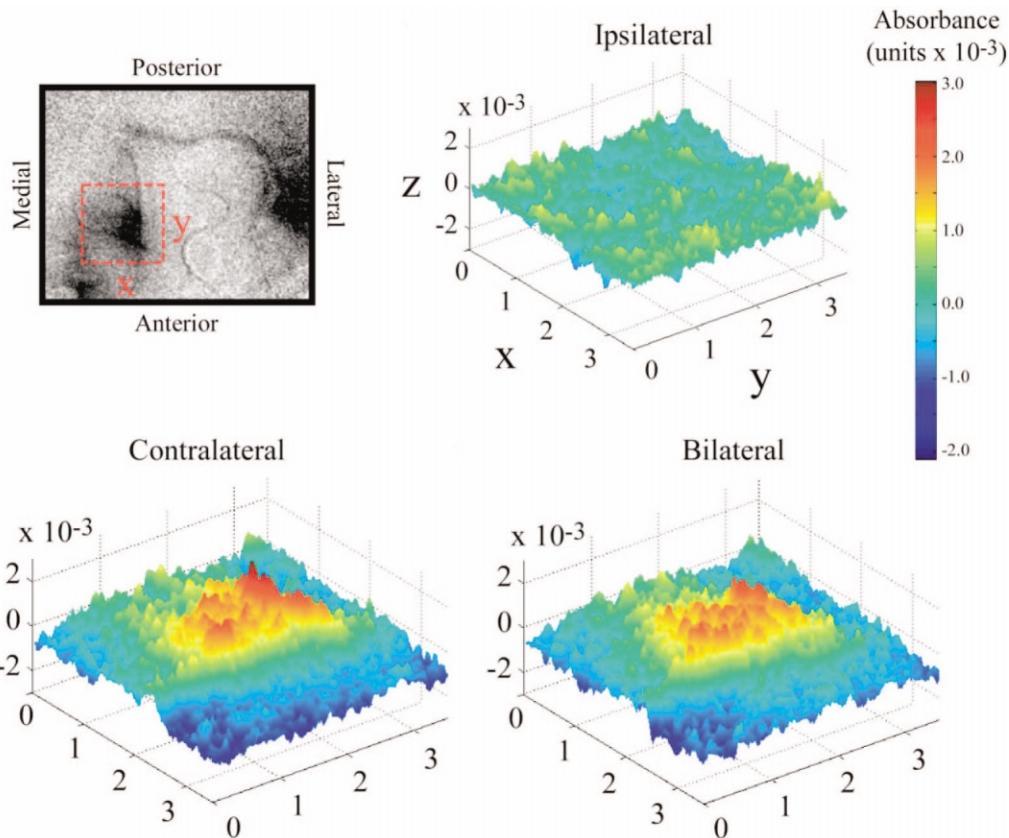


Figure 9. An example of the surface plots of absorbance evoked in somatosensory cortex by contralateral, ipsilateral, and bilateral flutter stimulation in the cat. From “Response of SI Cortex to Ipsilateral, Contralateral and Bilateral Flutter Stimulation in the Cat,” by M. Tommerdahl, S. B. Simons, J. S. Chiu, O. Favorov, and B. Whitsel, 2005, *BMC Neuroscience*, 6, p. 32.

hand, lowered production of an inhibitory neurotransmitter will play a similar function.

3. Neurons in the somatosensory system are “wired” in certain patterns. They are dynamic and subject to constant modification depending on incoming signals from various connections. Although different neurotransmitters may act on their specific receptors, they may share a similar intracellular cascade pathway or interact with different intracellular pathway. Some of these intracellular events are critical to modifying genetic expression that may have a long-term effect, like in chronic pain.

4. Chronic pain is also phasic depending on the psychosocial status of the patient; it may change within hours, days, or weeks, possibly related to various hormones and their concentrations in the system.

5. Noninvasive imaging tools (CT, fMRI) have greatly advanced our knowledge of the anatomical and pathological conditions of the nervous system. PET, SPECT, and MEG techniques have added a further step in understanding the dynamic changes of the brain in response to certain stimuli or tasks. However, interpretation of results from these relatively new technologies should be made with some caution, especially in dealing with chronic pain. A newly developed, much less expensive tool—optical imaging—is another new potential technique, but it may suffer from less resolution in terms of noninvasiveness. A critical component

of future research is to examine tonic neuronal activity, since some chronic pain conditions may possibly be associated with abnormalities in tonic levels of activity, in noxious evoked brain activation, or both.

6. Recent developments in nanotechnology could also contribute to the understanding of basic mechanisms (by using quantum dots labeling) and may provide a potential therapeutic mean (by targeted drug delivery).

Pain and Emotion

Historically, pain has been viewed as a symptom secondary to the presence of tissue pathology and, thus, as being of secondary importance. From this perspective, the amount of pain experienced and reported should be directly proportional to the amount of tissue pathology. Once the physical pathology has resolved, the pain should subside. Emphasis then should be on treating the cause of pain. Conversely, as noted previously, pain has also been viewed as being outside the senses and among the emotions (e.g., Aristotle). A new era in thinking about pain was ushered in by the conceptual model underlying the gate control theory by Melzack and Casey (1968) who, as we reviewed earlier in this article, suggested that the end experience of pain was a composite of

