

Depression and pain

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1. ABSTRACT

Depression and pain disorders are often diagnosed in the same patients. Here we summarize the shared pathophysiology between both disorders and the importance of addressing all symptoms in patients with comorbid pain and depression. We describe anatomical structures that are activated and/or altered in response to both depression and pain – examples include the insular cortex, the prefrontal cortex, the anterior cingulate cortex, the amygdala, and the hippocampus. Both disorders activate common neurocircuitries (e.g. the hypothalamic-pituitary-adrenal axis, limbic and paralimbic structures, ascending and descending pain tracks), common neurochemicals (e.g. monoamines, cytokines, and neurotrophic factors), and are associated with common psychological alterations. One explanation for the interaction and potentiation of the disease burden experienced by patients affected by both pain and depression is provided by the concept of allostasis. In this model, patients accumulate allostatic load through internal

and external stressors, which makes them more susceptible to disease. To break this cycle, it is important to treat all symptoms of a patient. Therapeutic approaches that address symptoms of both depression and pain include psychotherapy, exercise, and pharmacotherapy.

2. INTRODUCTION

Depression and pain disorders are common comorbidities. Epidemiological studies report a mean prevalence rate of major depressive disorder (MDD) in patients with chronic pain assessed in pain clinics of 52%, and a mean prevalence of pain in depressed patients of 65% (1). In a primary care setting, 69.1% of patients with MDD reported at least moderate pain symptoms, while only 38.6% of patients without MDD reported moderate pain symptoms (2).

Comorbidity of pain and depression has a negative impact on several outcome measures: health care

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Table 1. Brain structures involved in depression and pain

Brain Structure	Observations in MDD ¹	Observations in Pain
Amygdala	Primary role in processing and memory of emotional reactions ²⁴	Key role in attaching emotional significance to pain ¹⁸
Anterior Cingulate Cortex (ACC)	Role in rational cognitive functions like reward anticipation, decision making, empathy and emotion. Integrates emotional stimuli and attentional functions ²⁴	Involved in pain processing, anticipation, cognitive-attentional, and motor response to pain ¹⁸
Cerebellum	Reduced vermal volume ^{24,247} Hypoactive in depressed patients ²⁴⁸	Activations have been found after experimentally induced muscle pain, noxious thermal stimulation, capsaicin-induced pain, visceral pain, and during empathy for pain ¹⁸
Hippocampus	Important for the forming and perhaps storage of associative and episodic memories ²⁴ Reduced hippocampal volume in depression ^{50,63-67,69}	Dysfunction may be responsible for inappropriate emotional response to pain ²⁴⁹
Insular Cortex	Processes convergent information to produce an emotionally relevant context for sensory experiences ²⁴	Frequently activated in response to pain ¹⁸
Nucleus accumbens	Role in reward, pleasure and addiction; novelty detector, may be involved in the regulation of emotions ²⁴	Associated with increases in negative affects and fear ratings in response to pain challenge ²⁵⁰
Prefrontal Cortex (PFC)	Involved in the “executive functions” such as working memory, decision-making, planning and judgement ²⁴ Altered structure and function in depression ²⁹⁻³²	Activated in clinical pain conditions; involved in processing of affective aspects of sensory stimulation ¹⁸
Somatosensory Cortex	Involved in the processing of tactile sensory memories ²⁵¹	Major site for identifying noxious stimuli; participates in sensory-discriminative aspect of pain ¹⁸
Thalamus	Reduced volume ^{24,252}	Involved in the affective and sensory-discriminative aspects of pain processing ¹⁸ Reduced gray matter density in chronic pain patients ³⁴

Abbreviations: ¹Major depressive disorder

related costs are significantly higher (2), productivity is decreased with more days absent from work (3), and most importantly, the likelihood of remission of depressive symptoms is decreased (4). Achieving remission is critical in the treatment of depression. Patients with residual symptoms are more likely to experience a relapse of depressive episodes (5,6), and to do so earlier than patients without residual symptoms (7). Also, patients with MDD who do not reach remission experience substantial impairment in their physical, occupational, and social functioning (5,6). Residual depressive symptoms are associated with a higher rate of suicide attempts (8) and negatively impact marital interactions (9) and the mental health of children of depressed patients (10). One effect of the presence of major depression in chronic pain conditions is increased absenteeism in those patients resulting in economic implications (11).

Here we summarize the current knowledge in the literature with regard to the biological and psychological processes shared by depression and chronic pain disorders. We present how multiple overlapping anatomical structures, physiological pathways, and neurocircuitries are altered by both diseases. Beyond this evidence based science, we introduce the theoretical concept of allostasis to further demonstrate the complex interactions between depression and pain.

Allostasis is defined as the ability of the organism to maintain stability by reacting to external and internal stress with change. While this adaptation is beneficial for coping with stress and allows the individual to continue to function, high levels of activity in this system due to excessive stress induce the accumulation of allostatic load, which in turn makes the individual more susceptible to disease (12). The extent to which allostatic load is accumulated, and subsequently the susceptibility to disease, is highly variable between individuals and is influenced by many internal and external factors. Vulnerability factors that increase the risk of depression include genetic and environmental predispositions. Caspi and colleagues

demonstrated in a longitudinal birth-cohort study that a functional polymorphism in the promoter region of the serotonin transporter alters the response to stressful life events and the incidence of depression following such events (13). Another prominent environmental vulnerability factor is childhood trauma, which is reported by a high percentage of adults affected by depression (14).

