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Psychological Processing in Chronic Pain: A Neural Systems Approach

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Abstract

Our understanding of chronic pain involves complex brain circuits that include sensory, emotional, cognitive and interoceptive processing. The feed-forward interactions between physical (e.g., trauma) and emotional pain and the consequences of altered psychological status on the expression of pain have made the evaluation and treatment of chronic pain a challenge in the clinic. By understanding the neural circuits involved in psychological processes, a mechanistic approach to the implementation of psychology-based treatments may be better understood. In this review we evaluate some of the principle processes that may be altered as a consequence of chronic pain in the context of localized and integrated neural networks. These changes are ongoing, vary in their magnitude, and their hierarchical manifestations, and may be temporally and sequentially altered by treatments, and all contribute to an overall pain phenotype. Furthermore, we link altered psychological processes to specific evidence-based treatments to put forth a model of pain neuroscience psychology.

Keywords

chronic pain; psychology; anxiety; depression; anhedonia; cognition; attention; perception; interoception; motivation; fear; catastrophizing; imaging; reward; brain; allostatic load; nociception; neurocircuits; behavior; insula; amygdala; prefrontal cortex; hippocampus; parietal cortex; anterior cingulate cortex

Introduction

As organisms, we respond to external and internal milieu. In humans, such behavioral and physiological responses may be adaptive or maladaptive. In chronic pain, alterations in physical systems can result in changes in psychological processes observed as neural-circuit defined changes in behavior. Control of these processes may be viewed as a balance of

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excitatory and inhibitory events. Some processes may contribute to an escalating cascade or deescalating cascade of neural systems to produce altered behaviors in a sensitized or desensitized state. Chronic pain provides an ideal model to attempt to understand these types of processes in the context of localized and integrated neural networks. Brain regions consistently implicated include the primary and secondary somatosensory cortex (S1 and S2), spinal cord, thalamus, insula, anterior cingulate cortex, prefrontal cortex (Apkarian et al., 2005; Peyron et al., 2000; Tracey, 2008); midbrain areas including the periaqueductal gray (Linnman et al., 2011) and cerebellum (Moulton et al., 2010), and subcortical structures including the hippocampus, basal ganglia, and amygdala (Borsook et al., 2010; Maleki et al., 2011; Schweinhardt and Bushnell, 2010; Simons et al., 2012a); and see (Bushnell et al., 2013) for a recent review on brain regions involved in cognitive and emotional aspects of chronic pain) (see Figure 1). The brain's interconnected networks contribute to resting and active functions that are orchestrated with varying degrees of contributions from these and other brain regions.

Pain is *a response* to nociceptive stimuli, often the driving force leading individuals to seek treatment, when they ache, hurt, and/or *suffer*. As pain becomes chronic, there is a tendency to be different - ones psychological state of being (and mind) is altered. Physical and emotional pain exist on the same continuum (Borsook et al., 2007; Elman et al., 2011; Perl, 2007) with common brain networks involved (Bendelow and Williams, 2008), with duplication and redundancy abounding. For example, using both noxious heat and unpleasant pictures, overlapping activation was observed in the posterior cerebellum with significant inverse correlations with limbic structures (viz., anterior hypothalamus, subgenual anterior cingulate, and parahippocampal gyrus), suggesting that the cerebellum contains specific regions involved in encoding generalized aversive processing, not necessarily unique to affective or sensorimotor functions (Moulton et al., 2011). Figure 2 conceptualizes physiological and psychological processing of nociception and pain related processes that may lead to altered behaviors. There are two major points that need to be considered when trying to understand a brain-systems approach to psychological processes in pain: (1) experiencing pain can trigger a cascade of neurological (initially sensory) events that lead to an altered psychological state; and (2) prior psychological states can confer a heightened risk for pain chronicity due to processes such as cross sensitization, where exposure to stress in the past results in greater sensitivity to other seemingly unrelated stimuli (e.g., childhood trauma, loss of a parent, and addiction) (Elman et al., 2013; Goldberg et al., 1999; Nicolson et al., 2010).

In this review we evaluate some of the principle behavioral alterations in the context of neural circuits and how these may be altered as a consequence of chronic pain. Data extracted from original research and from seminal review articles were critically assessed and summarized within the following main sections: (1) *Pain, Neural Circuits, and Maladaptive Changes* that contribute to central sensitization and perturbations in allostasis (allostatic load); (2) Alteration of Psychological Processes in Chronic Pain with evidence-based treatments that map onto key areas such as cognition, reward state and fear learning; (3) *Premorbid Risk Factors and Pain* where vulnerabilities such as psychological trauma can confer heightened risk; and lastly, we bring together these concepts with (4) Integrating Dysfunction: Complex Behaviors with Reciprocal, or Multiple and Multiplying Effects and provide suggestions for (5) *Treatment and Training Approaches* aimed at psychologists' training in the basic tenets of pain neuroscience.

1: Pain, Neural Circuits, and Maladaptive Changes

1.1. Chronic Pain, Neurocircuits and Behavior—The evolution or transition to chronic pain is not obvious. For many chronic pain conditions, the transition follows a

specific insult (e.g., complex regional pain syndrome, post herpetic neuralgia, diabetic neuropathy, spinal cord injury, etc.), relates to a missing enzyme (e.g., Fabry's Disease) or is the result of a genetic condition (e.g., hemiplegic migraine), while in some cases pain emerges spontaneously. In cases of a specific insult the evolution of altered behaviors that are comorbid with pain unfold. Take for example, the individual who has a traumatic amputation from war or civilian injuries; prior to the injury, they were considered `normal'. Following their injury a sequence of altered behaviors that relate to or are comorbid with their pain unfold with varying temporal frequency. Thus, the subject who was not previously depressed is now. The subject who had no sleep-wake issues does now. The subject who had no problems related to anxiety may have components of post-traumatic stress disorder (PTSD). Similarly alteration in memory, cognition and even subtle changes in relating spatially to the environment may change. How do we understand these psychological changes in the context of neural plasticity, maladaptation and allostatic load?

Allostasis refers to the ability of complex physiological systems to maintain stability through change when confronted with a stressor (McEwen, 1998). Regulatory changes often engage multiple physiological systems, including the cardiovascular, neuronal, immunologic, and endocrine systems. When these processes are compromised, allostatic load occurs; manifested as chronic dysregulation of physiologic systems. Allostatic load has a direct impact on brain function. The brain reacts to stressors by modulating physiology and behavior, which in turn results in chemical and structural brain changes (McEwen, 2000a, b). Although pain is an inherently adaptive signal that warns an individual of real or potential damage, persistent pain leads to cumulative strain on the brain, allostatic load, and alterations in normative psychological processes such as perception, emotion, cognition, and motivation that are closely intertwined with physiological responses of interoception, brain system rest (sleep), and autonomic function (see Figure 3). Pre-clinical models are beginning to take into consideration the broad scope of behavioral responses associated with persistent pain and pain relief. A number of behaviors suppressed by pain in rodents (rearing, burrowing) mimic more closely the alterations in behavior observed in patients with chronic pain and are becoming targets to measure analgesic response. Specifically, burrowing has been conceptualized as an indicator of global `wellbeing' for the rat (Deacon, 2006). Andrews and colleagues successfully examined spontaneous burrowing behavior to detect the effects of traumatic peripheral nerve injury and tissue inflammation and were able to measure the analgesic efficacy of gabapentin (30mg/kg) and ibuprofen (30mg/kg), both of which reversed the burrowing deficits (Andrews et al., 2011). In other words, some behaviors may be difficult to evaluate, but clearly contribute to the process of either seeking pain relief or sequestering ourselves as a protective process from stress, the elements, social situations, etc.

1.2. Pain Behavior – Adaptive or Maladaptive—Escape or avoidance from painful or potentially painful stimuli is a normal process (i.e., even rapid withdrawal from a noxious stimuli) for acute threats. In chronic pain this drive is no longer adaptive. Clinical examples include resting the painful limb in complex regional pain syndrome that may be considered protective to limit pain sensory exacerbation with movement. However, the nature of this behavior is maladaptive, as the condition may be made worse with immobility. Similar, but perhaps more complex processing relates to how individuals have emotional equivalents of `protecting the limb' in trying to protect (or avoid) affective experiences. The high comorbidity of chronic pain and PSTD exemplifies this process where similar mechanisms (e.g., attentional biases, avoidance coping) "*mutually maintain*" (Liedl et al., 2010; Sharp and Harvey, 2001) both conditions/disorders.