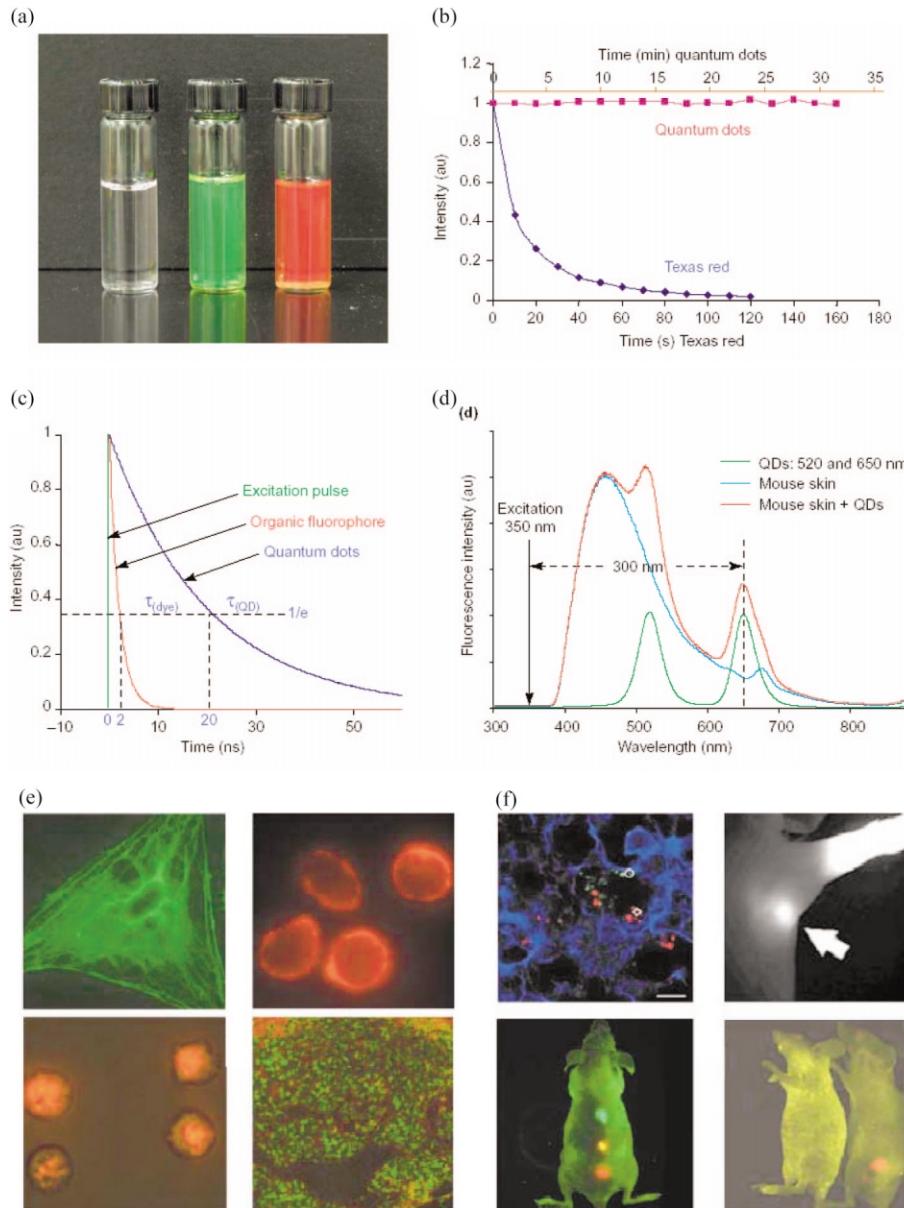


Figure 10. The optical properties of quantum dots (a-d) and potential applications in imaging cellular structures (e) and lymph nodes or prostate tumor in live animal (f). From “In vivo Molecular and Cellular Imaging With Quantum Dots,” by X. Gao, L. Yang, J. A. Petros, F. F. Marshall, J. W. Simons, and S. Nie, 2005, *Current Opinion in Biotechnology*, 16, p. 67. Copyright 2005 by Elsevier. Reprinted with permission.

sensory-discriminative, cognitive-evaluative, and motivational features. In this view, although the three components may be disentangled and assessed separately, they are interdependent. As noted, the integrative model postulated by Melzack and Wall (1965), and expanded by Melzack and Casey, has become the dominant paradigm in the specialized field of pain and pain management; however, there continue to be vestiges of mind-body, dualistic views in research on pain and clinical pain management.

Pain is ultimately a subjective, private experience, but it is invariably described in terms of sensory and affective properties. As defined by the International Association for the Study

of Pain, “[pain] is unquestionably a sensation in a part or parts of the body but it is also always unpleasant and therefore also an *emotional experience* [emphasis added]” (Merskey, 1986, p. 1). The central and interactive roles of sensory information and affective state are supported by an overwhelming amount of evidence (Fernandez, 2002; Robinson & Riley, 1999; Smeets, Vlaeyen, Kester & Knottnerus, 2006; Keogh & Asmundson, 2004; Turk & Monarch, 2002). The affective component of pain incorporates many different emotions, but they are primarily negative. Depression and anxiety have received the greatest amount of attention in chronic pain patients; however, anger has

recently received considerable interest as a significant emotion in chronic pain patients.

In addition to affect being one of the three interconnected components of pain, pain and emotions interact in a number of ways. Emotional distress may predispose people to experience pain, be a precipitant of symptoms, be a modulating factor amplifying or inhibiting the severity of pain, be a consequence of persistent pain, or be a perpetuating factor. Moreover, these potential roles are not mutually exclusive, and any number of them may be involved in a particular circumstance interacting with cognitive appraisals. For example, the literature is replete with studies demonstrating that current mood state modulates reports of pain as well as tolerance for acute pain (e.g., Fernandez & Turk, 1992; Turk & Monarch, 2002). Levels of anxiety have been shown to influence not only pain severity but also complications following surgery and number of days of hospitalization (e.g., DeGroot et al., 1997; Pavlin, Rapp, & Polisar, 1998). Individual difference variables, such as anxiety sensitivity (discussed later in this article), have also been shown to play an important predisposing and augmenting role in the experience of pain (Asmundson, 1999; Asmundson, Wright, & Hadjistavropoulos, 2000). Level of depression has been observed to be closely tied to chronic pain (Gatchel, 2005) and to play a significant role in premature termination from pain rehabilitation programs (Kerns & Haythornthwaite, 1988).

Emotional distress is commonly observed in people with chronic pain. People with chronic and recurrent (episodic) acute pain often feel rejected by the medical system, believing that they are blamed or labeled as symptom magnifiers and complainers by their physicians, family members, friends, and employers when their pain condition does not respond to treatment. They may see multiple physicians and undergo numerous laboratory tests and imaging procedures in an effort to have their pain diagnosed and successfully treated. As treatments expected to alleviate pain are proven ineffective, pain sufferers may lose faith and become frustrated and irritated with the medical system. As their pain persists, they may be unable to work or have financial difficulties, difficulty performing everyday activities, sleep disturbance, or treatment-related complications. They may be fearful and have inadequate or maladaptive support systems and other coping resources available to them. They may feel hostility toward the health care system in its inability to eliminate their pain. They may also feel resentment toward their significant others who they may perceive as providing inadequate support. And, they may even be angry with themselves for allowing their pain to take over their lives. These consequences of chronic pain can result in depression, anger, anxiety, self-preoccupation, and isolation—an overall sense of demoralization. Because chronic pain persists for long periods of time, affective state will continue to play a role as the impact of pain comes to influence all aspects of the pain sufferers' lives.

Although we provide an overview of research on the predominant emotions—anxiety, depression, and anger—associated with pain individually, it is important to acknowledge that these emotions are not as distinct when it comes to the experience of pain. They interact and augment each other over time.

Anxiety

It is common for patients with symptoms of pain to be anxious and worried. This is especially true when the symptoms are unex-

plained, as is often the case for chronic pain syndromes. For example, in a large-scale, multicentered study of fibromyalgia syndrome patients, between 44% and 51% of patients acknowledged that they were anxious (Wolfe et al., 1990). People with persistent pain may be anxious about the meaning of their symptoms and for their futures—will their pain increase, will their physical capacity diminish, will their symptoms result in progressive disability where they ultimately end in a wheelchair or bedridden? In addition to these sources of fear, pain sufferers may be worried that, on the one hand, people will not believe that they are suffering and, on the other, they may be told that they are beyond help and will just have to learn to live with it. Fear and anxiety also relate to activities that people with pain anticipate will increase their pain or exacerbate whatever physical factors might be contributing to the pain. These fears may contribute to avoidance, motivate inactivity, and ultimately greater disability (Boersma & Linton, 2006). Continual vigilance and monitoring of noxious stimulation and the belief that it signifies disease progression may render even low-intensity aversive sensations less bearable. In addition, such fears will contribute to increased muscle tension and physiological arousal that may exacerbate and maintain pain (Gatchel, 2005; Robinson & Riley, 1999).

Threat of intense pain captures attention in such a way that individuals have difficulty disengaging from it. The experience of pain may initiate a set of extremely negative thoughts, as noted previously, and arouse fears—fears of inciting more pain and injury or fear of their future impact (see Vlaeyen & Linton, 2000). Fear and anticipation of pain are cognitive-perceptual processes that are not driven exclusively by the actual sensory experience of pain and can exert a significant impact on the level of function and pain tolerance (Feuerstein & Beattie, 1995; Vlaeyen et al., 1999; Vlaeyen & Linton, 2000). People are motivated to avoid and escape from unpleasant consequences; they learn that avoidance of situations and activities in which they have experienced acute episodes of pain will reduce the likelihood of reexperiencing pain or causing further physical damage. They may become hypervigilant to their environment as a way of preventing the occurrence of pain.

Investigators (e.g., Lethem, Slade, Troup, & Bentley, 1983; Vlaeyen, Kole-Snijders, Rotteveel, et al., 1995) have suggested that fear of pain, driven by the anticipation of pain and not by the sensory experience of pain itself, produce strong negative reinforcement for the persistence of avoidance behavior and the putative functional disability in pain patients. Avoidance behavior is reinforced in the short term through the reduction of suffering associated with noxious stimulation (McCracken, Gross, Sorg, & Edmonds, 1993). Avoidance, however, can be a maladaptive response if it persists and leads to increased fear, limited activity, and other physical and psychological consequences that contribute to disability and persistence of pain.