Another source for increased allostatic load, and therefore a higher risk to develop a depressive disorder, is current stressors – either environmental, e.g. stressful life events, or internal, e.g. pain due to a medical illness. An example of an external stressor with a strong association to triggering a depressive episode is divorce (15). Chronic pain in longitudinal studies of community respondents has also been shown to be associated with a high risk for the development of depression (16). Therefore, the importance of allostasis for depression and pain is twofold: both depression and pain can increase allostatic load, and increased allostatic load can in turn trigger the manifestation of depression and pain.

The purpose of this review is to raise awareness in both mood and pain clinicians for the close interactions and commonalities in the pathophysiologies of pain and depression. Comorbidity with pain and depression potentiates the disease burden, which is reflected in longer symptom duration, more severe symptoms, and worse outcomes. To achieve optimal therapeutic success, it is essential to treat both pain and depression when they coexist.

3. MECHANISM OF THE MOOD AND PAIN LINK

3.1. Brain structures involved in mood and pain

Several brain regions have been implicated in both major depressive disorder (MDD) and pain (Table 1 and Figure 1). The most extensive research has been done on the insular cortex, prefrontal cortex (PFC), anterior cingulate cortex (ACC), amygdala and hippocampus.

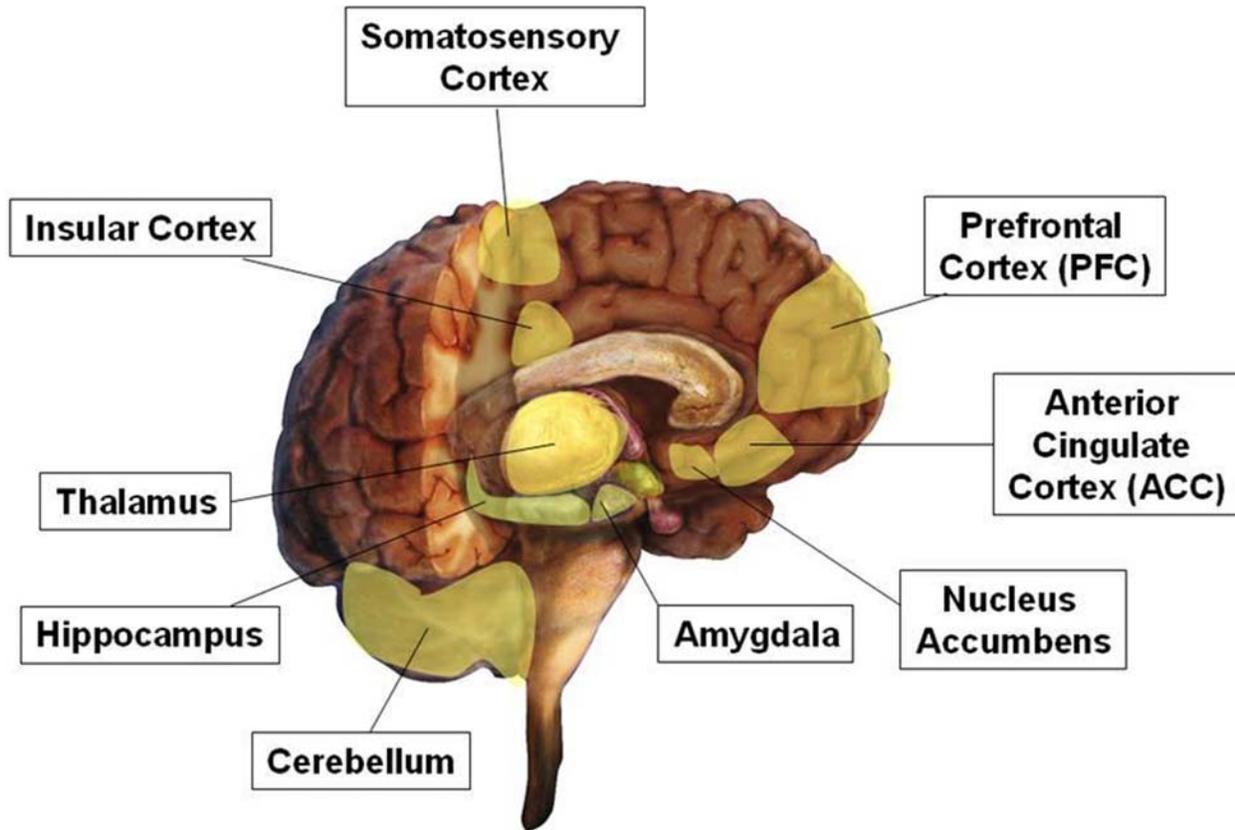


Figure 1. Areas of the brain implicated in major depressive disorder (MDD) and pain disorders.

3.1.1. Insular cortex

The insular cortex is frequently activated in response to pain (17,18). Tonic pain is an example of a pain sensation that is encoded by this brain structure (19). Imaging studies using functional magnetic resonance imaging (fMRI) confirmed the central role of the insular cortex in pain processing (20,21), and showed its importance during integration of sensory and cognitive components of pain perception (22).