A clear example of adaption and maladaptation related to pain is conditioned fear. It may be intimately linked to the onset of pain such as in the case of trauma or triggered by the

experience of increased pain with activity. Such processes contribute to an ongoing actual and perceived `threat' to the individual. In an adaptive process, individuals would allow for neuronal repair of neurons and functional circuits or implement physical and behavioral functions to restore their ability to interact with the environment. In a maladaptive process, feed forward mechanisms result in system failure (McEwen, 2012). Some of these perturbations are relatively easily measured such as alterations in sensation (sensitization, allodynia, hyperalgesia, hyperpathia, etc.) and may encompass peripheral and/or central sensitization. This dynamic and relatively quantitative approach is more difficult in non-sensory aspects of pain. As such, the term *centralization of pain* may be used to capture the process where the initial stimulus (e.g., surgical trauma) progresses to a chronic pain state (neuropathic pain) but also alters cognition (Berryman et al., 2013), affective and motivational states (Wiech and Tracey, 2013), potential for suicide (Elman et al., 2013) and may diminish normal inhibitory and enhanced facilitatory pain modulatory processes (Chalaye et al., 2012; Porreca et al., 2002). Taken together these may set up an unstable emotional state, frequently manifested as emerging comorbid conditions, most commonly, anxiety and depression. While certain vulnerability factors are clearly at play (see 3.0 *Premorbid Risk Factors and Pain*), most non-sensory processes (i.e., motivation, cognition, memory, etc.) are altered in pain as a consequence of centralization of nociceptive signaling. Nociception eventually invades neural processes that are altered to produce the centralized brain state of chronic pain. Figure 3 and Figure 4 encompasses two main themes: (1) that some psychological systems when altered have deleterious effects on others (e.g., cognition on memory and vice versa); and (2) that progressive cumulative failures of psychological function, as exemplified by the diminishing energy of activation in a bouncing ball, applies to chronification of pain where patients' neural systems are no longer adaptive and systems fail.

2. Alteration of Psychological Processes in Chronic Pain

In the following sections we describe how pain itself drives changes in psychological processes. While segregation of some of these processes is somewhat artificial since they are integrative or may overlap, the understanding of brain network involvement in these processes affords a model of how individual processes may contribute to altered behaviors in chronic pain. We also use this approach to explore how integrated system-focused treatments for chronic pain should be considered as depicted in Figure 5.

2.1. Cognition and Attention—Cognition is defined as *the act of knowing* (http://www.merriam-webster.com) and includes awareness, perception, reasoning, decision-making (van der Meer et al., 2012), and judgment. These processes are altered in chronic pain (for reviews in this area see (Hart et al., 2003; Moriarty et al., 2011; Wiech et al., 2008). Overall, the evidence supports the notion that pain has a negative effect on cognitive performance and attentional processes (Eccleston and Crombez, 1999) and that it may affect brain regions involved in cognition. For example, activation of the anterior cingulate cortex (ACC) and its role in attention can be altered by hypnotic suggestion in healthy subjects (Rainville et al., 1997). Cognitive changes have been reported in chronic pancreatitis (Jongsma et al., 2011), complex regional pain syndrome (CRPS) (Kolb et al., 2012), and fibromyalgia (Glass, 2008) amongst others (Hart et al., 2003). In another study comparing healthy participants to patients with osteoarthritis using a computerized sustained attention task (Continuous Performance Task [CPT]) and painful stimulus, investigators observed increased ACC activity when the painful stimuli was applied during the CPT task across all subjects, but activation patterns in the ACC were different between patients and healthy participants (Buffington et al., 2005). In acute pain models, cognitive processing is not significantly disturbed (Seminowicz and Davis, 2007; Van Essen et al., 2012)). In ongoing pain, alterations in cognition may relate to alteration in the dorsolateral prefrontal cortex

(DLPFC) (Apkarian et al., 2004b), the ventrolateral prefrontal cortex (VLPC) (Jensen et al., 2012), and reduced connectivity from the medial prefrontal cortex (mPFC) to the default mode network (Loggia et al., 2013). It is as if ongoing pain drives alterations in these regions to alter synaptic connectivity or function to diminish cognitive abilities resulting in altered perceptive and interoceptive states and inhibition of top-down cognitive control of emotional states (as described further in section 2.4.1.).

2.2. Altered Perception—Perhaps the best examples of the importance of bodily interpretation and chronic pain relate to the perception of missing limbs (Flor et al., 2013) where treatments such as mirror training and sensory stimulation provide visual or proprioceptive inputs to the brain. These seem highly salient as correction of these perceptual abnormalities can provide pain relief (Mercier and Sirigu, 2009; Moseley and Flor, 2012). More subtle forms of altered perception are seen in other chronic pain syndromes and include specific processes such as hemineglect.

Hemineglect has been defined as “a deficit in processing or responding to sensory stimuli in the contralateral hemispace, a part of the own body, the part of an imagined scene, or may include the failure to act with the contralesional limbs despite intact motor functions” (Kerkhoff, 2001). In chronic pain altered perception including hemiinattention-hemineglect are present. This was first reported in CRPS patients by Galer and colleagues wherein a series of 11 selected patients uniformly described an inability to move their affected limb without significant focus and effort and a sense of disconnection from their affected body part (Galer et al., 1995; Galer and Jensen, 1999). Now observed in others including those with chronic low back pain (Moseley et al., 2012), these patients have altered perception of the external environment and also, more difficult to define, alterations in their perception of their internal physiological environment. The latter is captured in the writings of Craig on `interoception' (Craig, 2002). Thus, these patients have diminished awareness of their body schema and surroundings (Kolb et al., 2012) that have been termed neglect-like symptoms. Other studies have also shown impaired evaluation of hand size in CRPS (Forderreuther et al., 2004; Peltz et al., 2011). More recent studies have not only confirmed neglect symptoms in CRPS patients, but observed this same phenomena in other chronic pain patients, although to a lesser degree (Frettloh et al., 2006; Kolb et al., 2012). Such disturbances, it has been argued, contribute to chronic pain (Lewis et al., 2007). Such alterations may have significant implications for treatment, endorsing the benefits of treatment plans that include physical therapy or the direct targeting of affected cortical areas. The main focus, based on our understanding from the neurological literature on hemi-inattention and neglect (Rizzo, 1993; Vallar, 1998), would be the parietal cortex that is clearly involved in functional changes in CRPS as defined in neuroimaging studies (Cohen et al., 2012; Lebel et al., 2008). The parietal lobe is involved in perception of both real and illusionary experimental pain (Seckel et al., 2012; Zaretskaya et al., 2013). Neglect like symptoms are more frequently observed in right parietal changes (i.e., in the case of pain patients, affecting the left painful limb). Given our understanding of cerebral dominance, such processes feed into the overall notion of right sided processing in affective changes vs. left. Alternatively, hyperfunctional changes in the intact left hemisphere may be a driver of neglect like symptoms in CRPS/ chronic pain (Koch et al., 2008). Neglect symptomology, seen predominantly after lesions of the right hemisphere, may be the result of an imbalance of lateral orienting processes that have a bias towards the ipsilesional side and a deficit in orienting attention (Gainotti et al., 1989; Karnath, 1988; Kucyi et al., 2012).

Altered perception has been relatively under-evaluated in the clinic, but when one considers the existence of these changes in other significant disease states, including schizophrenia (Cavezian et al., 2011) and Parkinson's disease (Ebersbach et al., 1996), the process seems fundamental to altered neurological function in diseases that affect the brain. Furthermore,

the deficits in visospatial processing can be *modulated* by other intersecting processes. For example, emotionally negative stimuli can overcome visiospatial neglect through activation of frontal and limbic networks (Dominguez-Borras et al., 2012; Grabowska et al., 2011) suggesting that emotionally laden information may overcome the deficit. Clearly, the neural pathways are complex and in a recent meta-analysis, multiple regions of the right hemisphere (viz., middle and superior temporal gyrus, inferior parietal lobule, intra-parietal sulcus, precuneus, middle occipital gyrus, caudate nucleus, and posterior insula) were found to be involved in spatial neglect (Molenberghs et al., 2012). It is unknown if sensory perceptual alterations in chronic pain can also manifest as psychological neglect (e.g., individuals are unaware of their depression). In hemi-neglect patients, with parietal lobe damage, emotional interpretation of sensory stimuli are reported to be intact (Dominguez-Borras et al., 2012). While these alterations of the perceptual circuitry may not be explicitly defined, evidence furthers the notion that psychological alterations such as attention and emotion are intimately connected.

