Stress and Sensitization in Chronic Pain

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Abstract and Keywords
Stress and sensitization are central concepts in chronic pain. Both can be a consequence and a contributor to the pain experience. This chapter describes the psychobiology of stress and sensitization within a multilevel perspective, indicating the impact of various forms of stress and sensitization on multiple psychoneurobiological processes (i.e., autonomic, endocrine, immune, and central processes) related to chronic pain. As a result of disordered stress regulation, sensitization may occur as a mechanism that explains how acute pain problems can become chronic and how acute pain problems can extend or generalize to other body parts or modalities. The evidence for stress and sensitization as consequences of or as contributors to chronic pain is reviewed, and possible underlying mechanisms are discussed. Next, strategies to reduce stress and sensitization and foster desensitization processes are described. The chapter concludes by introducing a motivational account of chronic pain informed by the stress and sensitization literature.

Keywords: chronic pain, sensitization, stress, interventions, psychoneurobiology, psychophysiology

5.1 Introduction
Stress and sensitization have been proposed to be both a contributor and a consequence of persistent pain. In this chapter, we focus on the psychobiology of stress and sensitization from an interactive multilevel perspective. We describe the impact of various forms of stress (e.g., daily versus chronic stressors) on multiple interdependent psychoneurobiological processes (i.e., autonomic, endocrine, immune and central processes) related to chronic pain. An important idea is that disordered stress regulation leads to sensitization that explains (1) the transition from acute to chronic pain, and (2) the extension and generalization to other body parts or modalities (Woolf, 2011). The evidence for stress and sensitization in chronic pain is reviewed together with possible mechanisms explaining these links. Next, strategies to reduce stress and sensitization, and to foster desensitization processes are described. The chapter concludes with introducing a motivational account of chronic pain informed by the stress and sensitization literature.

5.2 Stress
5.2.1 Stress, Stressors, and the Stress Response

Stress is omnipresent in our language and daily life, referring to a wide variety of situations and responses. Several definitions of stress have been proposed. Seminal research has been performed by Selye, who described stress as the non-specific (neuroendocrine) response of the body to an external physical, chemical, or psychological agent (Szabo, Tache, & Somogyi, 2012). In a later definition, the role of psychological factors, such as the appraisal of the situation and our judgments on whether we are able to adequately cope with the situation, was taken to the fore (Lazarus & Folkman, 1984). Currently, many researchers adhere to a psychophysiological account of stress, viewing stress as arising from the interaction between environmental demands (e.g., major life events or daily hassles) and individual resources (e.g., available coping mechanisms), eventually leading to psychophysiological responses (e.g., cognitive and emotional responses, as well as autonomic and neuroendocrine activation) to deal with the stressor (Cohen, Kessler, & Gordon, 1995; Lazarus & Folkman, 1984; Schneiderman, Ironson, & Siegel, 2005).
Stressors differ in their nature, number, and persistence. Different stress taxonomies exist, mostly categorizing stressors in terms of (1) acute time-limited stressors (e.g., laboratory challenges), (2) naturalistic stressors (e.g., minor or major life events), and (3) chronic (intermittent) stressors (e.g., enduring work stress, death of a loved one, financial problems, or childhood victimization; Geenen, Van Middendorp, & Bijlsma, 2006; Segerstrom & Miller, 2004). Chronic stress is common in humans, who display the unique ability to prolong the stress response by means of verbal-cognitive processes (see also the chapter 14 on ACT in this book). (p.179) This ability may lead to excessive stress anticipation, as in the case of worrying, or may lead to dwelling on stressors in the past, as in the case of rumination (Ottaviani et al., 2016; Schneiderman et al., 2005). It is reasonable to assume that chronic, major life stress has the largest impact on health, as it is accompanied by long-lasting activation of the physiological stress response (Ottaviani et al., 2016; Verkuil, Brosschot, Tollenaar, Lane, & Thayer, 2016).

From a physiological perspective, stress is an actual or potential threat to homeostasis, or stated otherwise, to internal stability in a constantly changing environment. Prolonged activation of the stress systems in response to stress has biological costs, termed allostatic load. In case of a healthy stress response, a primary activation of the stress system is followed by a cascade of responses that ultimately aims to restore homeostasis (McEwen, 1998; Schneiderman et al., 2005). The physiological stress system encompasses an intricate interconnected network of physiological pathways, both peripherally and centrally. It consists of the activation of the autonomic nervous system (ANS), of which the sympathetic-adrenal-medullary system (SAM) is part, and the activation of the neuroendocrine system, including the hypothalamus-pituitary-adrenal (HPA) axis. Both the ANS and neuroendocrine system are connected to the immune system (De Brouwer et al., 2010; Geenen et al., 2006). See Figure 5.1 for an overview of the psychophysiological stress response.
Overall, acute physiological responses to stress are considered adaptive. By producing catecholamines (e.g., epinephrine) through the SAM-system, and glucocorticoids (e.g., cortisol) through the HPA-axis, energy sources become increasingly available, and are redistributed to the skeletal muscles and the brain. Less critical activities, such as digestion, are temporarily suspended. Depending on the nature of the stressor, physiological responses may be regulated by different mechanisms. For example, stressors that can be actively dealt with may lead to myocardial responses that enhance cardiac output, enabling a fight-or-flight response. In contrast, stressors that require vigilant coping (e.g., drawing attention to potential danger signals) may lead to vascular responses that minimize potential damage in case of assault. When the stress has abated, feedback (p.180) (p.181) loops initiate an automatic turning-off of ANS responses and immune activation. This can be achieved for example by the release of cortisol. When the stress system is repeatedly or continuously activated, tissue damage (e.g., vascular hypertrophy and immune suppression) and disease (e.g., increased vulnerability to viral infections) may occur. For example, when people are confronted with intense and chronic stressors during childhood, such exposure may lead to long-term psychological, neurobiological, and immune effects (Kok et al., 2016; Schneiderman et al., 2005).

