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Perspective

Common Brain Mechanisms of Chronic Pain and Addiction

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While chronic pain is considered by some to be a CNS disease, little is understood about underlying neurobiological mechanisms. Addiction models have heuristic value in this regard, because both pain and addictive disorders are characterized by impaired hedonic capacity, compulsive drug seeking, and high stress. In drug addiction such symptomatology has been attributed to reward deficiency, impaired inhibitory control, incentive sensitization, aberrant learning, and anti-reward allostatic neuroadaptations. Here we propose that similar neuroadaptations exist in chronic pain patients.

Epidemiological and Clinical Context

Pain is critical for the survival of organisms. It is also, especially when chronic, a reason the lives of so many people become unbearable. In addition to immeasurable suffering, chronic pain remains one the most challenging problems faced by clinicians and health care policy makers by afflicting more than 120 million Americans and costing an estimated $600 billion annually (Gaskin and Richard, 2012; Nahin, 2015) due to loss of productivity, medical expenses, and long-term disability (Institute of Medicine, 2011). The following facts call for novel insights informing better prevention, diagnosis, and management of chronic pain patients. First, the preceding numbers are rising steadily (Freburger et al., 2009), notwithstanding the overall improving standard of health care. Second, the currently available analgesics, including opioids, are inefficient in about 70% of patients in pooled analyses of placebo-controlled trials (Gilron et al., 2005). Finally, even though CNS involvement in pain is well recognized and encoded in the International Association for the Study of Pain (IASP) definition as ''emotional experience associated with actual or potential tissue damage'' (Merskey and Boduk, 1994), there is still a black box between advances in the understanding of clinical symptomatology and effective analgesic strategies, along with basic mechanisms.

Pain and Reward

Sensory abnormalities are commonly understood to be central features of chronic pain. Here, however, pain is postulated to be a disorder of reward function. This is a time-honored perspective. Formulated around the 6^{th}–5^{th} century BCE by Anaximander, Heraclitus, and Pythagoras and refined about 2,500 years later by Fichte and Hegel, unity of opposites is a core tenet of dialectic philosophy, analogous to the yin and yang laws of nature that have been steering traditional Chinese healing practices for more than 3 millennia. Dostoevsky and Nietzsche expanded this concept to the holistic and indivisible pain-pleasure amalgamation, while Spinoza upheld the pain-pleasure continuum by designating them opposite anchors of the perfection scale. Despite being one of many legitimate ways in which pain might be operationalized, this approach has several advantages. First, the concepts of reward and motivation rest on a firm body of basic and clinical research. Second, their activities are regulated in accordance with homeostatic principles maintaining stability in response to environmental challenges. Third, avoiding pain and seeking pleasure are linked to opposing defense or avoidance versus approach motivational drives that shape the behavior of humans and other species. Fourth, pain relation to reward has been extensively documented.

Key Terms

Reward is defined as an integrated set of hedonic (i.e., pleasurable) and motivational processes occurring at both conscious and unconscious levels and eliciting cognitive and behavioral responses (Berridge and Robinson, 2003). In contrast, pleasure encompasses a variety of positive affective states, supporting gratification of immediate needs (e.g., food, water, and sex), along with social behaviors (e.g., attachments, community affiliation, and pursuit of excellence). Still, pleasure is distinct from euphoria, which is a more specific affective state of well-being, self-confidence, and sociability. Motivation refers to conscious and unconscious psychological constructs that normatively link biological, emotional, social, or cognitive needs with behaviors aimed at their fulfillment while optimizing pleasure and avoiding harm.

Stress is implicated across the entire spectrum of painful phenomena, be it chronic back pain (Vachon-Presseau et al., 2013), migraine (Hedborg et al., 2011), or fibromyalgia (Van Houdenhove and Luyten, 2006). Chronic pain may be viewed as a self-amplifying stressor that contributes to the allostatic load (described later) by impairing sleep and autonomic function, as well as by promoting systemic inflammation (Borsook et al., 2012). These may be worsened by ongoing psychosocial problems, including fear (De Peuter et al., 2011), catastrophizing (Quartana et al., 2009), and depression (Fishbain et al., 1997), on top of social, employment, or financial concerns. In

consequence, stress denotes a broad entity that is addressed here from cognitive, emotional, endocrine, psychopathological, molecular, and neurobiological standpoints.

Outline

Addiction serves as a comparison framework for understanding pain because of its distinctive disruptions of hedonic homeostasis. This comparison is taken as a basis for the hypothesis on the role of early-onset pain-induced neuroadaptations in the pathogenesis of chronic pain syndromes. To that end, we integrate prevailing and complementary theories on the nature of addiction. We also argue that dimensional and interactive measures, rather than a categorical adherence to a single theoretical framework, are essential for a comprehensive clinical and scientific formulation of the complex biopsychosocial pain phenomena.

Thus, in addition to a general introduction of the paper's main themes, we have provided the epidemiological and clinical context of the discussed entities and defined the key terms. The next section summarizes the current understanding of neurobiology of pain as it is involved in sensory, emotional, and reward function. The Reward and Addiction sections pertain to the prevailing models of reward and addiction, respectively. Homeostatic concepts are used here to illustrate normative hedonic function and to compare it to the allostatic load underlying chronic pain as discussed in the next section, which is the main portion of the paper. In the Therapeutic Considerations section, specific evidence for testable hypotheses on psychotherapeutic and psychopharmacological interventions is deliberated. The final section presents a summary and conclusions.

Pain Is a Complex Biopsychosocial Entity

Chronic Pain: Involvement of the CNS

Acute pain is essential for survival, because it calls for immediate action by retreating from the harmful factor or by preventing motion to promote healing. Acute nociceptive pain, caused by the activation of nociceptors, is a symptom of the underlying medical condition that tends to parallel its severity and to end with the disappearance of the primary cause (e.g., damaged and subsequently healed tissue).

This is not so for chronic pain, which per the current IASP definition lasts for more than 3 months and has no survival value (Kehlet et al., 2006). The transition from acute to chronic pain is not fully defined (Katz and Seltzer, 2009). It involves both spinal cord and brain alterations at numerous levels that were recently defined as the dynamic pain connectome (Kucyi and Davis, 2015). The symptoms may manifest in spontaneous pain or in exaggerated responses to painful (hyperalgesia) and normally non-painful (allodynia) stimuli, in combination with negative affective and cognitive states and a persistent desire to eliminate pain via behavioral or pharmacologic measures (Apkarian et al., 2009). Chronic neuropathic pain is caused by damage to the nervous system or by inadequately treated nociceptive pain (Apkarian et al., 2009). The demarcation of nociceptive and neuropathic types of pain may be blurred, however, because both are associated with sensitization of the peripheral and/or central neurons due to their recurring, forceful, and sustained stimulation by reason of tissue damage with ensuing release of toxic and inflammatory compounds. Whereas mixed pain conditions (both nociceptive and neuropathic) are quite common (Blond et al., 2015), it is important to segregate them, because the latter component does not respond well to conventional analgesic therapy (Gilron et al., 2005), presumably due to alterations of the CNS (Borsook et al., 2013).

Classification of Pain

In addition to the acute or chronic and nociceptive or neuropathic dichotomization, pain can be characterized based on its peripheral source, pathophysiology, nociceptive quality, location, distribution, or intensity (Table 1). All of these characterizations share the aversive component and are modulated by numerous factors, including genes, gender, cognitive interpretation, emotional or motivational context, neuropsychopathology, concentrations of endorphins, and other hormones, as well as cultural, social, and religious milieu (Institute of Medicine, 2011).

Hence, an attempt to understand pain faces an initial major question: How should one define and operationalize this hackneyed concept that has been given nearly as many definitions as there are treatises that have dealt with it? "Pain" may be used to describe phenomena ranging from the emotional consternation experienced by a rejected lover, i.e., psychache (Shneidman, 1998), to biological changes occurring in a wounded soldier pinned down by enemy fire. One meaningful classification is linked to syndromes with and without obvious medical etiology (Table 1), e.g., pain caused by mechanical, thermal, chemical, ischemic, inflammatory, or oncogenic tissue injury versus pain that is functional (i.e., biological function is affected by emotional factors) or psychogenic (without identifiable biological factors).

Neurocircuitry of Pain

Biological pain domain comprises the neural sensory apparatus, viz., nociceptors, afferent neurons (converging at the spinal cord's dorsal root ganglia) with their prolongation in afferent spinal and brainstem pathways (e.g., the lateral spinothalamic tract) and projections to the brain regions that include the thalamus, nucleus accumbens (NAc), and amygdala (Figure 1). Before interpretation by the primary and secondary somatosensory cortices, nociceptive signals may be inhibited or amplified (Eippert et al., 2009; Fields, 2004). This generates respective placebo or nocebo effects at the dorsal horn level by way of the descending modulation system that integrates internal body and environmental information with pain-related affective states and behaviors. Higher-level brain regions (e.g., the cingulate gyrus and insular cortex) are involved in the modulatory influences through connections to the brain stem nuclei, such as the periaqueductal gray matter (PAG; Lau and Vaughan, 2014). The same limbic structures, alongside the reticular formation nuclei (arousal), superior colliculus (motoric orientation), parabrachial nucleus, and hypothalamus (autonomic processes and neuroendocrine stress-like output), receive pain-related input from the medial spinothalamic tract via the medial thalamic and brain stem nuclei. They then mediate emotional, motivational, and cognitive aspects, including subjective averseness, and prompt defensive responses, salience, and fear. The prefrontal cortex (PFC) is entrusted with the pain's conscious appraisal, enhancement, and suppression, as well as with planning, learning, and contextualizing (Freund et al., 2007). Taken together, the preceding characteristics indicate that biological, psychosocial, and

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Table 1. Methods of Pain Classification

Etiology	Characteristic	Types	
Obvious medical	duration	acute and chronic	
		continuous and episodic	
	pathophysiology	nociceptive and neuropathic	
		physiological and pathological	
		cancer and non-cancer	
	source	peripheral	type of tissue (e.g., muscle, skeleton, blood vessels, or peripheral nerves) or location (e.g., back, head, or abdomen)
		CNS	immune, degenerative, or trauma (e.g., thalamic pain syndrome)
	type of injury	mechanical, thermal, chemical, ischemic, inflammatory, oncogenic, etc.	
	nociceptive quality (type of fibers)	burning, throbbing, or stabbing	
	distribution	diffused, focused, or referred	
	intensity	mild, moderate, severe, or excruciating	
Unobvious medical	functional	reward or motivational aberrations as the primary etiology for impaired biological function, e.g., headaches or cardiac ischemia due to blood vessels constriction in the context of stress or other negative affective states	
	psychogenic	reward or motivational aberrations as the primary etiology for pain without identifiable impaired biological function, e.g., fibromyalgia, irritable bowel syndrome, vulvodynia, temporomandibular disorders, or somatic symptom disorder with predominant pain	

behavioral manifestations of pain represent an inseparable and overlapping continuum. This continuum affects pain at both the spinal cord level, via nociceptive signal transduction, and the level of the brain circuits mediating reward, motivation, and cognition, via expectancy, interpretation, and emotional coloring.

A link between "unpleasant sensory and emotional experience" (Merskey and Boduk, 1994) of pain and gloomy perspectives forms the attitude of misery and suffering that is reinforced by pain behavior (e.g., facial expressions, stereotypic actions, and complaining). The assumed sick role with consequent secondary gains (e.g., attention, pity, and exemption from routine chores) eventually evolves in susceptible individuals into preoccupation and compulsive seeking of pain relief that inevitably engulfs significant others, colleagues, and members of the treatment team. Emotional pain is inherent in social setbacks and losses stemming from dysfunctional communication styles. Contrary to the schematic overview (Figure 2), in real life, it may be difficult to specifically account for each of the displayed components, because pain can be solely derived from emotional or social sources in the absence of nociception that may not produce pain (Navratilova and Porreca, 2014). In the words of William Styron (1989): "the gray drizzle of horror induced by depression takes on the quality of physical pain. It is also stated in "a forgotten poem…entitled 'The Author's Abstract of Melancholy'; or, 'A Dialogue between Pleasure and Pain.' Here pain is melancholy" (Burton, 2001).

