Available online at www.sciencedirect.com
SCIENCE DIRECT®
ELSEVIER
Progress in Neuro-Psychopharmacology & Biological Psychiatry 29 (2005) 1264 – 1280
Progress In Neuro-Psychopharmacology & Biological Psychiatry
www.elsevier.com/locate/pnpbp

Review article

Interface of physical and emotional stress regulation through the endogenous opioid system and μ-opioid receptors

Saulo C. Ribeiro [a], Susan E. Kennedy [a], Yolanda R. Smith [b], Christian S. Stohler [c], Jon-Kar Zubieta [a,*]

[a] *University of Michigan, Department of Psychiatry and Molecular and Behavioral Neuroscience Institute (MBNI), 205 Zine Pitcher Place, Ann Arbor, MI 48109-0720, USA*
[b] *University of Michigan, Department of Obstetrics and Gynecology, Ann Arbor, MI, USA*
[c] *University of Maryland, School of Dentistry, Baltimore, MD, USA*

Accepted 26 August 2005
Available online 26 October 2005

Abstract

Unraveling the pathways and neurobiological mechanisms that underlie the regulation of physical and emotional stress responses in humans is of critical importance to understand vulnerability and resiliency factors to the development of a number of complex physical and psychopathological states. Dysregulation of central stress response circuits have been implicated in the establishment of conditions as diverse as persistent pain, mood and personality disorders and substance abuse and dependence. The present review examines the contribution of the endogenous opioid system and μ-opioid receptors to the modulation and adaptation of the organism to challenges, such as sustained pain and negative emotional states, which threaten its internal homeostasis. Data accumulated in animal models, and more recently in humans, point to this neurotransmitter system as a critical modulator of the transition from acute (warning signals) to sustained (stressor) environmental adversity. The existence of pathways and regulatory mechanisms common to the regulation of both physical and emotional states transcend classical categorical disease classifications, and point to the need to utilize dimensional, "symptom"-related approximations to their study. Possible future areas of study at the interface of "mind" (cognitive–emotional) and "body" (physical) functions are delineated in this context.

Keywords: Affect; Amygdala; Emotion; Endogenous opioids; Mu-opioid receptors; Neurotransmitter release; Nucleus accumbens; Pain; Positron emission tomography; Sex differences; Stress; Substantia innominata; Ventral pallidum

Contents

Abbreviations: ACTH, adrenocorticotropic hormone; BP, binding potential; COMT, catechol-*o*-methyl transferase; CRH, cortico-releasing hormone; GABA, gamma-aminobutyric acid; PANAS, Positive and Negative Affectivity Scale; PET, positron emission tomography.

* Corresponding author.
E-mail address: zubieta@umich.edu (J.-K. Zubieta).

0278-5846/$ - see front matter © 2005 Elsevier Inc. All rights reserved.
doi:10.1016/j.pnpbp.2005.08.011

1. Introduction

Living beings are open systems with definite boundaries, characterized by relatively stable form and structure, which tends to persist over time. Thermodynamically, they might be defined as localized regions where there is a continuous increase in order, and genetically as systems with increasing levels of complexity, capable of evolution by natural selection (Sagan and The Editors, 1995). All living beings share a permanent dynamic activity organized around multiple mechanisms designed to maintain a stable internal milieu (Cannon, 1939). However, life can be maintained only through a continuous exchange with the environment, by which living systems increase their order at the expense of an increase in the entropy of the surrounding environment. These encounters with the surroundings bring permanent threats to life or internal homeostasis, and common mechanisms have evolved to deal with these stressors (Cannon, 1915; Selye, 1936). Sensations such as temperature (Craig et al., 2000b), itch (Andrew and Craig, 2001), visceral distention, muscle ache, hunger, thirst, 'air hunger', sensual touch (Craig, 2003a), emotions (Damasio et al., 2000), and pain (Craig et al., 2000a; Craig, 2002, 2003a,b,c) can be seen as closely connected to the preservation of homeostasis, contributing to the global representation of the physiological condition of the body and well-being.

2. Pain as warning signal and homeostatic emotion

Pain is operationally defined by the International Association for the Study of Pain as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage" (Merskey and Bogduk, 1994). This definition emphasizes its Janus-like dual elements, simultaneously encoded as a discriminative sensation and as a global sign of danger to physical or psychological equilibrium. Stemming from the specificity theory (von Frey, 1894; Iggo and Ogawa, 1971; Kumazawa and Perl, 1977; Sugiura et al., 1986) and from the gate control theory (Melzack and Wall, 1965), the studies of pain as a sensation show that physical pain starts in the tissues, where specialized high-threshold sensory neurons respond to potentially damaging environmental stimuli such as excessive pressure, heat, cold, distension, noxious chemicals, or tissue damage (Caterina et al., 2000). From these nociceptors, action potentials are transmitted to neurons in the dorsal horn of the spinal cord through fast A-sigma fibers and through slower C fibers, the former being responsible for the first, sharp, acute and well localized pain, and the latter by the so-called "second pain", characteristically more diffuse, widespread, dull, with a persistent character associated with unpleasantness and emotional response (Julius and Basbaum, 2001; Aguggia, 2003). Further processing in the dorsal roots, trigeminal nuclei and spinal cord involves intricate circuits, regulation by opioid and NMDA receptors, substances P and K, specific protein kinases, and further modulation by substances such as serotonin, extracellular protons, arachidonic acid, bradykinin, nucleotides, calcitonin gene-related peptide and neurotrophins (Malmberg et al., 1997; Mantyh et al., 1997; Sah et al., 2003). From the dorsal horn cells, ascending spinohypothalamic, spinopontoamygdaloid and spinothalamic pathways project into multiple brain areas (Price, 2000). Ventroposterior thalamus and the primary and secondary somatosensory parietal areas SI and SII further seem to be connected with the integration of pain as a discriminated perception (Coghill et al., 1994). Finally, the midbrain periaqueductal gray is thought to integrate the impulses from higher centers and modulates descending impulses to increase or decrease pain threshold, closing the loop via the nucleus raphe magnus (Hosobuchi et al., 1977, 1979). This perspective and body of work lends to the notion that injury and the sensory transmission and perceptions arising from it are the primary processes of interest. It therefore tends to emphasize the sensory elements of the pain experience, with other factors, such as processing in more complex supraspinal circuits, taking a more or less important secondary role (a bottom-up approach to the pain experience).

A different line of research, this time stemming from the pattern theory (Goldscheider, 1894), has placed more attention on the global character of pain as a homeostatic emotion that dominates attention, acting as a potent motivational drive that induces an automatic avoidance response, an increase in arousal and negative valence, and clear autonomic and neurochemical responses (Woolf and Salter, 2000; Scholz and Woolf, 2002). Once it is encoded affectively and cognitively as an emotion, pain loses its specific discriminative character and eludes even any clear definitions (Schott, 2004). This characteristic unpleasantness associated with pain is unrelated to its sensory characteristics (Price, 2000) and can be clearly dissociated from it: in pain associated with labor, for example, affective ratings vary independently of sensory ratings, depending on whether women focus on the birth of the child or on the pain (Price et al., 1987). Acute and more sustained pain also demonstrates similar dissociations: even when maintained at similar intensity (sensory-related) levels, its negative affective qualities increase as a function of the time exposed to the painful stimulus. The latter then becomes more comparable to the experience of pain as described by humans suffering from persistent, clinical pain conditions (Stohler and Kowalski, 1999). A profusion of skillful imaging studies have shown that the dorsal anterior cingulate cortex is activated in response to unpleasantness but not the actual painful stimuli (Talbot et al., 1991), to illusion of pain in the thermal-grill illusion paradigm (Craig and Bushnell, 1994; Craig et al., 1996), and to hypnotic changes in unpleasantness, but not intensity (Rainville et al., 1997). In addition to the dorsal cingulate, the anterior insula has also been implicated in studies involving mental anticipation of pain (Ploghaus et al., 1999), attentional manipulations (Peyron et al., 1999), and empathic pain (Singer et al., 2004). Placebo analgesia has been recently related to decreased brain activity in the contralateral thalamus, contralateral insula and rostral anterior cingulate cortex (Wager et al., 2004). A recent model of pain as a homeostatic threat tries to integrate these findings implicating two different circuits in the processing of pain and other homeostatic signals (Craig, 2002, 2003a,b,c): one circuit involves the parabrachial nucleus, the ventromedial thalamic nucleus (Lenz et al., 1993a,b; Craig et

al., 1994; Lenz et al., 1998; Blomqvist et al., 2000), the sensorimotor area 3a, postero-medial and anterior insula, where an interoceptive map is generated and feelings and affective responses related to the sensation of self are encoded (Bush et al., 2000; Damasio, 2003b; Singer et al., 2004). In a parallel circuit, the medial dorsal thalamic nucleus integrates lamina I input with brainstem homeostatic activity from the parabrachial nucleus and periaqueductal gray, projecting to the anterior cingulate or limbic motor cortex (Hsu and Shyu, 1997; Kung and Shyu, 2002) and generating the motivating, autonomic and driving components associated with pain (Critchley et al., 2003). Emotions, pain and the sense of self are seen as closely interconnected and related to interoception and to the feeling of homeostatic balance (Collet et al., 1997; Damasio, 1998, 2003a,b; Damasio et al., 2000; Churchland, 2002; Critchley et al., 2004). Only primates seem to have the neuroanatomical capacity to feel pain in the same way that humans do (Craig, 2003a), and in humans these emotional experiences become even more complex in view of the cognitive and linguistic abilities of our species. This "top-down" approach to pain neurobiology is then more akin to that taken by various disciplines in the study of various forms of physical and emotional stressors, where the more elaborate processing occurring in telencephalic regions takes precedence over the actual source of the unpleasant sensory process. This perspective may be particularly appealing to understand the individual experience of pain as initial pathological processes become established and impair the individual in multiple elements of their function.

3. Emotion regulation

Like its counterpart pain, emotion also has two facets that seem to be irreducible from each other, historically represented in the sharp distinction between dimensional or categorical models (Calder et al., 2001). Categorical models, analogously to studies derived from the pain specificity theory, see each emotion as a class with distinct pathways and integration centers in the brain. Fear, disgust, anger, happiness, surprise, and sadness are described as universal emotions, and multiple categories try to account for the multiple existential contexts, objects, situations and dispositions to act (Fuster, 2004) which are characteristic of everyday human experience, and that form the so-called "folk psychology" (Russell, 2003). Emotional classes do not seem to have sharp boundaries, but to appear as fuzzy sets of multiple similar feelings, which have indistinct borders, blending with neighboring categories as emotions become more distant from the prototypical class element (Chaplin et al., 1988; Russell and Fehr, 1994). Moreover, languages and cultures differ widely in how they carve categorically the domain of emotion: sadness, for example, does not exist in the Tahitian and Chewong lexicons, and is not distinguished from anger in Luganda (Russell, 1991), in spite of being well-known as a basic emotion and reliably reported as distinct from other emotions on the basis of facial (Ekman, 1993), autonomic (Ekman et al., 1983; Collet et al., 1997; Thayer and Faith, 2001; Levenson, 2003; Christie and Friedman, 2004), self-report (McNair et al., 1971), linguistic (Russell, 1991), and anatomical studies. As a reaction to these shortcomings, and as an attempt to find more fundamental and basic components of the emotional experience, dimensional theories, like the "pattern theories" of pain, have emphasized the global, immediate, affectively condensed character of emotions. In dimensional models, emotions are seen as points in spaces defined by orthogonal axes of pleasure–displeasure and activation–deactivation (Russell, 1980, 2003; Russell and Carroll, 1999; Remington et al., 2000), by varimax-rotated factors of positive and negative affect (Watson and Tellegen, 1985; Watson et al., 1988, 1999), or by evaluative valence axes of positivity and negativity (Cacioppo and Berntson, 1994; Cacioppo and Gardner, 1999; Larsen et al., 2001). As such, they become closely connected with pain or pleasure (Sartre, 1948; Aristotle, 1952; Abbagnano, 1982; Calder et al., 2001), with the well-being and homeostatic status of the total organism (Craig, 2003b; Damasio, 2003a,b; Damasio et al., 2000), with non-specific stress responses (Szabo, 1998) and with global reactions of approach or withdrawal. In contrast to exteroceptive (touch) or teloreceptive (vision) modalities, emotions are like "feelings from the body", endowed with a characteristic affect that motivates behavior, and generates autonomic responses (Craig et al., 2000a; Rainville, 2002). Teleologically, they may be seen as evaluative tools evolved to show the significance of certain encounters of the organism with the environment and with the stability of its internal milieu, in a process where pain and pleasure are transformed into emotional distress or satisfaction as a result of appraisals of their significance, context, action and posture tendencies and interpersonal relations (Lazarus, 1991).

