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Pain and depression comorbidity: a preclinical perspective

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Abstract

Pain and depression are two highly prevalent and deleterious disorders with significant socioeconomic impact to society. Clinical observations have long recognized the co-existence and interactions of pain and depression. However, the underlying mechanisms of pain-depression comorbidity and their dynamic interactions remain largely unknown. Preclinical animal studies may provide critical information for the understanding of this important comorbidity. This review analyzed the current preclinical evidence of interactions between pain and depression, which generally supports the causative relationship of the two conditions. In addition, the analysis proposed to apply domain interplay concept in future model development of pain-depression comorbidity and mechanism studies. The application of spectrum-centered animal models will better the understanding of pain-depression dyad and foster the development of more effective therapeutic strategies.

Keywords

Pain; Depression; Comorbidity; Animal Models; Domain interplay

1. Introduction

Pain is one of the most common reasons that patients seek medical treatment, representing a major clinical, social and economic problem. The estimated prevalence of various pain conditions ranges from 8% to as high as 60% [1-3]. In the United States alone, chronic pain is estimated to affect at least 116 million adults, reduces quality of life, and costs society at least $ 636 billion annually [4]. Similarly, depression is among the most common and costly of all psychiatric disorders, accounting for 4.4% of total disability-adjusted life years [5]. Up to 65% of individuals have recurrent episodes of depressive disorders in their lifetime [6, 7]. Even worse, a large proportion of patients with depressive disorders were not diagnosed or did not receive treatment, and for those who did receive treatment, approximately 50% of patients with depression did not experience a response to first-line antidepressant therapy

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and the proportion of patients achieving a response decreases to approximately 30% with second-line treatment [8-10]. Unsurprisingly, the highly prevalent and chronic nature of depression creates a substantial economic and societal burden to society. It was estimated that the total cost of depression in the United States in 2000 was $ 83.1 billion [11] and € 118 billion in Europe in 2004 [12].

Clinical observations have long recognized the comorbidity of pain and depression. These observations have led to some authors to label the comorbidity as the pain-depression syndrome or pain-depression dyad. Both conditions often coexist, respond to similar treatments, exacerbate one another, and share overlapping biological mechanisms [13, 14]. The comorbid nature of depression and pain has been extensively reviewed [15-18]; however, the exact neurobiological mechanisms remain unclear, and mechanism-based preclinical studies are rare [19]. The goal of this review was to briefly summarize the clinical findings of pain-depression comorbidity, analyze the limited preclinical studies, and propose to develop and use domain interplay concept to study pain-depression comorbidity in future investigations.

2. Clinical findings of pain and depression comorbidity

Although both pain (particularly various chronic pain conditions) and depression are highly prevalent conditions, a growing body of literature suggests that the prevalence of pain in depressed patients and the prevalence of depression in pain patients are higher than when these two conditions are separately evaluated [18]. The prevalence of pain is averaged 65% in depressed patients across a pooled analysis of multiple studies [18]. Compared to those patients without depressive symptoms, the depressive symptoms predict the future occurrence of various pain conditions such as low back pain, neck-shoulder pain and musculoskeletal symptoms [20]. Depressed patients frequently report specific pain-related complaints such as headache, abdominal pain, joint pain and chest pain [21, 22]. In addition, depressed patients are 2 times more likely to report low back pain than their control cohort [23]. Similarly, multiple studies have confirmed the increased odds for developing depressive symptoms in patients with chronic pain. Patients with more than one pain complaints (e.g., low back pain, headache, abdominal pain, chest pain and facial pain) are 3 to 5 times more likely to develop depression than those without pain [24]. Patients with chronic pain are 3 times more likely to meet the diagnosis criteria of depression than those without pain, and the odds of developing depression increases with increased number of pain symptoms [25-27]. This reciprocal relationship holds true across a broad range of pain conditions. A recent longitudinal analysis confirms that depression is a strong predictor for patients with depression to report intensive and enduring pain than non-depressed patients, and chronic pain strongly predicts the development of more depressive symptoms in patients with pain than those without [28].