Chronic pain is not a unitary problem mediated by an isolated mechanism or a neurotransmitter. On the contrary, this hierarchical, multidimensional entity, which is frequently devoid of recognizable nociceptive input (Baliki et al., 2010), represents integration of higher-order emotional and motivational functions and, derived from them, lower-order cognitive, behavioral, and social manifestations. Each of these plays a specific role within an extensive biopsychosocial system of chronic pain. It is therefore useful to segregate this multidimensional system into domains based on the underlying circuitry or function comparably to the Research Domain Criteria (RDoC): explicitly, positive valence, negative valence, cognition, social processing, and arousal (Cuthbert, 2015). Addressing each domain separately (e.g., reward and hedonic homeostasis, as discussed in the sections that follow) may provide a sound footing for understanding potential interactions among domains and their roles in the phenotypic expression of pain.

Reward

Neurobiology of Reward

The neurobiology of reward has been reviewed in detail elsewhere (Elman et al., 2006), but some elements are briefly presented here. Dopamine neurons in the ventral tegmental area (VTA) and their projections into the NAc, along with the striato-nigro-striatal circuit linking the NAc shell to the dorsal striatum, constitute the critical element of the brain reward and reinforcement circuitry. Dopamine level increase in the NAc is a common element of natural reward, as well as of drugs of abuse. The physiological and pathophysiological significance of this occurrence remains a subject of complementary hypotheses, including subjective pleasure or high (reward) sought by drug users. Others include motivation, salience, conditioned learning of stimulus-reward association (Gardner, 2011; Koob and Volkow, 2010), analgesia (Xie et al., 2014), descending CNS modulation of nociceptive peripheral stimuli

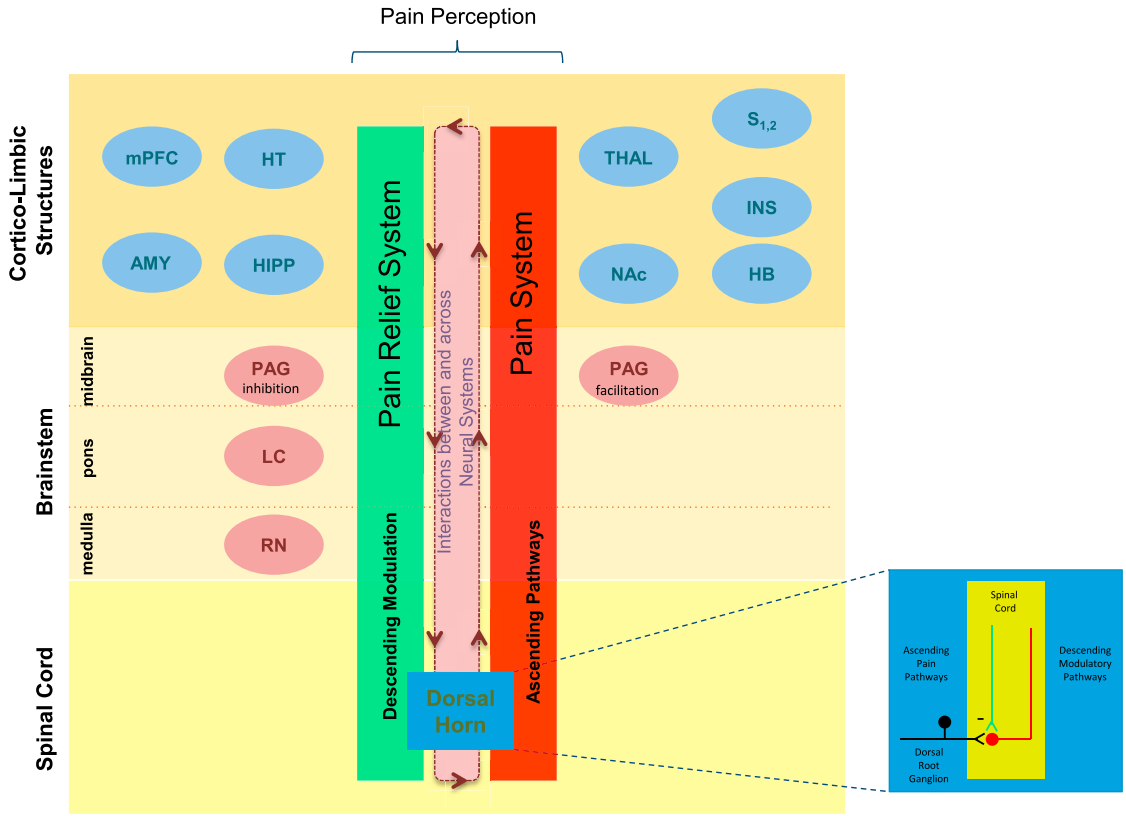

Figure 1. Putative Model of the Integrated and Reciprocally Coordinated Pain and Analgesia Systems Determining Net Pain Perception
Peripheral noxious stimuli are detected by nociceptors and propagated along primary afferent neurons to converge at the level of the dorsal root ganglion (DRG). The DRG is the origin of the spinothalamic tract relaying the nociceptive sensory information to the primary and secondary somatosensory cortices ($S_{1,2}$) via excitatory neurotransmission (e.g., glutamate and substance P). The flow of painful stimuli is diminished or amplified at the DRG level by the pain modulatory system composed of the dynamically communicating cortico-limbic structures and brain stem nuclei. Nociceptive stimuli are interpreted at the level of the cortico-limbic structures and, based on survival needs and other modulating variables, may activate the endogenous analgesia system, releasing opiates, serotonin (5-hydroxytryptamine), GABA, or norepinephrine suppressing the DRG nociceptive signals. The periaqueductal gray matter (PAG) integrates nociceptive data arriving from the ascending pain pathways—with an extensive contribution from the superior cortical and subcortical structures, including the medial prefrontal cortex (mPFC), amygdala (AMY), thalamus (THAL), nucleus accumbens (NAc), hypothalamus (HT), insula (INS), and habenula (HB)—to regulate the descending pain modulation system by the inferior brain stem nuclei, including the nucleus tractus solitarius, parabrachial nucleus, locus coeruleus (LC), and raphe nuclei (RN). The HB modulates pain intensity, aversion, and motor responses and is part of the anti-reward system that becomes activated with exposure to negative reinforcers (i.e., aversive stimuli). This is in contrast to the NAc, which is part of the reward system that becomes activated by positive reinforcers (i.e., reward). The hedonic value attributed by the AMY to a particular event weakens or strengthens particular memories stored in the hippocampus (HIPP).

(Elman et al., 2013), and discrepancy between stimuli actual and anticipated value, i.e., prediction error (Knutson and Cooper, 2005).

The VTA to the NAc pathway's activity is modulated by other cortical and subcortical structures, including those involved in pain, stress, emotions, mood, memory, and arousal (Hikosaka et al., 2008). Thus, the medial prefrontal cortex (mPFC), composed of the cingulate gyrus and orbitofrontal cortex, is involved in the coding of prediction error. Other key mPFC functions include integration of peripheral and environmental stimuli for exercising cognitive control over drives and emotions (Goldstein and Volkow, 2002) and for performing (in conjunction with more lateral cortical areas) contextual framing of time. This is done by discounting reward valuation proportionally to the predicted postponement in its delivery (i.e., delay discounting; Knutson and Cooper, 2005). The amygdala is also involved in reward (Janak and Tye, 2015) by processing both positive and negative reinforcement, in conjunction with the associations among arousing, sensory, and emotional stimuli properties (Janak and Tye, 2015).

Opioid neurotransmission within the scattered network of subcortical (e.g., NAc, VTA, ventral pallidum, and hypothalamus) and brain stem (e.g., PAG) nuclei is another fundamental reward component (Leknes and Tracey, 2008). In addition to facilitating dopamine release in the NAc, both endogenous and exogenous opioids encode valence that is consciously interpreted along the continuum of pleasure to aversion in the mPFC (Berridge and Kringelbach, 2015). Such opioids' actions are determined by the type of receptors that are activated. The μ and δ or κ opioid receptors, respectively, facilitate or suppress dopamine release while mediating pleasurable and aversive (e.g., dysphoria, irritability, and physical and emotional pain) effects (Wise and Koob, 2014). Another key functional reciprocity is between mesolimbic and habenula neurons

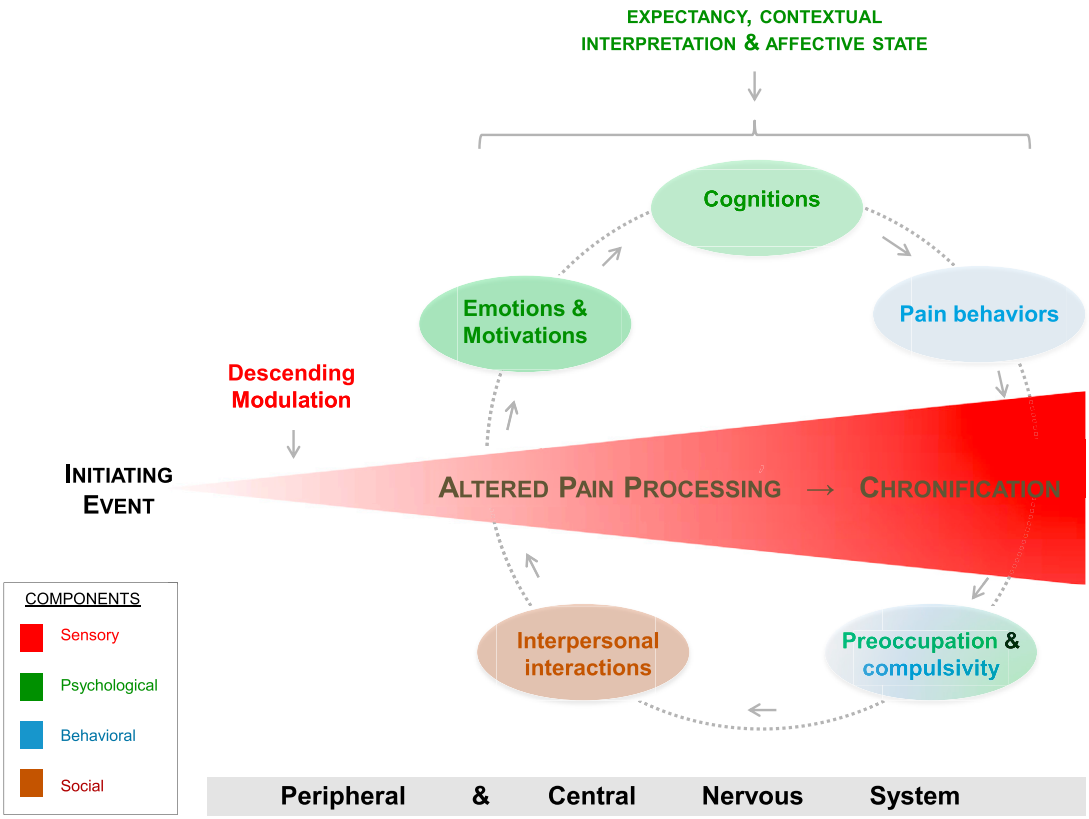

Figure 2. Typical Evolution of a Chronic Pain Syndrome

Tissue or nerve damage is detected by nociceptors. The flow of nociceptive information is amplified or diminished at the level of the spinal cord's dorsal horn (Eippert et al., 2009) by descending modulation from higher centers before interpretation as acute pain in the cortical and subcortical areas (Tracey, 2010). The figure depicts the transition from tissue or nerve damage, detected by nociceptors, to dysregulation of homeostatic reward processes leading to impairments in sensory, psychological, behavioral, and social functions.