4. Interfaces between pain and emotion regulation through stress circuitry

Prolonged, stressful conditions have been repeatedly associated with specific emotional reactions and physiological responses that are different from those observed when the organism faces an acute danger, an insight anticipated by Selye (1936) when he differentiated "stress" from the "flight or fight reaction" described by Cannon (1915). The latter reflects more closely sudden threatening environmental events, known to trigger within seconds a massive release of catecholamines, hypothalamic CRH, prolactin, growth hormone and glucagon, which act mostly through rapid second messenger cascades within seconds to a few minutes of the event. In contrast, and more akin to the broader "stress" concept of Selye, there is a second slower wave happening within minutes that involves both release of glucocorticoids and decline of gonadal steroid secretions, whose actions are mainly genomic and not fully exerted until hours of the onset of the stressor (Sapolsky et al., 2000). Thus, stress seems to involve both an acute global response and specific response dependent on type, location and pattern of stressors (including environmental context, duration of

stress, social status, and nature of social hierarchies) (Lopez et al., 1999; Korte et al., 2005; Sapolsky, 2005). When systems involved in the maintenance of balance are elevated in a sustained manner, the resulting allostatic, disrupted state, results in an imbalance of the primary mediators and in widespread physiological and anatomical changes and damages resulting from mechanisms evolutionarily well adapted to deal with physical, acute stressful situations (Sapolsky, 1996; McEwen, 2004; Korte et al., 2005). Specifically, prolonged, unpredictable, uncontrollable and intermittent stressors have been associated with detachment and withdrawal of the organism from the environment. In many widely used animal models, including the forced swim and tail suspension tests, learned helplessness to inescapable shock, exposure to chronic mild uncontrollable stresses, and the social defeat and variable foraging paradigms, rodents and primates display behaviors which resemble sadness and depression. These include "anhedonia" (decreased interest in sucrose), rapid eye movement sleep alterations, reduced body weight, diminished sexual behavior, and persistently elevated corticotropin-releasing factor and corticosterone levels (Nestler et al., 2002), with secondary effects on neuronal plasticity and connectivity (Sapolsky et al., 1985). As an example of this differentiation between mechanisms engaged during acute and prolonged challenges, animals subjected to prolonged, intermittent foot shock had analgesia of significantly longer duration and appeared behaviorally depressed, showing a decrease in acoustic startle, orientation to touch, and ability to cling to wall (Lewis et al., 1980). In these studies, foot shocks of short duration, or even when more prolonged but applied to the rear paws, as opposed to forepaws, did not activate suppressive, stress-induced analgesic endogenous opioid neurotransmission, which was otherwise engaged during the more threatening or prolonged stimuli, presumably as a homeostatic response (Watkins and Mayer, 1982). Along the same lines, alterations in other neurotransmitter systems, manifested as changes in the concentrations of receptors such as the serotonergic 1A and 2A appear in sustained and unpredictable forms of stress, and in human depression and postmortem material from suicide victims, but not in acute versions of the same challenges (Lopez et al., 1999). Numerous other examples can be cited, differentiating the biological consequences of acute, akin to the original "flight or fight" response, versus those engaged during more substantial allostatic loads. In humans, sadness appears as an all-inclusive feeling that colors the whole psychic life, reminding more of a "mood" than an acute emotion (Jaspers, 1977), and presenting as more associated with internal representations than with any present, here-and-now stimulus. As the prototype of a fuzzy category encompassing grief, longing, guilt, depression and others (Shaver et al., 1987), sadness is generally experienced at the end of a chain of struggles to cope, when the absence of commitments and meaning slowly leads to inaction or withdrawal from involvement in the world, culminating in a state of passivity, internalization, and prolonged suffering (Freud, 1917; Klein, 1978; Ey et al., 1989).

5. Endogenous opioids and the regulation of physical and emotional stressors

Opiates have been connected to pain and emotion for millennia: a Sumerian papyrus of circa 1500 B.C. describes a remedy for children made of poppy-plant and, in the eight century, opium was widely known and used in Asia and Europe (Watkins and Mayer, 1982). Opioid abuse and dependence are associated with euphoria, high and intense pleasure, ecstatic experiences, excitation, mood changes, and intense reward properties, while withdrawal is associated with irritability and dysphoria; these symptoms are thought to be mediated mainly through μ-opioid receptors in gamma-aminobutyric acid (GABA) neurons and their connections with the mesolimbic–mesocortical dopaminergic system (O'Brien, 2001; De Vries and Shippenberg, 2002; Kreek et al., 2002; Gerrits et al., 2003; Greenwald et al., 2003). The exogenous opioid morphine (named after Morpheus, the Greek god of dreams) was synthesized in 1804 (Brownstein, 1993) and, in the past decades, an endogenous opioid system was discovered and described in detail (Pert and Snyder, 1973; Terenius, 1973; Hughes et al., 1975, 1977; Kosterlitz and Waterfield, 1975; Bradbury et al., 1976; Waterfield et al., 1976; Walker et al., 1977; Hosobuchi et al., 1979). The opioid system consists of several G-protein receptors with multiple subtypes (Lembo et al., 2002; Hong et al., 2004), named mu (μ, for morphine), kappa (κ, for ketocyclazocine) (Martin et al., 1976), delta (δ, for vas *d*eferens) (Lord et al., 1977), and ORL-1 (for opioid receptor-like) (Bunzow et al., 1994; Chen et al., 1994; Fukuda et al., 1994; Mollereau et al., 1994; Wang et al., 1994; Wick et al., 1994; Lachowicz et al., 1995). The endogenous ligands for these receptors are peptides belonging to four families, the endorphins, the enkephalins (Hughes et al., 1975; Bradbury et al., 1976), the dynorphins (Goldstein et al., 1981) and the orphanin FQ or nociceptin (N/OFQ) family (Meunier et al., 1995; Reinscheid et al., 1995), respectively derived from four precursors, each of them encoded by a gene: prepropiomelanocortin (Nakanishi et al., 1979), preproenkephalin (Noda et al., 1982), preprodynorphin (Kakidani et al., 1982), and proorphanin (Nothacker et al., 1996; Pan et al., 1996). Each of these different subsystems has different distributions and functions in the brain (Gutstein and Akil, 2001; Bodnar and Hadjimarkou, 2002), being involved in the regulation of pain, reinforcement and reward, release of neurotransmitters, autonomic and neuroendocrine modulation. Several of the naturally occurring peptides preferentially bind to the μ-opioid receptor, but a specific and more selective endogenous ligand was found only in 1997 and was called endomorphin (Zadina et al., 1997). In animals, activation of μ-opioid receptors hyperpolarizes neurons in the lateral amygdala, periaqueductal gray and ventral pallidum (Sugita and North, 1993) by direct mechanisms, such as inhibition of cAMP and calcium currents, or by indirect mechanisms, such as modulation of GABA or glutamatergic transmission.

Multiple animal and human studies have confirmed the role played by the endogenous opioid system in the modulation of pain and stress. At the neuroendocrine level, the stress hormone

ACTH and the opioid peptide β-endorphin have a common precursor, respond to the same regulatory mechanisms, and are concomitantly secreted by the adenohypophysis in response to acute stress or pain, such as breaking the tibia and fibula (Guillemin et al., 1977). In the peripheral nervous system, pain induces the production of opioid peptides by the dorsal root ganglia neurons and by immune cells, which act by inhibiting calcium and sodium ion channels, blocking firing of nociceptors (Stein et al., 2003). Additionally, stimuli, such as deep brain stimulation, pain, and morphine, a selective μ-opioid receptor agonist, are thought to work through a common centrifugal system, by which signals originating in the central nervous system descend through the dorsolateral funiculus of the spinal cord and eventually inhibit nociceptive neurons located either in the dorsal horn or in the trigeminal nucleus caudalis (Watkins and Mayer, 1982). In the supraspinal central nervous system, opioids have been proposed to act on the affective part of the so-called "pain matrix". This assertion was based on observations that patients receiving exogenous opioids frequently report that the pain is still present, but that they feel more comfortable, and that continuous, dull pain is relieved more efficiently than sharp, intermittent pain (Gutstein and Akil, 2001). This effect mimicked early studies showing that resection of the anterior cingulate cortex reduced the distress associated with pain, but not the perception of pain itself (Foltz and White, 1962). This relatively restricted perspective has been challenged by studies demonstrating that both sensory and affective qualities of pain are suppressed by the activation of μ-opioid receptor mediated neurotransmission in humans, albeit in distinct anatomical localizations, many of them cortical (Zubieta et al., 2001). In animals, electrical stimulation of the rat central grey and midbrain structures was found to cause complete anesthesia to stimuli such as paw pressure, tail shocks, burning, ice water or abdominal surgery (Reynolds, 1969; Mayer et al., 1971); however, similar effects have also been obtained at higher levels of the telencephalon, such as the thalamus (Albe-Fessard et al., 1985) and central nucleus of the amygdala (Manning, 1998), suggesting that analgesia takes place at multiple levels of the neuraxis through similar mechanisms.

Aside from their involvement in pain regulation, opioids have been involved in the neurochemistry of social attachment, alleviating separation distress in dogs, guinea pigs, rats and primates (Panksepp, 2003). Global reactions such as stress-induced increases in pain-thresholds, catalepsy and changes in locomotor activity and body temperature resemble those produced by some opiates, are antagonized by naloxone, and are capable of producing cross-tolerance to μ-opioid receptor agonists (Yamada and Nabeshima, 1995). Intriguingly, only certain painful stimuli lead to μ-opioid mediated analgesia: hind paw shock-induced analgesia is *not* blocked by naloxone and does not resemble or is cross-tolerant with morphine-produced analgesia, whereas front paw shock-induced analgesia is (Watkins and Mayer, 1982), suggesting differences in the manner that pain is modulated depending on the type of pain in question, and perhaps related to its perceived threat to the organism. Similarly, animals subjected to prolonged, intermittent, foot shock show longer lasting analgesia which is blocked by naloxone, whereas animals subjected to brief, continuous foot shock display analgesia that is *not* blocked by naloxone (Madden et al., 1977; Lewis et al., 1980). As described above, only the former appeared behaviorally depressed and had naloxone-reversible analgesia (Lewis et al., 1980). These data then suggest that the activation of the endogenous opioid system is associated with the regulation of emotions and connected with detachment as a reaction to prolonged, repeated and intermittent (unpredictable or more troublesome), as opposed to brief and regular (predictable), stresses. All these data contributed to the intriguing hypothesis that the opioids may act by blunting the distressing, affective component of pain, modulating stress by attenuating or terminating stress responses that, if carried for a prolonged time, could be detrimental to the organism (Drolet et al., 2001). One of the caveats of pharmacological studies, however, is that the antagonists typically utilized to block opioid effects, naloxone and naltrexone, are not selective for the various opioid receptor types, particularly in the high doses ranges, bringing into question the participation of the various receptors for opioid peptides in these processes. The majority of the experimental evidence available, however, has specifically implicated the activation of μ-opioid receptors in analgesic effects (Watkins and Mayer, 1982; Akil et al., 1984; Rubinstein et al., 1996; Sora et al., 1997; Zubieta et al., 2001), reproductive and stress-related neuroendocrine functions (Smith et al., 1998; Drolet et al., 2001), and the adaptation and response to novel and emotionally salient stimuli in animal models (Kalin et al., 1988; Nelson and Panksepp, 1998; Filliol et al., 2000b; Moles et al., 2004) and more recently in humans (Zubieta et al., 2003b). For this particular system, the typical effects have been in the direction of suppression, whereby μ-opioid receptor activation reduced pain and affective ratings in humans (e.g., Zubieta et al., 2001, 2002, and references therein). Nevertheless, κ-opioid mediated neurotransmission has also been implicated in pain regulation in women, but not in men (Gear et al., 1996; Mogil et al., 2003), and in the regulation of ACTH and cortisol production (Williams et al., 2003). Delta-opioid mechanisms have also been recently associated with antidepressant-like effects in animal models (Jutkiewicz et al., 2003; Torregrossa et al., 2004), as well as with pronociceptive activity in neuropathic pain in the rodent model (Wang et al., 2001).

6. Endogenous opioid regulation of pain and emotion in humans as measured with positron emission tomography

The close relation between persistent pain states, prolonged stress, and emotional states led us to study their central regulation by the endogenous opioid system and μ-opioid receptors in humans, using positron emission tomography (PET) and experimental challenges in vivo. In these neuroimaging studies, activation of the endogenous opioid system is observed as a reduction in μ-opioid receptor availability (in vivo receptor binding) with the selective μ-opioid agonist radiotracer [^{11}C]carfentanil. These reductions are thought to reflect one or multiple processes associated with the release of

the endogenous neurotransmitter: competition between the radiolabeled tracer and the endogenous ligand for the receptor sites, receptor internalization and recycling, or both (Laruelle, 2000). In the case of agonists such as carfentanil, selective labeling of high affinity sites has been suggested to induce a more pronounced sensitivity to changes in endogenous neurotransmission, which may further include a conversion of high affinity sites to low affinity by the excess endogenous neurotransmitter (Sastre and Garcia-Sevilla, 1994; Kenakin, 1997; Narendran et al., 2004). This mechanism has also been invoked to explain the findings of more pronounced changes in dopamine D_2 binding measures after amphetamine challenges when evaluated with a agonist radiotracer, compared with a radiolabeled antagonist (Hwang et al., 2005).

In the first study examining the activation of the endogenous opioid system and μ-opioid receptors in humans, we utilized a sustained pain challenge, muscular pain in the masseter muscle, that was maintained at moderate, constant levels, through the infusion of small amounts of hypertonic saline (Zubieta et al., 2001). This stimulus was associated with a significant activation of the μ-opioid receptor system in multiple regions. These included the anterior cingulate and lateral prefrontal cortex, anterior insular cortex, anterior and lateral thalamus, ventral basal ganglia (nucleus accumbens and ventral pallidum), amygdala, hypothalamus and periaqueductal gray. The activation of this neurotransmitter system was furthermore variable between individuals in spite of the pain being maintained at constant levels of intensity for the duration of the study. These individual variations were correlated with the capacity to suppress both sensory (in the lateral thalamus, amygdala, and ventral basal ganglia) and affective ratings of the pain (in the dorsal anterior cingulate cortex, anterior–medial thalamus, and nucleus accumbens/ventral pallidum), as measured by the word descriptors of the McGill Pain Questionnaire (Melzack and Katz, 2000). These data demonstrated that the influence of the endogenous opioid system on the experience of pain was taking place at multiple "higher" level telencephalic regions, in addition to the more traditional theory that descending inhibitory inputs impacted on opioid receptor-regulated brainstem pain control regions (e.g., periaqueductal gray, ventromedial medulla). Some of the regions where μ-opioid modulation was shown had been traditionally involved in the "pain matrix" of pain sensory and affective representation (e.g., dorsal anterior cingulate, insular cortex, thalamus, and periaqueductal gray). Others, such as the amygdala, nucleus accumbens and ventral pallidum, had been more typically implicated in the assessment of intensity and valence of emotions (amygdala; Morris et al., 1996, 1998; Anderson et al., 2003), reward and reinforcement (nucleus accumbens; Koob and Moal, 1997; Robinson and Berridge, 2000), and in the regulation of sensory-motor integration (ventral pallidum; Mogenson and Yang, 1991). Subsequent work utilizing the capsaicin model of cutaneous hyperalgesia in a smaller sample (Bencherif et al., 2002) also demonstrated the activation of the μ-opioid receptor system at the level of the thalamus.