On the other hand, pathophysiological changes in the insular cortex might contribute to depression as this brain area is responsible for processing information from sensory experiences to create an emotionally relevant context. Imaging studies revealed focal changes of the serotonin 5HT₂ receptor status in the insular cortex of depressed patients (23).

3.1.2. Prefrontal cortex

The most prominent feature of the PFC is its role in executive functions like working memory, planning, and judgment; impairments of all of these functions are observed in patients with MDD (24,25). Positron emission tomography (PET) revealed increased blood flow in patients with MDD from the left ventrolateral PFC to the medial PFC (26), and decreased activity in the PFC ventral region to the genu of the corpus callosum combined with a gray matter volume reduction of 48% in this area (27).

Patients with MDD show altered activation of the PFC during the processing of emotions (28). fMRI imaging revealed an imbalance between right and left PFC in patients with MDD linked to negative emotional judgment compared to healthy controls (29). Consistent with altered brain structure in depression, human postmortem studies revealed reduced size and density of neurons and glial cells in the prefrontal cortex of patients with MDD (30-32). In a rodent model for depression, the PFC showed the greatest reduction in synaptic plasticity proteins in response to adolescent separation (33).

In patients with chronic back pain, reduced gray matter density has been described for the bilateral dorsolateral PFC (34). Activation of the PFC has been observed in clinical pain conditions and is associated with a role in attending to or ignoring painful stimulation (18). A critical role for the PFC on individual differences in pain perception (35), perceived control over pain (36), and spatial discrimination of pain was shown in fMRI studies (37).

3.1.3. Anterior cingulate cortex

The ACC plays an important role in conflict detection and emotional evaluation of error. In addition, it is connected to brain structures that influence the emotional valence of thought, autonomic and visceral responses, and mood regulation. All of these functions are disturbed during depression (38).

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Electroencephalographic examinations showed differences in the activity of the rostral ACC between responders and non-responders to antidepressant therapy (39). Magnetic resonance imaging (MRI) of medication-naïve female depressed patients showed a reduction in volume of the ventral ACC and the amygdala in comparison to healthy controls (40). Analysis of glucose metabolism demonstrated a significant negative correlation with age in patients with MDD, but not in healthy controls (41). Higher metabolic rates of the ACC in conjunction with higher loudness dependence of the auditory evoked potential (LDAEP) values are predictive for better treatment response in depressed patients (42). In rodent models, the modulation of depression by the rostral ACC has been shown by lesion studies (43).

The activation of the ACC in response to thermal and mechanical pain was shown in human fMRI studies with healthy volunteers (44). Migraine patients have significant decreases of gray matter in the cingulate cortex compared to healthy controls when examined by MRI (45). Single photon emission computed tomography (SPECT) demonstrated reduced blood flow in the ACC in patients with chronic pain conditions (46). Additional neuroimaging studies revealed that both felt pain in an individual and seen pain in another person activates the ACC, but not necessarily identical neurons (47).

3.1.4. Amygdala

The amygdala performs a primary role in the formation and storage of memories associated with emotional events (24), processes which are disturbed in patients with MDD. PET shows increased blood flow in the amygdala of patients with MDD (26). Conflicting results are reported in the literature regarding the amygdala volume in depressed patients. While some studies did not find differences between healthy control subjects and patients affected by MDD (48), others report a decrease (40,49) or an increase (50) of the amygdala volume in depressed patients. Within a group of depressed patients, suicidal patients with MDD have a larger amygdala volume than non-suicidal patients with MDD (51). Activity levels of the amygdala are increased during stress and in patients with anxiety and mood disorders (52).

The amygdala plays a key role in attaching emotional significance to pain (18). Imaging studies show an activation of the amygdala in response to different painful stimuli (53,54). Intervention studies in rodents confirmed the central role of the amygdala in pain perception (55-58).

3.1.5. Hippocampus

The hippocampus provides an important feedback inhibition of the hypothalamic-pituitary-adrenal gland (HPA) axis (59). A direct link exists between the hippocampus and the PFC, and it has been shown in rodent experiments that the hippocampus exerts a direct excitatory influence on PFC interneurons (60). The hippocampus is important in the control of mood (61) and for the formation of associative and episodic memories (62). Reduced hippocampal volume compared to controls has been

reported in adult patients with MDD (50,63-68), with a statistically significant inverse relationship between duration of untreated depression and degree of hippocampal volume loss (69). However, it is not clear if depressed patients have reduced hippocampal volume in the premorbid state, or if the reduction is caused by the disorder. A study in depressed children and adolescents did not detect any hippocampal volume reduction in comparison to a control group (49).

Activation of the hippocampus has been demonstrated in healthy volunteers in response to a pain stimulus (70). Patients with fibromyalgia show decreased presynaptic dopaminergic activity in several brain regions, including the hippocampus, compared to healthy controls (71). Changes in the hippocampal morphology and gene expression were observed in rodents in response to chronic pain (72-74). Similarly, chronic stress models of depression in rodents induce changes in synapse morphology in hippocampal subregions (75).

3.2. Shared neurocircuitries and neurochemicals between mood and pain

Shared neurocircuitries and neurochemicals play an important role connecting the pathophysiologies of depression and pain disorders. Those shared pathways enable cross talk between both disorders on several levels – within and between brain regions, intercellular and through neurochemical signaling. Therefore, alterations in the activity of neurocircuitries and the levels of neurochemicals due to either disorder can affect the other disorder.

