The Mesolimbic Dopamine System in Chronic Pain and Associated Affective Comorbidities

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Abstract

Chronic pain is a complex neuropsychiatric disorder, characterized by sensory, cognitive, and affective symptoms. Over the last two decades, researchers have made significant progress towards understanding the impact of mesolimbic dopamine circuitry in acute and chronic pain. These efforts have provided insights into the circuits and intracellular pathways in the brain reward center that are implicated in sensory and affective manifestations of chronic pain. Studies have also identified novel therapeutic targets as well as factors that impact treatment responsiveness. Dysregulation of dopamine function in the brain reward center may further promote comorbid mood disorders and vulnerability to addiction. This review discusses recent clinical and preclinical findings on the neuroanatomical and neurochemical adaptations triggered by prolonged pain states in the brain reward pathway. Furthermore, this discussion highlights evidence of mechanisms underlying comorbidities between pain, depression, and addiction.

Keywords

Introduction

The mesolimbic system is a central nervous system circuit in which dopaminergic inputs from the ventral tegmental area (VTA) innervate brain regions involved in executive, affective, and motivational functions, including the prefrontal cortex (PFC), amygdala, and nucleus accumbens (NAc). Dysfunctions within this system can contribute to neuropsychiatric diseases, including major depression disorder (MDD) and addiction (1–3). Emerging evidence points to a critical role of the mesolimbic system in the perception and modulation of chronic pain symptoms (4–9), highlighting the importance of this pathway in pain therapeutics.

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Understanding the function of the brain reward pathway under chronic pain states can also provide insight into clinically detrimental comorbidities, such as depression and addiction vulnerability. Indeed, clinical research has demonstrated substantial comorbidity between pain and depression, with one study estimating a prevalence of 30% comorbidity (10). Considering that approximately 9% and 20% of the U.S. population suffers from depressive or chronic pain disorders, respectively, this increased potential for comorbidity is not trivial (11, 12). Notably, patients with debilitating mental conditions, such as MDD, have a higher comorbid presence of chronic pain, with each of these conditions positively reinforcing the other (13–18). Managing chronic pain is challenging because symptoms often vary between patients, while the currently available medications target only a subset of symptoms. Furthermore, we have limited knowledge of the gender- and age-related mechanisms of pain modulation.

The misuse of opioid analgesics has also been a major concern in pain management. Morphine, oxycodone, and other synthetic opioids show limited efficacy in the treatment of *chronic* pain, they promote hyperalgesia, and they contain the risk of physical dependence and addiction (19–24). The 300% increase in opioid analgesic prescriptions for chronic non-cancer pain patients between 2000 and 2010 has contributed to the substantial rise in the incidence of physical dependence and substance use disorders (19–25). Based on the existence of affective and nociceptive comorbidities related to the mesolimbic system, it falls within reason that this network could underlie vulnerabilities to addiction and depression in chronic pain patients (26).

Mesolimbic Functional Magnetic Resonance Imaging (fMRI) in Chronic Pain Patients Compared to Depression and Addiction Populations

Functional imaging studies have been fundamental in documenting the impact of pain conditions on the brain reward circuitry (see Figure 1). By reviewing the literature on depression and addiction, below we summarize structural and functional commonalities between these conditions that may underlie comorbidities in chronic pain populations. Specifically, we focus on the ventral tegmental area (VTA), nucleus accumbens (NAc), prefrontal cortex (PFC), anterior cingulate cortex (ACC), and the amygdala, which play major roles in managing executive decision-making, emotional perception, and motivational drive.

Ventral Tegmental Area.