Figure 5.1 Psychophysiological stress response with possible links to disease outcome.

Numerous studies have found an association between stressors and unfavorable outcomes, such as increased morbidity and mortality. Much evidence shows a link between stress exposure on the one hand, and cardiovascular diseases and upper respiratory diseases on the other hand (Cohen et al., 1998). An impact on the progression of HIV-infection to AIDS has also been found (Schneiderman et al., 2005). In addition, stress exposure has been consistently associated with acute and chronic pain (e.g., Chapman et al., 2008; De Brouwer et al., 2010; Nicol et al., 2016; Ortego et al., 2016).

5.2.2 Stress Assessment

Several assessment procedures are available to measure stress-related constructs (Cohen, Kessler, & Underwood Gordon, 1995; Rodrigues, Kaiseler, & Queiros, 2015). First, the experience of potentially stressful events associated with substantial adaptive demands can be assessed by means of major stressful life events instruments such as the PERI life events scale (Dohrenwend, Krasnoff, Askenasy, & Dohrenwend, 1982). These instruments measure the occurrence of a number of major stressful situations, such as the death of a love one, job loss, and divorce, within a specific time period (mostly the past year; Turner & Wheaton, 1988). To assess general stress levels, validated self-report questionnaires such as the Perceived Stress Scale can be administered (Cohen, Kamarck, & Mermelstein, 1983; Fliege et al., 2005). Because stress is part of life and cannot always be prevented, measuring stress-vulnerability factors (p.182) can also be useful in order to identify individuals at risk. For example, investigators may screen for neuroticism, hyper-vigilance, worrying, fear-avoidance, and catastrophizing (Evers, Kraaimaat, Geenen, Jacobs, & Bijlsma, 2003; Evers, Gieler, Hasenbring, & Van Middendorp, 2014; Van Middendorp & Evers, 2016).
To gain insight into the number, severity, and consequences of daily stressors, ecological momentary assessment (EMA) procedures can be used to measure acute stress (and potential consequences such as pain) levels by means of (electronic) diaries over a specific period of time, varying from several days up to a year (McIntyre et al., 2016; Shiffman, Stone, & Hufford, 2008). Technological advances such as EMA allow investigators to gauge specific thoughts, actions, and emotions that might provide detailed insight into the stress experience and its consequences. For example, one may employ event-based diaries, in which participants complete a diary entry each time that they experience a specific stressful event. Such a procedure reduces recall bias and captures the frequency and severity of the stressful encounters across individuals (Cohen, Kessler, & Underwood Gordon, 1995; Rodrigues et al., 2015). As an example, a large diary study of 333 patients with fibromyalgia has shown that the experience of anger in response to an emotional event was predictive of higher end-of-day pain in the majority of patients (Van Middendorp, Lumley, Moerbeek, et al., 2010). The combination of EMA measures with non-invasive physiological measures, such as ambulatory monitoring systems to assess autonomic nervous system functioning (e.g., via heart rate) and endocrine functioning (e.g., via salivary cortisol), may also provide useful insights into within-person immediate and longer-term psychophysiological stress responsiveness (Almeida, McGonagle, & King, 2009; Houtveen, Hamaker, & Van Doornen, 2010).

Finally, in order to assess basal physiological stress activity and reactivity, physiological responses may be registered in the laboratory, either continuously (e.g., heart rate) or at specific intervals (e.g., salivary cortisol) before and after exposure to an experimental stressor. Different types of experimental stressors can be employed, among which are physiological stressors (e.g., injection of norepinephrine or the dexamethasone (p.183) suppression test), physical stressors (e.g., the cold pressor test), cognitive stressors (e.g., mental arithmetic), or psychosocial stressors (e.g., social-evaluative performance task such as the Trier Social Stress Test). Research has shown that social-evaluative threats, in which participants prepare and deliver a speech about their competencies in front of a critical audience and perform complex mental arithmetics while receiving negative feedback, are robust elicitors of psychological (e.g., stress levels) and physiological (e.g., heart rate and cortisol) stress responses (Dickerson, Mycek, & Zaldivar, 2008; Kirschbaum, Pirke, & Hellhammer, 1993). Of course, such laboratory studies take place in highly controlled circumstances (in contrast to real-life diary studies). Despite a potential lack of ecological validity, these studies nonetheless enable the identification of causal relationships and the validation of vulnerability factors (e.g., stress-vulnerability factors, early life or recent major stressors; De Brouwer et al., 2010; De Brouwer et al., 2014; Van Middendorp et al., 2013).