3.2.1. Hypothalamic-pituitary-adrenal axis

Both patients with MDD and those with chronic pain experience dysregulation of the HPA axis (76) (Figures 2A, 2B). The brain reacts to stress and depression with activation of the HPA axis. The hippocampus and the amygdala are two of several brain structures that control the activity of the HPA axis. The hippocampus exerts an inhibitory influence on hypothalamic neurons that contain corticotropin-releasing-factor (CRF), while the amygdala has a direct excitatory influence on these hypothalamic neurons. Glucocorticoid levels under physiological conditions seem to enhance hippocampal inhibition of HPA axis activity (via feedback loops coupled to glucocorticoid receptors) (76). Increased glucocorticoid levels, as seen in response to stressors like pain and potentially depression, may not only damage hippocampal neurons, but reduce neurogenesis (77). Additionally, the negative feedback mechanism between increased glucocorticoid levels and the HPA axis can be disrupted as a result of prolonged stress, which causes maladaptive responses of the HPA axis (76). Many psychiatric patients, including those with MDD, show abnormal, excessive activation of the HPA axis (78). It has been shown that the HPA axis normalizes in response to treatment with antidepressants (79). Rodent data show that increased glucocorticoid levels induce a loss of synapses within the hippocampus. In these animals, examination of the cellular volume in the hippocampal CA3 area revealed that increased glucocorticoid levels have no effect on the neuropil and glial volume in the proximal subfield of the CA3, but induce changes in the middle

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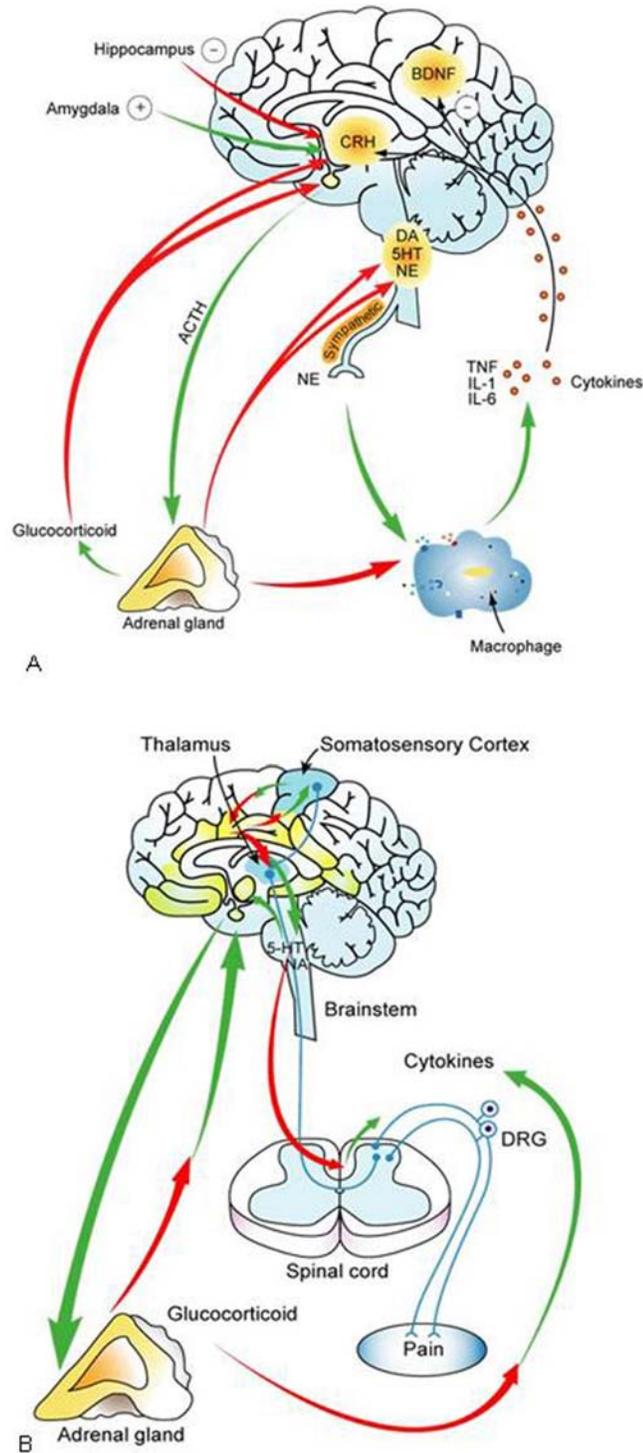


Figure 2. Dysregulation of the hypothalamic-pituitary-adrenal axis (HPA) and cytokines. 2A. HPA and cytokine dysregulation during stress and depression. Red = inhibitory pathways to the HPA axis; green = stimulatory pathways to the HPA axis. Abbreviations: BDNF = brain-derived neurotrophic factor; CRH = corticotrophin releasing factor; DA = dopamine; 5HT = serotonin; NE = norepinephrine; ACTH = adrenocorticotrophic hormone; TNF = tumor necrosis factor; IL-1 = interleukin 1; IL-6 = interleukin 6. Adapted from (77,84), reproduced with permission from (246). 2B. HPA and cytokine dysregulation during pain. Red = inhibitory pathways to the HPA axis; green = stimulatory pathways to the HPA axis. Abbreviations: 5-HT = serotonin; NA = noradrenaline; DRG = dorsal root ganglion. Adapted and reproduced with permission from (76).

subfield of the CA3. These changes include the occurrence of more astrocytic processes and a decrease of tissue volume made up of non-glial cells (80).