Normal mesolimbic function and affective processes, such as reward-mediated drive, are highly dependent on dopaminergic neurotransmission emanating from the VTA (27–29). Fibromyalgia and trigeminal neuralgia patient populations demonstrate a reduction in gray matter volume and decreased VTA activity (30, 31). Researchers have found that chronic migraine is associated with decreased connectivity between the extended amygdala and the VTA, which are both areas significantly involved in the management of executive function and emotional responses (32). Interestingly, studies on MDD populations have reported increased VTA connectivity to the ACC, a structure involved in pain processing (33). Decreased VTA activity also has been observed in MDD patients (33). The contribution of

reduced VTA activity to mesolimbic affective disorders is supported by the finding that deep brain stimulation (DBS) of the VTA is effective in treating chronic, refractory cluster headaches and treatment-resistant depression (TRD) (34–36). Alterations in VTA-NAc connectivity have also been observed in individuals suffering from substance abuse disorders, during active use as well as during abstinence phases; such changes may further impact executive or affective pain-processing centers (26, 37, 38). Specifically, changes in VTA-NAc connectivity in individuals suffering from substance abuse disorders occur in an opposite direction to those observed in individuals suffering from depression, as 3-day abstinent cocaine users show increased *effective* connectivity from the VTA to the NAc and medial PFC (mPFC) (37). However, another study found decreased functional connectivity between the VTA and NAc of active cocaine users (38). Differences between these studies may be related to the abstinent versus active status of the patients, or to the form of connectivity analyzed (effective connectivity analyzes a unidirectional influence of one brain area over another, while functional connectivity provides a broader bidirectional relationship between two regions).

Nucleus Accumbens.

The NAc projects to various executive, emotional, and motor regions and is considered a master regulator of motivational drive (39, 40). Although a decrease in NAc gray matter volume occurs in states of chronic pain (as with heroin addiction), the activity in this region collectively increases (31, 41–43). Human imaging studies also have helped elucidate the neurobiological mechanisms contributing to the transition from acute to chronic pain, which is fundamental for the development of efficient treatment tools. As shown by a longitudinal brain imaging study that followed subacute back pain patients for one year, increased functional connectivity of the NAc with the PFC predicts pain persistence, suggesting that this circuit contributes to the transition to chronic pain (44). A different study on chronic back pain patients indicated that the higher incidence of white matter and functional connections within the dorsal medial PFC (dmPFC)-amygdala-NAc circuit, and the observed reductions in amygdala volume, represent risk factors for pain persistence. This work demonstrated that the opioid receptor delta 1 (*OPRD1*) rs678849 single nucleotide polymorphism (SNP) is associated with amygdala volume, and the opioid receptor mu 1 (*OPRM1*) rs1799971 SNP is associated with incidence of connections within the dmPFC-amygdala-NAc white matter network (45). Interestingly, the status of NAc-PFC connectivity also contributes to depression and addiction, although these conditions arise from a net decrease in functional connectivity (33, 46, 47). Small-scale clinical studies have demonstrated promising efficacy of NAc DBS for depression and sustained heroin abstinence (48–51), suggesting that such approaches may be used for the treatment of comorbid conditions.

Prefrontal Cortex.

The PFC is a major component of the mesolimbic circuit, which affects several structures involved in pain perception, motivational drive, substance seeking, and anxiodepressive states (52–58). A resting-state fMRI study with rheumatoid arthritis patients revealed that prolonged pain states are associated with increased connectivity between the insula and the PFC (59). Using fMRI, Baliki et al. demonstrated that chronic back pain results in increased

PFC activity, and this activity is strongly related to pain intensity (60). The degree of change in BOLD (blood-oxygen-level-dependent) signal in the mPFC and the ACC were highly correlated with the severity of spontaneous pain in chronic back patients. In contrast, the level of insular activation was significantly associated with duration (years) of pain (60). A reduction in PFC thickness has also been reported in chronic pain populations (61, 62). Interestingly, effective treatment of low back pain (spinal surgery or facet joint injections) reverses the anatomical and functional maladaptations in ACC circuits (62). Since studies using repetitive transcranial magnetic stimulation (rTMS) and DBS of the PFC demonstrate significant and rapid improvement of fibromyalgia-induced chronic pain and TRD, along with a reduction of cue-evoked heroin cravings, it is possible that such therapeutic interventions may successfully manage comorbidities between these disorders (63–65).