5.2.3 Stress and Pain
5.2.3.1 Stress and acute pain

Stress can have an analgesic (pain-relieving) effect, or a hyperalgesic (pain-enhancing) effect in healthy people. During physical stress (e.g., an intensive sports game or war situation), endogenous opioids (endorphins) are secreted that decrease the activity of neurons transmitting nociceptive information, and hence reduce pain. However, stress may also increase pain. Individuals who are sensitive to stress, such as those who tend to be anxious (negative affectivity, or neuroticism), generally show an increased pain response or hyperalgesia (Sapolsky, 2004; Vachon-Presseau et al., 2013). Studies on brain activation have revealed that such stress-induced increases in pain experience are the consequence of enhanced emotional reactivity to the pain stimulus, rather than of an increased activity of nociceptors (Sapolsky, 2004; Vachon-Presseau et al., 2013).

Some inconsistent results have emerged about the effects of acute laboratory stressors on pain in healthy individuals. Some studies show an (p.184) analgesic effect of acute stress (Vachon-Presseau et al., 2013; Yilmaz et al., 2010), whereas others reveal a pain-enhancing effect (Choi, Chung, & Lee, 2012; Skovbjerg et al., 2017). Still other studies report no effects on pain, but reveal that stress reduces the ability to modulate pain, especially in high stress responders (Geva, Pruessner, & Defrin, 2014).

In addition, various mechanisms that underlie the pain-decreasing or pain-enhancing effect have been reported. Some studies show that acute stress-related cortisol responses are associated with pain reduction (Vachon-Presseau et al., 2013), whereas others have related cortisol activation to pain enhancement (Choi et al., 2012). One study has shown that the cortisol response to acute stress leads to reduced pain-related activity of the anterior midcingulate cortex (aMCC), a key brain structure involved in the motivational and affective dimensions of the pain experience, and to reduced functional connectivity between the aMCC and the midbrain and rostral ventromedial medulla (Vachon-Presseau et al., 2013). The conflicting findings regarding the effects of acute stress on pain may be explained by differences in the timing of the measures (e.g., during or immediately following a stressor versus at more than 30 minutes after a stressor) and the type of stressor employed (e.g., physical versus psychosocial; Vachon-Presseau et al., 2013). However, it is clear that a great deal still remains to be learned and investigated.

5.2.3.2 Stress and chronic pain
Many researchers and clinicians consider chronic pain (e.g., back pain, rheumatoid arthritis and fibromyalgia) to be an uncontrollable, long-term stressor. Chronic pain is often accompanied by distress, disability, other somatic complaints (e.g., fatigue, stiffness), and an unpredictable course. Often patients use medications with potentially serious side effects for a long time. Patients need also to adjust their lives and cope with functional disabilities in almost all areas of daily life (such as work, leisure activities, and social and family life). Their future is likely to change or is uncertain (Andersson, 1999; Banks & Kerns, 1996; Kool, Van Middendorp, Lumley, Bijlsma, & Geenen, 2013; Lumley et al., 2011; McBeth, Macfarlane, & Silman, 2002; Van Houdenhove et al., 2002; Van Middendorp & Evers, (p.185) 2016; Vriezekolk et al., 2010). All in all, this is fertile ground to increase stress, which may further exacerbate symptoms and flare-ups. Over time, this process can become a vicious, self-perpetuating cycle.

In line with this view, most studies of patients with chronic pain have reported an association between acute stressors and increased pain and physical disability (Andersson, 1999; Sturgeon, Finan, & Zautra, 2016; Van Middendorp, Lumley, Jacobs, Bijlsma, & Geenen, 2010). Also, many studies have provided evidence for a pain-augmenting association of stress and stress-vulnerability factors, such as neuroticism and a tendency to worry (Al-Allaf et al., 2002; Andersson, 1999; Davis, Luecken, & Zautra, 2005; Evers, Verhoeven, et al., 2014; Evers, Zautra, & Thieme, 2011; Geenen et al., 2006; Low & Schweinhardt, 2012; Niccol et al., 2016; Ortego et al., 2016; Raphael, Widom, & Lange, 2001; Van Middendorp & Evers, 2016). Intriguingly, a number of studies has revealed that major stressors might be associated with the development of chronic pain. However, most of these studies have been retrospective in nature, raising potential issues about recall and reporting bias (Afari et al., 2014; Davis et al., 2005; Geenen et al., 2006). The small number of prospective studies that are available on this matter are less conclusive and have revealed conflicting results. One study showed an overall positive association (Low & Schweinhardt, 2012). Another study was only able to reveal an association using a retrospective design, but not when using a prospective design (Raphael et al., 2001). Still another study reported an association only in individuals who developed posttraumatic stress disorder (PTSD) as a result of childhood adversity (Raphael & Widom, 2011).
To conclude, acute, daily, and chronic stressors can impact pain across various pain conditions, but more prospective studies are needed to unravel the precise relationship between stress and pain. Importantly, the relationship between stress and pain seems to be moderated or mediated by different cognitive-behavioral factors. Relevant cognitive-behavioral factors in the stress-pain relationship may include hypervigilance (see the chapter in this volume on attention and pain, chapter 6), dysfunctional cognitive strategies, such as catastrophizing, and behavioral fear-avoidance patterns (also see the chapter in this volume on coping, (p.186) chapter 12). All these factors have been found to be more prevalent in chronic pain patients and are relatively consistently associated with the amplification and persistence of chronic pain (Crombez, Eccleston, Van den Broeck, Goubert, & Van Houdenhove, 2004; Kroska, 2016; Turk & Okifuji, 2002; Van Houdenhove, Luyten, & Egle, 2009).