Of note, the vast majority of the subjects studied in these samples was male. In view of the possible influences of sex on brain functional responses to phasic and repetitive pain challenges (Paulson et al., 1998; Fillingim and Ness, 2000) and in the concentration of μ-opioid receptors (Zubieta et al., 1999), subsequent studies were designed to determine whether sex differences to sustained pain could be attributed to differences in the capacity to activate the endogenous opioid system and μ-opioid receptors (Zubieta et al., 2002). In these studies, women were studied in the early follicular phase of the menstrual cycle, when estradiol and progesterone were low, using the sustained muscle pain challenge described above. Sex differences were obtained in the thalamus, ventral basal ganglia (nucleus accumbens and ventral pallidum) and amygdala, whereby the magnitude of endogenous opioid system and μ-opioid receptor activation was more prominent in men than in women. These regional effects were associated with a more effective suppression of sensory (in the nucleus accumbens and amygdala), affective qualities of pain (in the anterior thalamus), and of the internal affective state (negative affect, ventral pallidum) in males than in females. Moreover, a significant reduction of μ-opioid system activation from baseline levels (a *deactivation* of neurotransmission, observed as increases in the in vivo binding measure) was detected in the nucleus accumbens in women, an effect associated with hyperalgesia. This was an unexpected result since responses of the endogenous opioid system were taking place in the direction of reduction of function in women, instead of simply showing lesser degrees of activation than males, or even no evidence of activation in response to the pain challenge. Interestingly, substantial opioid tone in this region had been previously described (Gear and Levine, 1995), with the local injection of naloxone being associated with hyperalgesic responses in animal models. Subsequent studies in a second sample of women studied again under conditions of low estradiol and low progesterone (early follicular phase of the menstrual cycle) confirmed the deactivation of μ-opioid receptor-mediated neurotransmission in the anterior–medial thalamus, nucleus accumbens and amygdala. Furthermore, that these reductions were reversed after increasing plasma levels of estradiol for 7–9 days by the administration of exogenous estradiol, whereby the response of the endogenous opioid system and μ-opioid receptors became comparable to that of males. Increases in the concentration of μ-opioid receptors as measured with PET were also obtained in the same regions (Zubieta et al., 2003a). The latter findings, whereby the capacity of activating endogenous opioid transmission impacting on μ-opioid receptors as well as the baseline concentration of these receptors was enhanced by estradiol, appears consistent with the published data in animal models. In the ovariectomized animal model, estrogen administration has been shown to increase μ-opioid receptor protein concentrations, immunoreactivity and mRNA (Hammer and Bridges, 1987; Dondi et al., 1992; Quinones-Jenab et al., 1997), the concentration of endogenous opioid peptides and their mRNA (Broad et al., 1993; Hammer et al., 1993) and the release of endogenous opioid peptides in cell cultures (Eckersell et al., 1998). Further study of the influence of gonadal steroids, and possibly their interaction with various forms of stress (whether physical, emotional, or both) in women appears

then justified, as various idiopathic pain syndromes (e.g., fibromyalgia syndrome, temporomandibular pain) are more frequently diagnosed in women, but only after gonadal maturation (Unruh, 1996). They also appear influenced by circulating gonadal steroids, with higher ratings of pain during times of low or rapidly changing levels of estradiol (LeResche et al., 2003).

We have also examined the response of the endogenous opioid system and μ-opioid receptors to a purely psychological challenge, the induction of a sustained (30 min) sadness state elicited by the cued recall of an autobiographical experience associated with that emotion (Zubieta et al., 2003b). In view of the sex differences in the μ-opioid system function described above, as well as sex differences in responses to emotional challenges (George et al., 1996), the sustained sadness induction studies were performed only in women. As was observed in the pain-stress challenges in women, the main effect of sustained sadness induction was one of reduction in μ-opioid receptor mediated endogenous opioid neurotransmission. These reductions reached statistically significant thresholds in the rostral anterior cingulate, ventral basal ganglia, amygdala and inferior temporal cortex. They were further correlated with the increases in negative affect during the challenge (anterior cingulate and ventral basal ganglia) and reductions in positive affect ratings (ventral basal ganglia and amygdala), as measured with the Positive and Negative Affectivity Scale (PANAS) (Watson et al., 1988). These studies, together with data acquired in animal models, demonstrate that the endogenous opioid system and μ-opioid receptors in telencephalic regions mediate the regulation of emotional responses in the face of both physical and psychological stimuli once they transition from an acute to a sustained state. While emotional regulatory processes are typically difficult to study in animal models due to their complexity, transgenic animal models devoid of μ-opioid receptors or the endogenous opioid peptide β-endorphin point to reductions in the capacity to suppress responses to pain signals (Matthes et al., 1996; Sora et al., 1997), stress-induced analgesia (Rubinstein et al., 1996), and more recently, exaggerated anxiety-like responses in the elevated maze model (Filliol et al., 2000a) and deficits in maternal-pup attachment behavior (Moles et al., 2004).

7. Similarities and differences in the response of the human μ-opioid system to physical and emotional challenges

To illustrate and further examine the responses of the endogenous opioid system and μ-opioid receptors to stressful physical (sustained, moderate levels of muscle pain, arguably a physical and psychological stressor; Stohler and Kowalski, 1999) and emotional stimuli (sustained sadness induction), we reanalyzed data from female volunteers involved in our previous studies with these two models. In this manner, we compared the commonalities and differences of the response of the μ-opioid system to these two different stressors (Ribeiro et al., 2004). In these analyses, we selected a matched sample of 22 healthy women (20–30 years of age), who were not taking psychotropic medications or hormone treatments, did not exercise in excess of 1 h three times per week, had regular menstrual cycles, and were scanned during the follicular phase of their menstrual cycles (2 to 9 days after the onset of menses), ascertained by plasma levels of estradiol and progesterone immediately before scanning. All studies were conducted in the morning, between 8 and 11 a.m. Written informed consent was obtained in all cases. All of the procedures used were approved by the University of Michigan Investigational Review Board for Human Subject Use and the Radiation Safety Committee.

All subjects underwent PET imaging with [^{11}C]carfentanil, a μ-opioid receptor specific radiotracer, 10–15 mCi i.v., with a bolus plus continuous infusion protocol. Quantification of μ-opioid receptor binding potential ($BP = B_{max}/K_d$) was performed with Logan plots and the occipital cortex as the input function (non-specific binding region). All subjects also received a T1 SPGR MRI scan for coregistration with PET and non-linear warping to the International Consortium for Brain Mapping (ICBM) stereotactic coordinate system (Meyer et al., 1997). During PET imaging, subjects underwent either a sustained sadness induction protocol ($n = 14$ subjects) or a sustained moderate pain protocol in the right masseter muscle ($n = 8$ subjects), in a single blind fashion. The control conditions were the recall of a neutral (non-emotional) event and the infusion of non-painful isotonic saline, respectively. Isotonic saline control (non-painful) and hypertonic saline painful challenges were introduced in the left and right sides, respectively. The order of active and control conditions were randomized and counterbalanced between subjects. The Positive and Negative Affectivity Scale (PANAS) was administered immediately following each condition, retrospectively rating the affective state of the volunteers during the condition (Watson et al., 1988).

Images were analyzed using SPM'99 software, as previously described (Zubieta et al., 2001, 2002). The effects of sustained sadness and sustained pain were evaluated on a voxel-by-voxel basis using paired (within subjects, between conditions), two-tailed t-tests [($BP_{PAIN} - BP_{CONTROL}$) or ($BP_{SADNESS} - BP_{NEUTRAL}$)]. The differential effects of each set of conditions were tested using unpaired (between subjects and conditions) two-tailed t-tests [($BP_{PAIN} - BP_{CONTROL}$) − ($BP_{SADNESS} - BP_{NEUTRAL}$)]. Regions were considered significant if $p < 0.0001$, since the regional effects had already been described in larger samples — in the face of a priori hypothesis.

The sustained painful and sustained sadness states were associated with similar ratings and increases in negative affective scores (as measured with the PANAS scale) (Table 1).

Table 1
Effects of sustained pain and sustained sadness states on the internal affective state of the volunteers as measured with the positive and negative affect scale (PANAS)

Condition	PANAS negative affect	PANAS positive affect
Neutral affect	1.6±2.4	14.6±7.3
Non-painful control	1.6±2.2	9.4±4.7
Sad affect	7.8±4.5	10.9±6.4
Pain state	8.5±6.9	11.6±6.4

Table 2A
Sustained pain-induced deactivation of μ-opioid neurotransmission in women ($n=8$)

Regions	Coordinates (x, y, z) (mm)	Cluster size (voxels)	% ΔBP (control – pain)	Z score
Thalamus (R)	−11, −13, 10	311	−11.3	3.95
Thalamus (L)	5, −5, 14	990	−16.0	5.09
Ventral basal ganglia (R)	−9, 13, −2	752	−13.7	5.43
Ventral basal ganglia (L)	21, 6, −11	97	−11.7	3.56
Amygdala (R)	−27, −1, −21	356	−15.8	4.11

Data represent the localization (ICBM coordinates) and magnitude of differences in μ-opioid binding potential (BP) from non-painful control to sustained pain states, a measure of endogenous opioid release and μ-opioid receptor availability. Significant reductions in endogenous opioid neurotransmission were observed. Sizes of significant clusters are expressed in mm^3. Z scores were deemed significant at $p<0.0001$.

However, the PANAS positive affect scores were significantly lower in the control condition for the pain challenge (unpaired, two-tailed t-test, $p<0.05$). These differences between the control conditions may be due to the higher level of invasiveness of the pain control state, or the expectation that pain may take place (anticipation of pain), since it involved the positioning of a needle in the masseter muscle and the infusion of non-painful isotonic saline for the duration of the pain control condition.

The induction of either a sustained painful state or a sustained sadness state in this sample of women was associated with a regional deactivation of μ-opioid receptor mediated neurotransmission, evidenced by increases in the in vivo BP measure, as observed in previous work (Zubieta et al., 2002, 2003b). Tables 2A and 2B show the regions where significant effects were observed in this sample.

As noted in Tables 2A and 2B, sustained pain and sadness challenges elicited similar effects on endogenous opioid neurotransmission and μ-opioid receptors in the ventral basal ganglia spanning both the nucleus accumbens and ventral pallidum, and in the amygdala. However, the effects of the emotional challenge were observed bilaterally, while only unilaterally (ipsilateral to pain) in the case of the pain stimulus (Fig. 1). Subtraction analyses between conditions $[(BP_{PAIN}-BP_{CONTROL})-(BP_{SADNESS}-BP_{NEUTRAL})]$ and $[((BP_{SADNESS}-BP_{NEUTRAL})-(BP_{PAIN}-BP_{CONTROL})]$ still demonstrated some significant differences in these overlapping regions. As would be expected in view of the bilateral effects of the sadness induction, the left amygdala μ-opioid neurotransmission was significantly more deactivated in response to the emotional challenge (x, y, z coordinates in mm, 17, 1, −23, $z=3.69$, $p<0.0001$). The pain challenge, on the other hand, induced a significantly greater deactivation in the right ventral basal ganglia (ipsilateral to the pain) (x, y, z coordinates in mm, −7, 10, −7, $z=6.86$. $p<0.0001$).

These findings point to both overlapping and differential effects of two distinct challenges, one involving a sustained negative emotional state (sadness induction), and another a sustained painful state (moderate levels of pain). Both experimental challenges were associated with similar increases in negative affect scores and changes in endogenous opioid neurotransmission. In the case of women studied during the follicular phase of the menstrual cycle these took place in the direction of deactivation, a permissive effect towards the experience of these challenges (Zubieta et al., 2002, 2003b). Furthermore, some overlap was observed in the regions involved (ventral basal ganglia and amygdala). These results then add to a growing body of literature suggesting that pain, emotion and other distress signs (stressors) share common psychological, neuroanatomical and neurochemical pathways. Areas of specialization also seem to emerge, whereby in this sample thalamic μ-opioid neurotransmission was exclusively modulated by the sustained pain challenge. Conversely, μ-opioid neurotransmission in the rostral anterior cingulate and the inferior temporal cortex were only modulated during the sadness state. In this regard, the involvement of μ-opioid receptors at the level of medial and anterior thalamus in the regulation of pain signals has been well documented in animal models (Albe-Fessard et al., 1985; Bushnell and Duncan, 1989; Harte et al., 2000) and humans (Casey et al., 2000; Zubieta et al., 2001), as ascending medial spinothalamic pathways synapse in this area prior to transmitting noxious information to higher order, integrative neocortical regions (Price, 2000). Conversely, the rostral anterior cingulate is typically activated by emotional stimuli (Mayberg et al., 1999), while more dorsal areas of the cingulate are implicated in the representation of the affective quality of pain (Rainville et al., 1997; Tolle et al., 1999), albeit both regions are modulated by μ-opioid receptor mediated neurotransmission (Schlaepfer et al., 1998; Zubieta et al., 2001; Petrovic et al., 2002). Similarly, μ-opioid receptors in the subamygdalar inferior temporal cortex have been recently implicated in the regulation of synaptic and emotional responses to the presentation of negative emotional stimuli (Liberzon et al., 2000).

The ventral basal ganglia and amygdala, areas where neurotransmitter responses overlapped between these two challenges, appear to form part of a less specialized, "motiva-

Table 2B
Sustained sadness-induced deactivation of μ-opioid neurotransmission in women ($n=14$)

Regions	Coordinates (x, y, z) (mm)	Cluster size (voxels)	% ΔBP (control – sad)	Z score
Anterior cingulate	−3, 31, 2	874	−23.1	5.77
Temporal cortex (L)	24, 7, −38	115	−33.2	4.95
Ventral basal ganglia (R)	−15, 2, 3	133	−18.8	3.66
Ventral basal ganglia (L)	14, 1, −2	39	−11.3	3.66
Amygdala (R)	−20, 0, −21	89	−12.3	3.44
Amygdala (L)	16, −4, −21	146	−19.3	4.09

Data represent the localization (ICBM coordinates) and magnitude of differences in μ-opioid binding potential (BP) from neutral to sustained sadness states, a measure of endogenous opioid release and μ-opioid receptor availability. Significant reductions in endogenous opioid neurotransmission were observed. Sizes of significant clusters are expressed in mm^3. Z scores were deemed significant at $p<0.0001$.