Anterior Cingulate Cortex:

Evidence suggests that the ACC and the periaqueductal gray (PAG) form a central network that is primarily involved in spontaneous pain, and that the connectivity between these regions is increased in chronic pain patients (66, 67). This hypothesis is substantiated by the practice of treating patients exhibiting comorbid neuropathic pain and MDD with bilateral anterior cingulotomy, which effectively relieves symptoms associated with both disorders (68). Indeed, studies have shown that the serotonin-norepinephrine reuptake inhibitor (SNRI) Milnacipran is effective for treating fibromyalgia patients, likely because of its ability to decrease functional connectivity within the ACC-insular cortex-PAG network (69). Enhanced ACC activity has been associated with chronic pain and depression, whereas decreased ACC gray matter volume coincides with these two conditions as well as with heroin dependence (70–75). Notably, clinical trials suggest that interrupting abnormal ACC signaling by DBS or transcranial direct current stimulation has promise for the management of neuropathic pain, TRD, and cue-evoked cocaine cravings (76–78).

Amygdala:

Nuclei of the amygdala help regulate emotional stress and pain perception (79–81). Elevated baseline activity in the amygdala is associated with fibromyalgia- and inflammatory bowel syndrome-induced chronic pain and depression. By contrast, reductions in amygdala gray matter volume have been noted across the comorbidities discussed above (82–84). The amygdala also appears to modulate affective abnormalities associated with chronic pain, such as catastrophizing, through exaggerated and abnormal functional connectivity with the central executive network (85). This is important because catastrophizing can further exacerbate chronic pain conditions and increase the likelihood of poor clinical outcomes (86, 87). Similar to the observations in chronic pain patients, studies have found that using oral morphine for one month leads to persistent decreases in amygdala gray matter volume (88). Other reports show decreased functional connectivity between the amygdala and the ACC in heroin-addicted individuals (89, 90). We expect that future work on the impact of pain-addiction comorbidities on the function of this circuitry will fill a major gap in our understanding of addiction mechanisms.

Common Clinical Alterations in Mesolimbic Dopamine Neurotransmission Among Chronic Pain-related Comorbidities

Both pre- and post-synaptic stages of dopaminergic neurotransmission are compromised during chronic pain (91, 92), as well as in other affective disorders (see Figure 2). In accordance with reduced VTA activity in chronic pain patients, a pilot study found that chronic pain states diminish the pre-synaptic metabolism of dopamine in the VTA, as well as in the anterior cingulate gyrus and the insular cortex (91). Furthermore, chronic back pain patients demonstrate blunted dopamine release in response to noxious challenges (92). Positron emission tomography (PET) imaging studies in chronic back pain and fibromyalgia patients have demonstrated a reduction in ventral striatal dopamine receptor subtype 2 and subtype 3 (D2/D3R) binding (92, 93). These studies also found that the reduction in dopamine receptor availability correlates with lower thermal pain thresholds. By contrast, a Serine-9-Glycine mutation in the DRD3 gene, which is known to increase D3R activity, restores thermal pain thresholds to healthy control levels (94). Activity-lowering polymorphisms in dopamine metabolism genes, such as DAT-1 (dopamine transporter-1) and MAO-A (monoamine oxidase-A), have been associated with increased sensitivity to noxious cold (95). Crucially, activity-reducing mutations in dopamine-clearing genes, such as COMT (catechol-O-methyltransferase), also appear to modify pain sensitivity by changing functional responses of μ-opioid receptors in the NAc and other pain-modulating circuits. Such maladaptations may ultimately impact pain tolerance and affective states (96).