5.2.4 Stress Response Mechanisms in Chronic Pain

A dysregulation of the stress system in patients with chronic pain may be the result of several physiological mechanisms. A popular idea is that physical or emotional stressors overburden the stress response system, which ultimately ends in enhanced chronic pain (e.g., McEwen & Kalia, 2010; Cohen et al., 2012; Van Houdenhove et al., 2009; Woda et al., 2016). According to this view, enduring stress leads to hyper(re)activity of the stress system, which, in the long term, may induce functional or structural changes in receptors. Such changes may involve receptor downregulation or increased negative feedback, for example, leading to glucocorticoid receptor resistance. By losing the ability to flexibly respond to an ever-changing environment, disturbances in neurotransmitter functions, immunological mechanisms, and central pain processing may appear. Immune cells may become resistant to cortisol effects, leading to a chronic activation of pro-inflammatory cytokine production (Schneiderman et al., 2005; Cohen et al., 2012). The resulting overactive immune-mediated sickness response may instigate a conglomerate of psychoneurobiological symptoms (Chapman et al., 2008; Cohen et al., 2012; McEwen & Kalia, 2010; Schneiderman et al., 2005; Sluka & Clauw, 2016; Van Houdenhove & Luyten, 2009; Van Houdenhove et al., 2009; Woda et al., 2016). Thus, the overburdening of the stress system is one possible pathway that results in increased pain and reduced pain tolerance. Nonetheless, other pathways have been proposed to explain the association between early life stress and chronic pain. These include long-lasting changes in developing neurotransmitter and endocrine circuits linked to anxiety and stress, nociceptive circuitry, and stress responsivity in addition to genetic polymorphisms (p.187) and epigenetics (Chapman et al., 2008; Low & Schweinhardt, 2012; Woda et al., 2016).
When we turn to the evidence in support of these ideas, a somewhat blurred picture emerges, with different studies reporting different findings regarding the activation of the stress system in patients with chronic pain. In support of the hyper(re)activity of the stress system, some studies have reported a hyper-reactivity in the ANS (e.g., decreased heart rate variability) and HPA-axis functioning in response to acute laboratory or naturalistic (chronic) stressors in patients with chronic pain (Chapman et al., 2008; Geenen et al., 2006; Koenig et al., 2016; McEwen & Kalia, 2010; Sluka & Clauw, 2016; Tracy et al., 2016; Woda et al., 2016). In response to lifetime stressors, such as childhood maltreatment, a basal hypercortisolism combined with a decreased circadian variability and hyper-reactivity in response to common stressors (Woda et al., 2016; Yeung et al., 2016) have been reported. Other studies have actually provided evidence for a hypo(re)activity of the stress system (e.g., Cohen et al., 2012; Sluka & Clauw, 2016; Van Houdenhove & Luyten, 2009; Woda et al., 2016). For example, a study in patients with fibromyalgia showed that self-reported childhood neglect was associated with a flattened cortisol profile under basal conditions (Yeung, Davis, & Ciaramitaro, 2016). Still other studies indicate that the SAM- and HPA-axis responses to acute experimental stressors in patients with chronic pain are similar to those of healthy controls (De Brouwer et al., 2010; Vachon-Presseau et al., 2013; Van Middendorp et al., 2013). These studies do not appear to support the idea of structural dysfunctions in the stress responses in patients with chronic pain (De Brouwer et al., 2010). Some researchers have, however, interpreted these allegedly “normal” ANS and neuroendocrine stress responses in chronic pain patients as actually representing a hypo-response to the overactive immune-mediated sickness response that could result from a chronic overburdening of the stress system due to the various and high-intensity stressors that patients experience (Geenen et al., 2006; Van Middendorp & Evers, 2016; Woda et al., 2016).
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Studies have not only investigated the ANS and neuroendocrine responsiveness to stress, but have also investigated immune responses to stress. Acute stressors have sometimes been found to induce immune suppression in healthy samples (Schneiderman et al., 2005). In patients with chronic pain, most evidence points to stress-based increases in pro-inflammatory cytokine levels (e.g., Interleukin-6) and disease activity (Affleck et al., 1997; Chapman et al., 2008; De Brouwer et al., 2014; Geenen et al., 2006; Huyser & Parker, 1998; Sluka & Clauw, 2016; Sturgeon et al., 2016; Walker, Littlejohn, McMurray, & Cutolo, 1999; Woda et al., 2016). For major stressors, there seems to be an interaction between potentially anti-inflammatory consequences of the stress response and the adverse effects of a long-term chronic condition, leading to chronic dysregulation of the Th1(pro-inflammatory)/Th2(anti-inflammatory) balance in favor of immuno-suppressive effects. Such interactions may potentially lead to a chronically enhanced inflammatory state, in line with the proposed overactivity of the immune-mediated sickness response in chronic pain patients (Chapman et al., 2008; Geenen et al., 2006; Huyser & Parker, 1998; Sluka & Clauw, 2016; Walker et al., 1999; Woda et al., 2016).