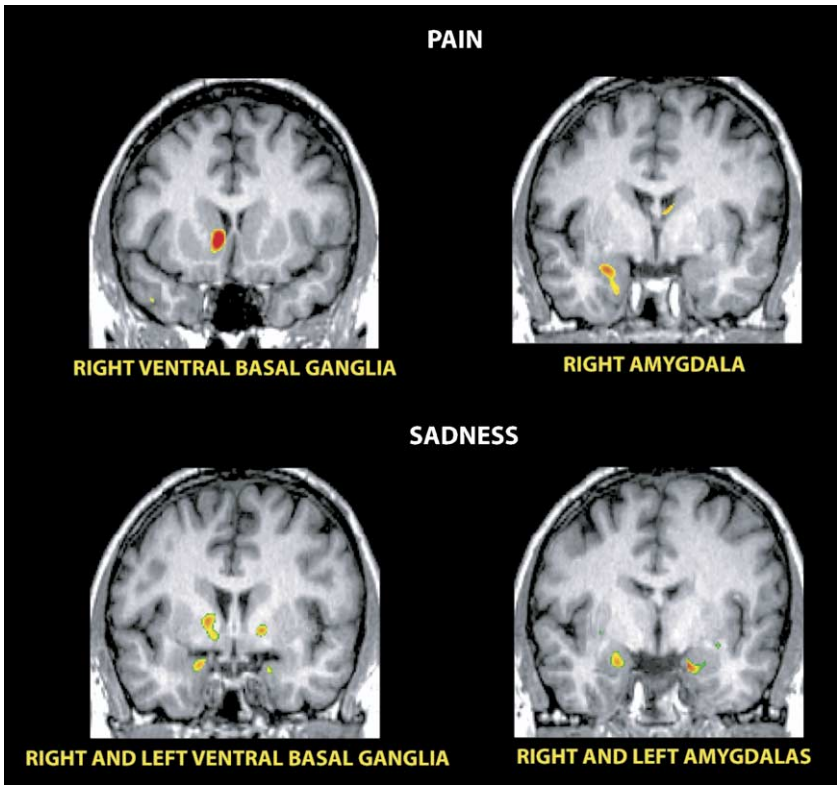

Fig. 1. Reductions in the state of activation of the μ-opioid system during intensity-controlled sustained muscle pain and sustained sadness in women. Brain areas where partially overlapping, significant changes in regional in vivo μ-opioid receptor availability from saline control to sustained pain ($n=8$) and from neutral to sustained sadness states ($n=14$) were obtained in women: ventral basal ganglia (nucleus accumbens and ventral pallidum) and amygdala. The left side of the image corresponds to the right side of the volunteers (radiological convention).

tional-integrative", stress–response circuit (Mogenson and Yang, 1991; Kalivas et al., 1999). Mu-opioid receptor mediated endogenous opioid inputs play an important regulatory role in both locations (Chen et al., 1993; Quirarte et al., 1998; Steiner and Gerfen, 1998; Napier and Mitrovic, 1999). At the level of the ventral basal ganglia, the nucleus accumbens and the ventral pallidum/substantia innominata are connected through the dopamine-enkephalinergic striatopallidal pathway. In this pathway, dopamine binding to D_2 receptors activate downstream enkephalinergic neurons (Chen et al., 1993; Steiner and Gerfen, 1998). While the dopaminergic system is better known for its involvement in reward and reinforcement (Koob and Moal, 1997; Robinson and Berridge, 2000), accumulating evidence in healthy humans using a social stress challenge (Pruessner et al., 2004), in patients diagnosed with chronic pain syndromes (Jaaskelainen et al., 2001; Hagelberg et al., 2003), and in animal models (Horvitz, 2000) demonstrates its additional involvement in responses to aversive stimuli, possibly explaining the activation of endogenous opioid neurotransmission and μ-opioid receptors in this pathway. The ventral pallidum, in turn, has been shown to receive inputs from multiple sources, both cortical (prefrontal cortex) and subcortical (amygdala and ventral tegmental area), and appears to represent an integrative "relay" region where multiple sensory modalities are processed and are further regulated by μ-opioid receptors (Mogenson and Yang, 1991; Chrobak and Napier, 1993; Johnson and Napier, 1997; Napier and Mitrovic, 1999). The amygdala, originally thought to be primarily implicated in the assessment and assignment of emotional valence (Morris et al., 1996) and in the modulation of emotional memory (LeDoux, 1993; Cahill et al., 1995), also appears to have a broader role related to the assessment of the intensity of sensory inputs, whether negative or positive (Anderson et al., 2003), and is also potently modulated by μ-opioid receptors (Quirarte et al., 1998; Schlaepfer et al., 1998; Manning et al., 2001).

8. Overview and possible research directions

The activation of endogenous opioid neurotransmission and μ-opioid receptors in response to sustained experimental pain (Bencherif et al., 2002; Zubieta et al., 2001, 2002, 2003c) and its psychophysical correlates in humans confirm the regulatory role played by this system in the attenuation or termination of the pain response to blunt a prolonged, detrimental reaction with no protective value to the organism (Drolet et al., 2001). However, these effects have only been clearly demonstrated in males and in a relatively small proportion of females (Zubieta et al., 2001, 2002). The observation that most women responded to the same sustained painful stimulus and to a sustained sadness states with *deactivation* of this neurotransmitter system, an effect associated with increased ratings of negative affect, hyperalgesia and more pronounced pain unpleasantness (Zubieta et al., 2002, 2003b), suggests a bidirectional role of this system in the generation or mainte-

nance of these states. In this regard, and as noted above, the existence of an endogenous opioid tone modulating both painful and non-painful stressful challenges has been suggested in animal studies: the administration of naloxone in the nucleus accumbens of rats has been shown to induces hyperalgesia (Gear and Levine, 1995); naloxone-induced conditioned place aversion in rats, a centrally mediated effect possibly localized in the amygdala (Yamamoto et al., 1994; Thielen and Shekhar, 2002), is absent in μ-opioid receptor knock-out mice (Skoubis et al., 2001). In addition, increases in the basal metabolic activity and c-Fos expression of the amygdala and brainstem nuclei, dopamine release in the nucleus accumbens and acetylcholine release in septo-hippocampal neurons have been shown after naloxone administration (Spanagel et al., 1992; Kraus et al., 1996; Mizuno and Kimura, 1996; Gestreau and Besson, 2000). Grounded in this baseline tonic activity, the ability to activate or deactivate the μ-opioid system, as suggested in our results, implies a broader regulatory and homeostatic role of this system, whereby increases or decreases of opioid activity serve different adaptive roles depending on specific circumstances.

Such a broad regulatory role is consistent with the marked behavioral variability observed in pain, stress and emotional responses. In order to work efficiently to sign homeostasis disruption, the nociceptive and emotional systems must be activated at a threshold sufficiently high to avoid impairment of normal functioning, but low enough to signal danger before it becomes effectively harmful (Scholz and Woolf, 2002). Timely activation and termination of the stress responses are essential for survival, since the acute responses to stress may be damaging to the organism if carried indefinitely (Sapolsky, 2003). The unpleasantness of stimuli varies according to subjectively perceived threat and temporal relations: for example, there is a significant and independent increase in the negative affect related to pain as it becomes more widespread and as it changes from tonic to chronic (Stohler and Kowalski, 1999), and stimulation of deep tissues, such as ischemic exercise or cold pressure pain, leads to more unpleasantness than electrical shocks or noxious contact heat (Rainville et al., 1992). Conditions of stress or adaptation to an extreme environmental demand may lead to decreased pain sensitivity or even analgesia (Basbaum and Jessell, 2000), and in other situations hypersensitivity may have a protective role, decreasing functional use during recovery from an injury (Iadarola and Caudle, 1997; Woolf and Salter, 2000). Pain must then be seen as a dynamic experience, by which peripheral stimuli originating from the nociceptor system are permanently modulated and reevaluated within a broader context of the organism and its interaction with the environment, which includes expectations, views of the future, and global value of the pain in comparison to other stimuli, leading to a constant resetting of the pain threshold. The same flexibility is necessary in the emotional responses. Failing to reach a goal, lack of success in major life enterprises, submission and restrain in social interactions (Waal, 1989; Price et al., 2004), humiliation and entrapment (Brown et al., 1995; Gilbert and Allan, 1998; Kendler et al., 2003), or facing death (Freud, 1917; Sartre, 1956; May et al., 1958; Heidegger, 1996; Pyszczynski et al., 1999; Goldenberg et al., 2001; Solomon et al., 2003) are potent elicitors of negative affect, which may serve the double function of decreasing current investment and preventing premature pursuit of alternatives (Nesse, 2000). Low mood may serve as a yielding sign in hierarchy conflicts, as a communication designed to manipulate others into providing resources signals the pursuit of unreachable goals, motivating consideration of alternative strategies, shifting cognition to more systematic and perhaps more realistic patterns, and leading to regulation of investment strategies as a function of changes in anticipated levels of payoffs (Nesse, 1990, 1991, 2001). Moreover, interoceptive awareness involves increased activity in insula, somatomotor and cingulate cortices (Critchley et al., 2004) and is associated with increased emotional expression (Ferguson and Katkin, 1996) and increased ability to experience emotional stimuli (Wiens et al., 2000). This ability has been used in art and theatre as the path for actors to draw on their "affective memory" to be able to respond genuinely to events that must be imagined on the stage, and to repeat performances (Strasberg and Chaillet, 1995), and may play a role in self-induced emotional states. In everyday social interactions, it may be in the core of social emotions involving sympathy, social cognition (Adolphs, 2003) and adequate selection and performance of social roles (the word "person" comes from the Greek "persona", meaning "mask") (Ferrater Mora, 1990). The Socratic dictum "know thyself" necessarily involves being in tune not only with one's thoughts and outside reality but also with the subtle or more severe emotional reactions, which are primary evaluative tools of meaning and value.

The extensively documented existence of defective states seems to point occasions in which the plastic nature of the pain may lead to permanent imbalance (Iadarola and Caudle, 1997; Anand, 2000; Ruda et al., 2000; Woolf and Salter, 2000; Ballantyne and Mao, 2003; Stein et al., 2003). Seemingly normal reactions to psychosocial stresses may trigger depressive episodes in susceptible individuals, which eventually become autonomous (Kendler et al., 2003; McEwen, 2003a,b). Chronic pain may be caused by auto- or heterosensitization of the nociceptor terminals, windup of action potential discharges in the dorsal horn, modulation of the peripheral terminals and synaptic transmission, or modification of primary sensory neurons and of pain transmission neurons (Woolf and Salter, 2000). Consistently with our results, showing more deactivation of stress-modulatory μ-opioid inputs in females, women are overrepresented in a number of clinical pain conditions, report more recent pain complaints and pain in a greater number of regions compared to men, show greater pain sensitivity than men in experimentally induced pain (Fillingim and Ness, 2000), and are clearly more prone to experience major depression (Kornstein et al., 2000; Angst et al., 2002). Interestingly, a common genetic polymorphism reducing the function of the enzyme catechol-*o*-methyl transferase (COMT) has been shown to be associated with a poorer activation of μ-opioid neurotransmission in response to sustained pain (Zubieta et al., 2003c) and with higher levels of trait anxiety in women, the latter being a risk factor for the development of depression (Enoch et al., 2003). The function of this enzyme is

reduced by estradiol (Xie et al., 1999) and may in fact represent a point of interaction between stress–response regulatory mechanisms and gonadal maturation. While it is known that sex steroids affect peripheral and central pain pathways in a cyclical fashion, with the balance shifting toward enhanced pain responses during the late luteal phase and toward decreased response during the follicular phase (Fillingim and Ness, 2000; LeResche et al., 2003), it remains to be studied if these defect states may be associated with an adaptive role in dealing with life events and stress. In this regard, there is evidence from animal models and humans that gonadal steroids, and in particular estrogen, modulates both μ-opioid receptor density and the concentration and release of endogenous opioid peptides activating these receptors (Dondi et al., 1992; Broad et al., 1993; Hammer et al., 1993; Eckersell et al., 1998; Zubieta et al., 1999, 2003a).

These findings generate interesting directions for future studies. The common circuits, neuroanatomical areas and neurotransmitter system involved in sadness, pain, and stress may be related not simply to a shared circuit but to underlying dimensional factors that transcend the traditional categorical separation of physical and emotional functions, responses and disease processes. In this regard, an important area of study involves the role played by the opioid system in the interactions between cognition, emotion and physical experiences, the so-called "top-down" processes. For example, in animal studies, analgesia can be classically conditioned; classically conditioned analgesia is mediated by the opioid system and blocked by naloxone: animals can learn to activate their endogenous opioid system to inhibit pain (Watkins and Mayer, 1982). In pain associated with labor, it was shown that affective ratings vary independently of sensory ratings, depending on whether women focus on the birth of the child or on the pain (Price et al., 1987). The mere anticipation of pain causes changes in the synaptic activity of the anterior cingulate, anterior insula and posterior cerebellar regions (Ploghaus et al., 1999), while the subjective reduction of pain associated with both placebo and opiate agonist administration has been associated with increased activity in rostral anterior cingulate cortex and anterior insula (Petrovic et al., 2002). If the placebo effect is taken as a model of these "top-down" regulatory processes, placebo effects under conditions of expectation of analgesia have long been shown reversed by the opioid receptor antagonist naloxone, implying a clear role of the opioid system in placebo analgesia (Levine et al., 1978). Placebo analgesia has also been associated with decreases in the synaptic activity of pain-representation regions including the thalamus, insula and rostral anterior cingulate cortex, albeit the mechanisms by which these regional effects induce analgesic effects is unknown. Anticipation of analgesia by itself was associated with increases in the activity of the dorsolateral prefrontal cortex, suggesting that this region may be implicated in regulating placebo effects through the expectation of pain relief (Wager et al., 2004).