Studies have demonstrated that fear of movement and fear of (re)injury are better predictors of functional limitations than biomedical parameters or even pain severity and duration (e.g., Crombez, Vlaeyen, & Heuts, 1999; Turk, Robinson, & Burwinkle, 2004; Vlaeyen, Kole-Snijders, Rotteveel, et al., 1995). For example, Crombez et al. (1999) showed that pain-related fear was the best predictor of behavioral performance in trunk-extension, flexion, and weight-lifting tasks, even after the effects of pain intensity are partialled out. Moreover, Vlaeyen, Kole-Snijders, Rotteveel, Rue-

sink, and Heuts (1995) found that fear of movement and (re)injury was the best predictor of self-reported disability among chronic back-pain patients and that physiological sensory perception of pain and biomedical findings did not add any predictive value. The importance of fear of activity appears to generalize to daily activities as well as the clinical experimental context. Approximately two thirds of chronic nonspecific low back-pain sufferers avoid back straining activities because of fear of (re)injury (Crombez et al., 1999). For example, fear-avoidance beliefs about physical demands of a job are strongly related to disability and work lost during the previous year, even more so than pain severity or other pain variables (Asmundson, Norton, & Norton, 1999; Vlaeyen & Crombez, 1999; Vlaeyen, Kole-Snijders, Boeren, & van Eek, 1995; Vlaeyen, Kole-Snijders, Rotteveel, et al., 1995). Interestingly, reduction in pain-related anxiety predicts improvement in functioning, affective distress, pain, and pain-related interference with activity (McCracken & Gross, 1998). Clearly, fear, pain-related anxiety, and concerns about harm-avoidance all play important roles in chronic pain and need to be assessed and addressed in treatment.

Pain-related fear and concerns about harm avoidance all appear to exacerbate symptoms (Vlaeyen, Kole-Snijders, Boeren, & van Eek, 1995). Anxiety is an affective state that is greatly influenced by appraisal processes; to cite the stoic philosopher Epictetus, "There is nothing either bad or good but thinking makes it so." Thus, there is a reciprocal relationship between affective state and cognitive-interpretive processes. Thinking affects mood, and mood influences appraisals and, ultimately, the experience of pain (Boersma & Linton, 2006; Gatchel, 2005).

Depression

Research suggests that 40%–50% of chronic pain patients suffer from depressive disorders (Banks & Kerns, 1996; Dersh, Gatchel, Mayer, Polatin, & Temple, 2006; Romano & Turner, 1985). Epidemiologic studies provide solid evidence for a strong association between chronic pain and depression but do not address whether chronic pain causes depression or depression causes chronic pain. Prospective studies of patients with chronic musculoskeletal pain have suggested that chronic pain can cause depression (Atkinson, Slater, Patterson, Gant, & Garfin, 1991), that depression can cause chronic pain (Magni, Moreschi, Rigatti Luchini, & Merskey, 1994), and that they exist in a mutually reinforcing relationship (Rudy, Kerns, & Turk, 1988).

One fact often raised to support the idea that pain causes depression is that the current depressive episode often began after the onset of the pain problem. The majority of studies appear to support this contention (Brown, 1990). However, several studies have documented that many patients with chronic pain (especially those disabled patients seen in pain clinics) have often had prior episodes of depression that predated their pain problem by years (Katon, Egan, & Miller, 1985). A small longitudinal study (Dworkin et al., 1992) followed patients with herpes zoster for 1 year. They observed that those who developed more severe pain (i.e., post-herpetic neuralgia) 3 months after the initial diagnosis scored higher on baseline levels of depressed mood. However, these results were not confirmed in a recent larger study conducted by this group (Katz et al., 2005). One important prospective study (Jarvik et al., 2005) demonstrated that levels of depression pre-

dicted the development of low back pain 3 years following the initial assessment. Patients with depression were 2.3 times more likely to report back pain compared to those who did not report depression. Depression was a much stronger predictor of incident back pain than any clinical or anatomic risk factors. This has led some investigators to propose that there may exist a common trait of susceptibility to dysphoric physical symptoms (including pain) and to negative psychological symptoms (including anxiety as well as depression). They concluded that "pain and psychological illness should be viewed as having reciprocal psychological and behavioral effects involving both processes of illness expression and adaptation" (Von Korff & Simon, 1996, p. 107).

Given the scenario of chronic pain above, it is hardly surprising that chronic pain patients are depressed. It is interesting, however, to ponder the flip side of the coin—why are not all chronic pain patients depressed? Turk and colleagues (Rudy et al., 1988; Turk, Okifuji, & Scharff, 1995) examined this question and determined that two factors appear to mediate the pain–depression relationship: patients' appraisals of the effects of the pain on their lives and appraisals of their ability to exert any control over their pain and lives. That is, those patients who believed that they could continue to function, and that they could maintain some control despite their pain, were less likely to become depressed. Here we see the interdependence of cognition and affect.

As noted previously, in the majority of cases, depression appears to be reactive, although some have suggested that chronic pain is a form of "masked depression," whereby patients use pain to express their depressed mood because they feel it is more acceptable to complain of pain than to acknowledge that one is depressed. Once a person has a chronic pain diagnosis, it no longer matters which is the cause and which is the consequence—pain or depression. Both need to be treated.

Anger

Anger has been widely observed in people with chronic pain (Schwartz, Slater, Birchler, & Atkinson, 1991). Even though chronic pain patients might present an image of themselves as even tempered, Corbishley, Hendrickson, Beutler, and Engle (1990) found that 88% acknowledged their feelings of anger when these were explicitly sought. Approximately 98% of the patients referred to a multidisciplinary pain rehabilitation center reported that they were feeling some degree of anger at the time of the assessment (Okifuji, Turk, & Curran, 1999). We must be cautious in interpreting data from patients recruited at pain centers, however, as there may be a referral bias such that the most distressed patients are sent to these facilities, and they do not represent the large number of people with persistent pain who are never evaluated in treatment facilities that specialize in pain management.

Since anger is frequently considered as socially undesirable, some patients in the studies cited previously may have found it difficult to admit that they were angry to the health care professionals. Thus, it is possible that the anger rates may actually be an underestimate. The high prevalence of anger observed is perhaps not surprising, given the frustrations related to persistence of symptoms, limited information on etiology, and repeated treatment failures, along with anger toward others (employers, insurance companies, the health care system, family members) and anger

toward themselves, perhaps, for their inability to alleviate their symptoms and to move on with their lives (Okifuji et al., 1999).

Several empirical studies provide preliminary support for the association between anger and pain intensity (Gaskin, Greene, Robinson, & Geisser, 1992; Summers, Rapoff, Varghese, Porter, & Palmer, 1991), unpleasantness of pain (Wade, Price, Hamer, Schwartz, & Hart, 1990), affective component of pain (Fernandez & Milburn, 1994), and emotional distress in chronic pain patients (Duckro, Chibnall, & Tomazic, 1995; Kinder, Curtiss, & Kalichman, 1992) as well as families of chronic pain patients (Schwartz et al., 1991).

Anger in chronic pain has been considered by some to be attributable to enduring personality dispositions associated with unconscious conflicts (Fromm-Reichman, 1937), whereas others have suggested that anger may be a reaction to the presence of recalcitrant symptoms that have been unsubstantiated by objective medical findings and unrelieved by medical treatments (Fernandez & Turk, 1995). There is some evidence supporting the latter hypothesis. For example, a laboratory study (Berkowitz & Thomas, 1987) demonstrated that the mere anticipation of pain was sufficient to provoke angry behavioral responses in healthy individuals. Using the cross-lagged design with a clinical sample, Arena, Blanchard, and Andrasik (1984) found that an increase in pain tends to precede anger, directly contradicting the anger-somatization association.

The relatively fruitless debate over the cause–effect relationship between anger and pain is reminiscent of the arguments on the associations between pain and depression (see Romano & Turner, 1985). In order to refine researchers' understanding of the association between anger and pain beyond this debate, several investigators have begun to examine individual differences in how anger is expressed. In an early study, Pilowsky and Spence (1976) found that chronic pain patients are less willing to express anger compared to outpatient medical patients. Similarly, individuals with chronic pain problems appear to inhibit their anger compared to pain-free, healthy persons (Franz, Paul, Bautz, Choroba, & Hildebrandt, 1986; Hatch et al., 1991). Furthermore, inhibition of anger seems to contribute to aversiveness of the chronic pain experience. Inhibition of anger has been found to be related to pain severity and overt pain behaviors (Kerns, Rosenberg, & Jacob, 1994) as well as to increased emotional distress (Duckro et al., 1995; Tschannen, Duckro, Margolis, & Tomazic, 1992).