(Elman et al., 2013). The latter increase their firing when an expected reward does not materialize to predictors of reward and decrease their firing when an expected reward does occur. Thus, the habenula (with input from the limbic system structures and the basal ganglia) provides an inhibitory tone to the mPFC and the NAc dopaminergic neurons through the interpeduncular and the rostromedial tegmental projections and turns off reward function during conditions of stress and pain (Lee and Goto, 2011). Other major neurotransmitter systems contributing to aversive states, including serotonin (Kalén et al., 1989), norepinephrine, and acetylcholine (Lecourtier and Kelly, 2007), are regulated by the habenula via, respectively, the raphe nuclei, locus coeruleus, and nucleus of Meynert. Reward function is also inhibited by the γ-aminobutyric acid (GABA) neurons extending from the NAc back to the VTA, the glutamatergic neurons extending from the mPFC and stria terminalis to the VTA and from the hippocampus to the NAc (Kalant, 2010), and the orexinergic pathways (Elman et al., 2006).

Hedonic Homeostasis

The body caloric and water content balances are maintained via tightly synchronized homeostatic processes. Therefore, a compelling a fortiori argument could be that the reward or motivation circuitry promoting behaviors necessary for survival, including eating and drinking, is also subject to homeostatic control (Elman et al., 2006). The major interface among homeostatic, motivational or emotional, and motor components is located within the lateral hypothalamus (LH). This brain region is involved in reinforcement and is interconnected with the major hypothalamic nuclei, implicated in the metabolic sensing, and with the brain stem nuclei, which mediate eating-related motor function and autonomic activity (Elman et al., 2006). The LH is also involved in pain through sensory mechanisms (Ezzatpanah et al., 2015) and learning mechanisms (Berthoud and Münzberg, 2011). Reward homeostat (i.e., hedonostat), located within the NAc, compares dopamine concentrations perturbed by proponent stimuli's primary emotional and motivational qualities—be they aversive, appetitive, pleasant, or unpleasant—with a set point for responding, as determined by integrated input from the LH, PFC, amygdala, habenula, insula, and other regulators (Figure 3). The negative feedback loop is closed. Deviations from such a set point are buffered by the opponent (i.e., opposite the original changes) hedonostat's effectors that readjust dopamine synthesis, its release, and signaling to the preperturbation level, in conjunction with emotional or motivational states driving approach or avoidance behaviors.

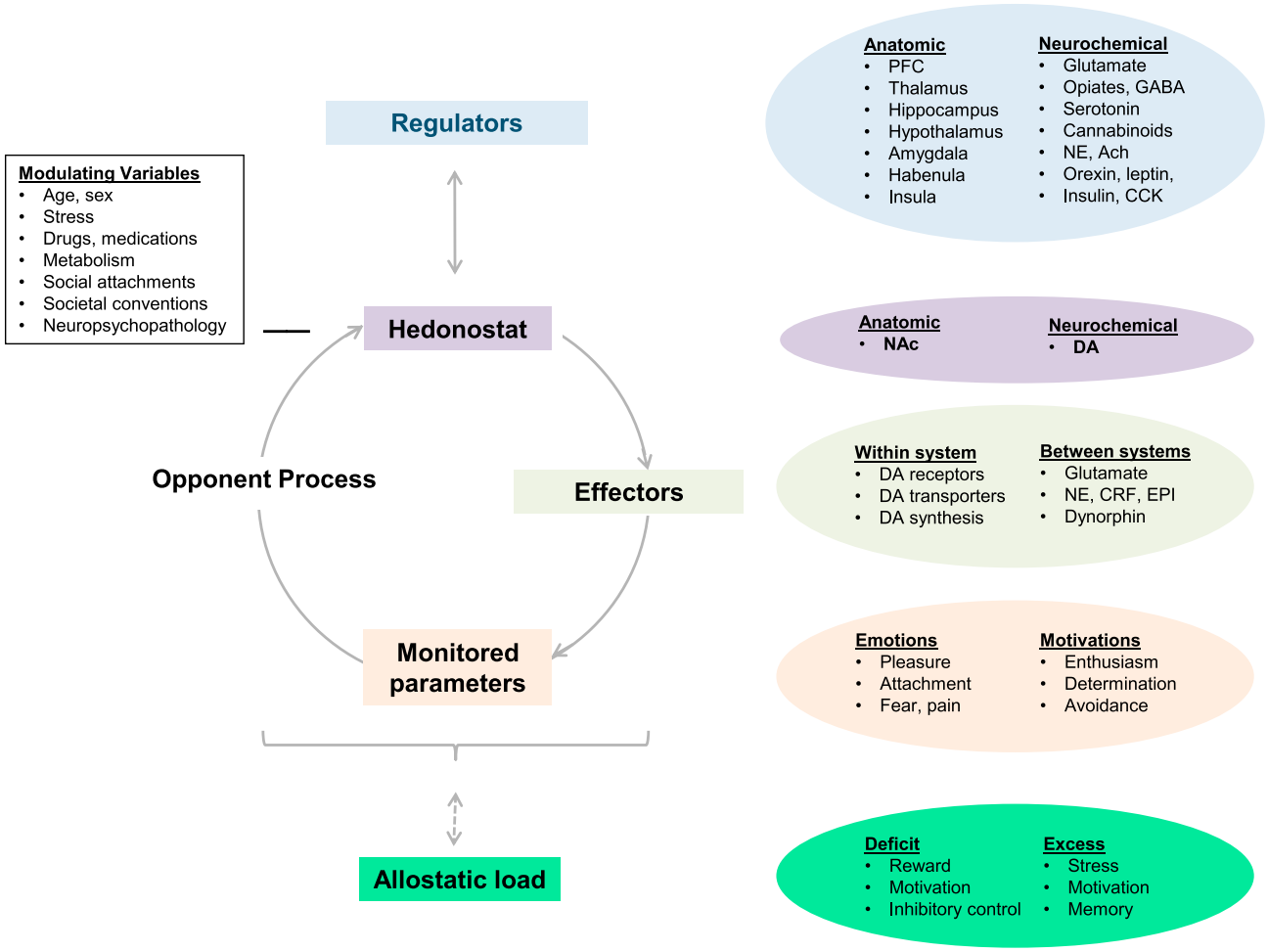

Figure 3. Schematic Overview of the Hedonostatic System of Emotions and Motivations

Anatomic and neurochemical regulators, i.e., the prefrontal cortex (PFC), exert top-down control for bottom-up dopamine (DA) signals coming from the medial forebrain bundle connecting the ventral tegmental area to the nucleus accumbens (NAc) in response to natural and pharmacological reward. The integrated information is compared to the regulated set point determined by the PFC, along with the amygdala, hypothalamus, habenula, and insula, and is modulated by countless variables (stress, drugs, metabolism, social attachments, societal taboos and prohibitions, and neuropsychopathology). In a case of discrepancy, DA changes are opposed via an opponent negative feedback loop by regulating within the DAergic system and between the system's effectors; all contribute to emotional or motivational states with resultant drives to seek pleasure and avoid aversion. Robust and sustained increases in DAergic trafficking induced by addictive substances or pain override homeostatic feedback control to generate excess- and deficit-type allostatic neuroadaptations of reward or motivational circuitry that is unchecked by physiological negative feedback mechanisms. Ach, acetylcholine; CCK, cholecystokinin; CRF, corticotropin-releasing factor; EPI, epinephrine; GABA, γ-aminobutyric acid; NE, norepinephrine.

Addiction

Addiction Is an Allostatic State

The well-orchestrated homeostatic opponent machinery (Figure 3) is infallible in the maintenance of reward equilibrium and for the stabilization of emotional states and motivational drives in the course of routine life events (Solomon and Corbit, 1974). However, robust and sustained increases in dopaminergic trafficking induced by addictive substances override homeostatic feedback control to generate allostatic neuroadaptations of reward or motivational circuitry that is unchecked by physiological negative feedback mechanisms (Figure 4).

Integration of Prevailing Theories on Addiction

Types of the interaction (i.e., competitive, additive, or synergistic), along with the nature of the neuroadaptations (e.g., reward deficiency, incentive sensitization, aberrant learning, or anti-reward, as explained later) and modulating variables (e.g., stress, pain, metabolism, and preexisting neuropsychopathology), determine the overall deficient or excessive (i.e., sensitized) directionality of the reward or motivational dysfunction (Table 2). Competition may be the most visible interaction, because addictive substances initially activate dopaminergic neurotransmission but over time produce the opposite within system adaptation. This is characterized by hypofunctionality of the brain circuits mediating reward and motivation and clinically noticeable as diminution of drives and capacity to experience pleasure (Volkow et al., 2005), viz., reward deficiency syndrome (Blum et al., 1996). In the reversed order, the deficient resting state in tonic dopaminergic neurotransmission in the NAc and PFC

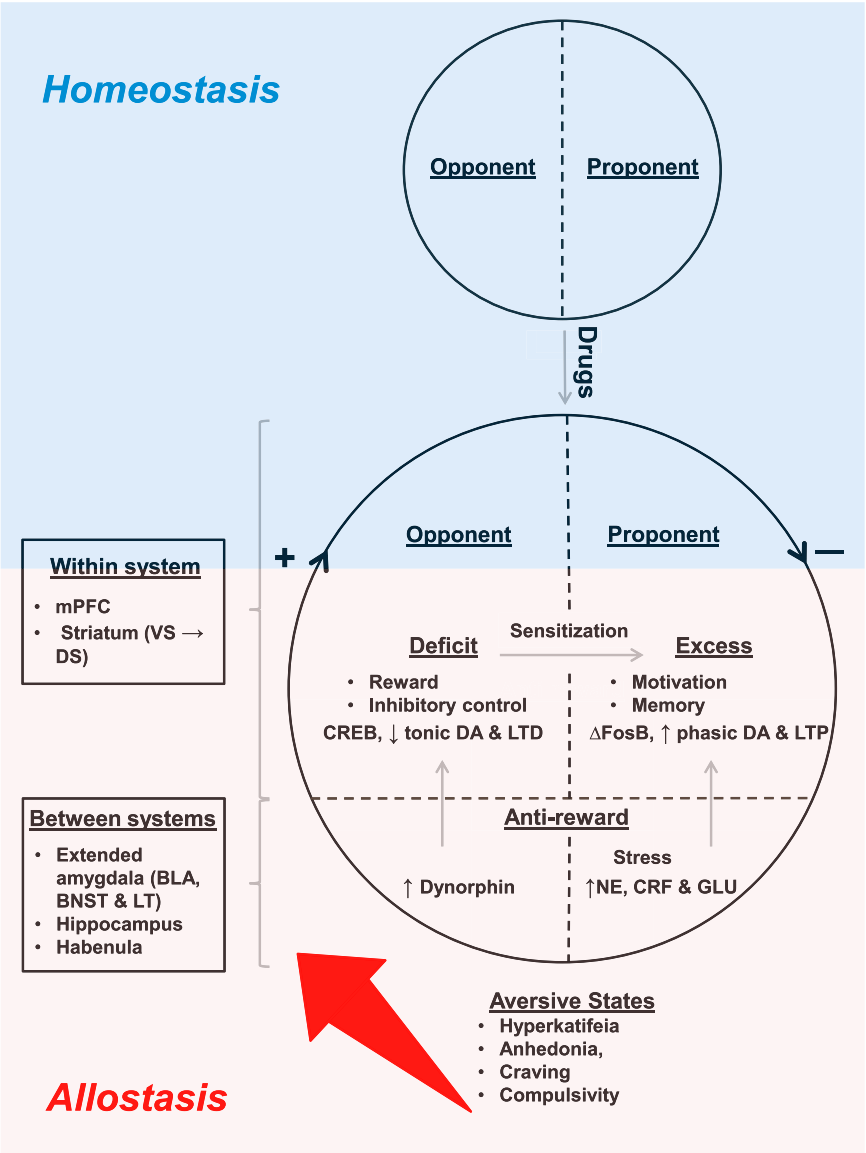

Figure 4. Schematic Overview Integrating Incentive Sensitization, Aberrant Learning, Impaired Inhibitory Control, Opponent and Anti-reward Addiction Theories

The circumference represents the spiraling distress cycle (Koob and Le Moal, 2001), whereby addictive drug consumption produces allostatic load in the form of reward deficiency and anti-reward aversive emotional states, leading to further drug consumption. This provides momentary relief but eventually increases averseness and craving, contributes to progressive worsening of the clinical condition, and evolves to bona fide addiction. + represents stimulation, and – represents inhibition. BLA, basolateral amygdala; BNST, bed nucleus of the stria terminalis; CREB, cAMP response element binding protein; CRF, corticotropin-releasing factor; DA, dopamine; DS, dorsal striatum; GLU, glutamate; LT, lateral tegmentum; LTD, long-term depression; LTP, long-term potentiation; mPFC, medial prefrontal cortex; NE, norepinephrine; ΔFosB, truncated splice variant of a protein encoded by the fosB gene; VS, ventral striatum.

sets in motion robust augmentation of phasic dopamine responses to drugs and, via conditioning, to drug-related cues (Volkow et al., 2005). These cues are manifested in their sensitized rewarding and reinforcing properties (Elman et al., 2002).