As opposed to the downregulation of inhibitory postsynaptic mechanisms in the chronic pain population, MDD patients can display an upregulation of D2/D3R availability, although evidence varies between studies. This conclusion would potentially support the finding that fibromyalgia patients with comorbid depression have higher ventral striatum D2/D3R binding potential than a non-depressed comparison group (93, 97, 98). Furthermore, Cannon et al. noted a depression-related reduction of excitatory D1R expression in the caudate, which strongly innervates the ACC, highlighting the importance of balanced dopamine activity in regulating affective processing (99). Similar to observations from chronic pain patients, the dopamine metabolism genes DAT-1 and COMT play a critical role in mediating susceptibility to depression. One study found that activity-enhancing polymorphisms in these genes protect against negative emotionality, further supporting the role of dopamine in resilience to affective disorders (100). Overall, evidence suggests that polymorphisms leading to a reduction in dopamine neurotransmission promote both chronic pain and depression. Notably, tricyclic antidepressants and SNRIs promote the activity of dopamine and effectively ameliorate sensory and affective symptoms of neuropathic pain (15, 101). Given the slow onset and several side effects of antidepressants, there is a pressing need for novel fast-acting therapeutic interventions that promote dopaminergic activity in the brain reward pathway.

Similar to chronic pain and depression, D2/D3R function plays a critical role in addiction vulnerability. [^{11}C]raclopride D2/D3R binding potential in heroin-dependent subjects both at baseline and after methylphenidate treatment is significantly lower than that of control subjects, particularly in the limbic striatum, caudate, and putamen (102). Researchers have

also observed a decrease in striatal D2R in opiate-dependent individuals upon naloxone-precipitated withdrawal (103). The DRD2 rs1800497 polymorphism, which attenuates D2R activity, also has been linked to vulnerability to heroin addiction (104). In accordance with reported changes in dopamine transport in MDD and chronic pain, patients on methadone maintenance or prolonged heroin abstinence also demonstrate lower presynaptic DAT activity in the striatum (105). In the next few years, the use of advanced PET imaging tools is expected to enhance our knowledge on the genetic and neurochemical substrates of chronic pain and its affective comorbidities.

Chronic Pain-induced Alterations in the Mesolimbic Pathway: Insights from Preclinical Studies

Studies on Neuronal Circuits

Several rodent studies have demonstrated that noxious stimuli affect the release of dopamine in the brain reward center. Consistent with observations in human studies, chronic pain states in rodents lead to a reduction in NAc dopamine release and pain relief is associated with increased dopamine levels in the NAc shell (106). In preclinical settings, compounds with pain-alleviating properties promote place preference when mice are conditioned to environmental cues. Pain relief promotes place preference in studies using the spared nerve injury (SNI) model of neuropathic pain, the complete Freund's adjuvant model of inflammatory pain, as well as models of post-surgical, cancer, and osteoarthritic pain (107). Thus, place preference to drugs with analgesic (but not rewarding) properties, such as lidocaine or the alpha-2 adrenoreceptor agonist clonidine, provides a valid model for evaluating spontaneous pain in rodents (108).

As mentioned earlier, there is major neurophysiological overlap between pain and depression (10, 17). Consistent with evidence from human studies, hypodopaminergic states in rodent models of neuropathic pain are associated with depression-like behaviors and reduced motivation (109–114). These affective deficits are linked to long-term depression of excitatory synaptic transmission in the medium spiny neurons of the indirect pathway (114).

Opto- and chemogenetic approaches have provided information on the functional role of brain reward circuits in affective and sensory pain symptoms. Ren and colleagues utilized fluorescent retrograde vectors and patch clamp electrophysiology to demonstrate that prolonged peripheral nerve injury using the SNI model leads to elevated intrinsic excitability of NAc shell medium spiny neurons of the indirect pathway (115). Long-term neuropathic pain states were also associated with a reduction in dendritic number and size, as well as with a decrease in extracellular dopamine levels. Furthermore, peripheral nerve injury caused a reduction in the spontaneous spiking of VTA dopamine cells projecting to NAc medium spiny neurons. Chemogenetic excitation of medium spiny neurons of the indirect pathway worsened SNI-induced mechanical allodynia, whereas inhibition alleviated allodynia (115). These results further support a role of the indirect dopamine pathway in modulating sensory hypersensitivity symptoms of peripheral nerve injury. Pharmacologic blockade of calcium-permeable AMPA receptors in the NAc core increased depression-like behaviors in models of neuropathic pain (116). The same study demonstrated that delivery