Denial of anger also appears to be common among chronic pain patients. However, awareness of anger should not be confused with anger expression. For example, Corbishley et al. (1990) observed that chronic pain patients tend to show strong reservations about expressing socially undesirable emotions that could create interpersonal conflict. For these individuals, it seems that expression of the emotion is under conscious control. They are aware of their anger but choose not to express it. On the other hand, some chronic pain patients may lack awareness of their angry feelings and have increased difficulties in recognizing and reporting these feelings (Braha & Catchlove, 1985).

Fernandez and Turk (1995) proposed that the specificity of targets toward which patients experience angry feelings may be important in understanding the relationship between pain and anger. When a pain sufferer is angry, there are a range of possible targets (e.g., employer, insurance company, health care providers). The presence or intensity of anger toward different targets may be

differentially related to chronic pain experience. That is, there may be some targets of anger that are more relevant to the chronic pain experience than others. As is discussed below, Okifuji et al. (1999) found that anger directed toward oneself was particularly common among chronic pain patients evaluated at a pain rehabilitation facility.

Another important issue regarding anger concerns gender differences. There is a growing literature suggesting the presence of important differences in the ways that males and females respond to pain (Unruh, 1996). Moreover, in the Western cultures, there appear to be social conventions regarding the expression of anger. In general, it seems acceptable for men to display angry feelings, whereas women are socialized to avoid overt expression of anger. However, research investigating gender differences in anger expression has revealed equivocal results. Some studies reported that women indicate significantly higher levels of generalized anger than men (e.g., Hashida & Mosche, 1988), some report the opposite results (Fischer, Smith, Leonard, & Fuqua, 1993; Kinder et al., 1992; Sternbach, Wolfe, Murphy, & Akeson, 1973), and still others reported no gender differences in anger expression (Averill, 1983; Stoner & Spencer, 1987). In the chronic pain population, some studies noted that male patients seem to acknowledge angry feelings more readily than do female patients (Kinder et al., 1992; Sternbach et al., 1973). In contrast, other investigators (Burns, Johnson, Devine, Mahoney, & Pawl, 1998; Curtiss, Kinder, Kalichman, & Spana, 1988; Okifuji et al., 1999) suggested that there may be substantial variability within groups of men and women. There seems to be a subgroup of female patients who do outwardly express anger, whereas some male patients may suppress their anger.

Although the effects of anger and frustration on exacerbation of pain and treatment acceptance has not received as much attention as anxiety and depression, Kerns et al. (1994) found that the suppressed feelings of anger accounted for a significant portion of the variance in pain intensity, perceived interference, and frequency of pain behaviors. Furthermore, Summers et al. (1991) found that anger and hostility were powerful predictors of pain severity in people with spinal cord injuries. It is thus reasonable to expect that the presence of anger may serve as a complicating factor, increasing autonomic arousal and blocking motivation and acceptance of treatments oriented toward rehabilitation and disability management rather than cure, which are often the only treatments available for chronic pain (Fernandez & Turk, 1995).

Frustrations related to persistence of symptoms, unknown etiology, and repeated treatment failures, along with anger toward employers, insurers, the health care system, family, and themselves, all contribute to the general dysphoric mood of patients (Okifuji et al. 1999). Okifuji et al. (1999) reported that 60% of patients expressed anger toward health care providers, 39% toward significant others, 30% toward insurance companies, 26% toward employers, and 20% toward attorneys. The target of anger most commonly acknowledged, however, was oneself (endorsed by approximately 70% of the sample). Internalization of angry feelings is strongly related to measures of pain intensity, perceived interference, and frequency of pain behaviors (Kerns et al., 1994). Overall, correlations between anger and pain severity have been shown to be statistically significant, ranging from .17 to .35 (Burns, Wiegner, Derleth, Kiselica, & Pawl, 1996; Kerns et al., 1994). Okifuji et al., (1999) reported that anger was significantly

correlated with pain intensity ($r = .30\text{--}.35$). Okifuji et al. also reported that anger was significantly correlated with disability ($r = .26$) and was highly associated with depression ($r = .52$).

The precise mechanisms by which anger and frustration exacerbate pain are not known. One reasonable possibility is that anger exacerbates pain by increasing physiological arousal (Burns, 1997; Cacioppo, Bernston, Klein, & Poehlmann, 1997). For example, Burns et al. (1996) reported the results of a study that demonstrated anger-induced stress produced increased muscle tension, which in turn predicted a greater level of pain severity in chronic back-pain patients. It was found that this effect was specific to anger; a measure of depression that was significantly correlated with pain was not associated with increased muscle reactivity.

Anger may also interact with depression to modulate perceived severity of pain. In addition, anger may block motivation for, and acceptance of, treatments oriented toward rehabilitation and disability management rather than cure. Yet, rehabilitation and disability management are often the only treatments available for these patients.

Negative Affect: A Summary

In summary, it is important to be aware of the significant role of negative mood in chronic pain patients, because it is likely to influence treatment motivation and compliance with treatment recommendations. For example, patients who are anxious may fear engaging in what they perceive as demanding activities, patients who are depressed and who feel helpless may have little initiative to comply, and patients who are angry with the health care system are not likely to be motivated to respond to recommendations from yet another health care professional. Finally, as noted by Robinson and Riley (1999),

Inhibition of negative emotion has also been suggested in the etiology of chronic pain through increased autonomic and central nervous system activity, which in turn weakens the cognitive processes that promote health, resulting in sleep disturbance, elevation of cortisol levels, and increased health care utilization. (p. 78)

Thus, clinicians who are treating people with persistent pain must focus on their mood states as well as on physical pathology and somatic factors. Pain cannot be treated successfully without attending to the patient's emotional state. This is true for acute pain, such as pain associated with surgery, and persistent pain states.

Pain and Cognitive Factors

As pointed out in the last section, pain and emotions interact in a number of ways that, in turn, may interact with cognitive appraisals of the pain state. A review of these cognitive factors is provided next.

Appraisal and Beliefs

Pain appraisal refers to the meaning ascribed to pain by an individual (Sharp, 2001). In accordance with the transactional stress model (Lazarus & Folkman, 1984), a distinction can be made between primary appraisal (evaluation of the significance of pain in terms of it being threatening, benign, or irrelevant) and secondary appraisal (evaluation of the controllability of pain and

one's coping resources). *Beliefs* refers to assumptions about reality that shape how one interprets events and can thus be considered as determinants of appraisal. Pain beliefs develop during the lifetime as a result of an individual's learning history and cover all aspects of the pain experience (e.g., the causes of pain, its prognosis, suitable treatments).

Appraisal and beliefs about pain can have a strong impact on an individual's affective and behavioral response to pain. If a pain signal is interpreted as harmful (threat appraisal) and is believed to be associated with actual or potential tissue damage, it may be perceived as more intense and unpleasant and may evoke more escape or avoidance behavior. For instance, pain associated with cancer is rated as more unpleasant than labor pain, even when the intensity is rated as equivalent (Price, Harkins, & Baker, 1987). Similarly, Smith, Gracely, and Safer (1998) demonstrated that cancer patients, who attributed pain sensations after physiotherapy directly to cancer, reported more intense pain than patients who attributed this pain to other causes. Perception of danger of an experimental pain stimulus (cold-pressor test) may also lead to avoidance of this stimulus (Cipher & Fernandez, 1997). Arntz and Claassens (2004) experimentally manipulated the appraisal of a mildly painful stimulus (a very cold metal bar placed against the neck) by suggesting that it was either very hot or very cold. It was assumed that heat would be more strongly associated with tissue damage than cold. As expected, participants rated the stimulus as more painful in the condition where they were informed that it was hot. In addition, the effect appeared to be mediated by the belief that the stimulus would be harmful. These studies demonstrate the important role of people's interpretations regarding the meaning of pain.