Treatment approaches to address perceptual alterations can include sensory stimulation (Marshall, 2009), specific visio-spatial training (Piccardi et al., 2006; Thimm et al., 2009), graded motor imagery (Moseley, 2006), and enhancing hypokinesia of the affected limb (Sapir et al., 2007). A fMRI study examined differential brain activation patterns after optokinetic stimulation training compared to alertness training; greater bilateral activation of the precuneus was observed after optokinetic training, whereas there was more activation bilaterally in the frontal cortex after alertness training. The data suggest that these two trainings may have differential effects on attentional intensity and spatial attention (Thimm et al., 2009). These treatment modalities align closely with physical therapy and psychological treatment.

2.3. Interoception—An individual's sense of the physiological condition of the physical body is directly associated with emotional well-being and stress levels (Craig, 2002). The anterior insula appears to play a significant role in this evaluative process (Craig, 2009). In the context of pain, this encompasses heightened awareness of or attentional bias toward general (e.g., increased heart rate) or threat-related (e.g., muscle tension) physiological cues. Interoceptive sensitivity can not only heighten acute pain sensitivity and decrease pain tolerance (Pollatos et al., 2012), it is theorized to be one of several mechanisms of fear learning for chronic pain patients (De Peuter et al., 2011). A related interoceptive bias is anxiety sensitivity (AS) where an individual interprets interoceptive information as potentially aversive or dangerous. AS has been found to have large effects on fear of pain and small to moderate effects on pain and disability (Ocanez et al., 2010). In the context of treatment, interoceptive sensitivity and AS can be manipulated to help patients improve their responses to the pain experience. In a randomized clinical trial for patients with irritable bowel syndrome, cognitive behavioral therapy with interoceptive exposure to visceral sensations was found to be superior to control conditions (Craske et al., 2011). This attentional bias can also be manipulated through mindfulness-based techniques where patients are taught to “pay attention in a particular way; on purpose, in the present moment, nonjudgmentally” (Kabat-Zinn, 2009). The benefits of this approach with chronic pain patients date back almost 30 years (Kabat-Zinn et al., 1985) and are now grounded in functional imaging. Meditation induced changes in pain have been associated with activity in the anterior insula and anterior cingulate cortex (Lutz et al., 2013; Zeidan et al., 2011), alterations which seem to be modulated top-down by cortical alpha rhythms (Kerr et al., 2013).

2.4. Reward, Aversion and Motivation—Rewarding and aversive stimuli have profound and dynamic abilities to modify behavior. In animals, a rewarding stimulus is defined by its ability to reinforce behaviors that produce the stimulus. In humans, we define

the conscious "*reward state*" as an affect bias towards positive emotions and motivation and "*aversive state*" or "*anti-reward*" as the opposite. The ability to derive pleasure from ordinary activities is important, as is aversion to potentially damaging stimuli and environments (Cabanac, 1971). The dopaminergic and opioidergic reward pathways of the brain are critical for survival, as they provide the pleasure drives, for example, the drives for food or sex (Gardner, 2011; Wise, 1989). These 'natural rewards' involve the release of dopamine in the nucleus accumbens and frontal lobes. In a general theory of reward and aversion processing, neural systems obtain information from the external (e.g., auditory, visual, or touch or pain) and internal (e.g., thirst, hunger, thermoregulation) environments to derive characteristics of the stimulus (Schultz, 2004; Wise, 2004). Integration of this information, including the specific weighting of properties (e.g. rate, intensity, delay, amount, proximity), allows the assignment of emotional salience (degree of motivational drive (Borsook et al., 2013)) and valence (rewarding or aversive) to the stimulus. Both conscious and unconscious processes are involved in the evaluation of the internal and external environments (Wise, 2002), including prediction of deficit states (e.g. lack of food or water), planning to obtain goal objects, and decision-making. Prior experience is a major determinant of the motivational impact of any given stimulus or trigger. In a normal state, the organism utilizes this information in a manner that optimizes biological fitness over time.

Emerging research suggests that even among healthy individuals, there is variability in reward circuitry activity that can directly predict opioid analgesia. Using fMRI, trait reward responsiveness and the response of brain reward circuitry (viz., orbitofrontal cortex, nucleus accumbens, and the ventral tegmental area) to predict analgesic effects of the μ-opioid remifentanil was evaluated (Wanigasekera et al., 2012). Significantly, the magnitude of opioid-induced behavioral analgesia (as measured by change in pain intensity) was positively correlated with trait reward responsiveness and was predicted by reward circuitry neuronal responses as measured by fMRI prior to the remifentanil infusion (Wanigasekera et al., 2012). A potential baseline reward circuitry deficit would only compound the impact of an ongoing aversive pain state producing alterations in mood, social interactions, cognition and potentially leading to a persistent hedonic deficit state (Elman et al., 2011). Individuals in chronic pain may seek pain relief (Leknes et al., 2013; Navratilova et al., 2012) and if this is not obtained, deterioration of adaptive systems (allostatic failure) may occur.

2.4.1. Depression and Anhedonia: In chronic pain the process of a `reward deficit syndrome' or anti-reward processes, may relate to ongoing circuit dysfunction. Increasing evidence suggests that plasticity of neural circuits are responsible for subtle changes over time that contribute to the behavioral manifestation of altered affective processes including blunting of reward or enhancing depression (Becker et al., 2012; Elman et al., 2011). Unquestionably, affective changes may evolve from normal reactive depression that relates to stress (Hammen, 2005) to more clinically related comorbid depression associated with chronic pain (Bair et al., 2003; DeVeaugh-Geiss et al., 2010). From an evolutionary point of view the down-regulation of affect is adaptive (Gilbert, 2006). While this may promote functioning in daily life, under circumstances of chronic pain altered affect is a common problem, and may be viewed as a loss of control over the aversive nature of the underlying pain problem. As such the loss of control unfolds into a failure to adapt to social and other environmental processes. Individuals may be preordained to be more sensitive to developing depression based on genetic (Lohoff, 2010), epigenetic (Sun et al., 2013), metabolic (Kim et al., 2012), or other less defined mechanistic processes. It is unclear what factors contribute to kindling (increased vulnerability after repeated exposure to stress) or confer direct diathesis (Willner et al., 2012) as depression evolves as a comorbid process in chronic pain. The vulnerability to depression in chronic pain is not well defined, but processes such as chronic stress contribute to the allostatic load of the disease (Borsook et al., 2012; McEwen,

2004). Whatever the etiology, the classification of the depressive state clearly has implications for treatment (Krishnan et al., 1985). The psychological tenant of reward deficiency syndrome present in chronic pain has been evaluated as anhedonia (the inability to feel pleasure) and is a core feature of depression. The evolution of sadness or mild mood alterations in chronic pain to meeting clinical criteria for major depressive disorder can be indistinct (Table 1). Some assert that the cognitive focus of negative thoughts can potentially distinguish `normal' depressed individuals marked with self-hatred and loathing from patients with pain and depressed mood whose negative thoughts center on their pain (Pincus and Morley, 2001). Regardless, preventing the progression from symptoms to full disorder is clearly an issue. Brain regions considered to be involved in depressive symptomatology involve an extensive network including the medial prefrontal cortex, limbic, striatal, thalamic, and basal forebrain structures (Price and Drevets, 2012). In a study where negative mood was induced in healthy volunteers, increased activity in prefrontal areas, ACC, and hippocampus, as well as significantly less deactivation in response to noxious thermal stimuli when compared to pain responses in a neutral mood (Berna et al., 2010). Subjects who reported greater increases in pain unpleasantness in this study showed greater inferior frontal gyrus and amygdala activation. Such findings underscore the compounding effect of the co-occurrence of depressed mood and a persistent pain state, suggesting that these systems may rapidly adapt, with persistent co-activation leading to altered circuits and behavior (emotional regulation).