of an AMPA receptor potentiator into the NAc ameliorates behavioral manifestations of depressive states. Thus, calcium-permeable AMPA receptors and their downstream pathways may provide new avenues for the management of pain-induced depression.

In a rat model of peripheral neuropathy, activation of PFC neurons projecting to the NAc core increased excitatory postsynaptic potentials and alleviated sensory hypersensitivity symptoms (117). In these experiments, light activation of neurons that were infected with adeno-associated viruses encoding channelrhodopsin-2 induced action potential spikes within the prelimbic PFC of rats. This optogenetic activation alleviated both mechanical and cold allodynia. Using the place-conditioning paradigm, the investigators demonstrated that optical activation of these neurons relieved pain and promoted a preference for the associated compartment. Optical stimulation of the prelimbic PFC also reversed depression-like behaviors that were observed several weeks after nerve injury. Subsequent experiments utilized photoactivation of channelrhodopsin-2-expressing NAc medium spiny neurons to confirm that the activation of projections from the prelimbic PFC to the NAc was responsible for these effects, pointing to this corticostriatal circuit as an important target of neuromodulation therapy. On the contrary, inhibiting rat pyramidal mPFC neurons projecting to the NAc core by halorhodopsin exacerbated acute pain symptoms, suggesting a role of this circuitry in the endogenous antinociceptive pathway (118). This intervention also heightened affective and sensory symptoms of peripheral nerve injury, suggesting that therapeutic interventions targeting the activity of this pathway may efficiently alleviate chronic pain symptoms.

Rodent models have also demonstrated a role of the ACC in mood disorders triggered by chronic pain states. Lesions of the ACC prevent the development of anxiodepressive behaviors without impacting hypersensitivity symptoms, whereas optogenetic activation of the ACC promotes depressive states (119). A study by Sellmeijer and colleagues applied the cuff model of peripheral nerve injury to demonstrate a potent role of the ACC in modulating anxiodepressive behaviors (120). Using *in vivo* electrophysiological recordings, the investigators observed an increased firing rate and bursting activity within the ACC at time points at which anxiety and depression-like behaviors had developed (120).

Using a rat neuropathic pain model, a recent study demonstrated that inactivation of amygdala nuclei alleviates hyperalgesia/allodynia and depression-like behaviors (121). More recently, Corder and colleagues combined circuit optogenetics with *in vivo* calcium imaging in mice to investigate the function of an amygdala-NAc circuit in pain-free and neuropathic pain states (122). These studies showed that while this amygdala-NAc circuit did not have a prominent role in nociceptive thresholds in pain-naïve mice, it played a major role in modulating affective pain symptoms in mice suffering from prolonged peripheral nerve injury. Inhibiting this pathway with opsins alleviated the aversive components of pain without impacting mechanical allodynia (122). Table 1 summarizes key preclinical findings on mesolimbic circuits in the modulation of chronic pain symptoms.

Studies on Transcriptional and Epigenetic Adaptations in the Brain Reward Center

Prolonged neuropathic pain states also promote adaptations in gene expression in the mPFC and the NAc. Evidence from next-generation RNA sequencing (RNA-Seq) and subsequent