Chronic pain is a persistent stressor, which in turn interrupts the negative glucocorticoid feedback on the HPA axis. This induces the generation of higher glucocorticoid levels by the HPA axis by down-regulation of the glucocorticoid receptors within the brain and the periphery (76). Dysfunction of the HPA axis has been shown to be predictive as to which individuals among psychologically at risk patients will develop chronic widespread pain (81). In a rodent model, a central role of the CRF-1 receptor in the amygdala for pain sensitization (82) and for the development of pain-related anxiety has been demonstrated (58).

3.2.2. Cytokines

Both patients with depressive symptoms and patients with pain disorders often display enhanced cytokine levels including interleukin-6 (IL-6), C-reactive protein (CRP), interleukin-1-beta (IL-1-beta), and tumor necrosis factor alpha (TNF-alpha) (83,84). Cytokines are small proteins released by cells and play an important role in intercellular communication. Examples include lymphokines, interleukins and other cell signaling molecules (Figures 2A, 2B). Activation of inflammatory pathways has been observed in otherwise medically healthy patients with MDD (85). Cytokines that are released in response to an activation of inflammatory pathways can enter the brain. There they may cause alterations of the metabolism of serotonin and dopamine (84). Additionally, cytokines activate CRF, which in turn leads to an increase of serum glucocorticoid levels (84). Under physiological conditions, increased serum glucocorticoid levels induce an inhibition of the HPA axis. After prolonged stress, this negative feedback mechanism is disrupted as detailed above. In patients with MDD, a positive correlation between inflammatory responses and long-term hyperactivity of the HPA axis has been observed (86), while during remission of depressive symptoms a normalization of both cytokine levels and HPA axis activity has been described (87). Additionally, in patients with MDD, correlations between cytokine levels and response to antidepressant treatment have been observed (88). Interestingly, patients whose HPA axis activity does not normalize during remission are more likely to experience an earlier relapse of their depressive symptoms (89). Support for the importance of cytokines in the pathophysiology of depression comes from observations in cancer patients who develop depressive symptoms after treatment with cytokines like interferon (76). Additionally, cytokine levels seem to differ between suicidal and non-suicidal patients with MDD (90).

Cytokines play a central role in the generation and transmission of pain (83,91,92). Patients with complex regional pain syndromes present with a pro-inflammatory cytokine profile with increased mRNA and protein levels of TNF-alpha and interleukin-2, and decreased levels of interleukin-4 and interleukin-10, compared to a control group (93). In patients with peripheral neuropathy, a similar

pro-inflammatory cytokine profile is associated with pain (94).

3.2.3. Limbic and paralimbic structures

As described above, several brain structures have been implicated in both depression and pain. Beyond anatomical co-localizations, evidence in the literature points to the common activation of neurocircuitry during pain and clinical signs of depression in those regions.

Eisenberger and colleagues demonstrated with an fMRI study that, during experiments that induce feelings of social exclusion, the same brain regions (ACC and right ventral PFC) are activated as in response to physical pain (95). Activation of the ACC is associated with the affective dimension of pain, and the degree of neuronal activation is correlated to levels of symptoms of depression (96). Compared to healthy controls, patients with MDD show a relative hyperactivation of the PFC in response to a thermal pain stimulus, which might explain their reduced thermal pain perception on the skin (97). Interestingly, patients with MDD and pain symptoms experience improvement of their pain symptoms in response to treatment with transcranial magnetic stimulation delivered to the left dorsolateral PFC (98).

The amygdala is essential for the interaction between pain and depression (99), and its central role in both pain and anxiety, a hallmark of depression, was recently illustrated in a rodent study. In this study, the investigators selectively blocked the CRF receptors in the amygdala, which inhibited anxiety-like behavior and nocifensive pain responses in animals that had received intraarticular injections with kaolin/carrageenan in 1 knee to induce arthritis (58). Additionally, anxiogenic effects of chronic pain have been demonstrated in rodents, and it was hypothesized that this phenomenon might be associated with changes in the opiodergic function of the amygdala (100). Neugebauer and colleagues proposed a hypothetical model in which the amygdala's role in facilitating pain perception is modulated by negative and positive emotions and so is directly influenced by the depressive state of a patient. In this model, negative emotions increase activity in the amygdala, while positive emotions deactivate the amygdala. The amygdala itself is linked to both facilitating and inhibitory pathways modulating pain; thus, an activation of the amygdala could both decrease and increase pain perception, dependent on which pathways within the amygdala are activated. The model differentiates between negative emotions that are associated with pain reduction, like fear and stress, which activate pain inhibitory pathways within the amygdala, and negative emotions that correlate with increased pain, like depression and anxiety disorders, which activate pain facilitating pathways within the amygdala. Positive emotions inhibit the pain facilitating pathway within the amygdala (99).

In a rodent study it was shown that chronic pain induces similar damage to the hippocampus as seen after stress, including changes in morphology and decreased brain-derived neurotrophic factor (BDNF) levels and neurogenesis, which might explain the development of

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depressive-like symptoms that are often observed in chronic pain patients (72), in cancer patients (101), and in patients with cardiovascular diseases (102). On a molecular level, similar decreased expression of BDNF and neurokinin 1 has been observed in the rodent hippocampus in models for pain and depression (103).