The mounting allostatic load may be added or synergized by the anti-reward cross-sensitization process (Elman et al., 2012). This is an autonomous, self-sustaining feedforward loop, whereby prior exposure to one stimulus (e.g., drug) increases subsequent response to itself and to a different stimulus (e.g., another drug, stress, or pain). The causality could run in the opposite direction so that a trivial stress instigates dopamine releases, thus priming craving and further escalating the vicious cycle of addiction. The involvement of sensitization in the pathophysiology of addiction is a matter of consensus (e.g., drug-induced locomotor effects). However, its varying roles and correspondingly affected brain regions are defined by complementary and partially overlapping theories addressing both within-system (dopaminergic) and between-system (i.e., anti-reward) neuroadaptations.

The former type of neuroadaptation encompasses incentive sensitization and aberrant learning pertaining, respectively, to sensitized motivational targets (Berridge and Robinson, 2003) and to overlearned motivational significance of conditioned cues (Hyman, 2005). According to incentive sensitization theory derived from rodent data, drug-induced changes in the mesolimbic dopaminergic circuitry, including dopamine terminal fields (e.g., the striatum, amygdala, and PFC), are responsible for assigning excessive motivational value to a particular object relative to the emotional experience that it evokes. This is construed to be an animal homolog of human craving (Berridge and Robinson, 2003).

A closely related learning theory, surmised primarily from primate work, postulates that learning of new reward or expectancy of old ones is encoded via interactions between tonic (baseline) and phasic spikes in dopaminergic neurons (Volkow et al., 2005; Schultz, 2001). Reinforcement learning directs behavioral choices en route for obtaining reward and avoiding punishments. Both are mediated via a series of prediction errors generated by the contrasted values of the experienced versus the expected stimuli and are encoded as phasic dopaminergic spikes in the striatum and midbrain neurons (Daniel and Pollmann, 2014; Samejima et al., 2005; Schultz et al., 1997). According to the principles of Bayesian probabilistic models (Rutledge et al., 2014), unexpected outcomes elicit prediction errors, shaping behavioral choices to become proportionally matched to the rates of

Table 2. Key Characteristics of the Prevailing Addiction Theories

Theory	Function	Mechanism		Clinical Features	Role in Addiction	Brain Regions	Type	
		Neural	Cellular					
Opponent	homeostasis	antagonistic response to the stimulus's primary qualities (be they aversive, appetitive, pleasant, or unpleasant)	adjustments in postsynaptic DA receptors, DA synthesis and release, and presynaptic DA transporters	low and sluggish at the onset; later grows to define the intensity and valence of the affective and motivational states	if fails → allostatic load → reward deficiency, sensitization, and anti-reward	not well defined: there are states that "have little or no opponent process" (Solomon and Corbit, 1974)	NA	within system
Inhibitory control	executive (salience attribution and processing of contingencies and outcomes)	hypofrontality: ↓ cerebral volume, metabolism, and blood flow at baseline when challenged by cognitive tasks or exposed to natural reinforcers (Garavan et al., 2000)	diminished DAergic tone with glutamate receptor restructuring and corresponding ↓ tonic glutamatergic activity (Lüscher and Malenka, 2011; Kalivas and Volkow, 2005)	↓ rational brakes on motivational drives	↓ control of drug urges and consumption	VTA and DAergic terminal fields (striatum, amygdala, and PFC)	deficit	
Cognition and decision making		impaired cognitive components of motivation and act-outcome representations (Robinson and Berridge, 2003)		↓ planning, problem solving, and cognitive flexibility	impulsivity and irrational choices (Heyman, 2013; Bari and Robbins, 2013)			
Reward deficiency	reward	repeated artificial ↑ DA → dysfunctional hypo-DAergic state	DA depletion-like state and ↑ CREB	emotional numbing, anhedonia, and ↓ responsivity to natural reinforcers	negative reinforcement: consumption of addictive drugs temporarily alleviates anhedonia			
					positive reinforcement: reward deficiency enhances drug use via amplification of its rewarding and reinforcing effects (Elman et al., 2002)			
Incentive sensitization	motivation	Pavlovian valuation system: value is assigned to the drug, but the motivation to pursue is disproportionally higher than that	hypo-DAergic state → sensitization: up- or downregulation in gene expression, potentiation and depression of synaptic strength,	excessive (relative to the hedonic valuation) motivation to pursue and to consume drugs	craving		excess	

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Table 2. ***Continued***

Theory	Function	Mechanism		Clinical Features	Role in Addiction	Brain Regions	Type	
		Neural	Cellular					
		value, i.e., wanting > liking (Robinson and Berridge, 2003; Rangel et al., 2008)	alterations in neuronal signaling, and ↑ ΔFosB	cross-sensitization with natural reward and stress (Robinson and Berridge, 2003)				
Aberrant learning	motor	habit-valuation system: value is assigned to the pursuit of the drug (based on prior hedonic experiences), and drug seeking is disconnected from its value, i.e., must do versus must have (Everitt, 2014)		disregard of natural reinforcers and of negative consequences	compulsivity and automatized drug use that are unrelated to the overriding goal (Wise and Koob, 2014)	cortico-striato-thalamo-cortical circuit		
Anti-reward	emotional	repeated artificial ↑ DA → ↑ dynorphin, CRF, NE, and glutamate	↑ neuronal excitability	aversive emotional state, anhedonia, and profound craving	negative reinforcement: consumption of addictive drugs temporarily alleviates anhedonia and distress	central and BLA, BNST, lateral tegmental NE nuclei, hippocampus, and habenula		between systems

Mesolimbic system: ventral tegmental area's (VTA's) projections to dopamine (DA) terminal fields (NAc, mPFC, amygdala, hippocampus, and insula). Nigrostriatal system: substantia nigra DAergic projections to the caudate, putamen, and globus pallidus. BLA, basolateral amygdala; BNST, bed nucleus of the stria terminalis; CREB, cAMP response element binding protein; CRF, corticotropin-releasing factor; ΔFosB, truncated splice variant of a protein encoded by the fosB gene; NA, not applicable; NE, norepinephrine; PFC, prefrontal cortex.

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reinforcement. When full matching is attained, the outcomes are predicted and no additional prediction error with consequential learning is occurring. As a consequence, in the context of learned natural reward phasic dopaminergic releases, underlying prediction errors are elicited by unexpected exposure to conditioned cues but not by rewards themselves (Huys et al., 2014).

The matching law (Herrnstein, 1997) posits that matched rates of the reinforced behavior are moderated by competing prediction errors and their correspondingly matched behavioral outcomes (Fernandez and McDowell, 1995; Fields, 2007; Leknes and Tracey, 2008). These outcomes are evoked by novel rewarding or aversive (Mirenowicz and Schultz, 1996) extraneous stimuli, which may be excessive, as is the case for aberrant learning. Drugs of abuse generate supraphysiological prediction errors that underlie enhanced learning of drug cues and their motivational significance (Schultz, 2011). Failure of such artificial prediction errors to become extinct even in the face of omitted reward explicates unrealistic expectations so that drugs are constantly expected to be better than they are actually experienced (Hyman et al., 2006). In due course, addictive drugs establish a habit-based valuation system with a gradual shift of prediction error mediation from the ventral to dorsal striatum. The hedonic value is consequently assigned not to the drug per se but to the actions inherent in obtaining and consuming it, cf., incentive sensitization conceptualization of the diminished hedonic drug's value relative to its motivational significance. The resultant habitual and compulsive behavioral patterns (Volkow et al., 2006) are undeterred by adverse outcomes (Bray et al., 2008) and so fit the definition of insanity attributed to Albert Einstein: ''doing the same thing over and over again and expecting different results.''

In some instances, it might be possible to suggest specificity of the incentive sensitization and aberrant learning mechanisms. Their difference is eloquently captured in must-do versus must-have adages (Rangel et al., 2008; Everitt, 2014). The dissociability is also supported by the preceding qualitatively different neuroanatomical and motivational characteristics. However, a logical alternative interpretation is that aberrant habitual learning (Thorn et al., 2010) represents an extreme end of the incentive sensitization continuum. Learned association is a basic tenant of the sensitization construct: novel memories are forged among emotions, motivations, and behaviors so that they can be re-enacted as a rigid ensemble by a seemingly discrete stimulation (Rome and Rome, 2000; Weiss and Post, 1994). Compatible with the latter assumption, key molecular elements of sensitization, namely, the transiently elevated cyclic AMP (cAMP) response element binding protein (CREB) and the long-standing transcription factors of a truncated splice variant of a protein encoded by the fosB gene (ΔFosB; Dong and Nestler, 2014), act at the incentive-, habit-, and declarative-type learning and memory structures (Koob and Volkow, 2010) of the ventral striatum (where the NAc is located), the dorsal striatum, and the hippocampus (Larson et al., 2010; Kandel, 2012). In this role, they alter the plasticity of the existing synapses (via long-term depression and long-term potentiation, LTD and LTP, respectively) and bolster the creation of new synapses (via neurotrophins, e.g., the brain-derived neurotrophic factor). CREB and ΔFosB roles coincide with additional theoretical formulations, including reward deficiency and excess effects promoting both negative and positive reinforcement (Koob and Volkow, 2010; Dong and Nestler, 2014). Hence, incentive sensitization and aberrant learning are not either-or situations with positive reinforcement and sensitized goal-directed motivational states extant, even in the face of co-occurring habitual and compulsive patterns of drug taking accompanied by reward deficiency (Koob and Volkow, 2010; Dong and Nestler, 2014).

Still, the habitual learning system may preponderate at advanced stages of addictive disorders because it is enabled by between-system adaptation in the form of cue-induced mPFC's phasic glutamatergic output to the already-hypofunctional NAc (Kalivas and Volkow, 2005). The ensuing supplemental decrease in dopaminergic production, amid the developing reward deficiency state, is progressively worsened by the release of the κ opioid receptors' agonist, dynorphin. This is another type of between-system anti-reward neuroadaptation, arising in conjunction with recruitment of the central amygdala (CeA) and basolateral amygdala (BLA) nuclei, the bed nucleus of the stria terminalis, the lateral tegmental noradrenergic nuclei of the brain stem, the hippocampus, and the habenula. These structures, in concert, contribute to massive outpouring of stressogenic norepinephrine, corticotropin-releasing factor (CRF), vasopressin, hypocretin, and substance P evident in stress-like emotional states (i.e., hyperkatifeia), metaphorically termed ''the dark side of addiction'' (Koob, 2015; Koob and Le Moal, 2005).