Although the general reciprocal interaction between pain and depression is well documented [28], the underlying neurobiological mechanisms are unclear. Depression is a persistent and highly heterogeneous disease and human neuroimaging studies reveal structural changes in multiple brain regions, including brain regions that involve pain perception and processing [29]. Chronic pain also fundamentally alters the brain structure and function as revealed by

growing neuroimaging studies [30]. It is postulated that the reciprocal interactions between pain and depression may be due to the overlapping (although separable [31]) neuroplasticity caused by both conditions [19]. Indeed, since 1960s antidepressants have been used to treat pain with the primary reason to treat concomitant depression [32], although later clinical studies have repeatedly demonstrated that the analgesic effects of antidepressants are separable from their antidepressant activities [33-35]. However, the above findings are only correlational at best, and few human studies have carefully examined the causative relationship between pain and depression. Adding to the complexity, patients with both conditions are highly heterogeneous. The odds of developing depression can be different for different pain conditions [18]. For depression, the spectrum of symptoms is not evenly developed in different pain conditions. In this regard, preclinical animal study is uniquely positioned to address this issue, because the experimental conditions can be carefully controlled and variables related to pain and depression can be precisely measured.

3. Animal studies of the pain-depression relationship

Given the well-recognized reciprocal interactions between pain and depression, emerging animal studies are beginning to address this issue [19]. Over the years, many animal models have been developed that are designed to model different aspects and/or origins of sensory pain and have good construct and face validity (e.g., inflammatory, nerve injury or cancer pain), although they are not without challenge [36, 37]. In addition, because pain is an integral subjective experience that is heterogeneous in nature and involves sensory, emotional and cognitive components as well as multiple sensory modalities, the animal models of pain begin to decipher components other than sensory modalities such as affective pain and cognitive impairments related to pain experience [19, 38]. Similarly, several animal models are developed to study the neurobiology of depression and screen potential antidepressants, including acute stress-related models (e.g., forced swimming test [FST], tail suspension test[TST], learned helplessness), models of iatrogenic depression (e.g., corticosterone drinking, forebrain glucocorticoid receptor knockout, chronic isotretinoin treatment), and models of chronic stress (e.g., chronic unpredictable mild stress [CUMS], social defeat) [39, 40]. In the past several years, a small body of literature began to examine the causal relationship between pain and depression in animal models. These studies can be generally categorized into three groups: studies that examine whether pain leads to depression-like behaviors, studies that examine whether behavioral manipulations related to depression alter pain responses, and studies that simultaneously examine pain and depression (Table 1).

3.1 Does pain exacerbate depression?

Using a mouse model of neuropathic pain (spared nerve ligation [SNL]), Suzuki and colleagues observed depression-like behaviors in the injured mice as evidenced by increased immobility in FST [41]. Importantly, although the nerve injury-induced mechanical and thermal hyperalgesia were evident 2 and 7 days after ligation, the increased immobility was not evident until 15 days after surgery, showing a clear delay on the development of depression-like behaviors [41]. This finding was successfully replicated in several other studies that involve different animal models of neuropathic pain [37-47]. For instance, in a