Pain appraisal and pain beliefs are also prominent determinants of adjustment to chronic pain (Jensen, Romano, Turner, Good, & Wald, 1999; Turner, Jensen, & Romano, 2000). The following pain beliefs have been identified as particularly maladaptive in dealing with pain: Pain is a signal of damage, activity should be avoided when one has pain, pain leads to disability, pain is uncontrollable, and pain is a permanent condition (Jensen, Turner, Romano, & Lawler, 1994; Turner et al., 2000). The belief that pain is a signal of damage and the belief that activity should be avoided in order to recover from pain appear to be widespread (Balderson, Lin, & Von Korff, 2004; Ihlebaek & Eriksen, 2003). Two months after seeking treatment, a large majority of back-pain patients believed that a wrong movement could have serious negative consequences for their back. Moreover, this belief was associated with reduced activity levels and increased disability (Balderson et al., 2004).

Catastrophizing and Fear-Avoidance Beliefs

In the last decade, chronic pain researchers have emphasized the role of a specific set of negative appraisal and beliefs (i.e., pain catastrophizing and fear-avoidance beliefs). *Pain catastrophizing* can be defined as an exaggerated negative orientation toward actual or anticipated pain experiences. There has been much debate about the specific nature of catastrophizing as a psychological construct (Sullivan et al., 2001; Turner & Aaron, 2001). However, current conceptualizations most often describe it in terms of appraisal or as a set of maladaptive beliefs (Severeijns, Vlaeyen, & van den Hout, 2004; Thorn, Rich, & Boothby, 1999). The evidence

for the role of pain catastrophizing in chronic pain adjustment is overwhelming and has been summarized in several review articles and studies (e.g. Keefe, Rumble, Scipio, Giordano, & Perri, 2004; Smeets et al., 2006; Sullivan et al., 2001). Cross-sectional studies have demonstrated that catastrophizing is associated with increased pain, increased illness behavior, and physical and psychological dysfunction across numerous clinical and nonclinical populations. Prospective studies indicated that catastrophizing might be predictive of the inception of chronic musculoskeletal pain in the general population (Picavet, Vlaeyen, & Schouten, 2002; Severeijns, Vlaeyen, van den Hout, & Picavet, 2005) and of more intense pain and slower recovery after surgical intervention (Granot & Ferber, 2005; Kendell, Saxby, Farrow, & Naisby, 2001; Pavlin, Sullivan, Freund, & Roesen, 2005).

The role of catastrophizing and the belief that pain means harm and activity should be avoided has been most articulated in fear-avoidance models of chronic pain (Asmundson, Norton, & Vlaeyen, 2004; Vlaeyen & Linton, 2000). Although fear-avoidance models are multifaceted and include affective (fear) and behavioral (avoidance) components, cognitions are identified as the core determinants of entering into a negative pain cycle. Philips (1987) was the first to stress the importance of beliefs in shaping avoidance behavior in response to pain. She identified memory of past pain experiences, the belief that activity will lead to a pain increase, and self-efficacy beliefs as the major determinants of avoidance behavior. The tenets of contemporary fear-avoidance models can be summarized as follows: When pain is perceived following injury, an individual's idiosyncratic beliefs will determine the extent to which pain is catastrophically interpreted. A catastrophic interpretation of pain gives rise to physiological (arousal), behavioral (avoidance), and cognitive fear responses. The cognitive shift that takes place during fear enhances threat perception (e.g., by narrowing of attention) and further feeds the catastrophic appraisal of pain (Asmundson et al., 2004).

The evidence that fear and avoidance are associated with increased pain and disability in chronic pain patients has been reviewed above in the section on pain and emotion. In addition, prospective studies have shown that fear-avoidance beliefs in patients seeking care for acute pain may be predictive of pain persistence, disability, and long-term sick leave (e.g., Boersma & Linton, 2005; Fritz, George, & Delitto, 2001). Fear-avoidance beliefs are also related to the future inception of (back) pain in the general population (Linton, Buer, Vlaeyen, & Hellsing, 2000; Picavet et al., 2002).

Health care providers are often not able to adequately address the fear-avoidance beliefs of patients (Balderson et al., 2004). In fact, some practitioners hold beliefs themselves that may encourage fear-avoidance in their patients (Houben et al., 2005; Linton, Vlaeyen, & Ostelo, 2002). Fear-avoidance beliefs of health care providers were found to be related to their treatment behavior and their recommendation for engaging in physical activities (Houben et al. 2004; J. Rainville, Carlson, Polatin, Gatchel, & Indahl, 2000). The beliefs of patients and health care providers may further interact with each other in a mutually reinforcing way, because a patient's beliefs may guide the choice of which health care provider is visited (Werner, Ihlebaek, Skouen, & Laerum, 2005).

Since catastrophizing and fear-avoidance beliefs appear to play such a prominent role in maladaptive responses to pain and in pain

perpetuation, it is of vital importance that these negative and maladaptive beliefs are corrected. Several investigators have demonstrated the therapeutic efficacy of doing so (Ehde & Jensen, 2004; Smeets et al., 2006; Thorn, 2004). Moreover, educational interventions in a primary care setting addressing fear-avoidance beliefs and encouragement to stay active have been found to reduce disability in back-pain patients (Burton, Waddell, Tillotson, & Summerton, 1999; J. E. Moore, Von Korff, Cherkin, Saunders, & Lorig, 2000). Also a population-based media campaign was shown to be effective in changing beliefs about back pain and reducing disability and worker's compensation costs related to back pain (Buchbinder, Jolley, & Wyatt, 2001). The improvement in population beliefs about back pain were sustained until 3 years after cessation of the campaign (Buchbinder & Jolley, 2005).

However, education alone may not be sufficient for reducing fear-avoidance beliefs in those patients with very high levels of catastrophizing and fear-avoidance beliefs (de Jong, Vlaeyen, Onghena, Goossens, et al., 2005). These patients may require a more tailored treatment approach, such as graded exposure to disconfirm their fear-avoidance beliefs (Vlaeyen, de Jong, Onghena, et al., 2002). In graded exposure therapy, first a hierarchy of fearful activities is established. Patients are encouraged to engage in a moderately feared activity until disconfirmation of harm beliefs for this particular activity has occurred. Then, patients proceed to the next item in the hierarchy until he or she is able to perform even the most feared activities. During the performance of activities, behavioral experiments are used to challenge the catastrophic interpretations of the consequences of the activity. Graded exposure appears to be a very effective treatment for altering fear-avoidance beliefs and catastrophizing and for reducing pain and disability in chronic pain patient who are characterized by high levels of fear-avoidance (Boersma et al., 2004; de Jong, Vlaeyen, Onghena, Cuypers, et al., 2005; Vlaeyen, de Jong, Geilen, Heuts, & van Breukelen, 2002).

Although graded exposure is the most specific treatment for reducing fear-avoidance beliefs, most cognitive behavioral treatment (CBT) packages for chronic pain patients contain at least some components (e.g., education, physical exercise, challenging negative cognitions) that are likely to be effective at reducing fear-avoidance beliefs (Williams & McCracken, 2004). Several studies have indeed demonstrated that CBT can lead to a reduction in fear-avoidance beliefs and that treatment success may be mediated by changes in fear-avoidance beliefs (e.g., Jensen, Turner, & Romano, 2001; McCracken, Gross, & Eccleston, 2002). CBT approaches are further reviewed later in this article.