Psychological treatment of depressive-like symptoms are likely most effective when mapped appropriately to the underlying mechanisms driving the dysfunction, such as interpersonal psychotherapy for individuals for whom relational strain or social isolation are prominent features (Klerman, 1984). As humans regularly use thoughts to generate more adaptive emotional and social reactions (Gross, 1998), cognitive regulation strategies, such as reappraisal and selective attention are typically taught within cognitive-behavioral therapy for depressive symptoms (Beck and Beck, 2011) and have a critical function in emotional responses (Fontaine et al., 2007). Reappraisal of negative scenes has been associated with increased activation of both dlPFC and vlPFC regions along with dorsal anterior cingulate, and decreased activation of a region of the orbitofrontal cortex and the amygdala (Ochsner et al., 2002) with other studies echoing these results (Ochsner and Gross, 2008). Additional findings implicate increased activity in the vmPFC (Delgado et al., 2008), underscoring the importance of reinitiating top-down cognitive control of emotion centers in the brain. For some, attempts to challenge their dysfunctional thought patterns can prove difficult, thus behavioral activation (BA), which aims to increase engagement in activities often associated with the experience of pleasure or mastery can be a more effective. BA predicates on the assertion that depressive symptoms persist through low rates of response-contingent positive reinforcement/pleasant activities (Dimidjian et al., 2011). Meta-analyses examining BA support this treatment approach among depressed patients (Cuijpers et al., 2008) and its application among individuals suffering with chronic pain fits well with the overall goals of pain rehabilitation to return to important activities of daily living.

2.5. Learning and Memory—Pain is an emotionally salient stressor that can trigger memory consolidation and learning. Both explicit and implicit learning processes have been implicated in the maintenance of chronic pain, with implicit processes more pronounced, and due to their unconscious nature, more difficult to extinguish (Flor, 2012). Prominent implicit processes include operant conditioning, social learning, and classical conditioning. Under operant contingencies, pain behavior (such as limping) can be directly maintained by escape from actual/anticipated noxious stimulation (negative reinforcement (Iwata, 1987)) or increased attention in the `sick role' (positive reinforcement). For example, social learning or modeling has been observed in pediatric chronic pain with an increased incidence of pain problems among children of parents who suffer with pain problems (Hoftun et al., 2013).

Lastly, classical conditioning underlies the acquisition of fear learning where a previously neutral stimulus (a medical exam) when initially paired with pain later elicits a conditioned response (increased heart rate when the physician approaches). Fear learning in the context of pain typically develops after few repetitions, generalizes quickly, and can be maintained simply through anticipation of increased pain transitioning to an operant process of reinforcement (Vlaeyen and Linton, 2012). In chronic pain, prediction error may be a key way to monitor stress and aversive situations. Heightened in pain sensitization (see (Ploghaus et al., 2000)), prediction error leads to impaired learning as well as the inability to attend to more constructive stimuli (Schultz and Dickinson, 2000). Under healthy conditions, coding of prediction errors may represent a basic mode of brain function in adaptive behaviors including normal learning.

2.5.1. Fear learning and pain-related fear: Broadly, fear is a normative response to a real or imagined threat with the primary function of promoting survival (e.g., (Gullone, 2000)). From separation anxiety manifested during infancy to fear of bodily injury emerging in school-age children and continuing into adulthood, we humans are hardwired to experience fear. These fears are protective, and in most cases, adaptive. Pain (an unconditioned, universally noxious stimulus; US) triggers our fear response and alerts our flight-or-fight system to act (an unconditioned response; UR). This is where pain and fear can collide. After exposure to painful stimuli or an injury, a previously neutral experience, such as movement or even anticipation of movement (a conditioned stimulus; CS) can elicit fear (a conditioned response; CR) even in the absence of pain. Although this can be adaptive in the short-term to promote healing, individuals who continue to perceive movement as threatening after the painful stimuli is no longer present or the initial injury has healed (conditioned fear) can experience a number of psychological and physical sequelae, including hypervigilance, muscular reactivity, escape/avoidance, and guarding behaviors that maintain or exacerbate pain and promote pain-related disability (Verbunt et al., 2003). The brain circuitry of fear learning has been extensively studied in animals (Johansen et al., 2010) and humans (Schiller and Delgado, 2010), although not explicitly among patients with chronic pain. Regions most prominently implicated are the amygdala, hippocampus, and prefrontal cortex (dlPFC and mPFC), with the amygdala serving as the primary hub of action. The amygdala circuitry provides an ideal example of pathways that may inform new approaches and metrics related to treatment. The CS and US learning pathways converge at the lateral nucleus of the amygdala (LA), where the LA receives afferent sensory input. The LA then connects with the central nucleus (CE) of the amygdala that controls the expression of the conditioned fear responses (CR), involving behavioral (e.g., freezing), autonomic nervous system (e.g., heart rate) and endocrine (pituitary-adrenal hormones) responses. Projections from the hippocampus to the basal nucleus (B) of the amygdala process contextual information during conditioning, and may gate fear expression through the CE (Hartley and Phelps, 2010). Results from fMRI studies of fear conditioning in healthy individuals show increased activity in the amygdala (Buchel et al., 1998; LaBar et al., 1998) with the magnitude of this response predictive of the strength of the conditioned response (LaBar et al., 1998; Phelps et al., 2004). Additionally, cognitive interpretation of a previously neutral stimulus through verbal instruction (LaBar et al., 1998; Phelps et al., 2004) or reappraising the meaning of an ambiguous scene so that it is more fearful (Ochsner et al., 2004) enhances amygdala activation. As many fears associated with pain are imagined and anticipated, but never actually experienced, these results support the neural pathways of these processes.

Reversing the impact of fear learning is complex and difficult. Extinction, or learning of an inhibitory response, of acquired fear is resistant to automatic generalization, requiring massed rehearsal in a variety of contexts during stressful and non-stressful circumstances to prevent renewal (Orsini and Maren, 2012; Quirk and Mueller, 2008). Graded in-vivo

exposure, a CBT developed by Vlaeyen and colleagues (Vlaeyen et al., 2002a; Vlaeyen et al., 2002b) effectively targets fear of pain and disability through exposing patients to activities previously avoided due to fear of pain or re-injury (de Jong et al., 2005). When patients experience how disengagement from safety behaviors does not lead to catastrophic consequences, their misinterpretations are challenged and disconfirmed and they correct their fear expectancies leading to fear extinction and cognitive regulation (Goubert et al., 2005; Leeuw et al., 2007; Smeets et al., 2006). Acceptance-based approaches also encourage exposure to a broader repertoire of avoided internal and external stimuli and are grounded in solid empirical evidence for their effectiveness among children (Wicksell et al., 2009) and adults (Vowles et al., 2011; Wicksell et al., 2013). FMRI results demonstrate increased top-down cognitive control (i.e., enhanced pain-evoked prefrontal cortex activation) after acceptance-based treatment (Jensen et al., 2012). From pre-clinical studies, we know that during extinction learning, inhibitory connections between the ventromedial prefrontal cortex (vmPFC) and the intercalcated (ITC) cell masses are established. During extinction recall, these connections inhibit fear expression through projections to the CE. Inhibitory connections between the vmPFC and the LA may also regulate fear expression through the CE. Contextual modulation of extinction expression is mediated by projections from the hippocampus to the vmPFC and/or LA. Imaging studies of extinction learning in healthy humans report a decrease in amygdala activation (Gottfried and Dolan, 2004; Knight et al., 2004; LaBar et al., 1998; Phelps et al., 2001) while BOLD signals in the vmPFC increase during extinction learning and extinction retrieval (Phelps et al., 2004). Preclinical data has provided further insights into the role fo the mPFC in these changes. For example, using a chronic neuropathic pain model, repeated administered D-cycloserine, a partial agonist of the NMDA receptor, can ehance learning and potentiate the extinction of acquired fear. Not only did D-cycloserine reduce mechanical sensitivity of the injured limb, the effect persisted after discontinuation of the drug (Millecamps et al., 2007). Specific infusions into the mPFC and amygdala acutely induced antinociception and infusions into the mPFC reversed place avoidance behavior induced by mechanical stimulation of the injured paw, together suggesting the potential efficacy of D-cycloserine in enhancing fear extinction and reducing neuropathic pain behavior (Millecamps et al., 2007). Persistent changes have also been observed in patients who have received a similar drug, ketamine that may reorder or restore neural circuits including the anterior cingulate (Becerra et al., 2009). Similarly, preliminary results suggest that the partial NMDAR glycine-site agonist, GLYX-13, may be a successful treatment agent for both tonic and neuropathic pain, but with an added antidepressant quality (Wood et al., 2008). Unlike ketamine, a non-competitive NMDAR antagonist, GLYX-13 does not seem to have the same sedative effect or abusive potential (Burgdorf et al., 2013). The increased positive emotional learning that occurs as result of mPFC infusions, suggests potential efficacy of GLYX-13 in deminishing neuropathic pain and it's associated pyschological consequences (Burgdorf et al., 2011). Overall, extinction learning in humans seems to depend on the integrated functioning of a neural circuit that is predominated by the amygdala and vmPFC. Such studies are insights to potential reordering of brain connectivity in a manner that may be therapeutic.