mouse model of neuropathic pain (partial sciatic nerve ligation [PSNL]), animals developed depression-like behavior 4 weeks after the surgery as evidenced by increased immobility in both FST and TST [42]. In a rodent model of neuropathic pain (chronic constriction injury [CCI]), animals developed depression-like behavior as demonstrated by an increased immobility 2 -4 weeks after the surgery and the magnitude of pain sensitivity was positively correlated with the duration of immobility [43-46]. In a rat model of neuropathic pain (spared nerve injury [SNI]), rats developed depression-like behaviors in a measure of anhedonia (decreased sucrose preference in the sucrose preference test [SPT]) and increased immobility in FST [47, 48]. Remarkably, a single injection of the fast-acting antidepressant ketamine reversed the depression-like behavior without altering the mechanical hypersensitivity [48]. In a similar study, 7 weeks after SNI surgery animals demonstrated increased immobility in the FST, which was accompanied by an increased cell proliferation in amygdala, a key brain nucleus in emotional behaviors [49]. In a mouse SNI model, increased immobility in the FST was observed 7 days after the surgery in the animals, together with an increased interleukin[IL]-1β gene expression within the frontal cortex and increased glial fibrillary acidic protein expression within the periaqueductal grey area [50]. Interestingly, the increased immobility in the FST was observed only in socially isolated but not in pair-housed animals in a similar study [51]. However, although most studies find that depression-like behaviors are observed in animal models of neuropathic pain, there are exceptions. For example, PSNL did not induce depression-like behavior as measured by TST up to 4 weeks after surgery [52]. In another study, L5-6 nerve ligated rats did not demonstrate depression-like behavior as measured by FST 2 weeks after the surgery [53]. One possibility for these negative findings could be due to the insufficient time after the surgery. Although pain hypersensitivity after nerve injury develops quickly, depression-like behavior is time-dependent and develops much slower (usually weeks after the primary injury) [54]. For instance, Hasnie et al did not observe changes in the TST test in PSNL-injured mice 4 weeks later [52], but another study observed significant increased immobility in TST in mice 7 weeks after the same injury [49]. Our own unpublished observation was that rats with CCI surgery developed significant depression-like behavior in the FST at least 4 weeks after the surgery. The time to develop depression-like behavior in animals may also depend on the neuropathic pain model used. Understanding why depression develops far behind pain hypersensitivity may have important implications to understand the neural mechanisms of pain-induced depressive and other mental disorders.

Besides neuropathic pain, other types of pain conditions also induce depression-like behaviors. In a rat model of complete Freund's adjuvant (CFA)-induced inflammatory arthritis, animals demonstrated increased duration of immobility in FST [55]. There is a high comorbidity between gastrointestinal diseases and depression, and patients with disorders such as irritable bowel syndrome, inflammatory bowel disease and functional dyspepsia often complain about visceral pain [56, 57]. Luo and colleagues induced experimental gastritis in rats and found increased depression- (decreased sucrose preference in SPT) and anxiety-like behaviors in female but not in male rats [58]. Wistar-Kyoto (WKY) rats is a genetic variation of Wistar rats with demonstrable depression like behavior. It was found that after CCI surgery or temporomandibular joint (TMJ) inflammation establishment, the

increased immobility in FST was significantly enhanced, suggesting that chronic pain exacerbates the depression-like behavior [59, 60].

Overall, these behavioral studies reported consistent findings. Using animal models of acute stress (FST and TST) and anhedonia measurement (SPT), these studies found that several animal models of nerve injury-induced neuropathic pain and inflammatory pain consistently induced depression-like behaviors.

FST is most often used as a tool to rapidly screen potential antidepressants [61]. Given the reliable correlational relationship between neuropathic pain and increased immobility in FST and TST assays, increasing studies used this assay to dually examine known and potential compounds for the treatment of both pain and pain-related depression. For example, subchronic treatment with an organoselenium drug, 3-(4-fluorophenylselenyl)-2, 5-diphenylselenophene, significantly reversed the pain sensitivity and depression-like behaviors in a mouse PSNL model [42]. A stimulator of brain-derived neurotropic factor (BDNF) synthesis ameliorated pain and depression-like behaviors in a rat CCI model [43]. Interestingly, the antidepressant desipramine decreased the depression-like behavior (decreased the duration of immobility in FST) without altering the pain sensitivity and a cannabinoid CB2 receptor agonist, GW405833, reversed both the increased immobility and pain sensitivity [44]. In a mouse CCI model, the antidepressant amitriptyline and a plant-derived phenolic compound curcumin both reversed the nociceptive hypersensitivity and depression-like behaviors [45, 46]. Moreover, behavioral manipulations such as social interaction also seems to affect the pain-depression comorbidity. For example, in a mouse SNI model, social interaction demonstrated a protective effect against the development of depressive-like behavior in animals with chronic neuropathic pain via oxytocin mechanism, a molecule that plays a key role in social bonding, [51].