bioinformatic analyses suggest that prolonged pain states affect several intracellular pathways within the mPFC and the NAc, including G protein, cAMP, and nitric oxide signaling, as well as immune, glutamatergic and glucocorticoid pathways (123). Several of the identified genes and pathways have documented roles in neuropsychiatric disorders. For example, recent studies pointed to the role of brain-derived neurotrophic factor and tumor necrosis factor-alpha (TNF-α) in regulating symptoms of chronic pain, depression, and addiction (124–127). RNA-Seq studies by Mitsi et al., which used the SNI model to monitor gene expression adaptations in response to desipramine treatment, showed that recovery from chronic pain states coincides with an upregulation of genes and intracellular cascades in neurons of the indirect pathway. In particular, recovery from chronic pain was associated with decreased phosphorylation of the transcription factor CREB (c-AMP response element binding) and the AMPA receptor subunit GluR1 (128) in the NAc. These studies also highlight a negative modulatory role of histone deacetylase 5 on the onset of action and efficacy of desipramine, suggesting that targeting histone function in the NAc may efficiently accelerate the expression of genes necessary for recovery from sensory and affective pain symptoms. Changes in the epigenetic landscape may also play critical roles in the transition from acute to chronic pain, the maintenance of pain, or the development of co-morbid depression. For example, there is a decrease in global gene methylation in the PFC six months after peripheral nerve injury, which is a time point at which both sensory deficits (mechanical and cold allodynia) and anxio-depressive behaviors are typically observed (129). This adaptation is particularly important as DNA methylation and other histone modifications may lead to the suppression of genes necessary for synaptic remodeling and recovery from chronic pain states (130). In this study, partial recovery from sensory hypersensitivity coincided with a return of global DNA methylation to normal levels. Thus, interventions in transcriptional or epigenetic processes may provide a powerful avenue for pharmacological management of chronic pain and comorbidities. Given the wide presence of gene expression modulators, a detailed understanding of the transcriptional and epigenetic adaptations underlying chronic pain and comorbidities is crucial for the development of medications with limited off-target effects.

Brain Reward Center Modulation of Opiate Actions Under Chronic Pain States

Recent studies assessed the impact of pain on opiate addiction vulnerability using a rat model of inflammatory pain in combination with heroin self-administration (131). In this study, rats showed decreased sensitivity to self-administration of low heroin doses, but increased intake with higher amounts of available heroin (131). It will be important to utilize animal models of chronic pain to determine if prior exposure to opioids or prolonged treatment regimens that cause physical dependence affect addiction-related behaviors. Various laboratories have observed a reduction in morphine reward sensitivity under long-term pain states. For instance, using the conditioned place preference test researchers have shown that the loss of morphine reward sensitivity is accompanied by cellular adaptations in the VTA, including adaptations in G protein-coupled extracellular kinase-2 (109, 110). Nerve injury in mice is also accompanied by upregulation of TNF-α in the NAc; genetic or pharmacologic inactivation of TNF-α restores sensitivity to morphine place preference (125). Work from our group demonstrated that three weeks after SNI, mice show a small but significant reduction in oxycodone reward sensitivity in the conditioned place preference

assay (132). Importantly, blocking intracellular modulators of mu opioid receptor function, such as regulator of G protein signaling-9–2, attenuated the rewarding effects of oxycodone and prevented the reinstatement of oxycodone place preference (132). Using a peripheral nerve injury paradigm, Taylor and colleagues demonstrated a potent role of VTA microglia in the rewarding effects of opioids and other drugs that increase dopamine levels in the NAc (133). These studies highlight various mesolimbic-related mechanisms that may affect sensitivity to the behavioral effects of opioids, and show that chronic pain states do not afford protection from physical dependence or addiction.