It is difficult to reverse the ongoing spiraling distress cycle (Goldstein and McEwen, 2002; Koob and Le Moal, 2001), whereby addictive substances' use via negative reinforcement mechanisms provides only momentary relief of reward deficiency and anti-reward symptomatology even as it amplifies substances' rewarding and reinforcing properties via positive reinforcement mechanisms (Elman et al., 2002; Tremblay et al., 2005). Both mechanisms, alongside incentive sensitization and aberrant learning, lead to unrelenting deterioration in emotional and behavioral problems and drive further consumption that eventually transitions from excessive drugging and drinking to bona fide addiction (Figure 4).

In sum, emotions and motivations are essential to adjusting to ever-changing environmental demands. Hedonic homeostasis buffers extreme fluctuations to assure continuous affective stability. Pathophysiological neuroadaptations engendered by addictive substances override homeostatic control. This results in both deficit- and excess-type alterations in reward or reinforcement and in stress systems underlying the multifaceted syndrome of addiction.

Harnessing Addiction Neurobiology for Understanding of Chronic Pain

Clinical and Neurobiological Similarities between Chronic Pain and Addiction

Presently, no clinical studies directly link chronic pain and addiction neurobiology. However, a cumulative body of evidence (discussed later) suggests two ideas. First, there is substantial overlap (Leknes and Tracey, 2008), but not identity (Schultz, 2013), between brain regions that are engaged by ongoing

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pain (Becerra et al., 2001; Scott et al., 2006), its onset (Baliki et al., 2010; Becerra and Borsook, 2008), its offset (Becerra and Borsook, 2008; De Felice et al., 2013), addictive drugs (Koob and Volkow, 2010), and analgesic drugs (Petrovic et al., 2002; Becerra et al., 2006). Second, proclivity for addictive behavior is ingrained in pain neuropathology because of neural changes that are comparable to long-term substance abuse even in the absence of prior drug consumption. The adaptation of these ideas lends strength to the subsequently discussed proposition that pain and addiction may be explained by recursive, partly shared neural systems.

Both types of stimuli are associated with massive dopaminergic surges in reward, motivation, and learning centers, albeit not entirely on the same timescale (Schultz, 2007; Becerra et al., 2013). By their chronic nature, this leads to pervasive effects (e.g., aversion and distress) with consequent rigidly focused motivational states, e.g., craving, or its pathophysiologic analogs of irresistible urges to seek and consume analgesic drugs, and catastrophizing (Elman et al., 2011). Moreover, placebo and nocebo effects are enhanced and diminished, respectively, by opioidergic and mesolimbic dopaminergic activity (Scott et al., 2008; Tracey, 2010; Peciña and Zubieta, 2015). In this regard, akin to behavioral and chemical addictions (Everitt, 2014), pain chronicity lacking discernible nociceptive input (e.g., fibromyalgia or somatic symptom disorder with predominant pain) may be attributable to evolutionary embedding within the neural network. Such embedding is responsible for repetitious actions essential for the existence of individuals and species via pursuit of food, water, and sex, as well as via learning, decision making, and harm avoidance.

A possible commonality area involves molecular and cellular mechanisms underlying reward and memory processes and relevant etiologic factors in both pain (Rahn et al., 2013; Melemedjian et al., 2014) and addiction (Dong and Nestler, 2014), including LTP, LTD (Rome and Rome, 2000), and transcription factors, e.g., CREB (Melemedjian et al., 2014) and ΔFosB (Luis-Delgado et al., 2006). Illustrating these concepts are fundamental observations that pain releases endogenous opioids (Bruehl et al., 2007) and, in mild-moderate intensity, may be perceived as reinforcing (Spealman and Kelleher, 1979). This is evidenced in the administration of mild electric shocks in nonhuman primates (Galbicka and Platt, 1984; Malagodi et al., 1981) and in repetitive acts of non-suicidal self-injury in clinical populations (Osuch et al., 2014).

Such reinforcing qualities may improve coping mechanisms and thus be adaptive from the phylogenetic standpoint. Accordingly, induction of emotional or physical pain in patients with complicated grief and back pain, via exposure to reminders of the deceased (O'Connor et al., 2008) or thermal pain (Baliki et al., 2010), engages the key reward and reinforcement structure, namely the NAc (Becerra et al., 2001), echoed in a poetic realization: "Love? What is it? Most natural painkiller" (Burroughs, 2000). Moreover, addicted patients consistently report emotional and physical pain symptoms arising in the context of drug or alcohol withdrawal (Shurman et al., 2010). Meanwhile, activation of the classic pain structure, PAG, elicits drug withdrawal-like symptomatology (Bozarth and Wise, 1984). Such reciprocal pain-reward interactions are exemplified by the effects of opioid medicines that provide analgesia when given at adequate doses but worsen pain (i.e., opioid-induced hyperalgesia; Lee et al., 2011) and create addiction when the dosing is either too high or too low with regard to the severity of the treated pain (Elman et al., 2011).

On the clinical level, among psychiatric patients, pain syndromes are most commonly diagnosed when reward alterations are also noted, including affective disorders (Nestler and Carlezon, 2006), stress-related disorders (Elman et al., 2009), and psychotic disorders (Elman et al., 2006). Furthermore, clinical features of pain syndromes analogous to the prototype psychiatric illness in which reward is implicated, namely, addiction, point to reward or motivation system dysfunction (Table 3). The most notable of these are the phenomena encoded in the *Diagnostic and Statistical Manual of Mental Disorders,* 5th edition (DSM-5; APA, 2013), diagnostic criteria, viz., tolerance of repeated painful stimuli (Sprenger et al., 2011; Grau et al., 2012) and the rewarding effect of pain termination (Baliki et al., 2010), social impairments (Cassidy et al., 2003; Elman et al., 2011), and withdrawal-like anti-reward symptomatology (e.g., hyperkatifeia; Shurman et al., 2010). It may be impossible to find a chronic pain patient without the presence of at least one such addiction-like characteristic.

Addiction-Informed Pain Models

The motivation-decision pain theory (Fields et al., 2007) on prioritizing neural choices based on homeostatic or survival values equates perceived pain to induced pain less simultaneous reward. Perceived reward is defined by subtraction of pain from the entire reward experience (see Figure 1 for the depiction of how reward may affect the pain relief system). In view of this thesis, pain and reward may be conceptualized as opponent processes (Becker et al., 2012). Individual differences in the NAc's responses to monetary reward expectation explained the variance of pain modulation by way of placebo-induced analgesia. Rewards that are olfactory (Villemure et al., 2012), gustatory (Lewkowski et al., 2003), auditory (Roy et al., 2008), visual (Meagher et al., 2001), and sexual (Forsberg et al., 1987) produced an analgesic effect that involves the ventral striatum (Villemure et al., 2012). However, pain usually eclipses its opponent effect, namely, euphoria that only becomes noticeable with the conclusion of the proponent painful condition. However, intersubject variability with respect to proponent-opponent pain interactions may be considerable. Therefore, a sense of pleasure derived from the experience of pain (i.e., algophilia) is also reported, and it may be a component of self-injurious behaviors typical of patients with borderline personality disorder (Sher and Stanley, 2008). Other observations consistent with that theory include cross-cultural variability in perceived childbirth pain (Rassin et al., 2009), as well as offset of excruciating pain from multiple daggers and hooks deeply penetrating the body (Kosambi, 1967) or from self-flagellation with chains via exhilaration derived from being a participant in a sacred ceremony.

From the neuroadaptational perspective (summarized in Table 4), similar to addictive substances, acute pain activates dopamine transmission in the brain reward circuitry, including the NAc (Scott et al., 2006; Boutelle et al., 1990), mPFC, and amygdala (Rouwette et al., 2012). In contrast, prolonged periods of pain increase endogenous opioidergic transmission.

Table 3. Key Clinical Characteristics of Pain and Addiction

Substance Use Disorder: DSM-5 Criterion	Pain: Clinical Characteristic	Neuroadaptation: Putative
Tolerance (increase in amount and decrease in effect of)	Tolerance of pain (Sprenger et al., 2011; May et al., 2012; Zheng et al., 2014), e.g., in athletes (Tesarz et al., 2012) or in victims of torture (Mumenthaler, 1976); of analgesics (Pohl and Smith, 2012); and of the rewarding effect pain termination (Baliki et al., 2010) may be acquired following respective exposures.	opponent process
Giving up or reducing important social, occupational, or recreational activities	Impaired social (Cassidy et al., 2003; Froud et al., 2014), occupational (Parthan et al., 2006), and recreational (Pickering et al., 2001) functions are hallmarks of chronic pain syndromes.	reward deficiency
Craving or a strong desire or urge to use a substance	Heightened incentive salience is attributed to pain and pain-related stimuli (Downar et al., 2003; Elman et al., 2011), so motivation to escape (the source of pain) or to seek pain relief is akin to the monofocused state of craving aimed at reducing the discomfort of withdrawal (Koob and Volkow, 2010).	incentive sensitization
Taking a substance in a larger amount and for longer period than intended	Compulsive seeking of opioid drugs is driven by the desire to ameliorate inadequately treated pain, i.e., pseudoaddiction (Weissman and Haddox, 1989), or to avoid a feared opioid withdrawal, i.e., therapeutic dependence (Portenoy and Foley, 1986).	
Persistent desire or repeated unsuccessful attempt to quit	Reinforcing qualities of acute pain are evidenced in the administration of mild electric shocks in non-human primates (Galbicka and Platt, 1984; Barrett and Spealman, 1978; Malagodi et al., 1981) and in repetitive acts of non-suicidal self-injury in clinical populations (Osuch et al., 2014).	
	Chronic spontaneous pain (without nociceptive input) or exaggerated responses to painful (hyperalgesia) and non-painful (allodynia) stimuli occur, in combination with negative affective states and a persistent yet unsuccessful drive to eliminate pain via behavioral or pharmacologic measures (Apkarian et al., 2009; Fishbain et al., 2015).	
Withdrawal symptoms	Pain patients exhibit withdrawal-like symptomatology, e.g., heightened levels of stress and arousal (e.g., hyperkatifeia; Shurman et al., 2010); stress also plays a key role in exacerbations of pain symptomatology (Finan and Smith, 2013; Lauche et al., 2013).	anti-reward
Taking a substance to relieve withdrawal	Pain may be inflicted to relieve negative affective states (Wilkinson and Goodyer, 2011).	aberrant learning
Continued use despite knowledge of adverse consequences	Pain relief is an exhilarating experience (Becerra and Borsook, 2008; Becerra et al., 2013; Leknes et al., 2011). Thus, non-suicidal self-injury (Osuch et al., 2014) may be perpetuated via backward conditioning. Accordingly, the *Merriam-Webster Dictionary and Thesaurus* defines "algophilia" as a morbid pleasure in the pain either of oneself or of others, while "algolagnia" is defined as perversion in which pleasure and especially sexual gratification are obtained by inflicting or suffering pain (Merriam-Webster Online, 2015).	
	Acute pain in the context of chronic pain may acquire positive reinforcing qualities (Seymour et al., 2005; Baliki et al., 2010).	
Spending much time to obtain, use, and recover	Catastrophizing or exaggerated prediction error (Sullivan et al., 2001), i.e., discrepancy between actual and anticipated pain (Elsenbruch et al., 2012), is a typical feature of chronic pain.	

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Table 3. ***Continued***

Substance Use Disorder: DSM-5 Criterion	Pain: Clinical Characteristic	Neuroadaptation: Putative
	The diagnostic criterion of excessive time and energy devoted to pain symptoms is encoded within the DSM-5 axis I definition of somatic symptoms disorder with predominant pain (APA, 2013).	