3. Premorbid Risk Factors and Pain

Some individuals seem more resistant to alterations in psychological function in the presence of persistent pain whereas others seems to swiftly transition into a downward spiral of dysfunction. Premorbid vulnerability factors likely contribute to some of the disparities in these outcomes. Here we briefly review some of the key risk factors that have emerged from the literature including prior physical and psychological trauma, social dysfunction, catastrophizing, social status, and gender.

3.1. Prior Physical and Psychological Trauma—While initially put forward in the late 1950's, the connection between psychological (e.g., emotional abuse, neglect) and physical (e.g., sexual) abuse in childhood has a strong connection with the subsequent development of chronic pain (Paras et al., 2009; Saariaho et al., 2011; Symes et al., 2013; Tietjen et al., 2010). Among types of abuse, sexual abuse amongst both men and women appears to confer the greatest diathesis or predisposition to chronic pain (Hart-Johnson and Green, 2012; Walling et al., 1994). It is unclear whether the heightened risk is derived in a similar fashion to that involving depression and pain where kindling of the underlying process of neural sensitization leads to the comorbidity (e.g., generalized pain in MDD patients who have not had pain previously).

3.2. Social Dysfunction—Recent studies support the notion that social pain (feelings associated with social disconnection) may have the same neurobiological underpinnings of physical pain (Eisenberger, 2012). Specifically, brain areas that are activated by social distress parallel those activated by acute experimental pain (Eisenberger et al., 2003; Onoda et al., 2009). The critical issue here in the clinical context is that social processes such as social exclusion (or bullying), isolation and lack of support may contribute to cross sensitization and affect physical pain i.e., one process may affect the other and vice versa. This is particularly applicable in the unfolding of a common process frequently encountered by chronic pain patients – rejection or social separation (Eisenberger and Lieberman, 2004; Macdonald and Leary, 2005). Although many of these studies have focused on regions such as the anterior cingulate cortex, the integration of social hurt may relate to how this region is involved in salience and how our salience network is disturbed in chronic pain. When socially rejected, psychological process of emotion and cognition may be adversely affected and pain exacerbated (Kashikar-Zuck et al., 2007) or behaviors such as intimacy and family relationships severely affected (Smith, 2003). Such changes may reinforce pain behaviors. This issue is also particularly important in children where early socializing, schooling, and interactions with family are so important.

3.3. Catastrophizing—Pain catastrophizing is a cognitive attributional style characterized by a negative mindset, magnification, and rumination about pain (Sullivan et al., 2001). For the patient, the worst is feared and the individual is left feeling helpless (Edwards et al., 2006). Catastrophizing is consistently and robustly associated with poor outcomes in adults and children post-surgically (Page et al., 2012; Sullivan et al., 2011) and across a broad spectrum of chronic pain conditions (Hirsh et al., 2010; Osborne et al., 2007; Turner et al., 2002). Catastrophizing is a cognitive vulnerability factor often found to precipitate depressive symptoms (Lee et al., 2008; Simons and Kaczynski, 2012). Furthermore, persistent pain catastrophizing may contribute to the ongoing pain process (intensity, disability, and other psychological changes) (Severeijns et al., 2001). While the importance of catastrophizing and the prediction of chronic pain are now established across many studies, a better understanding of its neurobiological correlates will provide insights into those components that may be more amenable to preventive treatments/psychological interventions (Campbell and Edwards, 2009). For example, a very recent study found increased dorsolateral prefrontal gray matter volume associated with reduced pain catastrophizing among patients who completed an 11-week CBT pain coping intervention (Seminowicz et al., 2013)

3.4. Social Status and Education Attainment—Across studies, low social standing usually has a negative effect on epidemiology of chronic pain (Gale et al., 2012; Gore et al., 2012; Rodarte et al., 2012; Zarei et al., 2012). Some issues that correlate with social status include obesity, lower level of education, and inequalities in the distribution of health care. Pre-clinical work has demonstrated decreased dopamine transporter binding and increased

D2 reception binding in the caudate putamen and nucleus accumbens in subordinate rats (Lucas et al., 2004) and increased dopamine D2 receptor availability/amount among socially dominant macaque monkeys (Morgan et al., 2002). Perhaps dopaminergic deficits in individuals of low social standing are predisposing them to chronic pain (Jarcho et al., 2012).

3.5. Gender—Post-pubertal women generally have a higher prevalence of chronic pain compared with men (Bjornsdottir et al., 2013; Fillingim, 2000; Keogh and Eccleston, 2006). A number of physiological factors including hormones (Kuba and Quinones-Jenab, 2005) and menopause (Martinez-Jauand et al., 2013) contribute to this discrepancy. Specifically, reduced mu opioid receptor activation (Zubieta et al., 2002) and the anti-dopaminergic effect of estrogen (Euvrard et al., 1980) (McEwen, 2001) may play such a role. It may also relate to issues such as a woman being more inclined to report their pain, especially considered the self-report nature of many chronic pain measures. While numerous reports of gender differences have been published, sex differences in psychological factors in chronic pain are inconclusive. Heightened pain-related anxiety has been identified in men with chronic back pain (Robinson et al., 2005), while recent work has identified pain-related anxiety as influential on pain intensity ratings in men and pain tolerance in women (Thibodeau et al., 2013). Thus the relationship between gender and pain is complex (Fillingim, 2013; Racine et al., 2012). This is further underscored by observations of heightened pain sensitivity and thalamocortical activity in women compared to men that is eliminated after controlling for trait anxiety (Goffaux et al., 2011). Comorbidities may contribute to a higher female prevalence including disorders of mood as estrogen has been implicated in depression (Fernandez-Guasti et al., 2012; Ryan and Ancelin, 2012). Recent data from imaging has shown differences in brain systems in response to chronic pain (Maleki et al., 2012) and this type of measure together with further epidemiological data may provide further insight into sex differences. What is clear however, is that more women present to pain clinics, particularly with certain pain disorders (migraine, fibromyalgia) and so at a practical level, we need to evaluate and understand psychological perturbations across men and women.

4. Integrating Dysfunction: Complex Behaviors with Reciprocal, or Multiple and Multiplying Effects

Together, the chronic pain state can trigger changes in psychological or mental functions that manifest as alterations in perception, attention, mood, motivation, learning and memory. The changes are ongoing, vary in their magnitude, and their hierarchical manifestations, and may be temporally and sequentially altered by treatments, and all contribute to an overall pain phenotype with some components of behavior having a stronger phenotypic influence. One may consider intact, normal behavior as that similar to an orchestra playing in harmony. In chronic pain, elements of the orchestra begin to fail, are missing or are playing out of tune. Obviously the nature of the quality of individual players is important, akin to the modifying effects of an individual's prior history – emotional, social, biological, education/ intellectual, and other components that form the composite of who we are and how we behave in response to chronic pain. These processes are integrated in what has now been termed the "*The Connectome*" – representing who we are intellectually, behaviorally and emotionally (D'Angelo, 2012; Van Essen et al., 2012).

As previously mentioned in Figure 4, the response to chronic pain may be akin to a bouncing ball, in that if left alone (no treatments) the system fails from energetic and resilient (healthy) to a non-energetic and dysfunctional status (clinical failure). In some respects this is akin to the cardiac failure model that continues to spiral out of control towards an untreatable or difficult to treat syndrome (i.e., allostatic load). Taking this view, early definition and understanding of those neural systems that are most salient in each

chronic pain patient needs to be identified and targeted. One of the missing keys to this is a lack of understanding of interactive processes that may be positive or negative. An example of this is complexities surrounding the use of opioids in chronic pain. In many cases they have short-term beneficial effects, but can have poor long-term effects on brain systems (Upadhyay et al., 2010).