A possible reason why the physiological stress response patterns differ across studies may be the heterogeneity of the patients with chronic pain (e.g., potentially reflecting various etiologies) and methodological differences in terms of the nature and timing of measurements (e.g., assessing basal versus stress-responsive activation) and types of stressors (e.g., lifetime, laboratory, daily, or chronic stressors; Chapman et al., 2008; Sluka & Clauw, 2016; Woda et al., 2016). Nevertheless, the conclusion seems warranted that the generally adaptive physiological stress system and immune responses have become dysregulated in chronic pain samples.

5.3 Sensitization

Sensitization, a process in which repeated exposure to a stimulus results in an amplified response to that stimulus, is one of the most pervasive mechanisms believed to be associated with both stress-related processes and chronic pain. Sensitization can occur either at the level of peripheral nerve terminals or at the level of the spinal cord and/or brain (peripheral and central sensitization, respectively; Woolf, 2011). Central sensitization involves dysfunctional central pain control mechanisms and stress-related inflammatory activation (Van Houdenhove et al., 2009). It represents enhanced neuronal signaling (Woolf, 2011) and has been discussed as a form of non-associative learning (Rahn et al., 2013; Ursin, 2014; see also the chapter on learning and conditioning in this volume, chapter 4). Central sensitization is considered an adaptive phenomenon as it reflects a “hyper-alert” system that can quickly signal risk of (further) damage (Latremoliere & Woolf, 2009).

5.3.1 Assessment of Sensitization
Various methods have been used to demonstrate (central) sensitization including quantitative sensory testing (QST) of altered sensory processing that focuses on hyperalgesia or temporal summation, enhanced activation in pain-related brain regions (as shown in imaging studies), and deficient pain modulatory pathways that could reflect enhanced pain facilitation, reduced pain inhibition, or both (Woolf, 2011). Studies examining sensitization have relied on advanced sensory testing methods, electrophysiology, or imaging to provide support for the amplification of the pain signal. Unfortunately, studies are not always comparable in their assessment of sensory thresholds and modalities, thus complicating the interpretation of findings. The publication of validated procedures for the choice of test modalities, for example by the German Research Network on Neuropathic Pain (DFNS), has significantly improved the standards in the field (Rolke et al., 2006a,b). However, testing pain hypersensitivity by using static paradigms (assessing sensory threshold) cannot simply be equated with central sensitization (Woolf, 2011).

Another approach to assess sensitization employs more dynamic sensory tests, based upon the idea that pain inhibits pain. One such paradigm is conditioned pain modulation (CPM), which assesses endogenous pain modulation. Patients report their pain to a test stimulus twice: once when the test stimulus is applied alone, and once when the test stimulus is presented against a background of another pain stimulus. One normally finds that pain to the test stimulus is less when applied along with another pain stimulus than when presented alone. The reduced efficacy of CPM has been found in several patient populations including fibromyalgia, irritable bowel syndrome (IBS), temporomandibular disorder (TMD), and whiplash-associated disorders (Wijk & Veldhuijzen, 2010; De Kooning et al., 2015; Kennedy et al., 2016).

5.3.2. Sensitization and Pain

Most evidence that supports the idea that sensitization underlies various chronic pain conditions derives from cross-sectional studies in patients with chronic low back pain, fibromyalgia, TMD, and gastrointestinal syndromes. Sensitization has also been suggested to play a role in neuropathic pain, post-surgical pain, and inflammatory pain (Woolf, 2011; Keefer et al., 2016; Sluka & Clauw, 2016). The question of whether sensitization results from pain, or whether it predicts pain remains largely unanswered in cross-sectional studies.
Fortunately, there are some prospective studies. A few of these studies have shown that enhanced pain sensitization as assessed by CPM can predict the development of chronic pain (Yarnitsky, 2010; Petersen et al., 2015). Nevertheless, a systematic review (O’Leary et al., 2017) was unable to find support for the role of central sensitization (assessed by QST or self-report questionnaires) in predicting treatment outcome in musculoskeletal conditions (including shoulder pain and osteoarthritis of the hip or knee). Several large-scale prospective studies with a follow-up of 12 months or more were also unable to find support for the predictive value of pain sensitization in the development of chronic pain. For instance, the Orofacial Pain Prospective Evaluation and Risk Assessment Study (OPPERA) is a large multicenter prospective study initiative that examined the development of TMD over a period of five years. The study found that pressure pain thresholds at baseline poorly predicted new cases (p.191) of TMD (Slade et al., 2014). Another prospective study found that pressure pain thresholds failed to predict the development of chronic widespread pain (CWP) over a period of 15 months, although a higher tender point count, in which a force of $4 \text{ kg/m}^2$ elicits pain in predefined body areas, was associated with the development of new CWP (Gupta et al., 2007). Similarly, in another prospective 12-month population-based study in tension headache, pressure pain thresholds did not predict pain development (Buchgreitz et al., 2008). These findings challenge the notion that sensitization as measured by QST is causally involved in the development of chronic pain. Nonetheless, these prospective studies found some support for central sensitization as a consequence of pain (or possibly associated distress) by establishing that increased pain sensitivity developed over time in response to pain. Given the variability in the quality of studies and the use of different measurements to indicate sensitization, it remains to be determined whether self-report questionnaires on centrally-mediated symptoms or specific QST modalities can predict the development of chronic pain. Large prospective studies with extended follow-up times (i.e., 12 months or more) are needed to unravel the complex interaction between possible sensitization pathways in pain development.