3.2.4. Ascending and descending pain tracks

Howard Fields and colleagues describe a pain modulating circuit including the amygdala, the periaqueductal gray, the dorsolateral pontine tegmentum (DLPT), and the rostral ventromedial medulla (RVM) (104). This circuit controls pain transmission through the dorsal horn of the spinal cord and the trigeminus through descending projections. The circuit is under bidirectional control by on- and off-cells. These cells are located in the RVM and extend their axons into the spinal cord where they induce or inhibit dorsal horn pain signals from nociceptive neurons. It is hypothesized that this circuit could also generate or enhance perceived pain intensity, which in turn might be a physiological mechanism through which mood can modulate pain perception (104-106).

3.2.5. Monoamines

Descending serotonin and noradrenergic pathways have been suggested as modulators of pain perception, i.e. they are associated with activating the "on" and "off" cells. The serotonergic neurons implemented in these descending pain tracks are in the raphe nuclei located in the RVM, while the noradrenergic neurons originate in the locus coeruleus part of the DLPT (106,107). Both tracts project over descending pathways into the spinal dorsal horn where they exhibit inhibitory influences. While under normal conditions these inhibitory influences are modest, in times of acute stress they can completely inhibit the perception of painful stimuli. In addition to these descending pathways, serotonergic and noradrenergic neurons project into various brain regions and are involved in the control of mood, movement, emotions, cognition, and several other processes. Dysfunction of these ascending projections may contribute to the classical symptoms of depression, and antidepressants facilitate these pathways. Therefore, the serotonergic and noradrenergic neurons of the raphe nuclei and the locus coeruleus, respectively, directly link pain and symptoms of depression, such that their dysregulation might provoke or enhance either or both (108).

3.2.6. Neurotrophic factors

The down-regulated expression of several neurotrophic factors has been implicated in the pathophysiology of depression and pain. The most prominent and widespread representative of this group is BDNF, a polypeptide that acts through the tyrosine kinase coupled receptor TrkB. BDNF plays a role in the brain, especially within the hippocampus, in neuronal differentiation (109) and survival (110), neurogenesis (111,112), synaptic plasticity (113-115), connectivity (116), maintenance of morphology (117), and learning and memory (118). In adults, it is important for maintenance of neuroplasticity that allows the brain to alter its structure in response to stimuli (119). Rodents that are subjected to

stress exhibit depressive-like activity and have decreased levels of BDNF (120). Intrahippocampal administration of BDNF decreases the stress-induced depressive-like activity (121), and antidepressants reverse the stress-induced decrease in BDNF levels (120,122). Human postmortem studies revealed that BDNF expression is suppressed in the hippocampus and the ventral PFC of depressed untreated suicide patients (123,124). Compared with untreated subjects, patients receiving antidepressant treatment at the time of death show increased expression of BDNF in the hippocampus (125). While BDNF serum levels are reduced in depressed patients (126-128), treatment with antidepressants can normalize them (129-131). In patients with panic disorder, BDNF serum levels are significantly higher in responders to cognitive behavioral therapy (CBT) than in non-responders (132). Humans heterozygous for a BDNF mutation present smaller hippocampal volumes (133-135) and seem to be impaired when performing hippocampal-dependent memory functions (136,137). No consensus has been reached as to if this mutation predisposes for anxiety and depressive disorders in humans (138). Homozygous mice with an equivalent BDNF mutation show increased anxiety-related behaviors that cannot be normalized with an antidepressant (138).

Similar to observations in depressed patients, hippocampal BDNF expression is reduced in rodents exposed to stress and pain (73,103). Contrasting to the hippocampal down-regulation, BDNF expression appears to be up-regulated in the spinal dorsal horn in response to pain stimuli (73,139) and seems to drive spinal noradrenergic sprouting following nerve injury (140). Continuous BDNF release after nerve damage stimulates faster peripheral nerve regeneration and potentially reduces neuropathy in rats (141). Evidence from neuronal cell culture models points to a possible role of BDNF in "central sensitization", an experimental paradigm paralleling human neuropathic pain (142). Interestingly, pretreatment of rodents with the antidepressant imipramine before pain challenge prevents alterations of BDNF gene expression in both the hippocampus and the spinal dorsal horn, without providing significant behavioral analgesia. Pretreatment of the same animals with the analgesic indomethacin reverses BDNF up-regulation only in the spinal cord, not in the hippocampus, and reduces peripheral hyperalgesia. The authors concluded that neither analgesic nor antidepressant treatment alone can completely protect against the behavioral and molecular effects of persistent pain (143).

Other examples of neurotrophic factors with implications in the pathophysiology of both pain and depression include nerve growth factor (NGF) (144-149), neurotrophin-3 (NT-3) (121,150-152) and neurokinin-1 (NK-1) (73,153,154).

3.2.7. Psychological overlaps

3.2.7.1. Catastrophizing in pain and depression

Catastrophizing (expecting the worst possible outcome) is a common phenomenon in both patients with depression and pain, and has negative implications for treatment outcomes. Patients that exhibit catastrophizing

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describe their situation as horrible and unbearable. Imaging studies in patients with fibromyalgia that exhibit catastrophizing of their pain symptoms revealed activation of brain areas involved in anticipation of pain (medial frontal cortex and cerebellum), attention to pain (dorsal ACC and dorsolateral PFC), emotional aspects of pain (claustrum) and motor control. These results support a role of catastrophizing in the perception of pain (155). In patients with lower back pain, catastrophizing is a predictor for higher long-term disability levels (156). Similarly, patients that catastrophize their pain expectations before knee replacement surgery experience greater postoperative pain (157). Generally, catastrophizing appears to be positively related to the severity of pain (158).