4.1. When the Butterfly Flaps its Wings—While speculative, local and distant changes in brain systems may be considered in the concept of *"When a butterfly flaps its wings*". These changes may be dependent on the current conditions, in this case brain networks that define these conditions. Thus a small change may produce significant changes in a non-linear process, particularly in pain where cross-sensitization may occur and a psychological effector (e.g., fear) enhances the pain experience. The effect is also determined by prior psychological and other factors (genetic, pain condition, age, gender etc.) that define baseline conditions that may contribute to this effect. These processes may result in relative resistance or resilience to a potential multiplying effect. Given the multiple psychological processes that may be altered in chronic pain, these interactions further contribute to the `butterfly effect' in complex yet ill-defined ways. Another way of looking at this is how these processes may contribute to a self-healing effect – the so-called Gaia effect that relates to how organisms interact to have self-regulating system that parallel allostasis in physiological systems – adapting to a stressor. Even In practical terms, the interaction of a patient's perceived limb pain and gaining motor function may alter other brain networks through these effects (see Figure 6).

4.2. Cross-Sensitization—Cross sensitization refers to how one process may exacerbate or enhance another. Common examples include drugs of abuse and repeated stress increasing glutamate receptors in the ventral tegmental area that alter dopamine function (Fitzgerald et al., 1996). Thus there are common, long term effects on function that occur in chronic pain. Pain-, stress-, and analgesic drug-induced opponent and proponent states of the mesolimbic dopaminergic pathways may render, in a similar manner altered reward/ motivation dysfunction that is now vulnerable to sensitization, cross-sensitization and aberrant learning. The affects are further amplified through the long-term neuroplasticity process of sensitization at the cortical and subcortical limbic structures (Rome and Rome, 2000). This is an autonomous, self-sustaining feed-forward loop generated by a variety of intermittent sensory (e.g., pain), emotional (e.g., altered mood, fear) and behavioral (e.g., social isolation) stimuli and characterized by conditionability, interchangeability as well as progressive intensification of the duration and magnitude of the responses (Pierce and Kalivas, 1997). Cross sensitization has significant implications in illness progression and treatment resistance that are independent of genetic or environmental (including epigenetic changes (e.g., (Hoffmann and Spengler, 2012)) vulnerability and increase the affliction level (Post, 2010; Post et al., 2012).

4.3. Allostatic Failure: Unsuccessful Perseverative Behavior—The concept of allostatic load in disease, initially promulgated by authors such as Bruce McEwen (recently reviewed in: (Karatsoreos and McEwen, 2011; McEwen and Gianaros, 2010) is increasingly being applied to disease states including chronic pain (Borsook et al., 2012). The notion of psychobiological allostasis has received attention (Karatsoreos and McEwen, 2011). Taken together, the homeostatic balance is altered in chronic pain and becomes unstable at a physiological (stress) and psychological level. When there is no adaptation or resilience to stressors, there are systemic failures that manifest as alteration in behaviors. Thus the comorbidity of a primary inciting process (i.e., pain) and the multitude of psychobiological processes that may subsequently ensue, contribute to alterations in brain plasticity that while part of resistance and allostatic load, may eventually lead to allostatic failure. Such failure

can be measured in a number of ways including progression from altered mood states to defined major depressive disorder (MDD).

4.4. Early Forme Fruste Markers of PsychoNeurological Changes—It is clear that alterations in neural networks occur with chronic pain. Many of these changes confer alterations in our psychobiological or psychoneurological behaviors. However, we need to have a better understanding of how we can define brain changes early, before these plastic changes, assumed to be adaptive become maladaptive. One example is when pain drives individuals to suicidal ideation and the act of suicide itself (Ritchie, 2012). The use of brain imaging has enormous potential in defining markers that may predate the evolution of behavioral changes or define relative states (e.g., state of resiliency to treatments; at risk states (Wood et al., 2013). Such information would have enormous implications for how we treat patients since early interventions have by and large proved to be better (since brain plasticity has not fully evolved into a resistant state) and innovative approaches for new therapies may become possible to enhance resiliency (Russo et al., 2012).

5. Treatment and Training Approaches

5.1. Integrating Psychological Science into Pain Neurobiology—It would seem that targeted research would contribute to a better understanding of psychological processes in chronic pain. Clearly, *Neuroscience Psychology* is advancing into clinical translation. However as in many fields some data sets such as functional imaging, while hugely appealing in terms of objective measures need reproducing to gain further acceptance. Clinical and research programs, and for that matter, drug trials, should further integrate psychological issues in pain to improve research strategies. Of course chronic diseases with multiple factors of primary and secondary (comorbid) etiologies are difficult studies to perform. As previously mentioned Figure 5 shows a correlation of psychological changes with brain function (regions, circuits and interactive circuits or networks) and treatments and Figure 7 summarizes the potential contributions of specific psychological processes to pain and behavioral responses to pain.

One approach to evaluating and planning for readapting the chronic brain using psychological and other approaches is `*Stripping Allostatic Load, One piece at a time*'. Table 2 links altered psychological processes to specific evidence-based psychological treatments. Current behavioral therapy approaches (e.g., Cognitive Behavioral Therapy, Acceptance and Commitment Therapy) have some, but relatively weak effects in controlled clinical trials (Wetherell et al., 2011; Williams et al., 2012) although somewhat better among pediatric patients (Eccleston et al., 2012). Therapeutic response can be enhanced by targeting the most susceptible processes initially that could then have the reversal of the `*Butterfly Effect*'. Just as most people adapt to a stressful situation, unadapting from a chronic condition needs a focused mechanism based, data driven approach.

**5.2. Training – Sub-Specialty in `Pain Neuroscience Psychology'—**While one could argue that most of clinical psychology may relate to `pain' or hurt, few clinical training programs have a focus on the neurobiology of pain. Given the tremendous advances in understanding the brain and the impact that this has and will have on our clinical practice, psychology is well positioned to take advantage of these in applying new developments in treating brain-related changes in chronic pain. It is here, with the huge advantages of a basic understanding of the brain and a sound basis in neurobehavioral processes that can be specifically targeted in patients with chronic pain. Thus, psychology could be a major contributor to advancing our understanding and treatment of chronic pain.

Conclusions

Although pain epitomizes the indivisible nature of physical and emotional suffering, it is rarely addressed from the psychological standpoint. This, however, is a timely endeavor because modern pain neuroscience research consistently implicates the key brain limbic and cortical structures respectively engaged in the generation and control of drives, impulses and affects experienced among chronic pain patients. Cyclical processes whereby pain-induced deterioration in cognitive, emotional, behavioral, perceptive and interoceptive functions worsens pain problems that in turn cause a transition from negative affective states and maladaptive behaviors to *bona fide* mental health disorders. While acute pain activates mesolimbic reward-related pathways and engenders sudden alterations in psychological states (e.g., fear, stress and avoidance), chronic pain is associated with progressive changes and relentless decline in psychological wellbeing paralleled by reward deficiency (i.e., diminished dopaminergic effects), pain sensitization and cross-sensitization (e.g., depression, anxiety, addiction, etc.) along with anti-reward (i.e., stress) allostatic neuroadaptations. Then again, negative affective states substantially worsen pain conditions further deteriorating psychological outcomes.

The notion of integrative psychological processes is not new (see Ryan, 1995). While the cognitive neurosciences have contributed enormous insights into brain function (e.g., consciousness (Feinberg, 2011; Goldfine and Schiff, 2011), chronic stress (Gourley et al., 2013; Hill et al., 2012), and resilience (Wu et al., 2013); while psychiatric research has furthered our understanding of disease states such as pathological anxiety and depression (Willner et al., 2012), the implementation of an integrative neural systems approach of psychological tenets into treatments for chronic pain are relatively limited. In some ways this is surprising. More data from combination treatments that involve drugs, behaviors, physical therapy and the like are making a bold statement: we need to view the brain as an orchestra and bring to it components that harmonize and enhance.

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Highlights

- The chronic pain state can trigger a cascade of changes in psychological processes.
- Changes occur in perception, attention, mood, motivation, learning and memory.
- We describe processes in the context of localized and integrated neural networks.
- We link altered behavioral processes to evidence-based psychological treatments.
- Pain neuroscience psychology can enhance our treatment of chronic pain.