5.3.3 Mechanisms of Sensitization
Sensitization may be related to stress. For example, Richebé et al. (2011) suggested that stress-induced hyperalgesia (SIH) is the result of a sensitization of the peripheral and/or central nervous system. It may be that chronic stress enhances inflammation, which in turn causes hyper-excitability of the receptors or neural structures involved in transmission of sensory stimuli through bidirectional immune-central nervous system communication pathways (Maier, 2003; Maier & Watkins, 2003). Additionally, stress has been shown to lead to hyperalgesia through adrenergic neurotransmission. For example, attenuation of central and peripheral $\alpha_2$-adrenergic receptor-inhibitory mechanisms has been linked to facilitation of pain hypersensitivity via a peripheral $\alpha_1$-adrenergic receptor (p.192) mechanism (Donello et al., 2011). Increased adrenergic levels can sensitize primary afferents to bradykinin, which can result in hyperalgesia-induced peripheral sensitization, as demonstrated in a rat model (Khasar et al., 2005). Corticotropin-releasing factor (CRF) is also involved in the physiological stress response, and has been shown to evoke hypersensitivity in pain syndromes such as IBS (Tanaka et al., 2011), presumably through central mechanisms involving limbic brain regions such as the amygdala (Myers et al., 2012). Moreover, stress can also decrease the function of endogenous pain modulating systems (Curatolo & Arendt Nielsen, 2015). As a result of this disordered stress regulation, sensitization may provide a powerful mechanism for explaining how acute pain problems become chronic, or how chronic pain extends or generalizes to other body parts or modalities.

The link between stress and sensitization to pain is further exemplified by studies reporting altered pain sensitization patterns in stress-related and pain disorders. For example, increased pain sensitivity patterns have been found in patients with stress-related disorders, such as in patients with PTSD for whom repetitive pressure stimuli yielded increased pain scores compared to controls (Moeller-Bertram et al., 2014). Additionally, stress also has been shown to be associated with increased pain sensitization in pain patients. Lower pressure pain thresholds, indicative of increased pain sensitivity, were found in chronic back pain patients who experienced psychological trauma compared to those without trauma (Tesarz et al., 2015). Also, a larger area of secondary mechanical hyperalgesia was reported after the experimental tonic application of capsaicin in women who reported having experienced more stressful life events (You et al., 2016), again stressing the potential link between stressors and pain sensitization (Lyon et al., 2011). High perceived stress was further associated with a site-specific (upper trapezius muscle) lowering of pressure pain thresholds, although not with endogenous pain modulation, in a general adult population, again indicating the relationship between stress and sensitized pain (Skovbjerg et al., 2017).
Other mechanisms of central sensitization have been described as well. For example, the process of long-term potentiation (LTP) is fundamental to synaptic plasticity contributing to learning and memory (see also the chapter on learning and conditioning in this volume, chapter 4), and has been argued to underlie, at least partly, the process of central sensitization (Ji et al., 2003). LTP encompasses a localized increase in synaptic strength (for example observed in the hippocampus and spinal cord; Bliss & Lomo, 1973; Randic et al., 1993), which can be potentiated for an extended time period (Ji et al., 2003). Although enhanced synaptic plasticity has many similarities with sensitization of pain, according to Woolf and colleagues (Latremoliere & Woolf, 2009; Woolf, 2011) LTP is one particular component of the more general process of central sensitization. These authors state that with LTP, enhanced synaptic plasticity is observed to be localized in the repeatedly activated synapses. For central sensitization, other synapses show enhanced efficacy, presumably due to recruitment of previously subthreshold synaptic input. This input is subsequently strengthened due to enhanced facilitation and/or reduced inhibition and can function autonomously, as these sensations can occur in the absence of noxious stimulation or peripheral tissue damage (Latremoliere & Woolf, 2009; Woolf, 2011). Additionally, the involvement of microglia, astrocytes, and gene transcription factors can also contribute to the process of peripheral and central sensitization (Woolf, 2011; Durham, 2016).