Perceived Control and Self-Efficacy

Perceived control over pain refers to the belief that one can exert influence on the duration, frequency, intensity or unpleasantness of pain. Perceived controllability of a pain stimulus may modify the meaning of this stimulus and directly affect threat appraisal (Arntz & Schmidt, 1989; Bandura, O'Leary, Taylor, Gauthier & Gossard, 1987). As a consequence, pain may be rated as less intense or less unpleasant, and pain tolerance may increase. However, studies in which the control over pain stimuli was experimentally manipulated yielded mixed results as to whether perceived controllability affects pain intensity or pain tolerance (Janssen, Spinhoven, & Arntz, 2004; Salomons, Johnstone, Back-

onja, & Davidson, 2004; Thompson, 1981). However, a recent study by Samwel, Evers, Crul, and Kraaimaat (2006) found that, in a group of 169 chronic pain patients treated at an interdisciplinary pain center, perceived helplessness appeared to be the strongest contributor to disability and pain level. Moreover, in another study, fMRI showed that manipulation of the controllability of a pain stimulus attenuated the neural response to pain (Salomons et al., 2004). Offering control in an experimental pain situation may interact with individual characteristics, such as self-efficacy and feeling of helplessness, in determining whether it is effective in reducing pain (Müller & Netter, 2000).

Outside of the laboratory, the relevance of perceived control over pain has also been examined. The belief that one has control over pain has a strong influence on disability in patients with chronic pain complaints (Jensen & Karoly, 1991; Turner et al., 2000), and an increase in this belief after multidisciplinary pain treatment may predict pain reduction and decreases in disability (Jensen et al., 2001; Spinhoven et al., 2004). However, there may be a downside to trying to gain control over pain. When repeated attempts to gain control over pain fail, this may lead to frustration and preoccupation with pain and, finally, to exacerbations of disability and distress (McCracken, Carson, Eccleston, & Keefe, 2004). Instead of trying to gain control over pain itself, it may be more effective to control the effect of pain on one's life. Of course, there is a fine line between controlling one's pain and controlling the impact of pain in one's life. These are not mutually exclusive. For example, relaxation may control both one's pain and the impact of pain on one's life. Regardless, though, as Tan et al. (2002) demonstrated, perceived control over the effects of pain was more strongly related to better adjustment and less disability than perceived control over pain itself. McCracken et al. (2004) proposed that the ineffective struggle to gain control over pain that is essentially uncontrollable should be abandoned, and that acceptance of pain may foster the sense of general life control. Indeed, a consistent relationship between pain acceptance and better adjustment has been found (e.g., McCracken & Eccleston, 2003; Viane et al., 2003), and preliminary evidence has been obtained for the efficacy of acceptance-based treatment for chronic pain patients (McCracken, Vowles, & Eccleston, 2005). On the other hand, however, there are growing data from imaging studies showing the positive physiological effects of cognitive coping (e.g., deCharms et al., 2005; Salomons et al., 2004). Thus, this issue still needs to be resolved. Afterall, on a pure clinical basis, to simply give up or give in would appear to be a certain route to depression.

Related to perceived control is the construct of self-efficacy. Self-efficacy is the conviction that one can successfully perform a certain task or produce a desirable outcome (Bandura, 1977). A major determinant of self-efficacy is prior mastery experience. In laboratory experiments, self-efficacy beliefs predict pain tolerance (e.g., Dolce et al., 1986; Keefe, Lefebvre, Maixner, Salley, & Caldwell, 1997). In chronic pain patients, self-efficacy positively affects physical and psychological functioning (Asghari & Nicholas, 2001; Rudy, Lieber, Boston, Gourley, & Baysal, 2003; Woby, Watson, Roach, & Urmston, 2005), and improvements in self-efficacy after self-management and cognitive-behavioral interventions are associated with improvements in pain, functional status, and psychological adjustment (Keefe et al., 2004; Marks, 2001). Recent reviews of psychological factors in chronic pain have concluded that the evidence for the role of self-efficacy

across a broad range of pain populations is impressive (Geisser, Robinson, Miller, & Bade, 2003; Keefe et al., 2004). Moreover, self-efficacy also influences the prognosis after acute physical interventions like surgery. Prospective studies in patients who underwent orthopedic surgery demonstrated that high self-efficacy before the start of rehabilitation and larger increases over the course of a rehabilitation speed recovery and predict better long-term outcome (Dohnke, Knauper, & Muller Fahrnow, 2005; Orbell, Johnston, Rowley, Davey, & Espley, 2001; Waldrop, Lightsey, Ethington, Woemmel, & Coke, 2001). A preoperative intervention (an instruction video demonstrating movement and breathing skills) in hysterectomy patients was able to enhance preoperative self-efficacy and decrease pain associated with post-operative activities and promote earlier mobilization (Heye, Foster, Bartlett, & Adkins, 2002).

Why is a high level of self-efficacy beneficial when people are confronted with an acute or chronic pain experience? For one thing, high self-efficacious people may be more motivated to engage in health promoting behaviors and adhere better to treatment recommendations because they have higher performance success expectancies. Also, they are less likely to give up an activity when facing barriers (e.g., pain), and this may prevent them from becoming trapped in the negative spiral of activity avoidance, physical deconditioning, loss of social reinforcers and depression. In addition, perceived self-efficacy can affect the body's opioid and immune systems (Weisenberg, 1998).

Vulnerability and Resilience

As discussed above, specific pain cognitions (appraisal and beliefs) are largely shaped by an individual's learning history, either through direct experience, modeling, or information from others. These learning experiences may interact with an individual trait characteristic and the global outlook on the world that an individual holds. That is, temperamental or personality factors may predispose some people to make certain kinds of maladaptive appraisals and to be more susceptible to some beliefs than to others. Temperament is supposed to be (at least partly) heritable and show continuity throughout life; personality in adulthood reflects the molding of underlying temperament by life experiences. Temperament and personality can be a vulnerability factor that predisposes toward catastrophic misinterpretation of pain sensations and maladaptive pain beliefs, or they can be a resilience factor protecting against maladaptive cognitions and promoting self-efficacy beliefs. Some potential vulnerability and resilience factors for chronic pain adaptation are reviewed here.

Trait characteristics that have received most attention as potential vulnerability factors leading to maladaptive cognitions are negative affectivity, anxiety sensitivity and, more recently, illness/injury sensitivity (Keogh & Asmundson, 2004). In the earlier section on Pain and Emotion, we discussed some of the basic emotional states associated with chronic pain. These negative emotions may be particularly prominent in patients with a high level of negative affectivity. Negative affectivity is considered a heritable, stable, and general tendency to view the world as threatening and distressing, and a high level of negative affectivity may evoke experiencing a broad range of negative emotions (Watson, Clark, & Harkness, 1994). Negative affectivity has been associated with heightened vigilance to bodily sensations and interpretation

biases toward ambiguous internal signals (Stegen, Van Diest, Van de Woestijne, & Van den Bergh, 2000; Watson & Pennebaker, 1989). Studies in nonclinical populations found negative affectivity to predict lower pain tolerance (Fillingim et al., 2005). However, studies in chronic pain populations have so far not provided consistent evidence for a role of trait negative affectivity. Negative affectivity does not seem to account for heightened pain vigilance in patients with various chronic pain syndromes (Crombez, Eccleston, Van den Broeck, Van Houdenhove, & Goubert, 2002; Peters, Vlaeyen, & van Drunen, 2000). There are also a few prospective studies on the prognostic role of negative affectivity in recovery after whiplash trauma. Again, the role of negative affectivity was not substantiated (Radanov, di Stefano, Schnidrig, & Ballinari, 1991; Scholten-Peeters et al., 2003). In conclusion, although negative affectivity has often been implicated as a vulnerability factor in chronic pain, convincing evidence is still waiting.