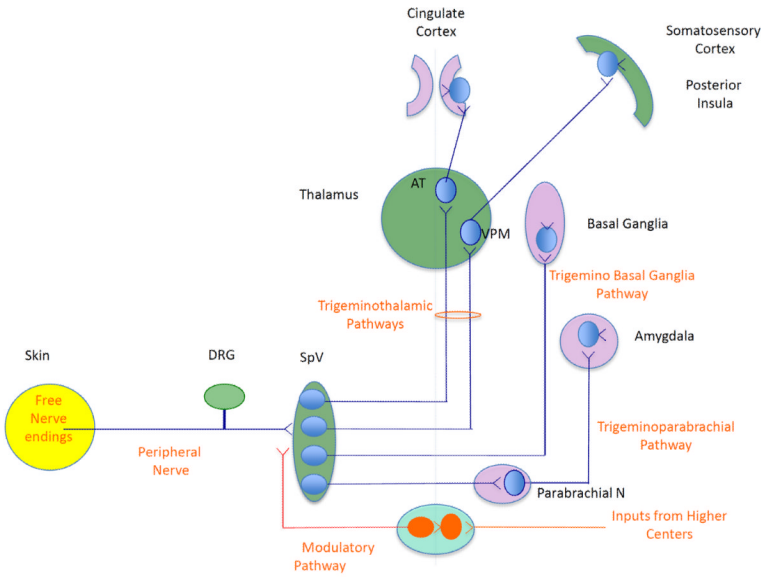

Figure 1. Neural Pathways involved in Pain

The figure conceptualizes brain regions involved in sensory and emotional processing of chronic pain. DRG = dorsal root ganglion, SpV = spinal nucleus of trigeminal ganglion (dorsal horn), AT = anterior thalamus; VPM = ventroposteromedial thalamus

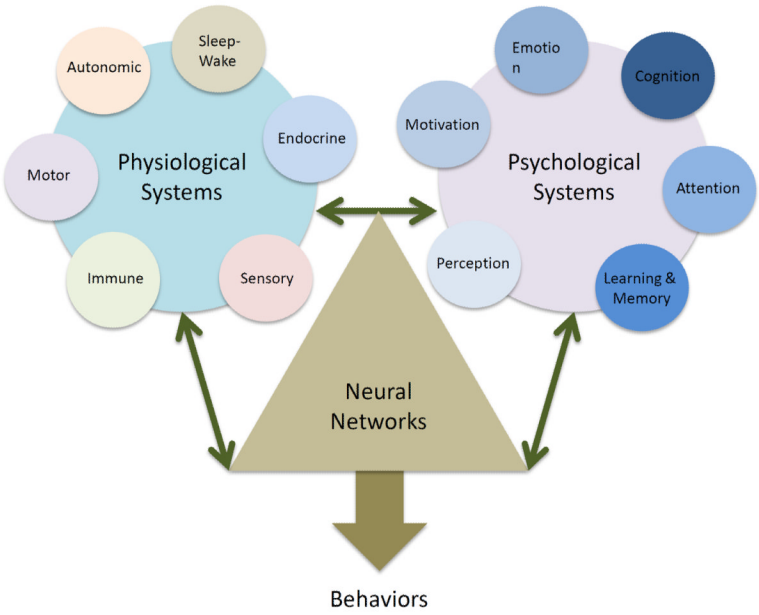

Figure 2. Physiological and Psychological Systems that integrate Pain Behaviors

Physiological systems including stress-related hormones and brain systems that control these, sleep-wake processes as well as those sensory systems that respond to tissue damage clearly contribute to alterations in neural networks. Some physiological changes can be either objectively measured or reasonably easily interpreted (e.g., pain intensity). Psychological systems to so in a less obvious manner until a *forme fruste* behavioral aberration is present. These changes alter our normal network profile that is dependent on genetic, epigenetic and live experience to modify behaviors. Clearly the two processes in pain are integrated and result in aberrant behaviors.

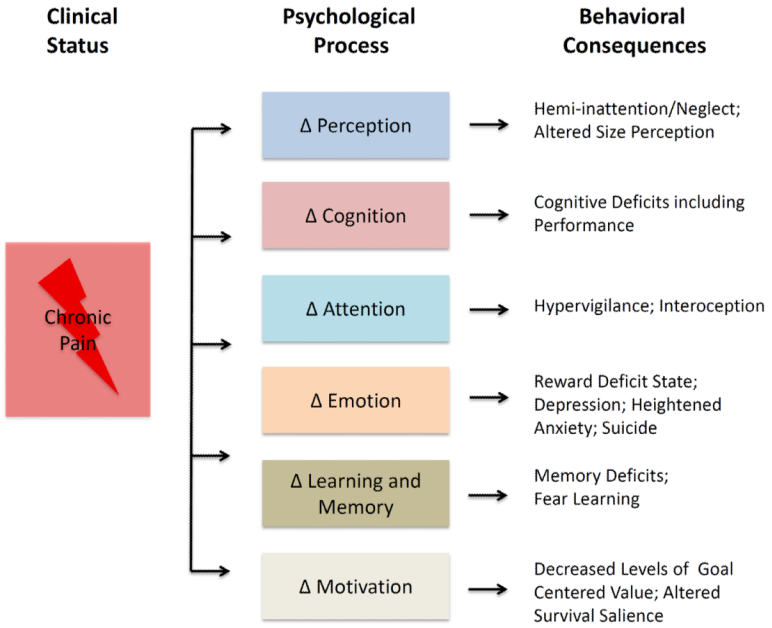

Figure 3. Pain, Psychological Processes and Behavioral Consequences

Following a pain (a sensory or emotional experience to an actual trauma or perceived bodily threat), a number of psychological processes including those listed here are involved in response. These change processes may be resilient or resistant to the inciting events or become altered as noted in examples of behavioral consequences. Additionally, alterations in one system may have consequences in another. The understanding of how these systems interact and can be targeted will have significant implications on treatment approaches.

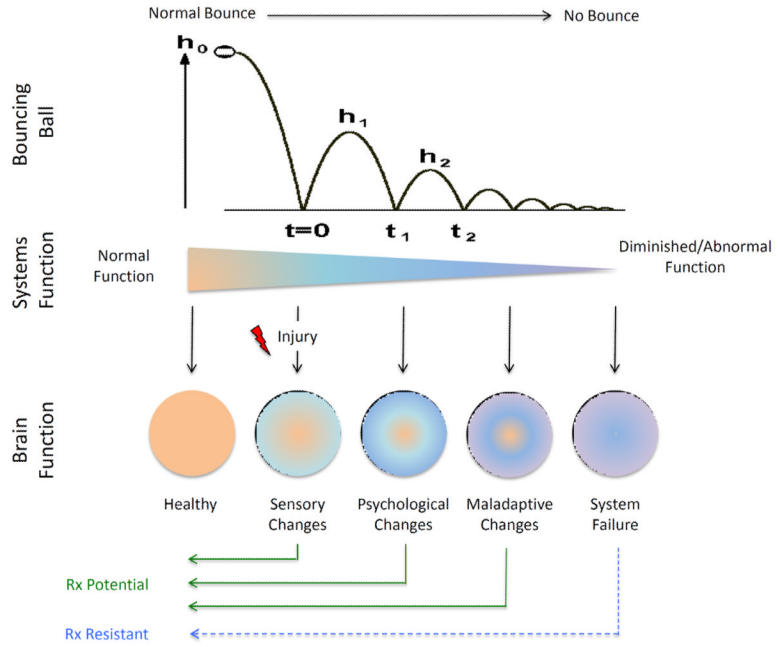

Figure 4. Pain Progression – Complex interactions leading to maladaptive changes and system failure (allostatic load)

The upper part of the figure shows the loss of energy in a bouncing ball – after a while all potential/kinetic energy (height, h) diminishes over time. The comparison is similar for chronic pain (middle figure) where normal function evolves to diminished normal or increased aberrant or abnormal function. Multiple changes in brain function (altered networks, see Figure 6) occur over time following injury as shown in the lower part of the figure where there is a sequential alteration in function (physiological and psychological) that eventually leads to maladaptive changes and system failure.

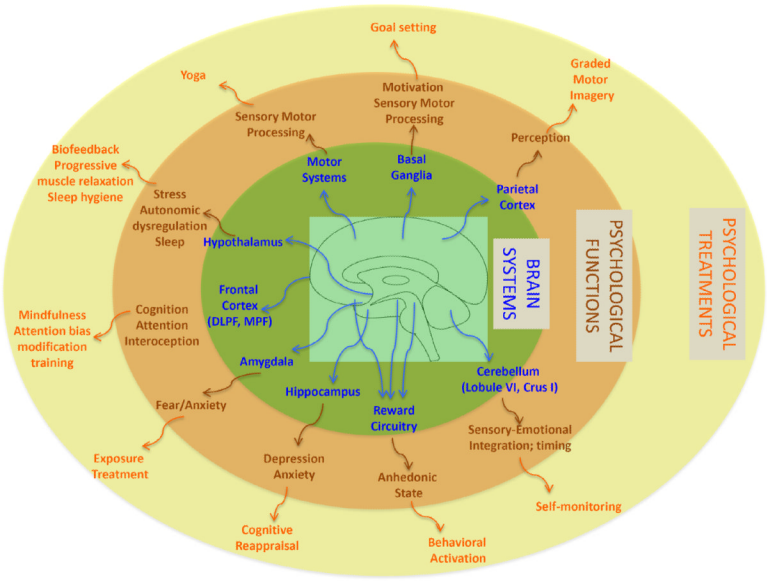

Figure 5. From Brain Systems to Psychotherapeutic Targets

A network of brain systems underlies alterations in psychological function in the chronic pain state. This figure shows specific psychological treatments that target alterations in psychological function across brain systems.