Several molecular pathways of sensitization have been identified. For example, peripheral sensitization can induce changes in the central nervous system by altering the activation threshold of nociceptor terminals in the periphery (e.g., via bradykinin or calcitonin gene-related peptide, CGRP), which leads to increased neuronal responsiveness (Wang et al., 2006; Durham, 2016). Moreover, brain-derived neurotropic factor (BDNF) can activate kinases including protein kinase C (PKC) and extracellular receptor kinase (ERK) that can change the activation of N-methyl-D-aspartate (NMDA) and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors. This may result, among other things, in decreased gamma-aminobutyric acid (GABA) neurotransmission and reduced release of glycine (for a detailed discussion, see Latremoliere & Woolf, 2009; Rahn et al., 2013). The clinical significance of these findings is exemplified by a report showing that brain GABA levels in migraine patients were associated with pain scores (Aguila et al., 2016).

In sum, several mechanisms have been implicated in the process of sensitization among which stress can potentially be an initial trigger or an exacerbating factor. Next to the significance of stress in the sensitization process, a close relationship between learning and memory processes and pain sensitization provides an argument for similarities in plastic changes in response to valent (pain) stimuli.

5.4 Stress- and Sensitization-Based Interventions in Chronic Pain
5.4.1 Psychological Interventions

The potentially harmful effects of stress on chronic pain can be counteracted by psychological interventions, as individual differences in stress appraisal and coping have shown to influence stress and pain responses (De Brouwer et al., 2010; Ehde et al., 2014; Evers et al., 2011, 2014). Increasing evidence suggests that psychological interventions including stress management techniques are able to change psychophysiological stress parameters or stress responsiveness in patients with chronic pain conditions. Specifically, psychosocial interventions, such as cognitive-behavioral stress-management, have shown to have a positive effect on the quality of life and related psychological and physical functioning. In some studies, these interventions have also been shown to affect psychophysiological stress responsiveness and possibly relevant inflammatory parameters (e.g., De Brouwer et al., 2011; De Brouwer et al., 2013; Van Middendorp, Geenen, Sorbi, Van Doornen, & Bijlsma, 2009). In addition to psychological mechanisms such as improved coping skills to explain these effects, physiological changes including decreased SAM-arousal and lowered cortisol and pro-inflammatory cytokine responses have been found to account for these positive effects (De Brouwer et al., 2011; De Brouwer et al., 2013; Ehde et al., 2014; Geenen, Newman, Bossema, Vriezekolk, & Boelen, 2012; Schneiderman et al., 2005). Small to moderate effects in patients with various chronic pain conditions have been found for different types of cognitive-behavioral interventions, including coping skills training, stress management, mindfulness, and motivational exercises (Davis, Zautra, Wolf, Tennen, & Yeung, 2015; De Brouwer et al., 2013; De Ridder, Geenen, Kuijer, & Van Middendorp, 2008; Ehde et al., 2014; Lumley et al., 2014; Mattukat et al., 2014; Turner et al., 2016). Another cognitive-behavioral intervention that could reduce pain sensitization is written emotional disclosure (You et al., 2014). A study involving 78 participants with a trauma history demonstrated that written emotional disclosure initially increased capsaicin-induced secondary hyperalgesia 1 day after writing, whereas the area and intensity of secondary hyperalgesia was found to be reduced at 1 month after disclosure (You et al., 2014).

5.4.2 Pharmacotherapeutic Approaches

As our knowledge is increasing of the psychophysiological factors that influence the stress experience and the neurobiological effects of (chronic) stress on pain, pharmacological interventions might be employed to correct dysregulated stress- and pain-processing mechanisms (Van Houdenhove & Luyten, 2009).
Several pharmacotherapies aim to target sensitization processes underlying chronic pain syndromes, although the evidence of (central) sensitization involvement of these treatments is not yet well established, especially in humans (Nijs et al., 2011). Among the pharmacotherapeutic approaches targeting the mechanisms involved in sensitization are: tricyclic antidepressants (TCAs) such as nortriptyline or amitriptyline, NMDA receptor antagonists, such as ketamine, that target temporal summation and secondary (mechanical) hyperalgesia, and selective balanced serotonin and noradrenaline-reuptake inhibitors (SNRIs), such as duloxetine, which influence descending modulation and potentially opioids, gabapentoids, or calcium channel alpha(2)delta ligands (Nijs et al., 2011; Woolf, 2011). Novel pharmacological developments include the potential for CRF modulators in the treatment of prolonged pain syndromes associated with HPA-axis irregularities (Lariviere & Melzack, 2000; Taguchi et al., 2017). Although drugs have shown to have modest beneficial effects in the treatment of chronic pain syndromes, it should be noted that since drugs act centrally, they can also elicit serious side effects. Therefore, non-pharmacological treatment options for sensitized pain syndromes should be considered, including neuro-technological approaches such as transcranial magnetic stimulation (TMS), manual therapy or stress management techniques, or other cognitive-behavioral interventions as described earlier (Nijs et al., 2011).