DSM-5, *Diagnostic and Statistical Manual of Mental Disorders*, 5th edition.

Consequences are lowered brain opioid binding potential (Maarrawi et al., 2007; Harris et al., 2007) and a NAc and mPFC hypodopaminergic state, accompanied by reduced motivation toward normally pleasurable stimuli, i.e., reward deficiency (Marbach et al., 1983).

Dopaminergic agents improve pain symptomatology (Miley et al., 1978) and produce analgesia (Dennis and Melzack, 1983). In contrast, inactivation of mesolimbic dopaminergic regions (the striatum, substantia nigra, and VTA), e.g., with Parkinson's disease (Sophie and Ford, 2012), results in excessive pain (Saadé et al., 1997). Hypofrontality or decrease in cerebral metabolism and blood flow in the mPFC and more lateral areas have been observed in pain patients (Khan et al., 2014). This is an example of not only the opponent process but also the impairment of inhibitory control, corresponding to impulsive and reckless behavior combined with faulty decision-making and learning processes (Becker et al., 2011; Berger et al., 2014).

As discussed earlier, incentive sensitization theories integrate neurobiological and psychological aspects of motivation by distinguishing core motivational and emotional components of pain. The former is defined by the extent to which pain and its relief are unwanted or anticipated, e.g., nocebo pain (Tracey, 2010) or placebo analgesia (Wager et al., 2004), whereas the latter refers to the subjective aversive pain experience (Becker et al., 2012). Psychological aspects of such undesirability and subjective valuation are mediated via distinct neurobiological pathways, which play different roles within the motivational and reward systems. The mesolimbic dopaminergic pathways, defining the motivational value of a particular object beyond the emotional experience it evokes, are involved in the incentive salience of pain (Baliki et al., 2010) and in the expectation of its relief, i.e., placebo analgesia (Eippert et al., 2009; Fields, 2004).

The tonic opponent hypodopaminergic state in the NAc and in the PFC results from recurrent dopaminergic stimulation by chronic pain. In the face of this, there is robust augmentation of proponent phasic dopamine responses to pain and to pain-related cues, i.e., incentive sensitization (cf., denervation hypersensitivity; Jones and Vrbová, 1974). Such phasic dopaminergic surges profoundly increase PFC's glutamatergic output (Kalivas et al., 2005) to hitherto hypoactive NAc (Taylor et al., 2015), thus further decreasing its dopaminergic activity. Synaptic plasticity induced by long-lasting and excessive release of dopamine by pain in the motivational system, but not in the valuational system, renders the former hypersensitive to pain and conditioned cues. This occurs without corresponding increases in the sensory perceptions (Becker et al., 2012) so that corticolimbic sensitization (Rome and Rome, 2000), also known as centralization (Borsook and Becerra, 2007), is theorized to play a key role in chronic pain symptomatology. Together with poor inhibitory control from the hypofunctional mPFC and aberrant learning produced by faulty prediction errors (i.e., pain is expected to be worse than it actually is), this promotes catastrophizing.

Various types of addictive drugs, e.g., opioids, sedative hypnotics, alcohol (Egli et al., 2012), and nicotine (Umana et al., 2013), that may provide pain relief can likewise become sensitized motivational targets that capture greater attentional resources and result in drug craving. This is clinically manifested in the expenditure of greater behavioral effort relative to normal reinforcers to seek and obtain drugs (Elman et al., 2011). The effort is driven by the desire to ameliorate inadequately treated pain (i.e., pseudoaddiction) or to avoid a feared opioid withdrawal (i.e., therapeutic dependence). This is probably why numerous epidemiologic surveys have documented that some substance use disorders (e.g., of nicotine and alcohol) are particularly prevalent among patients with pain (Ditre et al., 2011; Apkarian et al., 2013). These patients may receive treatment with opioid analgesics and develop tolerance and dependence on those drugs (Compton and Volkow, 2006).

The opponent to pain effect is evident in pain-induced analgesia (Gear et al., 1999; Tambeli et al., 2012). Such hedonically opposite of pain experiences, although overshadowed by the ongoing powerful pain stimuli, become conspicuous with pain termination in the form of pleasurable feeling, joy, and reward (Becerra and Borsook, 2008; Becerra et al., 2013; Leknes et al., 2011). Thus, through the evasion of aversive stimuli (i.e., negative reinforcement) and through the opponent to pain responses (i.e., positive reinforcement), learning serves as the fundamental determinant of pain-related behaviors (Navratilova and Porreca, 2014). Pain paired with early bonding and attachment (e.g., an outpouring of love and warmth on a hurting baby; Kolb, 1982), affection from friends and family, and compassion from strangers may be employed as a means of communicating social needs and eliciting acceptance, pity, or admiration. Learning new behaviors may thus occur when unconditioned stimulus (pain) triggers unconditioned responses in the form of exemption from work and family responsibilities. As a consequence, conditioned pain cues eventually come to elicit a conditioned response, viz., absenteeism.

The pain-pleasure continuum is a key theory in outlining interfacing sensory and emotional pain components (Elman et al., 2013) so that pain may be directly learned as a rewarding stimulus. For instance, pain of physical punishment may be the only sign of attention. Some pain may be an integral component of many pleasurable activities, be it sexual intercourse or consumption of a sizzling and spicy food. Conditioned cue-induced effects can also evoke pain symptomatology through backward

Table 4. Applicability of the Prevailing Addiction Theories to Understanding of Pain

Neuroadaptation	Mechanism	Manifestation	Role in Pain
Opponent process	pain and reward as opponent processes	exhilaration and euphoria with discontinuation of pain	pain potentially becoming a motivational target via backward conditioning
Impaired inhibitory control	prolonged periods of pain: ↓ DA in NAc and mPFC	emotional numbing, anhedonia, and ↓ responsivity to natural reinforcers	↓ control of drug urges and consumption
Reward deficiency			↑ pain as reward buffers pain according to motivation-decision theory
			↑ in proponent phasic DA responses to pain → sensitization (cf., denervation hypersensitivity)
			↓ placebo and ↑ nocebo effects
Incentive sensitization	pain- and analgesic drug-induced changes in the mesolimbic DAergic circuitry encompassing DA terminal fields (e.g., striatum, amygdala, and PFC)	pain and analgesia becoming sensitized motivational targets	chronic pain devoid of discernible nociceptive input that is a centralization phenomenon
			pseudoaddiction, therapeutic dependence, and catastrophizing
			stress-induced pain episodes
			rigid motivational states
			backward conditioning
Aberrant learning	neural adaptations to excessive DAergic trafficking in response to pain and analgesic drugs → up- or downregulation in gene expression LTD and LTP, with ensuing profound alterations in neuronal signaling evidenced in overlearning of the motivational significance	overlearned motivational significance of cues that predict delivery of drugs, i.e., exaggerated PE	positive reinforcement qualities of acute pain in the context of chronic pain
	ventral-to-dorsal striatum shift of behavioral control		
Anti-reward	repeated artificial ↑ DA by pain: ↑ NE, CRF, vasopressin, hypocretin, and substance P	aversive emotional state and anhedonia, as well as ↑ isolation and social withdrawal	↓ reward and ↑ pain
			↓ placebo and ↑ nocebo effects

CRF, corticotropin-releasing factor; DA, dopamine; LTD, long-term depression; LTP, long-term potentiation; mPFC, medial prefrontal cortex; NAc, nucleus accumbens; NE, norepinephrine; PE, prediction error; PFC, prefrontal cortex.

conditioning (Andreatta et al., 2013). That is, euphoria of pain termination, particularly when combined with euphoria produced by an opioid analgesic, constitutes an intense teaching signal reinforcing more pain and pain behavior. Conversely, after repeated pairing, pain-related stress and negative affective states can grow into a conditioned stimulus eliciting future painful episodes (Johnson and Greenwood-Van Meerveld, 2014; Li et al., 2014).

The aberrant learning theory postulates that Pavlovian and instrumental learning of new rewarding, aversive, or painful experiences is encoded via interactions between tonic (baseline) and phasic dopaminergic spikes in both ventral and dorsal striata (Everitt, 2014; White, 1996). In a fashion comparable to addictive drugs, pain and stress also produce abnormal magnitude and duration of dopamine elevations. This results in correspondingly heightened prediction errors signals evading normal learning and extinction mechanisms (Iordanova et al., 2006; McHugh et al., 2014). The initially homeostatic adjustments to diminished resting state tonic dopaminergic neurotransmission following chronic pain exposure (Tracey, 2008; Wood et al., 2007) set in motion up- or downregulation in gene expression, LTD, and LTP. Corresponding alterations occur in neuronal signaling with overlearning of the motivational significance of cues that either predict painful episodes or are associated with painful experience. These alterations are evidenced in irrationally catastrophic expectations with consequent devising of non-constructive coping strategies, e.g., drug seeking.

Such memory consolidation processes (Sandkühler and Lee, 2013) are pharmacologically modulated by psychostimulants (Fofi et al., 2014) and by anti-reward stress hormones (Schwegler

et al., 2010). In addition, ventral-to-dorsal striatum shift (Becerra et al., 2001; Osuch et al., 2014) of behavioral control gradually limits the behavioral repertoire to create habit-based, rather than value-based, compulsive motivational states fixated on pain-related content. This occurs with diminution of the mesolimbic neurons' ability to detect signals for normal salience (e.g., social reward) and loss of normal modulation of the reinforcers' values by pain-unrelated contexts (Rangel et al., 2008).

A similar example could be consolidation of traumatic memories in the BLA (Nader et al., 2000) and the CeA (Ciocchi et al., 2010; Haubensak et al., 2010). Consolidation is mediated by stress hormones (McGaugh, 2015) and subserving flashbacks, intrusive recollections, and psychological or physiological distress with exposure to the reminders of trauma (Pitman and Delahanty, 2005). Thus, chronic pain may be regarded as a variant of post-traumatic stress disorder (Gibson, 2012; Liedl et al., 2010) due to persistent relieving of stress, responding with hopelessness, catastrophizing (Quartana et al., 2009), or horror (Haugh, 2005) and avoidance of pain-related situations (Asmundson and Katz, 2009; Liedl et al., 2010). According to the fear-avoidance model (Crombez et al., 2012; Vlaeyen and Linton, 2000), pain, paired with emotional trauma and its recollections, can become a conditioned stimulus that evokes fear, anxiety, and catastrophizing responses. These, in turn, augment subjective pain perception and its neural correlates (Crombez et al., 1998; Ploghaus et al., 2001), setting in motion the mutual maintenance cycle (Asmundson and Katz, 2009; Crombez et al., 1998; Liedl et al., 2010).

The CeA's laterocapsular division, dubbed the nociceptive amygdala, is a part of the descending pain modulation system (Figure 1). It determines pain-related affective states and behaviors by means of nociceptive input integration with the internal body and environmental information (Neugebauer, 2015). Synaptic plasticity engendered by chronic pain in the BLA and the CeA is apparent in the sensitization of both sensory and emotional pain constituents (Veinante et al., 2013). The BLA sensitization brings about bottom-up mPFC inhibition, furthering cognitive and inhibitory deficits and giving rise to a positive feedback situation. The mPFC's failure to produce top-down amygdala's inhibition results in hyperalgesia, fear, anxiety, and dysfunctional pain behaviors (Neugebauer, 2015; Veinante et al., 2013).

Some pain behaviors (e.g., stooped posture and muscle tension) may provide temporary relief of pain but add severity to long-term pain (Knost et al., 1999). In the context of chronic or experimentally induced prolonged pain, acute pain could become reinforcing; its termination under such circumstances is processed by the mPFC (Seymour et al., 2005) and NAc (Baliki et al., 2010) by evoking aversion prediction error as pain does in healthy people (Becerra and Borsook, 2008; Baliki et al., 2010). Lastly, anti-reward stress and other negative affective states repeatedly paired with pain become conditioned stimulus for future painful episodes (Johnson and Greenwood-Van Meerveld, 2014; Li et al., 2014).