The anterior cingulate cortex, an area with high affinity for opiates (Vogt et al., 1979) has been involved in a number of multiple higher-order functions. These have included performance monitoring (MacDonald et al., 2000), cognitive monitoring and cognitive control (Kerns et al., 2004), decision making (Sanfey et al., 2003), error detection (Carter et al., 1998), remote memory for contextual fear conditioning (Frankland et al., 2004), cognitive conflict and memory suppression (Anderson et al., 2004), and emotional regulation (Mayberg et al., 1999). Both the anterior cingulate cortex and the prefrontal cortex have been seen as crucial neural substrates of the global work space that enables consciousness and control and detection of cognitive conflict (Mayr, 2004). Effects of emotional and painful challenges on the opioid system and μ-opioid receptors have been shown for both of these regions (Zubieta et al., 2001, 2003b,c); however, they are not consciously modulated. The inhibitory effects of this neurotransmitter system may then have an adaptive function to *reduce* conscious cognitive control, which requires work (Matsumoto and Tanaka, 2004). Although this conscious control is necessary when we block a habitual behavior and instead execute a less-familiar behavior, it may be less efficient when responding to salient threatening or pleasurable stimuli that may require automatic and less conscious modulation. The possible role played by the opioid system in these processes is an exciting area of research.

In summary, findings in human subjects and animal models demonstrate the involvement of the endogenous opioid system and μ-opioid receptors in the regulation of stressful states irrespective of their modality (physical, such as pain, or emotional). Furthermore, substantial sex differences exist in the function of this system, representing a point of interaction between gonadal maturation and the neurobiologies of pain, stress and affective regulation. Further delineation of the function and regulation of these and related circuits is necessary to understand the mechanisms by which humans maintain homeostasis and protect against substantial environmental insults.

Acknowledgements

Supported by grants R01 AT 001415, R01 DA 016423 and R21 MH 069612 to J.K.Z. and R01 DE 15369 to C.S.S. The authors also wish to acknowledge the contributions of the PET Center Nuclear Medicine Technologists to the performance of the studies (Jill M. Rothley, Edward J. McKenna, Andrew R. Weeden, Paul Kison and Shayna Huber).

References

Abbagnano, N., 1982. Emoção. In: Abbagnano, N. (Ed.), Dicionario de Filosofia. Mestre Jou, Sao Paulo.

Adolphs, R., 2003. Cognitive neuroscience of human social behaviour. Nat. Rev., Neurosci. 4, 165–178.

Aguggia, M., 2003. Neurophysiology of pain. Neurol. Sci. 24, S57–S60.

Akil, H., Watson, S., Young, E., Lewis, M., Khachaturian, H., Walker, J., 1984. Endogenous opioids: biology and function. Annu. Rev. Neurosci. 7, 223–255.

Albe-Fessard, D., Berkley, K.J., Kruger, L., Ralston, H.J., Willis, W.D., 1985. Diencephalic mechanisms of pain sensation. Brain Res. Rev. 9, 217–296.

Anand, K.J.S., 2000. Pain, plasticity, and premature birth: a prescription for permanent suffering? Nat. Med. 6, 971–973.

Anderson, A.K., Christoff, K., Stappen, I., Panitz, D., Ghahremani, D.G., Glover, G., Gabrieli, J.D., Sobel, N., 2003. Dissociated neural representations of intensity and valence in human olfaction. Nat. Neurosci. 6, 196–202.

Anderson, M.C., Ochsner, K.N., Kuhl, B., Cooper, J., Robertson, E., Gabrieli, S.W., Glover, G.H., Gabrieli, J.D.E., 2004. Neural systems underlying the suppression of unwanted memories. Science 303, 232–235.

Andrew, D., Craig, A.D.B., 2001. Spinothalamic lamina I neurons selectively sensitive to histamine: a central neural pathway for itch. Nat. Neurosci. 4, 72–77.

Angst, J., Gamma, A., Gastpar, M., Lepine, J.P., Mendlewicz, J., Tyleee, A., 2002. Gender differences in depression: epidemiological findings from the European DEPRES I and II studies. Eur. Arch. Psychiatry Clin. Neurosci. 252, 201–209.

Aristotle, 1952. Nicomachean Ethics. Encyclopaedia Britannica, Chicago.

Ballantyne, J.C., Mao, J., 2003. Opioid therapy for chronic pain. N. Engl. J. Med. 349, 1943–1953.

Basbaum, A.I., Jessell, T.M., 2000. The perception of pain. In: Kandel, E.R., Schwartz, J.H., Jessell, T.M. (Eds.), Principles of Neural Science, 4th ed. McGraw-Hill, New York, pp. 472–491.

Bencherif, B., Fuchs, P.N., Sheth, R., Dannals, R.F., Campbell, J.N., Frost, J.J., 2002. Pain activation of human supraspinal opioid pathways as demonstrated by [11C]-carfentanil and positron emission tomography (PET). Pain 99, 589–598.

Blomqvist, A., Zhang, E-T., Craig, A.D., 2000. Cytoarchitectonic and immunohistochemical characterization of a specific pain and temperature relay, the posterior portion of the ventral medial nucleus, in the human thalamus. Brain 123, 601–619.

Bodnar, R.J., Hadjimarkou, M.M., 2002. Endogenous opiates and behavior: 2001. Peptides 23, 2307–2365.

Bradbury, A.F., Smyth, D.G., Snell, C.R., 1976. Biosynthetic origin and receptor conformation of methionine enkephalin. Nature 260, 165–166.

Broad, K.D., Kendrick, K.M., Sirinathsinghji, D.J., Keverne, E.B., 1993. Changes in pro-opiomelanocortin and pre-proenkephalin mRNA levels in the ovine brain during pregnancy, parturition and lactation and in response to oestrogen and progesterone. J. Neuroendocrinol. 5, 711–719.

Brown, G.W., Harris, T.O., Hepworth, C., 1995. Loss, humiliation and entrapment among women developing depression: a patient and non-patient comparison. Psychol. Med. 25, 7–21.

Brownstein, M.J., 1993. A brief history of opiates, opioid peptides, and opioid receptors. Proc. Natl. Acad. Sci. U. S. A. 90, 5391–5393.

Bunzow, J.R., Saez, C., Mortrud, M., Bouvier, C., Williams, J.T., Low, M., Grandy, D.K., 1994. Molecular cloning and tissue distribution of a putative member of the rat opioid receptor gene family that is not a mu, delta or kappa opioid receptor type. FEBS Lett. 347, 284–288.

Bush, G., Luu, P., Posner, M.I., 2000. Cognitive and emotional influences in anterior cingulate cortex. Trends Cogn. Sci. 4, 215–222.

Bushnell, M.C., Duncan, G.H., 1989. Sensory and affective aspects of pain perception: is medial thalamus restricted to emotional issues? Exp. Brain Res. 78, 415–418.

Cacioppo, J.T., Berntson, G.G., 1994. Relationship between attitudes and evaluative space: a critical review, with emphasis on the separability of positive and negative substrates. Psychol. Bull. 115, 401–423.

Cacioppo, J.T., Gardner, W.L., 1999. Emotion. Annu. Rev. Psychol. 50, 191–214.

Cahill, L., Babinsky, R., Markowitsch, H.J., McGaugh, J.L., 1995. The amygdala and emotional memory. Nature 377, 295–296.

Calder, A.J., Lawrence, A.D., Young, A.W., 2001. Neuropsychology of fear and loathing. Nat. Rev., Neurosci. 2, 352–363.

Cannon, W.B., 1915. Bodily Changes in Pain, Hunger, Fear and Rage: An Account of Recent Researches Into the Function of Emotional Excitement. D. Appleton, New York.

Cannon, W.B., 1939. The Wisdom of the Body. W.W. Norton, New York.

Carter, C.S., Braver, T.S., Barch, D.M., Botvinick, M.M., Noll, D., Cohen, J.D., 1998. Anterior cingulate cortex, error detection, and the online monitoring of performance. Science 280, 747–749.

Casey, K., Svensson, P., Morrow, T., Raz, J., Jone, C., Minoshima, S., 2000. Selective opiate modulation of nociceptive processing in the human brain. J. Neurophysiol. 84, 525–533.

Caterina, M.J., Leffler, A., Malmberg, A.B., Martin, W.J., Trafton, J., Petersen-Zetz, K.R., Koltzenburg, M., Basbaum, A.I., Julius, D., 2000. Impaired nociception and pain sensation in mice lacking the capsaicin receptor. Science 288, 306–312.

Chaplin, W.F., John, O.P., Goldberg, L.R., 1988. Conceptions of states and traits: dimensional attributes with ideals as prototypes. J. Pers. Soc. Psychol. 54, 541–557.

Chen, J.F., Aloyo, V.J., Weiss, B., 1993. Continuous treatment with the D_2 dopamine receptor agonist quinpirole decreases D_2 dopamine receptors, D_2 dopamine receptor messenger RNA and proenkephalin messenger RNA, and increases mu opioid receptors in mouse striatum. Neuroscience 54, 669–680.

Chen, Y., Fan, Y., Liu, J., Mestek, A., Tian, M., Kozac, C.A., Yu, L., 1994. Molecular cloning, tissue distribution and chromosomal localization of a novel member of the opioid receptor gene family. FEBS Lett. 347, 279–283.

Christie, I.C., Friedman, B.H., 2004. Autonomic specificity of discrete emotion and dimensions of affective space: a multivariate approach. Int. J. Psychophysiol. 51, 143–153.

Chrobak, J., Napier, T., 1993. Opioid and GABA modulation of accumbens-evoked ventral pallidal activity. J. Neural Transm. Gen. Sect. 93, 123–143.

Churchland, P.S., 2002. Self-representation in nervous systems. Science 296, 308–310.

Coghill, R.C., Talbot, J.D., Evans, A.C., Meyer, E., Gjedde, A., Bushnell, M.C., Duncan, G.H., 1994. Distributed processing of pain and vibration by the human brain. Neuroscience 14, 4095–4108.

Collet, C., Vernet-Maury, E., Delhomme, G., Dittmar, A., 1997. Autonomic nervous system response patterns specificity to basic emotions. Auton. Nerv. Syst. 62, 45–57.

Craig, A.D.B., 2002. How do you feel? Interoception: the sense of the physiological condition of the body. Nat. Rev., Neurosci. 3, 655–666.

Craig, A.D.B., 2003a. A new view of pain as a homeostatic emotion. Trends Neurosci. 26, 303–307.

Craig, A.D.B., 2003b. Interoception: the sense of the physiological condition of the body. Curr. Opin. Neurobiol. 13, 500–505.

Craig, A.D.B., 2003c. Pain mechanisms: labeled lines versus convergence in central processing. Annu. Rev. Neurosci. 26, 1–30.

Craig, A.D.B., Bushnell, M.C., 1994. The thermal grill illusion: unmasking the burn of cold pain. Science 265, 252–255.

Craig, A.D., Bushnell, M.C., Zhang, E.T., Blomqvist, A., 1994. A thalamic nucleus specific for pain and temperature sensation. Nature 372, 770–773.

Craig, A.D.B., Reiman, E.M., Evans, A.C., Bushnell, M.C., 1996. Functional imaging of an illusion of pain. Nature 384, 217–218.

Craig, A.D., Chen, K., Bandy, D., Reiman, E.M., 2000a. Thermosensory activation of insular cortex. Nat. Neurosci. 3, 184–190.

Craig, A.D.B., Chen, K., Bandy, D., Reiman, E.M., 2000b. Thermosensory activation of insular cortex. Nat. Neurosci. 3, 184–190.

Critchley, H.D., Mathias, C.J., Josephs, O., O'Doherty, J., Zanini, S., Dewar, B.-K., Cipolotti, L., Shallice, T., Dolan, R.J., 2003. Human cingulate cortex and autonomic control: converging neuroimaging and clinical evidence. Brain 126, 2139–2152.

Critchley, H.D., Wiens, S., Rotshtein, P., Ohman, A., Dolan, R.J., 2004. Neural systems supporting interoceptive awareness. Nat. Neurosci. 7, 189–195.

Damasio, A.R., 1998. Emotion in the perspective of an integrated nervous system: 1. Brain Res. Rev. 26, 83–86.

Damasio, A., 2003a. Feelings of emotion and the self. Ann. N.Y. Acad. Sci. 1001, 253–261.

Damasio, A.R., 2003b. The person within. Nature 423, 227.

Damasio, A.R., Grabowski, T.J., Bechara, A., Damasio, H., Ponto, L.L.B., Parvizi, J., Hichwa, R.D., 2000. Subcortical and cortical brain activity during the feeling of self-generated emotions. Nat. Neurosci. 3, 1049–1056.

De Vries, T.J., Shippenberg, T.S., 2002. Neural systems underlying opiate addiction. Neuroscience 22, 3321–3325.

Dondi, D., Limonta, P., Maggi, R., Piva, F., 1992. Effects of ovarian hormones on brain opioid binding sites in castrated female rats. Am. J. Physiol. 263, E507–E511.

Drolet, G., Dumont, E.C., Gosselin, I., Kinkead, R., Laforest, S., Trottier, J.-F., 2001. Role of endogenous opioid system in the regulation of the stress response. Prog. Neuro-Psychopharmacol. Biol. Psychiatry 25, 729–741.

Eckersell, C., Popper, P., Micevych, P., 1998. Estrogen-induced alteration of μ-opioid receptor immunoreactivity in the medial preoptic nucleus and medial amygdala. J. Neurosci. 18, 3967–3976.

Ekman, P., 1993. Facial expression and emotion. Am. Psychol. 48, 376–379.

Ekman, P., Levenson, R.W., Friesen, W.V., 1983. Autonomic nervous system activity distinguishes among emotions. Science 221, 1208–1210.

Enoch, M.A., Xu, K., Ferro, E., Harris, C.R., Goldman, D., 2003. Genetic origins of anxiety in women: a role for a functional catechol-*O*-methyltransferase polymorphism. Psychiatr. Genet. 13, 33–41.

Ey, H., Bernard, P., Brisset, C., 1989. Manuel de Psychiatrie, 6 ed. Masson, Paris.

Ferguson, M.L., Katkin, E.S., 1996. Visceral perception, anhedonia, and emotion. Biol. Psychol. 42, 131–145.

Ferrater Mora, J., 1990. Persona. In: Ferrater Mora, J. (Ed.), Diccionario de Filosofia. Alianza Editorial, Madrid, pp. 2550–2555.