The neurobiological mechanisms regarding how chronic pain leads to depression have not been extensively studied, although it is clearly that the mechanism is multifaceted. Pharmacological investigations clearly show that pain and pain-induced depression are two separable processes [44]. In a mouse SNI model, chronic restraint stress for 2 weeks before SNI surgery markedly exacerbated mechanical allodynia and depression-like behavior, and increased IL-1β gene expression in the brain. The increased cytokine in the brain induced by peripheral nerve injury may contribute to the depressive-like behavior [50]. In a rat inflammatory arthritis model, it was found that the brain indoleamine 2, 3-dioxygenase 1 (IDO 1), a rate-limiting enzyme in tryptophan metabolism, plays a critical role in this pain-depression comorbidity. Inflammatory arthritis led to depression-like behavior and up-regulation of IDO 1 in bilateral hippocampus, and either *ido1* gene knockout or pharmacological inhibition of hippocampal IDO 1 activity attenuated both the pain and depression-like behaviors [55]. In another study, SNI-induced chronic neuropathic pain selectively increased the level of GluA1 subunits of AMPA-type glutamate receptors at the synapses of the nucleus accumbens (NAc), a key component of the brain reward system, and this increase in GluA1 levels led to the formation of calcium-permeable AMPA receptors (CPARs), which was thought to contribute to the pain-induced depression-like behaviors as pharmacological blockade and enhancement of these CPARs increased and decreased the depression-like behaviors, respectively [47]. Moreover, the BDNFERK1/2 signaling

pathway deficiency may also be involved in the depression-neuropathic pain comorbidity [43].

3.2 Does depression exacerbate pain?

Although the baseline threshold to a mechanical stimulus in WKY rats is not different from that in Wistar rats, WKY rats showed more significant mechanical allodynia than Wistar rats after CCI surgery or after TMJ inflammation establishment, suggesting that the presence of depression-like behavior exacerbated pain response [59, 60]. This study provided genetic evidence that depression may induce pain. Bilateral olfactory bulbectomy (OB) is a widely used rodent model of depression [62]. Following OB surgery, animals demonstrate hyperactivity in an open field test, which can be reversed by antidepressants. It was found that animals receiving OB surgery had a significantly higher pain threshold as measured by Randall-Selitto paw pressure method or by plantar test [63, 64]. In two studies from the same lab that employed different depression models (CUMS and OB), depressed animals demonstrated higher pain threshold to thermal stimuli either under normal condition or under CFA-induced chronic pain condition. However, these animals showed increased response in formalin-induced spontaneous nociceptive behaviors [65, 66]. The changes in depressed animals were prevented by chronic antidepressant fluoxetine treatment [65]. In another study, the same authors reported that CUMS-operated animals showed significantly higher pain threshold to thermal stimulus (plantar test) and mechanical stimulus (von Frey test in CCI rats), extending their previous findings [67]. Burke et al. examined the pain responses in two rat models of depression (OB and WKY rats). They found that OB rats demonstrated mechanical allodynia (von Frey test) but not thermal hyperalgesia (hot plate and tail flick tests), while the spontaneous nociceptive behaviors were heightened (formalin test) [68]. In addition, WKY rats exhibited thermal hyperalgesia (hot plate test) and increased response to formalin, while the response to von Frey filament stimulus and tail flick test did not change [68]. In a subsequent study, these authors reported that OB rats exhibited mechanical (von Frey test) and cold (acetone drop test) allodynia but not thermal hyperalgesia (plantar test) after these rats received SNL surgery [69]. In the acetone test, there was a positive correlation between the pain-like responses and the level of IL-1β and IL-10 gene expression in amygdala of the brain [69]. Besides the commonly used animal models of sensory pain, one study reported that CUMS-induced depression exacerbated trigeminovascular nociception, a rodent model of migraine [70].