Anti-reward stress symptomatology in chronic pain patients is evident in their hypersensitive responses to conditioned stressful stimuli (Marcinkiewcz et al., 2009; Miguez et al., 2014), i.e., stress sensitization and cross-sensitization (Marvizon et al., 2015). Clinically, pain patients exhibit heightened levels of stress and arousal (Thieme et al., 2006). Stress also plays a key role in exacerbations of pain symptomatology (Finan and Smith, 2013; Lauche et al., 2013; Marvizon et al., 2015), including sympathetically maintained pain (Nickel et al., 2012) and nocebo effect (Tracey, 2010). Furthermore, an exaggerated sympathoadrenal tone is evidenced by frequent clinical findings in chronic pain patients of increased (1) heart rate (Chalaye et al., 2014), (2) norepinephrine concentrations in samples obtained from plasma (Buscher et al., 2010) and cerebrospinal fluid (Buvanendran et al., 2012), and (3) skin conductance level (Bonnet and Naveteur, 2004). In addition, CRF receptor type 1 is implicated in visceral hyperalgesia (Larauche et al., 2012), while heightened CRF plasma concentration tends to parallel both sensory and affective pain components (McLean et al., 2006). Thus, anti-reward may fulfill a purpose in dissuading people from engagement in hazardous situations by eliciting pain and fear (Henchoz et al., 2013). However, the allostatic load generated by anti-reward is clearly dysfunctional. It increases pain and promotes isolation and social withdrawal that jeopardize adequate coping and adjustment.

Therapeutic Considerations

Therapeutic approaches (summarized in Table 5) to chronic pain patients are on a par with the complexities of their syndromes, personalities, social milieus, and neurobiological diathesis and makeups. There is no one-pill-fits-all strategy. The viewpoints to follow highlight potential directions for systematic thinking and for positing novel ideas and questions aimed at understanding the course of chronic pain syndromes and what makes many patients partially or completely resistant to conventional analgesic modalities.

Reward Deficiency

Reward deficiency can be addressed via improved coping mechanisms and/or by trying to correct the deficit state. The former strategies may involve cognitive behavioral therapy, fostering acceptance, social skills training, and mindfulness meditation (Kabat-Zinn, 2005). While most other forms of psychotherapy have traditionally targeted negative emotions, recent data (Dunn, 2012) point to their utility for relieving reward deficiency (e.g., anhedonia). Positive psychology focused on the attainment of life's joy and satisfaction (not on the cure of psychopathology) may likewise be helpful (Duckworth et al., 2005). Moreover, given considerable overlap of brain reward circuitry that evolved for the maintenance of emotional attachments and is impaired by chronic pain, remediation of emotional attachments via interpersonal therapy (Luty et al., 1998) may strongly stimulate reward circuitry, helping to buffer anti-reward processes associated with pain and depression. Mesolimbic dopaminergic structures, including the NAc, play a substantial role not only in reward function but also in stress and anxiety (Elman et al., 2009). This raises the possibility of a functional reciprocity between heightened stress reactivity and emotional numbing in pain patients. This is a testable hypothesis that could be evaluated by measuring reward function before and after stress-reducing psychotherapeutic interventions.

Several purportedly safe and non-addictive agents restore dopaminergic function and thereby may normalize pathological

Table 5. Therapeutic Implications of the Prevailing Addiction Theories

Neuroadaptation	Therapy			
		Pharmacological		
			Findings	
	Non-pharmacological	Type	Clinical	Preclinical
Impaired inhibitory control	alternative reinforcement	NE reuptake blockade: atomoxetine	Berigan (2004)	Shen et al. (2013)
Reward deficiency	CBT, expressive-supportive, interpersonal, positive psychology, stress management (Dunn, 2012; Duckworth et al., 2005; Luty et al., 1998; Elman et al., 2009)	DA receptors D2 or D3 agonists: lisuride, bromocriptine, pramipexole	Qiu et al. (2009)	Brewer et al. (2014)
		nutraceuticals: acetyl-L-carnitine, DA precursors plus inhibitors of the DA degrading enzyme catechol-O-methyl transferase	Blum et al. (2010)	Hoefer et al. (2006)
		antidepressants: fluoxetine, maprotiline, bupropion	Mika et al. (2013); Walitt et al. (2015)	Muscat et al. (1992), Hajhashemi and Khanjani (2014)
		atypical antipsychotics: clozapine, olanzapine, risperidone	reviewed in Elman et al. (2006)	
Incentive sensitization	psychodynamically informed therapy	anti-sensitization: lithium	Tfelt-Hansen and Jensen (2012)	Banafshe et al. (2012)
		anti-craving: acamprosate, disulfiram, baclofen, ondansetron, vigabatrin	Keppel Hesselink et al. (2014); Laaksonen et al. (2013); Moulin (2001)	Luszczki and Czuczwar (2008)
Aberrant learning	therapies integrated with behavioral economics and decision-making theories	anti-compulsivity: SSRIs	Leombruni et al. (2015)	—
		anti-reconsolidation: blockade of zif268 protein synthesis		Théberge et al. (2010)
		anti-adrenergics: clonidine, lofexidine	Chang et al. (2015); Giovannitti et al. (2015)	Bruijnzeel et al. (2010)
Anti-reward	stress management, muscle relaxation techniques, cognitive restructuring, systemic desensitization	anti-glutamatergics: N-acetyl-cysteine, lamotrigine, riluzole, topiramate	Truini et al. (2013); Hama and Sagen (2011); Johannessen Landmark (2008); Webb and Kamali (1998)	Gegelashvili and Bjerrum (2014); Vuckovic et al. (2015)
		CRF and κ-opioid antagonists		Chen et al. (2010); Chartoff et al. (2012); Bruijnzeel et al. (2012)
		diminution of heightened stress and arousal: antidepressants, neuroleptics, anticonvulsant agents	Elman et al. (2011, 2013); Simons et al. (2014)	Zychowska et al. (2015); Muscat et al. (1992); Hajhashemi and Khanjani (2014)

CBT, cognitive behavioral therapy; CRF, corticotropin-releasing factor; DA, dopamine; NE, norepinephrine; SSRIs, selective serotonin reuptake inhibitors.

pain response (Blum et al., 2015) beyond direct dopamine receptor agonism (Brewer et al., 2014; Kaleli et al., 2001). For example, antidepressant drugs (fluoxetine, maprotiline, and bupropion; Muscat et al., 1992); a dietary supplement, acetyl-L-carnitine (Hoefer et al., 2006); and an investigational nutraceutical combination of dopamine precursors with inhibitors of the dopamine-degrading enzyme catechol-O-methyl transferase may hold promise for patients with reward deficiency (Blum et al., 2007). In this respect, atypical antipsychotic drugs, which have been suggested to correct reward deficiency symptoms of schizophrenic patients (Green et al., 2008), were also shown to possess analgesic or antinociceptive properties in both human and

rodent models (Elman et al., 2006). It would be of interest to test whether the preceding agents are able to reverse reward deficiency symptoms in pain patients.

Impaired Inhibitory Control

The hypodopaminergic state in the mPFC is yet another deficit state evident in poor cognitive control. It is a common clinical impression that patients with addictions are undeterred by the grave consequences of their irresistible urges to seek and consume drugs. Such consequences include heightened risk for death from overdose, increased morbidity, incarceration, dwindled productivity and breakup of family and societal ties. These impressions potentially explain limited success of negative reinforcement techniques in the treatment of addictions and underscore the empirical value of the alternative reinforcement methodologies, e.g., monetary reward for drug-free urine (Volkow et al., 2004). Such motivational enhancement techniques can be applied to chronic pain patients, fostering compliance and active participation in pain treatment plans. Impulsivity in pain patients (Berger et al., 2014) can be treated by blocking norepinephrine reuptake (Berigan, 2004; Shen et al., 2013).

Anti-reward

Although numerous stress management techniques are reportedly helpful for chronic pain, the NIH Technology Assessment Panel (1996) assigned the highest score to the effectiveness of muscle relaxation techniques. The anti-reward process could be directly addressed by anti-adrenergic agents (Elman et al., 2013), in conjunction with (not yet approved) κ-opioid and CRF antagonists (Bruijnzeel et al., 2012; Chartoff et al., 2012). Glutamate inhibition is an additional therapeutic strategy, because pain-induced activation of dopaminergic pathways leads to sensitization of excitatory glutamatergic neurotransmission (Coderre, 1993). Accordingly, anti-glutamatergic agents reduce pain in laboratory animals (Gegelashvili and Bjerrum, 2014; Vuckovic et al., 2015). Less direct reduction of glutamatergic activity in humans by N-acetyl-cysteine (Truini et al., 2013), lamotrigine, riluzole, or topiramate also provides effective pain relief (Hama and Sagen, 2011; Johannessen Landmark, 2008; Webb and Kamali, 1998).

Proponent mechanisms remain the most extensively investigated entity in pharmacotherapy of pain. However, seemingly obvious analgesic therapy could further deteriorate the anti-reward processes. As a result, changes in the mesolimbic dopaminergic circuitry induced by opioids, administered at doses exceeding the homeostatic need for pain alleviation, may be responsible for the amplification of hyperkatifeia and pain (Elman et al., 2011). Hence, cognitive and behavioral strategies (e.g., cognitive restructuring, stress management, and systemic desensitization), alongside non-addictive alternatives to opioids with substantial analgesic properties (e.g., antidepressants, neuroleptics, and anticonvulsant agents), have been related to clinical improvement in pain patients (Elman et al., 2011; Simons et al., 2014).

Incentive Sensitization

In addition to its sensitization and cross-sensitization with stress (i.e., anti-reward), chronic pain (Marvizon et al., 2015) is a sensitized motivational target, as evident in disproportionate (relative to the sensory experience) motivational drives and compulsive preoccupations. This is largely an unconscious process (Berridge and Kringelbach, 2015), so uncovering repressed material while fostering insight and healthy defenses is the critical goal for psychodynamically informed therapy.

Incentive sensitization involvement in the craving phenomena (Gantchev, 1978) also argues for a combination of psychotherapy with anti-craving medications (O'Brien, 2005). Thus, patients with alcohol use disorder treated with acamprosate or disulfiram reported improvement in pain symptoms (Laaksonen et al., 2013). Other anti-craving medications, e.g., baclofen (Keppel Hesselink et al., 2014), ondansetron (Moulin, 2001), and vigabatrin (Luszczki and Czuczwar, 2008), offer cautious optimism for pain patients. Likewise, the non-anticonvulsant mood stabilizer, lithium, mitigates sensitization (Ago et al., 2012) and has beneficial features as an analgesic drug (Banafshe et al., 2012; Tfelt-Hansen and Jensen, 2012).

Aberrant Learning

Evaluation of analgesic potency and probability determination for analgesic effect, which are essential for patients' decision making and behavioral choices (Lin, 2013), may be empirically evaluated by borrowing behavioral economics concepts. A rich set of emotional, motivational, and cognitive processes are applicable for planning a pain patient's visit to the physician's office, in weighing the prospects of pain relapse or deterioration, and in evaluating the outcomes of ongoing therapy. Impairments in the functioning of these mechanisms may determine whether an individual ascertains control over pain or whether pain attains control over an individual.

According to prospect theory (Tversky, 1979), outcomes are subjectively evaluated according to distinct mental operations, namely, editing, assignment of subjective values, and transformation of decision weights into probabilities. The editing operation readjusts a prospect of continued pain or successful analgesia with respect to a tolerable amount of pain. Patients may reformulate coping strategies in accordance with the amount of pain they are capable of tolerating, thus altering the prediction error and consequent matching. Pain up to the limit of this new neutral state is not perceived as an aversive experience (Kahneman and Miller, 1986). Chronic pain-induced adaptations in the mesolimbic dopaminergic pathways render them sensitized to pain and to the conditioned cues (i.e., incentive sensitization). Therefore, the neutral point is shifted into what was previously perceived as pain-free domain, resulting in exaggerated prediction errors and aberrant learning.