Fillingim, R.B., Ness, T.J., 2000. Sex-related hormonal influences on pain and analgesic responses. Neurosci. Biobehav. Rev. 24, 485–501.

Filliol, D., Ghozland, S., Matthes, H.W., Simonin, F., Befort, K., Gaveriaux-Ruff, C., Dierich, A., Le Meur, M., Valverde, O., Maldonado, R., Kieffer, B.L., 2000a. Mice deficient for delta- and mu-opioid receptors exhibit opposing alterations of emotional responses. Nat. Genet. 25, 195–200.

Filliol, D., Ghozland, S., Chluba, J., Martin, M., Matthes, H., Simonin, F., Befort, K., Gaveriaux-Ruff, C., Dierich, A., Le, M.M., Valverde, O., Maldonado, R., Kieffer, B., 2000b. Mice deficient for delta- and mu-opioid receptors exhibit opposing alterations of emotional responses. Nat. Genet. 25, 195–200.

Foltz, E.L., White, L.E.J., 1962. Pain "relief" by frontal cingulumotomy. J. Neurosurg. 19, 89–100.

Frankland, P.W., Bontempi, B., Talton, L.E., Kaczmarek, L., Silva, A.J., 2004. The involvement of the anterior cingulate cortex in remote contextual fear memory. Science 304, 881–883.

Freud, S., 1917. Mourning and Melancholia. Hogarth Press, London.

Fukuda, K., Kato, S., Mori, K., Nishi, M., Takeshima, H., Iwabe, N., Miyata, T., Houtani, T., Sugimoto, T., 1994. cDNA cloning and regional distribution of a novel member of the opioid receptor family. FEBS Lett. 343, 42–46.

Fuster, J.M., 2004. Upper processing stages of the perception–action cycle. Trends Cogn. Sci. 8, 143–145.

Gear, R., Levine, J., 1995. Antinociception produced by an ascending spino-supraspinal pathway. J. Neurosci. 15, 3154–3161.

Gear, R., Miaskowski, C., Gordon, N., Paul, S., Heller, P., Levine, J., 1996. Kappa-opioids produce significantly greater analgesia in women than in men. Nat. Med. 2, 1248–1250.

George, M.S., Ketter, T.A., Parekh, P.I., Herscovitch, P., Post, R.M., 1996. Gender differences in regional cerebral blood flow during transient self-induced sadness or happiness. Biol. Psychiatry 40, 859–871.

Gerrits, M.A.F.M., Lesscher, H.B.M., van Ree, J.M., 2003. Drug dependence and the endogenous opioid system. Eur. Neuropsychopharmacol. 13, 424–434.

Gestreau, C., Besson, J., 2000. Is there tonic activity in the endogenous opioid systems? A c-Fos study in the rat central nervous system after intravenous injection of naloxone or naloxone–methiodide (In Process Citation). J. Comp. Neurol. 427, 285–301.

Gilbert, P.F., Allan, S., 1998. The role of defeat and entrapment (arrested flight) in depression: an exploration of an evolutionary view. Psychol. Med. 28, 585–598.

Goldenberg, J.L., Pyszczynski, T., Greenberg, J., Solomon, S., Kluck, B., Cornwell, R., 2001. I am not an animal: mortality salience, disgust and the denial of human creatureliness. J. Exp. Psychol. Gen. 130, 427–435.

Goldscheider, A., 1894. Ueber den Schmerz in physiologischer und klinischer Hinsicht. Hirschwald, Berlin.

Goldstein, A., Fischli, W., Lowney, L.I., Hunkapiller, M., Hood, L., 1981. Porcine pituitary dynorphin: complete amino acid sequence of the biologically active heptadecapeptide. Proc. Natl. Acad. Sci. U. S. A. 78, 7219–7223.

Greenwald, M.K., Johanson, C-E., Moody, D.E., Woods, J.H., Kilbourn, M.R., Koeppe, R.A., Schuster, C.R., Zubieta, J.K., 2003. Effects of buprenorphine maintenance on mu-opioid receptor availability, plasma concentrations, and antagonist blockade in heroin-dependent volunteers. Neuropsychopharmacology 28, 2000–2009.

Guillemin, R., Vargo, T., Rossier, J., Minick, S., Ling, N., Rivier, C., Vale, W., Bloom, F.E., 1977. Beta-endorphin and adrenocorticotropin are secreted concomitantly by the pituitary gland. Science 197, 1367–1369.

Gutstein, H.B., Akil, H., 2001. Opioid analgesics. In: Hardman, J.G., Limbird, L.E., Goodman-Gilman, A. (Eds.), Goodman and Gilman's The Pharmacological Basis of Therapeutics, 10th edition. McGraw-Hill, New York, pp. 569–619.

Hagelberg, N., Forssell, H., Rinne, J.O., Scheinin, H., Taiminen, T., Aalto, S., Luutonen, S., Nagren, K., Jaaskelainen, S., 2003. Striatal dopamine D_1 and D_2 receptors in burning mouth syndrome. Pain 101, 149–154.

Hammer RP, Jr., 1987. Preoptic area opioids and opiate receptors increase during pregnancy and decrease during lactation. Brain Res. 420, 48–56.

Hammer, R.P. Jr., Bogic, L., Handa, R.J., 1993. Estrogenic regulation of proenkephalin mRNA expression in the ventromedial hypothalamus of the adult male rat. Brain Res. Mol. Brain Res. 19, 129–134.

Harte, S., Lagman, A., Borszcz, G., 2000. Antinociceptive effects of morphine injected into the nucleus parafascicularis thalami of the rat. Brain Res. 874, 78–86.

Heidegger, M., 1996. Being and Time: a Translation of Sein und Zeit. State University of New York Press, Albany, NY.

Hong, Y., Dai, P., Jiang, J., Zeng, X., 2004. Dual effects of intrathecal BAM22 on nociceptive responses in acute and persistent pain—potential function of a novel receptor. Br. J. Pharmacol. 141, 423–440.

Horvitz, J., 2000. Mesolimbic and nigrostriatal dopamine responses to salient non-rewarding stimuli. Neuroscience 96, 651–656.

Hosobuchi, Y., Adams, J.E., Linchitz, R., 1977. Pain relief by electrical stimulation of the central gray matter in humans and its reversal by naloxone. Science 197, 183–186.

Hosobuchi, Y., Rossier, J., Bloom, F.E., Guillemin, R., 1979. Stimulation of human periaqueductal gray for pain relief increases immunoreactive beta-endorphin in ventricular fluid. Science 203, 279–281.

Hsu, M.M., Shyu, B-C., 1997. Electrophysiological study of the connection between medial thalamus and anterior cingulate cortex in the rat. NeuroReport 8, 2701–2707.

Hughes, J., Smith, T.W., Kosterlitz, H.W., Fothergill, L.A., Morgan, B.A., Morri, H.R., 1975. Identification of two related pentapeptides from the brain with potent opiate agonistic activity. Nature 258, 577–580.

Hughes, J., Kosterlitz, H.W., Smith, T.W., 1977. The distribution of methionine–enkephalin and leucine–enkephaline in the brain and peripheral tissues. Br. J. Pharmacol. 61, 639–647.

Hwang, D.R., Narendran, R., Laruelle, M., 2005. Positron-labeled dopamine agonists for probing the high affinity states of dopamine subtype 2 receptors. Bioconjug. Chem. 16, 27–31.

Iadarola, M.J., Caudle, R.M., 1997. Good pain, bad pain. Science 278, 239–240.

Iggo, A., Ogawa, H., 1971. Primate cutaneous thermal nociceptors. J. Physiol. 216, 77P–78P.

Jaaskelainen, S.K., Rinne, J.O., Forssell, H., Tenovuo, O., Kaasinen, V., Sonninen, P., Bergman, J., 2001. Role of the dopaminergic system in chronic pain — a fluorodopa–PET study. Pain 90, 257–260.

Jaspers, K., 1977. General Psychopathology. The Johns Hopkins University Press, Baltimore (Original 1913).

Johnson, P., Napier, T., 1997. Morphine modulation of GABA- and glutamate-induced changes of ventral pallidal neuronal activity. Neuroscience 77, 187–197.

Julius, D., Basbaum, A.I., 2001. Molecular mechanisms of nociception. Nature 2003, 203–210.

Jutkiewicz, E.M., Rice, K.C., Woods, J.H., Winsauer, P.J., 2003. Effects of the delta-opioid receptor agonist SNC80 on learning relative to its antidepressant-like effects in rats. Behav. Pharmacol. 14, 509–516.

Kakidani, H., Furutani, Y., Takahashi, H., Noda, M., Morimoto, Y., Hirose, T., Asai, M., Inayama, S., Nakanishi, S., Numa, S., 1982. Cloning and sequence analysis of cDNA for porcine beta-*neo*-endorphin/dynorphin precursor. Nature 298, 245–249.

Kalin, N., Shelton, S., Barksdale, C., 1988. Opiate modulation of separation-induced distress in non-human primates. Brain Res. 440, 285–292.

Kalivas, P.W., Churchill, L., Romanides, A., 1999. Involvement of the pallidal–thalamocortical circuit in adaptive behavior. Ann. N.Y. Acad. Sci. 877, 64–70.

Kenakin, T., 1997. Differences between natural and recombinant G protein-coupled receptor systems with varying receptor/G protein stoichiometry. Trends Pharmacol. Sci. 18, 456–464.

Kendler, K.S., Hettema, J.M., Butera, F., Gardner, C.O., Prescott, C.A., 2003. Life event dimensions of loss, humiliation, entrapment, and danger in the prediction of onsets of major depression and generalized anxiety. Arch. Gen. Psychiatry 60, 789–796.

Kerns, J.G., Cohen, J.D., MacDonald, A.W. III, Cho, R.Y., Stenger, V.A., Carter, C.S., 2004. Anterior cingulate conflict monitoring and adjustments in control. Science 303, 1023–1026.

Klein, M., 1978. Love, Guilt, Reparation and Other Works. The Free Press, New York.

Koob, G.F., Moal, M.L., 1997. Drug abuse: hedonic homeostatic dysregulation. Science 278, 52–58.

Kornstein, S.G., Schatzberg, A.F., Thase, M.E., Yonkers, K.A., McCullough, J.P., Keitner, G.I., Gelenberg, A.J., Ryan, C.E., Hess, A.L., Harrison, W., 2000. Gender differences in chronic major and double depression. J. Affect. Disord. 60, 1–11.

Korte, S.M., Koolhaas, J.M., Wingfield, J.C., McEwen, B.S., 2005. The Darwinian concept of stress: benefits of allostasis and costs of allostatic load and the trade-offs in health and disease. Neurosci. Biobehav. Rev. 29, 3–38.

Kosterlitz, H.W., Waterfield, A.A., 1975. In vitro models in the study of structure–activity relationship of narcotic analgesics. Annu. Rev. Pharmacol. 15, 29–47.

Kraus, M., Piper, J., Kornetsky, C., 1996. Naloxone alters the local metabolic rate for glucose in discrete bran regions associated with opiate withdrawal. Brain Res. 724, 33–40.

Kreek, M.J., LaForge, K.S., Butelman, E., 2002. Pharmacotherapy of addictions. Nat. Rev., Drug Discov. 1, 710–726.

Kumazawa, T., Perl, E.R., 1977. Primate cutaneous sensory units with unmyelinated (C) afferent fibers. J. Neurophysiol. 40, 1325–1338.

Kung, J.-C., Shyu, B.-C., 2002. Potentiation of local field potentials in the anterior cingulate cortex evoked by the stimulation of the medial thalamic nuclei in rats. Brain Res. 953, 37–44.

Lachowicz, J.E., Shen, Y., Monsma, F.J. Jr., Sibley, D.R., 1995. Molecular cloning of a novel G protein-coupled receptor related to the opiate receptor family. J. Neurochem. 64, 34–40.

Larsen, J.T., McGraw, P., Cacioppo, J.T., 2001. Can people feel happy and sad at the same time? J. Pers. Soc. Psychol. 81, 684–696.

Laruelle, M., 2000. Imaging synaptic neurotransmission with in vivo binding competition techniques: a critical review. J. Cereb. Blood Flow Metab. 20, 423–451.

Lazarus, R.S., 1991. Progress on a cognitive–motivational–relational theory of emotion. Am. Psychol. 46, 819–834.

LeDoux, J.E., 1993. Emotional memory systems in the brain. Behav. Brain Res. 58, 69–79.

Lembo, P.M.C., Grazzini, E., Groblewski, T., O'Donnell, D., Roy, M.-O., Zhang, J., Hoffert, C., Cao, J., Schmidt, R., Pelletier, M., Labarre, M., Grosselin, M., Fortin, Y., Banville, D., Shen, S.H., Strom, P., Payza, K., Dray, A., Walker, P., Ahmad, S., 2002. Proenkephalin A gene products activate a new family of sensory neuron-specific GPCRs. Nat. Neurosci. 5, 201–209.

Lenz, F.A., Seike, M., Baker, Y.C., Rowland, F.H., Graceley, L.H., Richardson, R.H., 1993a. Neurons in the area of human thalamic nucleus ventralis respond to painful heat stimuli. Brain Res. 623, 235–240.

Lenz, F.A., Seike, M., Richardson, R.T., Lin, Y.C., Baker, F.H., Khoja, I., Jaeger, C.J., Graceley, R.H., 1993b. Thermal and pain sensations evoked by microstimulation in the area of human ventrocaudal nucleus. J. Neurophysiol. 70, 200–212.

Lenz, F.A., Garonzik, I.M., Zirh, T.A., Dougherty, P.M., 1998. Neuronal activity in the region of the thalamic principal sensory nucleus (ventralis caudalis) in patients with pain following amputations. Neuroscience 86, 1065–1081.

LeResche, L., Mancl, L., Sherman, J.J., Gandara, B., Dworkin, S.F., 2003. Changes in temporomandibular pain and other symptoms across the menstrual cycle. Pain 106, 253–261.

Levenson, R.W., 2003. Blood, sweat, and fears: the autonomic architecture of emotion. Ann. N.Y. Acad. Sci. 1000, 348–366.

Levine, J.D., Gordon, N.C., Fields, H.L., 1978. The mechanism of placebo analgesia. Lancet 2, 654–657.