To sum up, the available studies that examined whether depressive status altered pain sensitivity used three different types of depression models (WKY rats, OB and CUMS), and reported drastically different results: some pain measures were increased, some were decreased but some did not change. These inconsistencies appear to be assay- and modality-dependent but no clear conclusion can be drawn. In relevance to this, human studies suggest that the pain sensitivity in depressed patients depends on the pain modality measured such that the cold sensitivity in depressed patients was significantly decreased as compared to healthy controls while the mechanical pain threshold was not different [71]. In addition, human studies indicate that acute mood alteration (threat of brief electric shock-induced anxiety) increases pain reactivity in healthy subjects, supporting the view that emotional state modulates human pain reactivity [72].

Little is known of the neural mechanisms about how depressive status alters pain sensitivity. A multiple-channel recording study showed that in CUMS-induced depression model, the processing of neurons in the thalamo-cortical circuits in the lateral and medial pain pathways were altered in the opposite direction by formalin-induced spontaneous pain and noxious thermal stimulus (plantar test)-evoked pain [73].

3.3 Models of pain-depression dyad

Several studies examined the interaction between pain and depression in the same models, which offers another perspective of the pain-depression dyad. Reserpine is a monoamine depletor, and repeated reserpine treatment leads to a battery of behavioral phenotypes that indicate the presence of pain and depression, including mechanical allodynia, thermal hyperalgesia and increased immobility in the FST [74, 75]. Because clinically used analgesics such as pregabalin, duloxetine, pramipexole reversed the pain-like behavior, it was proposed as an animal model of fibromyalgia [75]. This model has been used to study the pain-depression dyad and several plant-derived compounds including curcumin, ferulic acid and berberine reversed reserpine-induced pain and depression-like behaviors [74, 76, 77]. Another study first established neuropathic pain (SNI) and then established dopamine deficiency model of depression by MPTP treatment [78]. They found that the neuropathic pain index (autotomy) was exacerbated in rats that received MPTP as compared to those without MPTP treatment and the depressive-like behavior (sucrose preference) was more pronounced in SNI rats than sham rats.

Bravo et al. combined CCI and CUMS in the same animals and found that CUMS enhanced CCI-induced cold allodynia (acetone drop test) but not mechanical allodynia (von Frey test) [79]. In contrast, they found that CCI did not heighten depression-like behaviors [79]. This result is interesting because this is the only study that examined the effect of a neuropathic pain condition on depressive-like behaviors by using a model of chronic stress (CUMS), and may suggest the involvement of a complicated interaction between the presence of pain and repeated stress treatment.

3.4 Synthesis

Multiple studies have consistently demonstrated that chronic neuropathic pain leads to depressive-like behaviors in rats and mice, using measures such as increased immobility time in FST and TST and decreased sucrose preference in SPT. Other types of experimental pain are rarely examined. Clinical studies have demonstrated increased vulnerability of depression in patients with various painful conditions, and it is suggested that future preclinical studies need to extend the findings from neuropathic pain to other types of pain to establish the generality of these findings. In addition, preclinical work relied heavily on the test of behavioral despair (FST and TST) to detect the existence of depression. FST and TST are most successfully used to rapidly screen novel potential antidepressant agents and phenotype of genetically manipulated mice [40, 61]. Recent molecular and behavioral analysis suggested that other more sophisticated animal models (e.g., social defeat model) better model human depressive conditions [40, 80]. Future studies should incorporate multiple types of pain and more sophisticated models of depression to better model clinically relevant pain-depression dyad.

Studies that examine the causative role of depression to pain are less consistent. Notably, all studies employed more sophisticated and chronic models of depression (CUMS, OB and WKY rats). This is intuitively understandable because chronicity is likely needed and critical to lead to behavioral and neuroplasticity that ultimately alters pain processing and perception. Current data fail to reach consistency in the measures of pain, with some studies reporting increased pain sensitivity while others showing decreased or unaltered pain perception. One way to address this issue in future studies is to focus on one validated model of depression (e.g., social defeat) and one relevant model of chronic pain (e.g., CCI or SNI) and examine a broad spectrum of sensory and affective pain perceptions. Incorporating multidisciplinary techniques to examine the neural mechanisms will provide further evidence to elucidate the mechanisms by which depression increases susceptibility to pain.