More convincing has been the research on another potential vulnerability factor: anxiety sensitivity. *Anxiety sensitivity* is defined as the fear of anxiety-related sensations and is conceived as a partly heritable personality trait (Reiss, Peterson, Gursky, & McNally, 1986; Stein, Jang, & Livesley, 1999). Individuals with high anxiety sensitivity interpret unpleasant physical sensations (like rapid heart beating, feeling faint) more often as a sign of danger than do individuals with low anxiety sensitivity. Elevated levels of anxiety sensitivity have been found in several emotional disorders but especially in panic disorder (Taylor, 1995). There is growing evidence that anxiety sensitivity may also be a risk factor for the maintenance and exacerbation of chronic pain and disability (Asmundson et al., 2000). Anxiety sensitivity correlates with measures of fear avoidance and is associated with distress, analgesic use, and physical and social functioning in patients across a wide range of different pain-related conditions (for reviews see Asmundson et al., 2000; Keogh & Asmundson, 2004). Moreover, path analyses and mediation models suggest that anxiety sensitivity exacerbates fear-avoidance beliefs and the negative interpretation of bodily sensations, which in turn leads to enhanced pain experience and pain avoidance (Asmundson & Taylor, 1996; Keogh, Hamid, Hamid, & Ellery, 2004). It should be noted, though, that because anxiety sensitivity is quite highly correlated with a more general factor of neuroticism (Taylor, 1993), future research is required to determine whether it contributes any unique variance in explaining outcomes.

To determine whether anxiety sensitivity is really a vulnerability factor that is causally associated with maladaptive pain cognitions and poor behavioral and psychological adjustment to pain, and not merely a correlate of the chronic pain experience, researchers have examined the predictive value of anxiety sensitivity in relation to cognitive and behavioral reactions to experimentally induced pain in nonclinical samples. In agreement with its supposed role as a vulnerability factor, anxiety sensitivity predicted pain threshold and reported pain intensity after cold-pressor pain induction (Keogh & Birkby, 1999; Keogh & Mansoor, 2001; N. B. Schmidt & Cook, 1999). Moreover, individuals high in anxiety sensitivity show attentional and interpretational biases for physical threat-related material (Asmundson, Carleton, & Ekong, 2005; Keogh & Cochrane, 2002), and the negative interpretational bias regarding bodily sensations mediated the effect of anxiety sensitivity on affective pain responses (Keogh & Cochrane, 2002). Thus, anxiety

sensitivity may indeed be causally implicated in maladaptive cognitive and behavioral pain responses.

Recently, researchers have begun to consider yet another vulnerability factor: illness/injury sensitivity (Carleton, Asmundson, & Taylor, 2005; Vancleef, Peters, Roelofs, & Asmundson, 2006). According to Reiss (1991), illness/injury sensitivity is one of the three fundamental fears besides anxiety sensitivity and fear of negative evaluation. It may be proposed that illness/injury sensitivity, not anxiety sensitivity, is the fundamental fear that qualifies most as a specific vulnerability factor for chronic pain and disability. Illness/injury sensitivity is conceptually more strongly related to the content of fear-avoidance beliefs of chronic pain patients than anxiety sensitivity. This can be illustrated by the items of the inventories that are used to measure anxiety sensitivity and illness or injury sensitivity—the Anxiety Sensitivity Index (Peterson & Heilbronner, 1987) and the Injury/Illness Sensitivity Index (Taylor, 1993), respectively. The Anxiety Sensitivity Index contains items that very specifically apply to panic symptoms (e.g., fear of heart beating fast), whereas the Injury/Illness Sensitivity Index contains items that reflect worries about one's future physical condition (e.g., worrying about getting injured). In his analyses of the relationship between fundamental fears and common fears, Taylor (1993) showed that anxiety sensitivity was most predictive of agoraphobia, and illness/injury sensitivity was most predictive of medical fears. Fear-avoidance beliefs and catastrophizing were not included in this analysis.

Recent studies in healthy volunteers demonstrated that, indeed, illness/injury sensitivity may be a more specific vulnerability factor for maladaptive pain responses than anxiety sensitivity (Vancleef et al., 2006). In a cross-sectional study, illness/injury sensitivity, anxiety sensitivity, fear of negative evaluation, and trait anxiety were tested for their independent contribution to pain catastrophizing and fear-avoidance beliefs. Illness/injury sensitivity appeared to be the single best predictor of pain catastrophizing, fear of pain and pain avoidance. Moreover, when healthy volunteers were subjected to three different pain induction procedures (ischemic pain, electrical pain, and heat pain), only illness/injury sensitivity predicted anticipatory fear for the pain stimulus and not anxiety sensitivity (Vancleef et al., 2006). Another study examined whether illness/injury sensitivity is also predictive of behavior in physically threatening situations. Vignettes were used that described situations that could potentially signal damage to the body (e.g., having pain in the wrist after a fall) and the likelihood of performing safety behaviors was assessed (e.g., going to the general practitioner). As hypothesized, illness/injury sensitivity was the best predictor of safety behavior regarding physical health, superior to anxiety sensitivity and general trait anxiety (Vancleef, Peters, & de Jong, in press). In short, research has begun to demonstrate that the fundamental fear illness/injury sensitivity may be a vulnerability factor for negative pain appraisal and beliefs and avoidant pain behaviour in nonclinical populations. More research is needed to substantiate its role in chronic pain adjustment.

In contrast to a rather extensive search after negative predisposing factors, there has been relatively little research on protective factors for chronic pain and disability. Three potential resilience factors will be discussed here: optimism, hope, and benefit finding. Review of the literature suggests that optimism may be one of the most important personality traits in relation to adjustment to

chronic pain. *Dispositional optimism* is defined as "the tendency to believe that one will generally experience good vs. bad outcomes in life" (Scheier & Carver, 1985, p. 219) and is distinguishable from neuroticism and trait anxiety (Scheier, Carver, & Bridges, 1994). In cross-sectional and prospective studies, optimism was found to be associated with better general health, adaptation to chronic disease and recovery after various surgical procedures (Scheier & Carver, 1992). Also, optimism predicted ischemic pain tolerance and unpleasantness in patients with temporomandibular disorder (Costello et al., 2002).

Trait hope is a personality construct that is closely related to optimism (Snyder, Rand, & Sigmund, 2005), and recently, at least, some research has begun to address its association with adjustment to pain. Using the cold-pressor test to induce experimental pain, Snyder, Berg, et al. (2005) found that high hope people experienced less pain and tolerated the pain stimulus longer than low hope people.

Only a few studies have been looking at the role of dispositional optimism or hope in adaptation to chronic pain. Novy, Nelson, Hetzel, Squitieri, and Kennington (1998) found that optimism was related to less catastrophizing and more use of active coping strategies in chronic pain patients. Affleck, Tennen, and Apter (2001) reported that dispositional optimism predicts pleasant daily mood in fibromyalgia but that it is not related to daily pain. Finally, in studying rheumatoid arthritis patients, Trehanne, Kitas, Lyons, and Booth (2005) found that optimism was associated with less depression and higher life satisfaction and to less pain for patients in the early and intermediate stages of disease.

The main mechanism of the beneficial effect of optimism may be differences in coping behaviour between optimistic and pessimistic people (Garofalo, 2000). In general, pessimists turn to avoidant coping strategies and denial more often, whereas optimists use more problem-focused coping strategies. When problem-focused coping is not possible, they turn to coping strategies such as acceptance, use of humor and positive reframing of the situation (Garofalo, 2000; Scheier et al., 1994). Thus, it may not be the use of specific coping strategies but rather flexibility of coping that protects against disability and distress (Carver & Scheier, 2005). Snyder, Rand, and Sigmund (2005) have described a similar pathway for hope, with people with low hope showing a tendency to catastrophize, whereas people with high hope seek means to encounter future challenges and show flexibility in finding alternative life goals when their original goals are blocked.

Although not a personality trait, another resilience factor in dealing with the problem of chronic pain receiving attention in recent years is benefit finding (Tennen & Affleck, 2005). Some people are able to identify positive aspects of adverse life circumstances (e.g., that it made them more aware of their purpose in life). Benefit finding has been found to lead to less distress and superior psychological adjustment in a range of medical conditions and less activity limitations in rheumatoid arthritis (Tennen & Affleck, 2005). A diary study in fibromyalgia patients indicated that benefit finding influenced mood but not pain intensity (Affleck & Tennen, 1996). Clearly, more research on the role of these and other potential resilience factors for chronic pain (e.g., humor, sense of coherence) is needed.