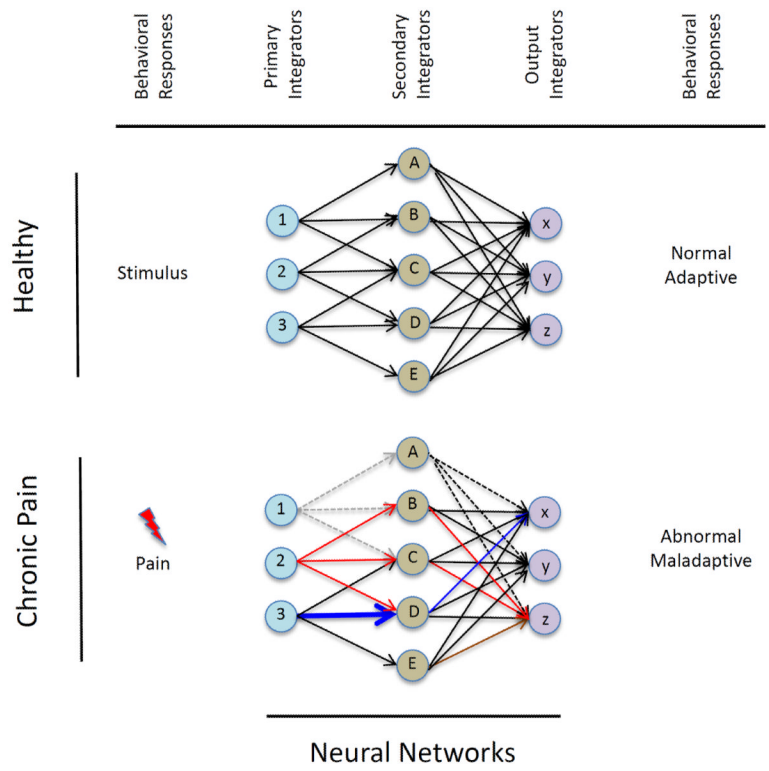

Figure 6. Altered Networks

The figure shows a model of brain network changes as a consequence of a stimulus in a healthy subject (top) and the same networks in response to pain (bottom). Using tissue damage as an example of a pain stimulus (viz., surgery), there are alterations in sensory inputs (Primary Integrators) that produce changes in Secondary Integrators (these may initially be adaptive e.g., enhanced modulation of pain by higher cortical centers such as the anterior cingulate cortex (See Figure 1), but eventually become maladaptive through individual networks or across networks resulting in altered behavioral responses.

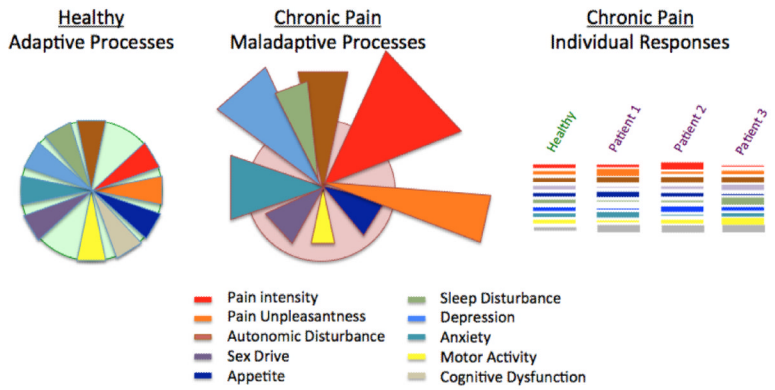

Figure 7. Treatment Paradigm – Neural Network-Directed Decreases in Allostatic Psychological Load with Readout Measures (from (Borsook and Kalso, 2013) with permission)

The figure shows containment and normal adaptive processing to various stressors (noted below in the key); these normal responses are balanced and adaptive (adapt to `homeostatic set-point') over time. In chronic pain responses may be exaggerated (out of `homeostatic set-point') or inhibited. In a multidimensional biological process such as chronic pain each of these stressors may affect an individual differently as represented in the `bar-code' noted on the right.

Table 1

Diagnostic criteria for Major Depression and Generalized Anxiety and the altered psychological state in chronic pain

Process	Psychiatric Condition	Altered Psychological State in Pain
Depression	Major Depressive Disorder*	
	1. Depressed mood or irritable.	Depressed mood (Ohayon and Schatzberg, 2010; Tang et al., 2008)
		Anger (Bruehl et al., 2009)
		Catastrophizing (Wood et al., 2012)
	2. Decreased interest or pleasure in activities	Anhedonia (Nicholas et al., 2009)
	3. Weight or appetite change	Weight gain/obesity (Ursini et al., 2011)
	4. Insomnia or hypersomnia	Sleep disturbance (Palermo et al., 2012; Palermo et al., 2011; Tang et al., 2012a)
	5. Psychomotor agitation or retardation	Motor control (Gerdle et al., 2010; Tang et al., 2012a)
	6. Fatigue or loss of energy	Fatigue (Dansie et al., 2012)
	7. Feelings of worthlessness or excessive guilt	Self-perceived burden (Kanzler et al., 2012; Kowal et al., 2012)
	8. Difficulty concentrating	Cognitive impairment (Reyes Del Paso et al., 2012)
		Decision-making deficits (Apkarian et al., 2004a)
	9. Thoughts of death or suicide	Suicidal ideation (Fishbain et al., 2012; Ilgen et al., 2008; van Tilburg et al., 2011)
Anxiety/Fear	Generalized Anxiety Disorder*	
	“Excessive anxiety and worry” that is difficult to control	Anxiety (Lucchetti et al., 2013; Simons et al., 2012b)
		Catastrophizing (Sullivan et al., 2001)
		Pain-related anxiety/fear (Vlaeyen and Linton, 2012)
	1. Feeling wound-up, tense, or restless	Anxiety sensitivity (Ocanez et al., 2010; Payne et al., 2013)
	2. Easily becoming fatigued or worn-out	#6 above
	3. Concentration problems	#8 above
	4. Irritability	#1 above
	5. Significant tension in muscles	Muscle tension (Klinger et al., 2010)
	6. Difficulty with sleep	#4 above

*To meet DSM-IV-TR diagnostic criteria must have 5 of 9 symptoms for MDD and 3 of 6 symptoms (1 of 6 for children) for GAD.

Table 2

Psychological Processes and Treatment Approaches

Process	Psychological Treatment	References
Physiological Systems		
Autonomic dysregulation	Progressive muscle relaxation	(Emery et al., 2008)
Stress	Biofeedback	(Nestoriuc and Martin, 2007)
Sleep	Sleep Hygiene	(Tang et al., 2012b)
Sensory-Emotional Integration Timing	Self-monitoring; self-regulation	(Sauer et al., 2010)
Sensory motor processing	Yoga	(Ward et al., 2013) (Cramer et al., 2012)
Psychological Systems		
Cognition	Mindfulness and acceptance	(Veehof et al., 2011)
Interoception	Attention modification	(Carleton et al., 2011; Sharpe et al., 2012)
Anxiety Sensitivity		
Perception	Graded motor imagery	(Bowering et al., 2013; Walz et al., 2013)
Pain-related fear	Exposure	(Bailey et al., 2010)
Anxiety	Cognitive reappraisal	(Ochsner et al., 2006)
Motivation	Goal setting	(Sauer et al., 2010)
Reward and Aversion	Values based action	(Vowles et al., 2011)
	Motivational enhancement therapy	(Vong et al., 2011)
Anhedonic state Depression	Behavioral activation	(Dimidjian et al., 2011)
Catastrophizing	Cognitive reappraisal	(Lawrence et al., 2011; Thorn et al., 2007)