The result of the subjective valuation process is the distinct slope for pain and analgesia function. The slope is steeper in the pain versus analgesia domains, e.g., catastrophizing. Transformation of decision weights to probabilities may also be a nonlinear function. Low probabilities may be overestimated, while reasonable probabilities may be underestimated in comparison to certain outcomes, e.g., pseudo-opioid resistance or self-reported pain with adequate analgesia because of unwarranted anxiety about an impending opioid dose reduction (Evers, 1997) or therapeutic dependence (Portenoy and Foley, 1986). Pain occurs against a backdrop of expectancy for pain and analgesia, which alters the value of the experienced pain. Current theory predicts that states of analgesia expectancy should be associated with diminished experience of pain and states of lowered expectancy should be associated with enhanced

experience of pain. This normative relationship may be impaired by chronic pain (Tamburin et al., 2014; Vase et al., 2015).

The delay discounting phenomenon bears remarkable parallels to Herrnstein's matching law (Dallery, 2012). It pertains to decision making concerning the choice between the instantaneous pain relief and a more delayed array of such deterring consequences as addiction to pain killers, opioid-induced hyperalgesia, and comorbid mood or emotional disturbances (Elman et al., 2011; Lee et al., 2011; Story et al., 2013). These parallels may also be applicable to apparent preference for instant pain in the present over lingering dread of forthcoming anguish (Story et al., 2013).

Existing non-pharmacological interventions for chronic pain range from self-help and peer support to brief and motivational interventions, as well as to more intensive therapy approaches. None of the professionally delivered therapies seems to be superior, although cognitive-behavioral methods are most commonly used (Monticone et al., 2015). Suboptimal efficacy of the existing interventions is probably related to their generic nature, e.g., treating observable behavioral or cognitive patterns, improving conscious control, and relaxation and awareness of physical and emotional states. More specific therapeutic approaches modeled on behavioral economics and other decision-making theories may improve therapeutic outcomes.

There are well-established psychopharmacological strategies for the management of pain-related compulsivity (Kroenke et al., 2013; Proctor et al., 2013) via inhibition of serotonin reuptake (Leombruni et al., 2015; but see Banzi et al., 2015). An additional aberrant learning target is stable memory established by recurrent painful episodes and Pavlovian associations with environmental cues (Hamlin et al., 2007; Price and Inyang, 2015). Such memory traces, recalled into a labile state by conditioned stimuli, can be prevented from reconsolidation by anti-adrenergic agents (Martin et al., 2006) and anti-glutamatergic agents (Hama and Sagen, 2011; Johannessen Landmark, 2008; Webb and Kamali, 1998). These agents have been successfully used in pain patients, along with the blockade of protein (viz., zif268) synthesis involved in reconsolidation (Théberge et al., 2010).

Synopsis and Conclusions

According to Hippocrates, pain alleviation is a divine act (viz., *divinum opus est sedare dolorem*). As such, it may be rewarding for both patients and their therapists. To generate new leads for the discovery of improved preventive and therapeutic strategies, clinicians and scientists are striving for formulation of coherent principles that explain the gamut of pain phenomena. This review compares the roles played by reward circuits in chronic pain and addiction to indicate that some reward and motivational features are shared yet other features may not generalize (Wiech and Tracey, 2013). For instance, there are no parallels in the substance abuse literature for the acute harm prevention motivation typical of acute pain. Other differences include beneficial analgesic properties of opioid drugs and the mutual maintenance cycle of pain and emotional trauma. More importantly, some addictive drugs (e.g., cocaine and alcohol) may cause diffused brain damage, e.g., subarachnoid or parenchymal injury reflected in impaired brain functions (Elman et al., 2008) that does not occur in pain patients.

The realization that pain and addiction may share a common neurobiological foundation could have important mechanistic and therapeutic implications. For instance, if the effects of pain and addictive drugs tend to sensitize over time, then cross-sensitization might transpire as well. If so, exposure to addictive drugs (not just to opioids) could increase susceptibility to the development of pain, and vice versa. Identifying cross-sensitization mechanisms could help in understanding and preventing relapse. Administration of a priming dose of an addictive drug can reinstate addictive behaviors in laboratory animals and humans; this effect is apparent even when the priming drug used is drawn from class different from that of the previously used addictive substance. If the neural circuitry underlying this reinstatement plays a role in both pain and addiction, then pain could trigger relapse in abstinent patients with substance use disorders; such cross-sensitization could be bi-directional. In sum, a better understanding of pain's neural basis and its relationship to that of addiction could further support the conceptualization of pain as a disorder of emotion, motivation, reward, and cognition.

The tremendous progress of basic pain research has shed light on key mechanisms engaged in complex interactions at the genetic, epigenetic, and molecular levels. One possible interpretation positing a unitary nosology is suggested by overlapping changes in reward, motivation, emotion, and stress processing in subcortical and cortical limbic structures for general categories of painful disorders, e.g., fibromyalgia, irritable bowel syndrome, migraine, and somatic symptom disorder with predominant pain (Landa et al., 2012; Schwedt et al., 2015). This interpretation may, however, be analogous to Hans Selye's largely refuted speculation of stereotyped stress response to any type of a challenge (Carter and Goldstein, 2015).

An alternative view is a specific pattern responses affecting multiple brain networks and systems (Carter and Goldstein, 2015) and involving different types of limbic or other changes so that pathophysiology of pain syndromes is derived from diverse allostatic sources. Pain may be then considered an intervening variable associating various stimuli and pathophysiological changes with behavioral responses (Tolman, 1938). Accordingly, tissue injuries and emotional setbacks are not directly related to neuropsychopathological changes but are rather undergo intervention by modulating variables (e.g., conditions of the hedonostat), regulators, effectors, and predisposing factors (e.g., foregoing neuropsychopathology and comorbid addiction or medical illness). To be precise, while patterns of pain symptomatology are critically dependent on the nature and intensity of causative factors, their clinical manifestations are determined by constitutional and lifestyle elements, available coping resources, and history of prior exposure to the same or similar stimuli, drugs, stress, etc.

The long-standing recognition of inseparable pain or reward amalgamation supports clinical and scientific formulations on the interface between the two systems. The prevailing theories on reward and addiction are germane here, because they form a basis for RDoC-like classification (Cuthbert, 2015). This allows exploration of the dynamic states of interactions between pain neuroadaptations, such as diametrically opposite diminished and enhanced dopaminergic responsivity to salient stimuli that are respectively predicted by reward deficiency and by incentive sensitization and aberrant learning (Robinson and Berridge, 2003; Elman et al., 2009).

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Thus, pain neuroadaptations may be classified in terms of the directionality and nature of dopaminergic alterations. Pain sensitivity predominates when hypodopaminergia is circumscribed to the nigrostriatal pathway, e.g., in Parkinson's disease (Rana et al., 2013). Pain becomes a sensitized motivational target in patients with generally low brain dopamine content, such as Lesch-Nyhan, Prader-Willi, and Cornelia de Lange syndromes, as evident in recurrent urges for self-inflicted pain (Devine, 2012). Hyperfunctionality of the limbic dopaminergic system in schizophrenia may manifest in pain insensitivity (Elman et al., 2006).

Dopaminergic alterations evoked by chronic pain are only part of a constellation of allostatic adjustments. Secretion of anti-reward sympathoadrenomedullary hypothalamic-pituitary-adrenal axis (e.g., CRF) hormones, along with dynorphin (Pacak et al., 1998; LeBlanc et al., 2015), predominates alterations of other stress- and metabolism-related neurohormones. Distress experienced by pain patients may be a combination of reward deficiency worsened by anti-reward hormones. At the same time, these hormones drive chronicity by sensitizing motivational circuits and by consolidating pain-related memories. For others, this may merely be a manifestation of a vicious cycle wherein hyperkatifeia due to opioid analgesic overuse increases pain. In this case, the pain is driving additional opioid consumption and, in consequence, amplifying the hyperkatifeia, etc. Simultaneous assessments of reward and stress functions should disentangle such mixed presentations. This would enable the elaboration of central mechanisms and eventually the emergence of neuroadaptation patterns specific for different types of pain.

In clinical work with patients, one hears that, although at times excruciating, acute pain may be exciting and even rewarding (Franklin, 2010). This echoes the psychological concepts of repetition compulsion and death drive (Freud, 1950) and the notion that active avoidance of punishment is reinforcing. Pop culture depicts addiction to pain and self-mutilation (Tolle, 2007). Many patients, despite their chronically depressed and anxious states, despair of ever being able to regain the attention and affection poured onto them when they were in pain and/or the intense highs they felt during self-inflicted pain or upon pain termination. The vulnerability of a substantial minority to experience pain as acutely reinforcing and even addicting is a yet unexplored area. These patients may perceive pain-free periods as bland, stressful, and unfulfilling and themselves as numb. They may turn to addictive drugs and alcohol as a means of overcoming this stress and numbing and recreating the seemingly paradoxical highs they felt while in pain.

Identification of the pathophysiological basis for the reward and stress abnormalities in chronic pain can suggest hypothesis-driven clinical interventions. This is an important and timely endeavor given that most pain syndromes are only partially responsive to opioids, so innovative approaches are essential. Identifying relative contributions of reward, motivation, and anti-reward abnormalities in pain patients could be translated into effective intervention strategies via identification of vulnerable individuals and assessing treatment response in hypothesis-driven clinical trials.

The proposed model is based on allostatic adjustment to recurrent activation of the dopaminergic reward circuitry evoked by pain and its conditioned cues. This model postulates maintenance of hedonic homeostasis in the face of perturbations via various effectors; all oppose and thereby initially balance abrupt reward circuit changes. Acute pain is associated with excessive dopaminergic activity. However, the function of the homeostatic regulator, homeostat, and the effector systems may vary from person to person (e.g., fewer dopamine receptors). Hence, it is necessary in multidimensional clinical assessments to formulate personalized therapeutic plans by matching clinical features to underlying central mechanisms. Biopsychosocial vulnerability factors could then be used to screen persons at risk. Those possessing high vulnerability due to prior reward deficiency and/or reward or stress sensitization might be counseled to avoid potentially addictive substances or targeted for early intervention even in presence of mild pain problems.

In addition to describing amenable to laboratory testing and modeling interactions among various aspects of reward, motivation, stress, and pain, this paper points to unresolved issues with consequential directions for further scientific inquiry. First, the principles regulating sensory, psychological, behavioral, and social components of chronic pain remain unclear. The same issue pertains to the interactions among numerous effectors and the hedonostat, including what triggers the initiation and determines the progression pace of allostatic load buildup. The reasons behind the evolution of a specific neuroadaptation are also not elucidated; that is, we still do not know why some people are prone to develop reward deficiency in response to pain of certain intensity while others succumb to incentive sensitization, aberrant learning, or anti-reward types of neuroadaptation following the same type of a stimulus. It would be also important to test whether patients who are destined to develop a specific neuroadaptation in the context of chronic pain present an identifiable pattern during acute pain challenge that may be mechanistically linked to the eventual neuropsychopathology.

While pain medicine has evolved as a highly specialized discipline requiring meticulous training, the ideas reviewed in this paper suggest that pain transcends the boundaries of a single field. It bonds multiple professionals entrusted with the alleviation of patients' suffering and with the promotion of their health. Other fields, such as psychiatry, neurology, anesthesiology, neuroradiology, neuropathology, psychology, behavioral economics, and medical humanities, will be undoubtedly enriched by increased efforts to include pain in their agendas and curricula. Such an addition will provide a critical perspective for the advancement of patient care, along with comprehensive clinical and scientific thinking, training, and education.

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