The development of animal models of pain-depression comorbidity is still in its infancy. Reserpine treatment induced increased pain sensitivity and increased immobility in FST test. These behavioral phenotypes seem appealing to suggest the co-existence of pain and depression. However, whether reserpine treatment leads to depression remains a highly debatable topic [81]. This model could be more useful and convincing if it is better validated in future studies by incorporating the measurement of a spectra of pain and depression phenotypes.

Overall, the preclinical data are surprisingly consistent with the clinical observations. It seems there exists a reciprocal interaction between pain and depression, with depressive-like conditions exacerbating pain perception and the presence of chronic pain aggravating depressive-like behaviors. With these promising behavioral findings available, future studies should begin to explore the neural and molecular mechanisms underlying this reciprocal relationship, which may eventually lead to better and more refined therapeutic strategies for pain-depression dyad.

4. Pain-depression dyad and domain interplay modeling

Pain and depression both have characteristic behavioral phenotypes. Besides the complaint of sensory pain, patients with chronic pain also have altered psychological status, such as depressed mood, anger, catastrophizing, anhedonia, sleep disturbance, fatigue, cognitive impairment and suicidal ideation [82]. Many of these symptoms are consistent with the clinical diagnostic criteria of depression, which usually utilizes a checklist of 9 symptoms (DSM-V). Although the preclinical studies reviewed above provide valuable information and established the reciprocal relationship between pain and depression, a better understanding of pain-depression dyad and its underlying mechanisms must utilize better animal models which simultaneously incorporate behavioral phenotypes of pain and depression. Although FST and TST are widely used to study depression, they are most successfully used in the assessment of potential antidepressants and genetic phenotypes [40]. In contrast, defeated animals in a social defeat paradigm demonstrate a battery of behavioral phenotypes such as social avoidance, anhedonia, decreased circadian amplitude, social hyperthermia and decreased body weight that have close human analogy of psychological stress and depression and thus may have better construct and predictive validity than “simple” behavioral assays such as FST [80]. By the same token, simply focusing on reflex-

based measures such as mechanical allodynia and thermal hyperalgesia have drawn increasing criticism in pain studies [36, 38]. Because overall pain experience comprises sensory, affective and cognitive components [83], emerging efforts have been incorporating the measurement of affective and cognitive components in the assessment of overall pain experience in preclinical studies [19, 38]. In this regard, the domain interplay concept may help the development and future study of pain-depression dyad.

Domain interplay refers to the dynamic interactions among the shared (overlapped) domains (traits) of different neuropsychiatric disorders [84, 85]. Animal models of pain-depression dyad may have better validities by combining multiple shared components of pain and depression as compared to those modeling single domain such as pain spectrum (hypersensitivity) or depression (FST or TST). For example, anhedonia is one of the core symptoms of depression, and chronic pain patients also report anhedonia [86]. Sleep disturbance is also a symptom that is observed both in depressed patients and in patients with chronic pain [87]. The incorporation of animal models of chronic pain (e.g., nerve injury and chronic inflammation) with multiple behavioral measures such as pain hypersensitivity, anhedonia and sleep pattern [88] may better reveal the existence of pain and depression and predict the therapeutic value of potential pharmacotherapies. In preclinical development of models of comorbidity, assessing the key overlapping behavioral phenotypes will minimize the incorrect interpretations of animal behaviors, improve the validity of animal modeling based on spectrum-and/or dimension-oriented psychiatric theories [84, 89] and better our understanding of pathogenesis of complex brain disorders.