5.5 A Motivational Account of Stress, Sensitization, and Chronic Pain
As demonstrated in the previous paragraphs relating to the role of stress and sensitization in pain, it is widely accepted that nociceptor input is not the only or even the main determinant of pain or disability (Curatolo & Arendt-Nielsen, 2015). Nociceptor activation and resulting central nervous activation are closely related to the sensory characteristics of pain, but the experience of pain also importantly involves emotional and cognitive factors (Navratilova & Porreca, 2014). For example, evidence of perseverative cognition, such as worrying and rumination, has been found in chronic pain patients and negative affect is considered to be a catalyst in the process of cognitive-emotional sensitization, which has been proposed to overlap with physiological sensitization (Brosschot, 2002). These perseverative cognitions can lead to a cognitive bias, which provides an alternative motivational account of sensitization processes in pain. This motivational account emphasizes the role of emotional and cognitive processes in addition to the processing of sensory information in the interpretation of stimuli as painful. For example, frequent and intense physical signals are not only prioritized at the level of the central nervous system, but also at higher levels of information processing, leading to attentional and memory biases for pain-related information (see also the chapter on attention and pain in the current volume, chapter 6). These biases can lead to long-lasting activation and continuous reactivation of pain- or related cognitive networks or schemata, which are associated with (1) increased attention to and detection of internal and external pain cues, (2) the interpretation of ambiguous internal and external information in terms of pain, (3) more misattribution of harmless signals as pain, and resultantly (4) more and stronger memory traces, which lead to a vicious cycle of detecting and experiencing pain at increasingly lower intensity levels. In this context, chronic pain should not be regarded merely as a reflection of an enhanced acute neural pain state.

A motivational view is supported by different brain-based functional, morphological, and connectivity changes found in chronic pain conditions compared to acute pain experiences (Baliki et al., 2006; Neugebauer et al., 2009; Vachon-Presseau et al., 2016a,b). Changes in structures of the corticolimbic system importantly involved in cognitive-emotional processing have been identified as possible key modulators in the development of pain (Lumley et al., 2011; Navratilova & Porreca, 2014). The corticolimbic system, comprising areas including the mPFC, NAc, amygdala, hippocampus, and ventral tegmental area (VTA; see Figure 5.2), is central in reward and motivated behavior and it has, therefore, been recently suggested that a persistent pain condition can arise from a change in the value attributed to nociceptive input through corticolimbic reward/motivational circuits (Vachon-Presseau et al., 2016a).
Supportive of this notion is the finding that the reward value of pain cessation is distorted in chronic back pain and is related to the enhanced connectivity found between the nucleus accumbens (NAc) and the medial prefrontal cortex (mPFC; Baliki et al., 2012; Navratilova & Porreca, 2014). The significance of corticolimbic structures for the development of chronic illness is further suggested by a recent study that proposed that the development of psychopathology is linked to individual genetic variations in the neuroendocrine stress system interacting with environment events (Bogdan et al., 2016). According to this line of reasoning, the transition from acute to chronic pain can be explained by pre-existing individual differences in functional, anatomical, and network properties of corticolimbic structures and by the resulting emotional responses and cognitive abilities and re-organizational properties following an event in this corticolimbic circuitry. Vachon-Presseau et al. (2016a) speculate that the potential emotional response to an injury can be exaggerated through reduced inhibition of the corticolimbic system as evidenced by deficient cortical inhibitory control mechanisms. Or, alternatively, it is possible that the inability to properly use inhibitory control results in reorganization of corticolimbic structures through emotional learning processes in vulnerable individuals. This view postulates that the transition to chronic pain is mediated by corticolimbic learning mechanisms (Vachon-Presseau et al., 2016a), and initial support for this idea was demonstrated in subacute back pain patients who were longitudinally followed for alterations in neuroanatomical structures (Vachon-Presseau et al., 2016b).
Consistent with this viewpoint, impaired corticolimbic modulation has been suggested to be an important mechanism of stress-induced hyperalgesia (Wang et al., 2013). Interestingly, this corticolimbic system was found to be related to strain differences in stress-coping behavior in mice (Andolina et al., 2014). Hence, reward/motivational circuits can be targeted by employing real-time feedback of neural activity, by fMRI (Chapin et al., 2012) or brain stimulation using TMS or deep brain stimulation; and these procedures hold promise for advancing future pain management (Navratilova & Porreca, 2014). A strategy to dampen the sustained arousal response induced by stress responses motivated by fear can be, for example, to learn to re-evaluate the motivational aspects, such as the controllability over a situation (Ursin, 2014).

5.6 Conclusions
In conclusion, stress and sensitization pose mechanistic explanations based on multi-factorial models for the development, maintenance, and exaggeration of chronic pain. The interaction between stress and sensitization has been explored only marginally. One of the possible reasons is that stress and sensitization are frequently studied from a psychological or physiological perspective only, without integrating both perspectives in a multilevel system approach. This holds also true for the singular use of pharmacological or psychological interventions to reduce stress and foster desensitization in chronic pain. Approaches that are able to combine these perspectives may hold promise for identifying novel mechanisms and for developing treatment possibilities in future studies. Furthermore, it can be concluded that high-quality large prospective cohort studies that incorporate methodologically rigorous measures (including QST and electrophysiology/imaging) and that include a long follow-up are needed to clarify the exact roles of stress and sensitization in the initiation and/or maintenance of different chronic pain conditions. The motivational account of pain promises to enhance our understanding of stress and sensitization processes underlying chronic pain.

References

Bibliography references:


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