Lewis, J.W., Cannon, T., Liebeskind, J.C., 1980. Opioid and nonopioid mechanisms of stress analgesia. Science 208, 623–625.

Liberzon, I., Taylor, S., Fig, L., Decker, L., Koeppe, R., Minoshima, S., 2000. Limbic activation and psychophysiologic responses to aversive visual stimuli. Interaction with cognitive task. Neuropsychopharmacology 23, 508–516.

Lopez, J.F., Akil, H., Watson, S.J., 1999. Neural circuits mediating stress. Biol. Psychiatry 46, 1461–1471.

Lord, J.A., Waterfield, A.A., Hughes, J., Kosterlitz, H.W., 1977. Endogenous opioid peptides: multiple agonists and receptors. Nature 267, 495–499.

MacDonald, A.W., Cohen, J.D., Stenger, V.A., Carter, C.S., 2000. Dissociating the role of the dorsolateral prefrontal and anterior cingulate cortex in cognitive control. Science 288, 1835–1838.

Madden, J., Akil, H., Patrick, R.L., Barchas, J.D., 1977. Stress-induced parallel changes in central opioid levels and pain responsiveness in the rat. Nature 265, 358–360.

Malmberg, A.B., Chen, C., Tonegawa, S., Basbaum, A.I., 1997. Preserved acute pain and reduced neuropathic pain in mice lacking PKC. Science 278, 279–283.

Manning, B., 1998. A lateralized deficit in morphine antinociception after unilateral inactivation of the central amygdala. J. Neurosci. 18, 9453–9470.

Manning, B.H., Merin, N.M., Meng, I.D., Amaral, D.G., 2001. Reduction in opioid- and cannabinoid-induced antinociception in rhesus monkeys after bilateral lesions of the amygdaloid complex. J. Neurosci. 21, 8238–8246.

Mantyh, P.W., Rogers, S.D., Honore, P., Allen, B.J., Ghilardi, J.R., Li, J., Daughters, R.S., Lappi, D.A., Wiley, R.G., Simone, D.A., 1997. Inhibition of hyperalgesia by ablation of lamina I spinal neurons expressing the substance P receptor. Science 278, 275–279.

Martin, W.R., Eades, C.G., Thompson, J.A., Huppler, R.E., Gilbert, P.F., 1976. The effects of morphine- and nalorphine-like drugs in the nondependent and morphine-dependent chronic spinal dog. J. Pharmacol. Exp. Ther. 197, 517–532.

Matsumoto, K., Tanaka, K., 2004. Conflict and cognitive control. Science 303, 969–970.

Matthes, H.W.D., Maldonado, R., Simonin, F., Valverde, O., Slowe, S., Kitchen, I., Befort, K., Dierich, A., LeMeur, M., Dolle, P., Tzavara, E., Hannoune, J., Roques, B.P., Kieffer, B.L., 1996. Loss of morphine-induced analgesia, reward effect and withdrawal symptoms in mice lacking the μ-opioid-receptor gene. Nature 383, 819–823.

May, R., Angel, E., Ellenberger, H. (Eds.), 1958. Existence: A New Dimension in Psychiatry and Psychology. Basic Books, New York.

Mayberg, H., Liotti, M., Brannan, S.K., McGinnis, S., Mahurin, R.K., Jerabek, P., Silva, J.A., Tekell, J.L., Martin, C.C., Lancaster, J.L., Fox, P.T., 1999. Reciprocal limbic–cortical function and negative mood: converging PET findings in depression and normal sadness. Am. J. Psychiatry 156, 675–682.

Mayer, D.J., Wolfle, T.L., Akil, H., Carder, B., Liebeskind, J.C., 1971. Analgesia from electrical stimulation in the brainstem of the rat. Science 174, 1351–1354.

Mayr, U., 2004. Conflict, consciousness, and control. Trends Cogn. Sci. 8, 145–148.

McEwen, B.S., 2003a. Interacting mediators of allostasis and allostatic load: towards an understanding of resilience in aging. Metabolism 52, 10–16.

McEwen, B.S., 2003b. Mood disorders and allostatic load. Biol. Psychiatry 54, 200–207.

McEwen, B.S., 2004. Protection and damage from acute and chronic stress: allostasis and allostatic overload and relevance to the pathophysiology of psychiatric disorders. Ann. N.Y. Acad. Sci. 1032, 1–7.

McNair, D.M., Lorr, M., Droppleman, L.F., 1971. Manual: Profile of Mood States. Educational and Industrial Testing State, San Diego.

Melzack, R., Katz, J., 2000. The McGill Pain Questionnaire: appraisal and current status. In: Turk, D., Melzack, R. (Eds.), Handbook of Pain Assessment. Guilford, New York, pp. 152–168.

Melzack, R., Wall, P.D., 1965. Pain mechanisms: a new theory. Science 150, 971–979.

Merskey, H., Bogduk, N. (Eds.), 1994. Classification of Chronic Pain. Descriptions of Chronic Pain Syndromes and Definitions of Pain Terms, 2nd ed. IASP Press, Seattle.

Meunier, J.-C., Mollereau, C., Toll, L., Saudeau, C., Moisand, C., Alvinerie, P., Butour, J.-L., Guillemont, J.-C., Ferrara, P., Monsarrat, B., Mazarguil, H., Vassart, G., Parmentier, M., Costentin, J., 1995. Isolation and structure of the endogenous agonist of opioid receptor-like ORL1 receptor. Nature 377, 532.

Meyer, C.R., Boes, J.L., Kim, B., Bland, P.H., Zasadny, K.R., Kison, P.V., Koral, K., Frey, K.A., Wahl, R.L., 1997. Demonstration of accuracy and clinical versatility of mutual information for automatic multimodality image fusion using affine and thin-plate spline warped geometric deformations. Med. Image Anal. 1, 195–206.

Mizuno, T., Kimura, F., 1996. Medial septal injection of naloxone elevates acetylcholine release in the hippocampus and induces behavioral seizures in rats. Brain Res. 713, 1–7.

Mogenson, G., Yang, C., 1991. The contribution of the basal forebrain to limbic–motor integration and the mediation of motivation to action. In: Napier, T., Kalivas, P., Hanin, I. (Eds.), The Basal Forebrain: Anatomy to Function. Plenum Press, New York, pp. 267–290.

Mogil, J.S., Wilson, S.G., Chesler, E.J., Rankin, A.L., Nemmani, K.V., Lariviere, W.R., Groce, M.K., Wallace, M.R., Kaplan, L., Staud, R., Ness, T.J., Glover, T.L., Stankova, M., Mayorov, A., Hruby, V.J., Grisel, J.E., Fillingim, R.B., 2003. The melanocortin-1 receptor gene mediates female-specific mechanisms of analgesia in mice and humans. Proc. Natl. Acad. Sci. U. S. A. 100, 4867–4872.

Moles, A., Kieffer, B.L., D'Amato, F.R., 2004. Deficit in attachment behavior in mice lacking the mu-opioid receptor gene. Science 304, 1983–1986.

Mollereau, C., Parmentier, M., Mailleux, P., Butour, J.-L., Moisand, C., Chalon, P., Caput, D., Vassart, G., Meunier, J.-C., 1994. ORL-1, a novel member of the opioid receptor family. Cloning, functional expression and localization. FEBS Lett. 341, 33–38.

Morris, J.S., Frith, C.D., Perrett, D.I., Rowland, D., Young, A.W., Calder, A.J., Dolan, R.J., 1996. A differential neural response in the human amygdala to fearful and happy facial expressions. Nature 383, 812–815.

Morris, J., Friston, K., Büchel, C., Frith, C., Young, A., Calder, A., Dolan, R., 1998. A neuromodulatory role for the human amygdala in processing emotional facial expressions. Brain 121, 47–57.

Nakanishi, S., Inoue, A., Kita, T., Nakamura, M., Chang, A.C., Cohen, S.N., Numa, S., 1979. Nucleotide sequence of cloned cDNA for bovine corticotropin-beta-lipotropin precursor. Nature 278, 423–427.

Napier, T., Mitrovic, I., 1999. Opioid modulation of ventral pallidal inputs. Ann. N.Y. Acad. Sci. 877, 176–201.

Narendran, R., Hwang, D.R., Slifstein, M., Talbot, P.S., Erritzoe, D., Huang, Y., Cooper, T.B., Martinez, D., Kegeles, L.S., Abi-Dargham, A., Laruelle, M., 2004. In vivo vulnerability to competition by endogenous dopamine: comparison of the D_2 receptor agonist radiotracer (−)-*N*-[^{11}C]propyl-norapomorphine ([^{11}C]NPA) with the D_2 receptor antagonist radiotracer [^{11}C]-raclopride. Synapse 52, 188–208.

Nelson, E.E., Panksepp, J., 1998. Brain substrates of infant–mother attachment: contributions of opioids, oxytocin, and norepinephrine. Neurosci. Biobehav. Rev. 22, 437–452.

Nesse, R.M., 1990. Evolutionary explanations of emotions. Human Nat. 1, 261–289.

Nesse, R.M., 1991. What good is feeling bad? Sciences, 30–37.

Nesse, R.M., 2000. Is depression an adaptation? Arch. Gen. Psychiatry 57, 14–20.

Nesse, R.M., 2001. Motivation and melancholy: a Darwinian perspective. Neb. Symp. Motiv. 47, 179–203.

Nestler, E.J., Gould, E., Manji, H., 2002. Preclinical models: status of basic research in depression. Biol. Psychiatry 52, 503–528.

Noda, M., Furutani, Y., Takahashi, H., Toyosato, M., Hirose, T., Inayama, S., Nakanishi, S., Numa, S., 1982. Cloning and sequence analysis of cDNA for bovine adrenal preproenkephalin. Nature 295, 202–206.

Nothacker, H.-P., Reinscheid, R.K., Mansour, A., Henningsen, R.A., Ardati, A., Monsma, F.J. Jr., Watson, S.J., Civelli, O., 1996. Primary structure and tissue distribution of the orphanin FQ precursor. Proc. Natl. Acad. Sci. U. S. A. 93, 8677–8682.

O'Brien, C.P., 2001. Drug addiction and drug abuse. In: Hardman Jr., J.G., Limbird, L.E., Goodman-Gilman, A. (Eds.), Goodman and Gilman's The Pharmacological Basis of Therapeutics. McGraw Hill, New York, pp. 621–642.

Pan, Y.-X., Xu, J., Pasternak, G.W., 1996. Cloning and expression of a cDNA encoding a mouse brain orphanin FQ/nociceptin precursor. Biochem. J. 315, 11–13.

Panksepp, J., 2003. Feeling the pain of social loss. Science 302, 237–239.

Paulson, P., Minoshima, S., Morrow, T., Casey, K., 1998. Gender differences in pain perception and patterns of cerebral activation during noxious heat stimulation in humans. Pain 76, 223–229.

Pert, C.B., Snyder, S.H., 1973. Opiate receptor: demonstration in nervous tissue. Science 179, 1011–1014.

Petrovic, P., Kalso, E., Petersson, K.M., Ingvar, M., 2002. Placebo and opioid analgesia — imaging a shared neuronal network. Science 295, 1737–1740.

Peyron, R., Garcia-Larrea, L., Gregoire, M.-C., Costes, N., Convers, P., Lavenne, F., Mauguiere, F., Michel, D., Laurent, B., 1999. Haemodynamic brain responses to acute pain in humans: sensory and attentional networks. Brain 122, 1765–1780.

Ploghaus, A., Tracey, I., Gati, J.S., Clare, S., Menon, R.S., Matthews, P.M., Rawlins, J.N.P., 1999. Dissociating pain from its anticipation in the human brain. Science 284, 1979–1981.

Price, D.D., 2000. Psychological and neural mechanisms of the affective dimension of pain. Science 288, 1769–1772.

Price, D.D., Harkins, S.W., Baker, C., 1987. Sensory–affective relationships among different types of clinical and experimental pain. Pain 28, 297–307.

Price, J.S., Gardner, J., Russell,, Erickson, M., 2004. Can depression, anxiety and somatization be understood as appeasement displays? J. Affect. Disord. 79, 1–11.

Pruessner, J.C., Champagne, F., Meaney, M.J., Dagher, A., 2004. Dopamine release in response to a psychological stress in humans and its relationship to early life maternal care: a positron emission tomography study using [^{11}C]raclopride. J. Neurosci. 24, 2825–2831.

Pyszczynski, T., Greenberg, J., Solomon, S., 1999. A dual-process model of defense against conscious and unconscious death-related thoughts: an extension of terror management theory. Psychol. Rev. 106, 835–845.

Quinones-Jenab, V., Jenab, S., Ogawa, S., Inturrisi, C., Pfaff, D.W., 1997. Estrogen regulation of mu-opioid receptor mRNA in the forebrain of female rats. Brain Res. Mol. Brain Res. 47, 134–138.

Quirarte, G., Galvez, R., Roozendaal, B., McGaugh, J., 1998. Norepinephrine release in the amygdala in response to foot shock and opioid peptidergic drugs. Brain Res. 808, 134–140.

Rainville, P., 2002. Brain mechanisms of pain affect and pain modulation. Curr. Opin. Neurobiol. 12, 195–204.

Rainville, P., Feine, J.S., Bushnell, M.C., Duncan, G.H., 1992. A psychophysical comparison of sensory and affective responses to four modalities of experimental pain. Somatosens. Motor Res. 9, 265–277.

Rainville, P., Duncan, G.H., Price, D.D., Carrier, B., Bushnell, M.C., 1997. Pain affect encoded in human anterior cingulate but not somatosensory cortex. Science 277, 968–971.

Reinscheid, R.K., Nothacker, H.-P., Bourson, A., Ardati, A., Henningsen, R.A., Bunzow, J.R., Grandy, D.K., Langen, H., Monsma, F.J. Jr., Civelli, O., 1995. Orphanin FQ: a neuropeptide that activates an opioidlike G protein-coupled receptor. Science 270, 792–794.

Remington, N.A., Fabrigar, L.R., Visser, P.S., 2000. Reexamining the circumplex model of affect. J. Pers. Soc. Psychol. 79 (2), 286–300.