CBT and Chronic Pain

As discussed earlier, the findings that cognitive factors play an important role in chronic pain has led to the development of CBT methods as a means of more effectively managing it. These CBT techniques proceed from the view that an individual's interpretation, evaluation, and beliefs about his or her health condition and coping repertoire, with respect to pain and disability, will affect the degree of emotional and physical disability associated with the pain condition (Sullivan, Feuerstein, Gatchel, Linton, & Pransky, 2005). In a very influential early study, Morley, Eccleston, and Williams (1999) reported the results of their systematic review and meta-analysis of the existing randomized trials of CBT for chronic pain. Their findings concluded that such treatment is effective for a variety of chronic pain conditions. Again, the major goals of such treatment are to replace maladaptive patient cognitions and behaviors with more adaptive ones. Most recently, Linton and Nordin (2006) reported a 5-year follow-up of a randomized controlled trial of early CBT intervention for back pain. Results demonstrated that this intervention resulted in significantly less pain, produced more active and better quality of life, and resulted in better general health, relative to the comparison group. There were also significantly greater economic benefits associated with the CBT intervention group.

A recent study by Brox et al. (2003) was an exceptional randomized controlled trial that compared the relative efficacy of lumbar spinal fusion versus CBT for back-pain patients who had documented underlying pathophysiology. A total of 64 patients were randomized into one of these two treatments. At the 1-year follow-up, the "difference between the groups given lumbar instrumental fusion and cognitive intervention and exercise was neither clinically important nor significant" (p. 1920). Both groups displayed significant clinical improvement on a wide range of measures. These findings were similar to those of the Fairbank et al. (2005) research study, which reported outcomes at 2 years. Even more recently, Brox et al. (2006) conducted randomized clinical trial demonstrating the effectiveness of CBT with lumbar instrumental fusion patients who had chronic low back pain and who also had a previous surgery for disc herniation. Again, no differences in treatment efficacy were found. Finally, the following are a number of other studies documenting the efficacy of CBT: Astin, Beckner, Soeken, Hochberg, and Berman (2002); Keefe and Caldwell (1997); Bradley (2003); Burns, Kubilis, Bruehl, Harden, and Lofland (2003); E. Chen, Cole, and Kato (2004); Cutler et al. (1994); Spinhoven et al. (2004); Weydert, Ball, and Davis (2003); and Turner, Mancl, and Aaron (2006).

It should also be noted that the usage of the term *cognitive behavioral therapy* varies widely and may include self-instructions (e.g., distraction, imagery, motivational self-talk), relaxation or biofeedback, development of coping strategies (e.g., increasing assertiveness, minimizing of negative self-defeating thoughts), changing maladaptive beliefs about pain, and goal setting. A patient referred for CBT may be exposed to varying selections of these strategies. Finally, it should also be pointed out that these CBT techniques are embedded in more comprehensive pain management programs that also include functional restoration, pharmacotherapy, and general medical management. Evidence-based scientific data documenting the treatment- and cost-effectiveness

of such comprehensive pain management programs for chronic nonmalignant pain patients has been recently well documented (Gatchel & Okifuji, 2006).

Summary and Conclusions

The biopsychosocial approach is now widely accepted as the most heuristic perspective to the understanding and treatment of chronic pain disorders (Gatchel, 2004a, 2004b). The biopsychosocial model views physical illnesses such as pain as the result of the dynamic interaction among physiologic, psychological, and social factors, which perpetuates and may even worsen the clinical presentations. Each individual experiences pain uniquely, and a range of psychological and socioeconomic factors can interact with physical pathology to modulate a patient's report of symptoms and subsequent disability. As we pointed out, such a comprehensive conceptual model of the biopsychosocial interactive processes involved in pain can be quite complex. The goal of the present article was to provide a review of the major breakthroughs in recent years concerning the basic neuroscience processes of pain (the *bio* part of biopsychosocial), as well as the psychosocial factors.

A number of investigators have provided excellent overviews of biopsychosocial interactions and how social and behavioral factors can act on the brain to influence health, illness, and even death (S. Cohen & Rodriguez, 1995; Gatchel, 2004a, 2004b; Ray, 2004). In the present article, we have discussed research that is starting to delineate the pathways involved in the complex interaction processes. For example, Melzack's neuromatrix model of pain (Melzack, 2001, 2005) emphasizes the importance of the HPA axis and stress system in pain. Chronic pain is a stressor that will tax the stress system. Prolonged activation of the stress regulation system will ultimately generate breakdowns of muscle, bone, and neural tissue that, in turn, will cause major pain and produce a vicious cycle of pain-stress-reactivity (Gatchel, 2004). One important measure of this pain-stress cycle is cortisol. Indeed, cortisol is the main hormonal product of the HPA axis in humans. Although increased cortisol secretions are considered an adaptive response of the organism when stressed (for purposes of energy mobilization), prolonged secretion can lead to negative effects such as muscle atrophy, impairment of growth and tissue repair, immune system suppression, and so forth. Melzack (2005) has suggested that cortisol can serve as a good marker of the degree of stress that should closely parallel the development of chronic pain. Gatchel, Garofalo, and Robinson (in press) have recently confirmed this relationship.

We also discussed the development of new technologies, such as brain imaging, that have provided novel insights into brain-pain mechanisms. This is also leading to potentially new effective methods for better managing pain. For example, a recent study by deCharms et al. (2005) addressed the following question: If a person is able to learn to directly control activation of localized regions within the brain associated with pain (e.g., the rostral anterior cingulate cortex, which is a region involved in pain perception and regulation), would that change the person's perception of pain? To test this, these investigators provided real-time fMRI to participants in order to guide their training. It was found that when subjects learned to control this activation, they were also able to control the perception of pain. When they voluntarily

increased activation, there was a corresponding increase in the perception of pain in response to an applied noxious thermal stimulus; when they decreased activation, there was a corresponding decrease in pain. Such results clearly demonstrated that subjects can gain voluntary control over activation in a specific brain region (when provided appropriate training), indicating that direct control over the neurophysiological mechanisms that mediate pain may provide an important new route for treating illness and pain behavior.

Neuroscience research has also made major inroads into better understanding basic neural and biochemical mechanisms involved in pain processing. These mechanisms, in turn, have led to important clinical applications, such as the development of analgesic agents for managing chronic pain. This is further evidenced by the potentially common pathogenic mechanisms involved in chronic pain and the comorbid psychiatric disorders such as depression (Polatin, 1991). For example, both nociceptive and affective pathways coincide automatically. Furthermore, norepinephrine and serotonin—the two neurotransmitters most implicated in the pathophysiology of mood disorders—are also involved in the pain process.

Finally, the emergence of the biopsychosocial model of chronic pain has led to the development of the most heuristic approach to the management of chronic pain—the interdisciplinary pain management approach. As noted earlier, patients with chronic pain are at increased risk for emotional disorders (such as anxiety, depression, and anger), maladaptive cognitions (such as catastrophizing and poor coping skills), functional deficits and physical deconditioning (due to decreased physical activity and fear of reinjury), as well as basic nociceptive dysregulation. All of these aforementioned variables, in turn, are often interdependent so that one cannot simply treat one to the exclusion of the others. Interdisciplinary pain management embraces the fact that the comprehensive assessment-treatment of all these dimensions is needed in order to be effective. Such an approach has been demonstrated to be the most therapeutic and cost-effective means of managing the often recalcitrant chronic pain syndromes. There is usually not a documentable isomorphic relationship between a specific nociceptive event and pain. Instead, as we have reviewed, multiple other dimensions, involving emotion, cognition, and behavioral and brain processing (i.e., total biopsychosocial functioning) must be carefully considered in order to maximize the probability of treatment success. Future breakthroughs in the understanding of such biopsychosocial mechanisms will hopefully lead to even greater understandings in the areas of etiology, assessment, treatment, and prevention of chronic pain. The role of the genetic factors is also an especially promising new area of research that should provide even greater insights into etiological mechanisms of pain that may account for important individual differences in the pain experience and one's response to it.

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