5. Concluding remarks

Pain and depression represent two highly prevalent and deleterious neuropsychiatric disorders. Both conditions often co-occur, share some similar symptoms, and exacerbate one another, suggesting overlapping neurobiological underpinnings. Both clinical observations and animal studies point to the reciprocal causative relationships between pain and depression. However, the neural mechanisms of this interaction are largely unknown and there are no well-validated animal models to recruit core symptoms of both disorders. The application of domain interplay concept in future development of animal models of pain-depression comorbidity may lead to animal models with better construct and predictive validity. Such models should incorporate the assessment of core symptoms of both pain (e.g., pain hypersensitivity, pain aversion and cognitive deficit) and depression (anhedonia, social avoidance and circadian rhythm change). These models will be invaluable in the understanding the mechanisms of pain-depression comorbidity and developing more refined and effective treatments.

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Research Highlights

► Pain and depression co-exist and exacerbate one another both in clinical and preclinical findings.

► Pain and depression seem to have a reciprocal causative relationship.

► Domain interplay concept may foster future development of new pain-depression comorbidity models.

Table 1

Preclinical studies that examined the pain-depression interactions.

Studies examining whether pain induces and/or exacerbates depression				
Pain model	**Species**	**Depression test**	**Key findings**	**References**
SNL	Mouse	FST	Increased immobility	[41]
PSNL	Mouse	FST, TST	Increased immobility	[42]
PSNL	Mouse	TST	No change in immobility	[52]
CCI	Mouse	FST	Increased immobility	[45]
CCI	Mouse	FST, TST	Increased immobility	[46]
CCI	Rat	FST	Increased immobility	[43]
CCI/TMJ	WKY rat	FST	Increased immobility	[59, 60]
SNI	Rat	FST	Increased immobility	[47, 48]
		SPT	Decreased sucrose preference	
SNI	Rat	FST	Increased immobility	[49]
SNI	Mouse	FST	Increased immobility	[50]
SNI	Mouse	FST	Increased immobility in socially isolated mice	[51]
CFA	Rat	FST	Increased immobility	[55]
Experimental gastritis	Rat	SPT	Decreased sucrose preference	[58]

Studies examining whether depression induces and/or exacerbates pain				
Depression model	**Species**	**Pain test**	**Key findings**	**References**
Genetic	WKY rat	CCI, von Frey	Increased allodynia	[59]
		TMJ, algometer	Increased allodynia	[60]
Genetic	WKY rat	hot plate, formalin	Increased sensitivity	[68]
		tail flick, von Frey	No change	
OB	Rat	Paw pressure	Decreased sensitivity	[63]
OB	Rat	Plantar test	Decreased sensitivity	[64]
OB	Rat	von Frey, formalin	Increased sensitivity	[68]
		plantar test	No change	
OB	Rat	CCI, von Frey, acetone	Increased sensitivity	[69]
		plantar test	No change	
OB, CUMS	Rat	plantar test	Decreased sensitivity	[65, 66]

Studies examining whether depression induces and/or exacerbates pain				
Depression model	**Species**	**Pain test**	**Key findings**	**References**
		formalin	Increased sensitivity	
CUMS	Rat	plantar test	Decreased sensitivity	[67]
		CCI, von Frey	Decreased sensitivity	
CUMS	Rat	migraine-like	Increased sensitivity	[70]

Studies simultaneously examining pain and depression				
Model	**Species**	**Tests**	**Key findings**	
Reserpinization	Rat	FST	Increased immobility	[74, 76,
	Mouse	von Frey, plantar test	Increased sensitivity	77]
CCI+CUMS	Rat	acetone	CCI increased sensitivity	[79]
		von Frey, SPT, FST	No change	
SNI+MPTP	Rat	autotomy	Increased intensity	[78]
		SPT	Decreased sucrose preference	

Note: SNL, spared nerve ligation; PSNL, partial sciatic nerve ligation; CCI, chronic constriction injury; TMJ, temporomandibular joint; SNI, spared nerve injury; CFA, complete Freund's adjuvant; FST, forced swimming test; TST, tail suspension test; SPT, sucrose preference test; OB, olfactory bulbectomy; CUMS, chronic unpredictable mild stress.