In elderly patients, a strong correlation between magnitude of depressive symptoms and catastrophizing has been found (159). In children that experienced physical traumas, the child's catastrophic appraisal of persistent vulnerability after the trauma strongly correlates with the experienced stress reaction (160). Similarly, children with recurrent abdominal pain develop more depressive symptoms the more they catastrophize the pain (161). Chronic pain patients' increased catastrophizing is linked to increased depression (162). Further support for the strong interactions between depression and pain was also found in patients with chronic pain, in whom catastrophizing of pain symptoms and levels of depressive symptoms are predictors for suicidal behavior (163). Greater pain catastrophizing has been associated with future depressive symptoms in pain patients (164), as well as in spouses of chronic pain patients (165).

3.2.7.2. Learned helplessness

Learned helplessness is defined as a state in which the individual has learned that a condition is out of the individual's control and therefore no attempts are undertaken to change a given situation. Chronic pain patients and depressed patients often display signs of learned helplessness. In fibromyalgia patients, it has been demonstrated that learned helplessness mediates between pain and depressive symptoms (166). In chronic pain patients, the degree of helplessness is a predictor for the level of pain experienced (167).

Close association between the level of helplessness and depressive symptoms has been described in patients with scleroderma (168) or multiple sclerosis (169), but also in healthy volunteers (170). In a rodent model it was demonstrated that learned helplessness is associated with decreased neurogenesis in the hippocampus, an effect that is reversed by treatment with an antidepressant (171).

3.2.7.3. End-organ sensitization

Irritable bowel syndrome (IBS) is an example for an end-organ sensitization observed in patients with depression in which the degree of pain experienced is influenced by catastrophizing (172). IBS is one of several central hypersensitivity pain disorders that are associated with depression (173,174); other examples are fibromyalgia

(175), headache (176), and pelvic pain (177). A role for serotonin mechanisms in the pathophysiology of these conditions has been suggested, and successful treatment with antidepressants is described in the literature (178).

4. MULTIDIMENSIONAL TREATMENT OF DEPRESSION AND PAIN

4.1. Theory of allostasis

Allostasis has been defined as "the ability to achieve stability through change" (12,179). Allostasis protects the body in response to internal and external stress through activation of the HPA axis, the autonomic nervous system, and the cardiovascular, metabolic and immune systems (12). An allostatic load accumulates when this system is chronically challenged (180). McEwen differentiates 4 mechanisms that lead to the accumulation of allostatic load: frequent stress, lack of adaptation to repeated stressful stimuli, inability to terminate an allostatic response after the stressful stimulus ceased, and inadequate response by some allostatic system that triggers compensatory increases in others (12). This model illustrates the importance of addressing all symptoms of a patient. Pain and depression are examples of comorbidities frequently diagnosed in the same patients. Besides common pathways in their pathogenesis, both disorders can lead to an accumulation of allostatic load, which in turn can trigger the manifestation of depression or pain syndromes. Successful treatment acknowledges the interdependence of both conditions and addresses the whole patient instead of isolated disease manifestations.

4.2. Optimization of treatment

4.2.1. Treating depression and pain

In the case of pain and depression comorbidity, it is common for patients to attribute their disease burden to either one or the other condition, and then seek help from respective specialists. As such, it is imperative that physicians carefully evaluate patients presenting with either pain or depression for symptoms of both disorders and tailor their treatment accordingly. Failure to address each comorbidity adversely impacts outcome. For example, the presence of pain predicts a longer time to remission in patients with MDD (181). Similarly, improvement of associated painful symptoms in patients with MDD significantly (p-value less than .001) increased the chances of remission of depression (182). Multiple treatment approaches are available.

4.2.1.1. Psychotherapy

Several psychotherapeutic approaches are being explored to treat patients with comorbid depression and pain. To date randomized controlled trials have supported the efficacy of CBT in treating both MDD (183,184) and pain disorders (185,186). CBT for pain or CBT for depression may be part of a comprehensive treatment plan for the patient with comorbid symptoms or disorders.

For the treatment of MDD, the combination of pharmacotherapy with CBT is optimal in some patient populations, such as chronic depression (187-189) and adolescents (190).

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Similarly, current treatment recommendations emphasize the value of CBT in the treatment of chronic pain conditions in combination with other treatment strategies (186,191). Several studies also provide evidence for the efficacy of CBT monotherapy for patients with chronic pain (192,193) and CBT has been recommended for the treatment of comorbid psychiatric symptoms in headache patients (194). A meta-analysis of psychotherapeutic approaches for chronic lower back pain showed improvements of pain and depression in response to CBT and self-regulatory treatment (192). Similarly, a study in highly disabled chronic pain patients confirmed efficacy of CBT for improvement of their depression and pain symptoms (195). Interdisciplinary CBT has been proven to be beneficial for adolescent pain patients and their families (196).