Reynolds, D.V., 1969. Surgery in the rat during electrical analgesia induced by focal brain stimulation. Science 164, 444–445.

Ribeiro, S.C., Kennedy, S.E., Bueller, J.A., Xu, Y., Koeppe, R.A., Stohler, C.S., Zubieta, J.K., 2004. Endogenous opioid neurotransmission regulates responses to stress and affective stimuli in overlapping circuits. Society of Biological Psychiatry 2004 Annual Meeting. Biological Psychiatry, New York, p. 5S.

Robinson, T.E., Berridge, K.C., 2000. The psychology and neurobiology of addiction: an incentive–sensitization view. Addiction 95 (Suppl. 2), S91–S117.

Rubinstein, M., Mogil, J.S., Japon, M., Chan, E.C., Allen, R.G., Low, M.J., 1996. Absence of opioid stress-induced analgesia in mice lacking β-endorphin by site directed mutagenesis. Proc. Natl. Acad. Sci. U. S. A. 93, 3995–4000.

Ruda, M.A., Ling, Q.-D., Hohmann, A.G., Peng, Y.B., Tachibana, T., 2000. Altered nociceptive neuronal circuits after neonatal peripheral inflammation. Science 289, 628–630.

Russell, J.A., 1980. A circumplex model of affect. J. Pers. Soc. Psychol. 39, 1161–1178.

Russell, J.A., 1991. Culture and the categorization of emotions. Psychol. Bull. 110, 426–450.

Russell, J.A., 2003. Core affect and the psychological construction of emotion. Psychol. Rev. 110, 145–172.

Russell, J.A., Carroll, J.M., 1999. On the bipolarity of positive and negative affect. Psychol. Bull. 125, 3–30.

Russell, J.A., Fehr, B., 1994. Fuzzy concepts in a fuzzy hierarchy: varieties of anger. J. Pers. Soc. Psychol. 67, 186–205.

Sagan, C. The Editors, 1995. Life. The New Encyclopaedia Britannica, 15th ed. Encyclopaedia Britannica, Chicago, pp. 964–981.

Sah, D.W.Y., Ossipov, M.H., Porreca, F., 2003. Neurotrophic factors as novel therapeutics for neuropathic pain. Nat. Rev., Drug Discov. 2, 460–472.

Sanfey, A.G., Rilling, J.K., Aronson, J.A., Nystrom, L.E., Cohen, J.D., 2003. The neural basis of economic decision-making in the ultimatum game. Science 300, 1755–1758.

Sapolsky, R.M., 1996. Why stress is bad for your brain. Science 273, 749–750.

Sapolsky, R.M., 2003. Stress and plasticity in the limbic system. Neurochem. Res. 28, 1735–1742.

Sapolsky, R.M., 2005. The influence of social hierarchy on primate health. Science 308, 648–652.

Sapolsky, R.M., Krey, L.C., McEwen, B.S., 1985. Prolonged glucocorticoid exposure reduces hippocampal neuron number: implications for aging. J. Neurosci. 5, 1222–1227.

Sapolsky, R.M., Romero, L.M., Munck, A.U., 2000. How do glucocorticoids influence stress responses? Integrating permissive, suppressive, stimulatory, and preparative actions. Endocr. Rev. 21, 55–89.

Sartre, J.P., 1948. The Emotions: Outline of a Theory. The Philosophical Library, New York.

Sartre, J.P., 1956. Being and Nothingness: An Essay in Phenomenological Ontology. Citadel Press, New York.

Sastre, M., Garcia-Sevilla, J., 1994. Density of alpha-2A adrenoceptors and Gi proteins in the human brain: ratio of high-affinity agonist sites to antagonist sites and effect of age. J. Pharmacol. Exp. Ther. 269, 1062–1072.

Schlaepfer, T., Strain, E., Greenberg, B., Preston, K., Lancaster, E., Bigelow, G., Barta, P., Pearlson, G., 1998. Site of opioid action in the human brain: mu and kappa agonists' subjective and cerebral blood flow effects. Am. J. Psychiatry 155, 470–473.

Scholz, J., Woolf, C.J., 2002. Can we conquer pain? Nat. Neurosci. 5, 1062–1067.

Schott, G.D., 2004. Communicating the experience of pain: the role of analogy. Pain 108, 209–212.

Selye, H., 1936. A syndrome produced by diverse nocuous agents. Nature 138, 32.

Shaver, P., Schwartz, J., Kirson, D., O'Connor, C., 1987. Emotion knowledge: further exploration of a prototype approach. J. Pers. Soc. Psychol. 52, 1061–11086.

Singer, T., Seymour, B., O'Doherty, J., Kaube, H., Dolan, R.J., Frith, C.D., 2004. Empathy for pain involves the affective but not sensory components of pain. Science 303, 1157–1162.

Skoubis, P.D., Matthes, H.W., Walwyn, W.M., Kieffer, B.L., Maidment, N.T., 2001. Naloxone fails to produce conditioned place aversion in [mu]-opioid receptor knock-out mice. Neuroscience 106, 757–763.

Smith, Y., Zubieta, J., Del Carmen, M., Dannals, R., Ravert, H., Zacur, H., Frost, J., 1998. Brain mu opioid receptor measurements by positron emission tomography in normal cycling women: relationship to LH pulsatility and gonadal steroid hormones. J. Clin. Endocrinol. Metab. 83, 4498–4505.

Solomon, S., Greenberg, J., Pyszczynski, T., 2003. Fear of death and human destructiveness. Psychoanal. Rev. 90, 457–474.

Sora, I., Takahashi, N., Funada, M., Ujike, H., Revay, R.S., Donovan, D.M., Miner, L.L., Uhl, G.R., 1997. Opiate receptor knockout mice define μ receptor roles in endogenous nociceptive responses and morphine-induced analgesia. Proc. Natl. Acad. Sci. U. S. A., 94.

Spanagel, R., Herz, A., Shippenberg, T.S., 1992. Opposing tonically active endogenous opioid systems modulate the mesolimbic dopaminergic pathway. Proc. Natl. Acad. Sci. U. S. A. 89, 2046–2050.

Stein, C., Schaffer, M., Machelska, H., 2003. Attacking pain at its source: new perspectives on opioids. Nat. Med. 9, 1003–1008.

Steiner, H., Gerfen, C.R., 1998. Role of dynorphin and enkephalin in the regulation of striatal output pathways and behavior. Exp. Brain Res. 123, 60–76.

Stohler, C., Kowalski, C., 1999. Spatial and temporal summation of sensory and affective dimensions of deep somatic pain. Pain 79, 165–173.

Strasberg, L., Chaillet, N., 1995. The art of the theatre. The New Encyclopaedia Britannica. Encyclopaedia Britannica, Chicago, pp. 521–536.

Sugita, S., North, R.A., 1993. Opioid actions on neurons of rat lateral amygdala in vitro. Brain Res. 612, 151–155.

Sugiura, Y., Lee, C.L., Perl, E.R., 1986. Central projections of identified, unmyelinated (C) afferent fibers innervating mammalian skin. Science 234, 358–361.

Szabo, S., 1998. Hans Selye and the development of the stress concept. Ann. N.Y. Acad. Sci. 851, 19–27.

Talbot, J.D., Marrett, S., Evans, A.C., Meyer, E., Bushnell, M.C., Duncan, G.H., 1991. Multiple representations of pain in human cerebral cortex. Science 251, 1355–1358.

Terenius, L., 1973. Stereospecific interaction between narcotic analgesics and a synaptic plasma membrane fraction of rat brain cortex. Acta Pharm. Toxicol. 32, 317–320.

Thayer, J.F., Faith, M.L., 2001. A dynamic systems model of musically induced emotions: physiological and self-report evidence. Ann. N.Y. Acad. Sci. 930, 452–456.

Thielen, S.K., Shekhar, A., 2002. Amygdala priming results in conditioned place avoidance. Pharmacol. Biochem. Behav. 71, 401–406.

Tolle, T., Kaufmann, T., Siessmeier, T., Lautenbacher, S., Berthele, A., Munz, F., Zieglgansberger, W., Willoch, F., Schwaiger, M., Conrad, B., Bartenstein, P., 1999. Region-specific encoding of sensory and affective components of pain in the human brain: a positron emission tomography correlation analysis. Ann. Neurol. 45, 40–47.

Torregrossa, M.M., Isgor, C., Folk, J.E., Rice, K.C., Watson, S.J., Woods, J.H., 2004. The delta-opioid receptor agonist (+)BW373U86 regulates BDNF mRNA expression in rats. Neuropsychopharmacology 29, 649–659.

Unruh, A., 1996. Gender variations in clinical pain experience. Pain 65, 123–167.

Vogt, B.A., Rosene, D.L., Pandya, D.N., 1979. Thalamic and cortical afferents differentiate anterior from posterior cingulate cortex in the monkey. Science 204, 205–207.

von Frey, M., 1894. Ber. K. Sachs. Ges. Wiss. 46, 185.

Waal, F.B.M.d., 1989. Peacemaking Among Primates. Harvard University Press, Cambridge, MA.

Wager, T.D., Rilling, J.K., Smith, E.E., Sokolik, A., Casey, K.L., Davidson, R.J., Kosslyn, S.M., Rose, R.M., Cohen, J.D., 2004. Placebo-induced changes in fMRI in the anticipation and experience of pain. Science 303, 1162–1167.

Walker, J.M., Berntson, G.G., Sandman, C.A., Coy, D.H., Schally, A.V., Kastin, A.J., 1977. An analog of enkephalin having prolonged opiate-like effects in vivo. Science 196, 85–87.

Wang, J.B., Johnson, P.S., Imai, Y., Persico, A.M., Ozenberger, B.A., Eppler, C.M., Uhl, G.R., 1994. cDNA cloning of an orphan opiate receptor gene family member and its splice variant. FEBS Lett. 348, 75–79.

Wang, Z., Gardell, L.R., Ossipov, M.H., Vanderah, T.W., Brennan, M.B., Hochgeschwender, U., Hruby, V.J., Malan, T.P. Jr., Lai, J., Porreca, F., 2001. Pronociceptive actions of dynorphin maintain chronic neuropathic pain. J. Neurosci. 21, 1779–1786.

Waterfield, A.A., Hughes, J., Kosterlitz, H.W., 1976. Cross tolerance between morphine and methionine–enkephalin. Nature 260, 624–625.

Watkins, L., Mayer, D., 1982. Organization of endogenous opiate and nonopiate pain control systems. Science 216, 1185–1192.

Watson, D., Tellegen, A., 1985. Toward a consensual structure of mood. Psychol. Bull. 98, 219–235.

Watson, D., Clark, L.A., Tellegen, A., 1988. Development and validation of brief measures of positive and negative affect: the PANAS Scales. J. Pers. Soc. Psychol. 54, 1063–1070.

Watson, D., Wiese, D., Vaidya, J., Tellegen, A., 1999. The two general activation systems of affect: structural findings, evolutionary considerations and psychobiological evidence. J. Pers. Soc. Psychol. 76, 820–838.

Wick, M.J., Minnerath, S.R., Lin, X., Elde, R., Law, P.Y., Loh, H.H., 1994. Isolation of a novel cDNA encoding a putative membrane receptor with high homology to the cloned mu, delta, and kappa opioid receptors. Brain Res. Mol. Brain Res. 27, 37–44.

Wiens, S., Mezzacappa, E.S., Katkin, E.S., 2000. Heartbeat detection and the experience of emotions. Cogn. Emot. 14, 417–427.

Williams, K.L., Ko, M.C., Rice, K.C., Woods, J.H., 2003. Effect of opioid receptor antagonists on hypothalamic–pituitary–adrenal activity in rhesus monkeys. Psychoneuroendocrinology 28, 513–528.

Woolf, C.J., Salter, M.W., 2000. Neuronal plasticity: increasing the gain in pain. Science 288 (Jun 9).

Xie, T., Ho, S.L., Ramsden, D., 1999. Characterization and implications of estrogenic down-regulation of human catechol-*O*-methyltransferase gene transcription. Mol. Pharmacol. 56, 31–38.

Yamada, K., Nabeshima, T., 1995. Stress-induced behavioral responses and multiple opioid systems in the brain. Behav. Brain Res. 67, 133–145.

Yamamoto, T., Shimura, T., Sako, N., Yasoshima, Y., Sakai, N., 1994. Neural substrates for conditioned taste aversion in the rat. Behav. Brain Res. 65, 123–137.

Zadina, J.E., Hackler, L., Ge, L.-J., Kastin, A.J., 1997. A potent and selective endogenous agonist for the mu-opiate receptor. Nature 386, 502–505.

Zubieta, J.K., Dannals, R., Frost, J., 1999. Gender and age influences on human brain mu opioid receptor binding measured by PET. Am. J. Psychiatry 156, 842–848.

Zubieta, J.K., Smith, Y., Bueller, J., Xu, Y., Kilbourn, M., Meyer, C., Koeppe, R., Stohler, C., 2001. Regional mu opioid receptor regulation of sensory and affective dimensions of pain. Science 293, 311–315.

Zubieta, J.K., Smith, Y., Bueller, J., Xu, Y., Woike, T., Kilbourn, M., Meyer, C., Koeppe, R., Stohler, C., 2002. Mu-opioid receptor mediated antinociception differs in men and women. J. Neurosci. 22, 5100–5107.

Zubieta, J.K., Stohler, C., Bueller, J., Xu, Y., Heitzeg, M., Smith, Y., 2003a. Estradiol regulation of μ-opioid mediated pain stress responses. Abstr.-Soc. Neurosci., 660–663.

Zubieta, J.K., Ketter, T.A., Bueller, J.A., Xu, Y., Kilbourn, M.R., Young, E.A., Koeppe, R.A., 2003b. Regulation of human affective responses by anterior cingulate and limbic mu-opioid neurotransmission. Arch. Gen. Psychiatry 60, 1145–1153.

Zubieta, J.K., Heitzeg, M.M., Smith, Y.R., Bueller, J.A., Xu, K., Xu, Y., Koeppe, R.A., Stohler, C.S., Goldman, D., 2003c. COMT val158met genotype affects mu-opioid neurotransmitter responses to a pain stressor. Science 299, 1240–1243.