4.2.1.2. Exercise

Beneficial effects of physical exercise have been described for patients with both depression and pain disorders. In women with fibromyalgia, group exercise improves both pain and depressive symptoms (197). Within this patient group, muscle strengthening and aerobic exercise programs seem to be equally beneficial (198); aquatic exercise improves pain symptoms to a comparable extent as aerobic exercise, but produces superior results with regard to depressive symptoms (199). Similarly, aerobic exercise improves depression and pain symptoms in patients with rheumatoid arthritis (200) and ankylosing spondylitis (201).

4.2.1.3. Pharmacotherapy options

As described above, serotonin and noradrenalin are involved in the pathophysiologies of both pain and depression. Tricyclic antidepressants (TCA) and the newer serotonin and norepinephrine reuptake inhibitors (SNRIs) duloxetine, venlafaxine (202) and milnacipran (203) have shown efficacy in the treatment of both conditions, an effect that might be due partially to their facilitating influence on both serotonin and norepinephrine. Selective serotonin reuptake inhibitors (SSRIs) seem to be less efficient in the combined treatment of pain (particularly neuropathic pain) and depression (202).

Significant empirical evidence is available for the efficacy of SNRIs in the treatment of pain disorders, pain symptoms and depression (204,205). Data from placebo-controlled trials suggest that SNRIs have direct analgesic effects independent of their antidepressant effects (206). Improvement of depression (207-212) and pain symptoms (182,208,209,213,214,215,216) in response to SNRIs has been observed in patients with MDD overall, and in subgroups including postmenopausal women (217), elderly patients (218,219), elderly patients with arthritis (220), and patients with melancholic depression (221). Patients with pain disorders that showed clinical improvement in response to treatment with SNRIs include women with fibromyalgia (222,223,203,224), patients with MDD and multisomatoform disorder (225), and patients with trigeminal neuralgia (226). In patients with atypical facial pain, SNRIs seem to be only modestly effective for pain relief (227). Limited information is available regarding the

efficacy and safety of SNRIs in pediatric patients. Case reports of depressed children and adolescents with pain describe improvement of both pain and depressive symptoms in these patients in response to SNRIs (228,229).

Mixed results regarding their efficacy for the treatment of pain and depression are available for SSRIs. A study in patients with IBS found no improvement over placebo for pain and depressive symptoms in response to SSRIs (230). On the other hand, some studies showed efficacy of SSRIs in improving pain symptoms in depressive patients. Examples are a study in adult patients with IBS (231) and a trial in children and adolescents with abdominal pain (232).

Extensive data in the literature support the efficacy of TCAs for the alleviation of pain symptoms in chronic pain patients; examples include patients with postherpetic neuralgia (233), neuropathic pain after spinal cord injury (234), fibromyalgia (235), diabetic peripheral neuropathic pain (236), somatoform pain disorder in the orofacial region (237), chronic headaches (238), especially tension-type headaches (239), and central post-stroke pain (240). Limiting the use of TCAs in the treatment of pain syndromes is the relatively high frequency of treatment emergent adverse events (compared to other antidepressants) (241,242), and potential lethality after intentional and accidental overdoses with TCAs (243,244).

Only 1 open-label observational study examined the efficacy of a tetracyclic antidepressant in treating depression and pain comorbidity; it showed improvement of depression and pain symptoms in response to treatment with a tetracyclic antidepressant (245).

5. PERSPECTIVES

In summary, the pathophysiologies of depression and pain overlap in many aspects. Empirical evidence illustrates the importance of shared brain structures and common neurocircuits and neurochemicals in the development of both disorders. The presence of both pain and depressive symptoms worsens the overall outcome of affected patients with longer treatment durations, more severe symptoms, and lesser likelihood of remission. One explanation for the observed interactions of pain and depression is based on the concept of allostasis, in which the accumulation of allostatic load is hypothesized to be responsible for greater vulnerability caused by external and internal stressors – which can include pain and depression. Therefore, it is essential for treatment success to recognize the comorbidity with pain and depression in affected patients and to treat both disorders. Examples of therapeutic options that target both disorders include cognitive behavioral therapy, exercise, and pharmacotherapy. Future research is needed to further clarify the multiple interactions of pain and depressive disorders, including effects on neurotrophins, which will aid in the development of more effective treatment strategies addressing all symptoms with which a patient might present.

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Abbreviations: ACC: anterior cingulate cortex; BDNF: brain-derived neurotrophic factor; CBT: cognitive behavioral therapy; CRF: corticotropin-releasing-factor; CRP: C-reactive protein; DLPT: dorsolateral pontine tegmentum, fMRI: functional magnetic resonance imaging; HPA: hypothalamic-pituitary-adrenal gland; IBS: Irritable bowel syndrome; IL-1-beta: interleukin-1-beta; IL-6: interleukin-6; LDAEP: loudness dependence of the auditory evoked potential; MDD: major depressive disorder; MRI: Magnetic resonance imaging; NGF: nerve growth factor; NK1: neurokinin-1; NT-3: neurotrophin-3; PET: Positron emission tomography; PFC: prefrontal cortex; RVM: rostral ventromedial medulla; SNRI: serotonin and norepinephrine reuptake inhibitor; SPECT: Single photon emission computed tomography; SSRI:

selective serotonin reuptake inhibitors; TCA: Tricyclic antidepressants; TNF-alpha: tumor necrosis factor alpha

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