Future Directions

Substance abuse-related deaths have reached an alarming level, with the National Institutes of Health reporting over 70,000 U.S. total deaths in 2017, ~68% of which were attributed to opioids (134). With the rising prevalence of chronic pain and depression, this death toll is likely to be exacerbated by prescription or comorbidity-related substance abuse (135, 136). The current situation necessitates a better understanding of structural changes within brain networks that manage executive/cognitive function, emotion, and perception. Various studies have linked the mesolimbic pathway to chronic pain, depressive, and addictive disorders. Given the limited comorbidity-specific preclinical models, human imaging studies provide a means to highlight and compare adaptations in the mesolimbic system that are associated with the symptomatology of specific diseases. These studies, in turn, can guide the development of new models that better reflect the human condition. Comorbidity analyses are also crucial for directing therapeutic approaches, such as TMS and DBS (76, 137–139). Information from clinical imaging analyses could also provide insight for translational research directed towards synaptic and cell type-specific mechanisms of chronic pain and comorbid disorders. The identification of circuits and cellular populations of the brain reward pathway may guide drug development efforts towards a range of new targets, from neuropeptide receptors to epigenetic modifiers. Collectively, these research and technological directions will help address a pressing challenge in therapeutics: the development of tailored, effective, and safe treatment approaches that reverse hypodopaminergic states and other pathological adaptations to chronic pain and related comorbidities.

Acknowledgements:

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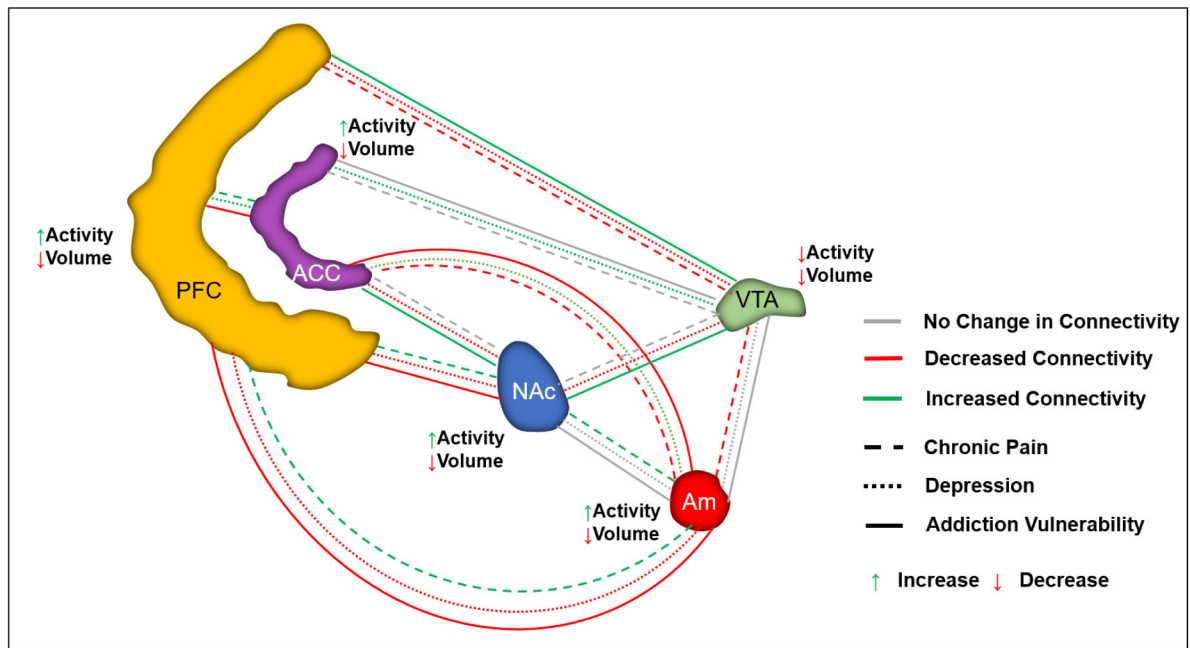
Figure 1:

fMRI studies have provided data on structural and functional changes within the mesolimbic circuitry underlying chronic pain and depression, independently and within comorbid states. This schematic highlights intra-regional changes in collective baseline activity and gray matter volume within chronic pain populations, as well as changes in functional connectivity within chronic pain, depression, and addiction populations. PFC=prefrontal cortex; ACC=anterior cingulate cortex; NAc=nucleus accumbens; VTA=ventral tegmental area; Am=amygdala.
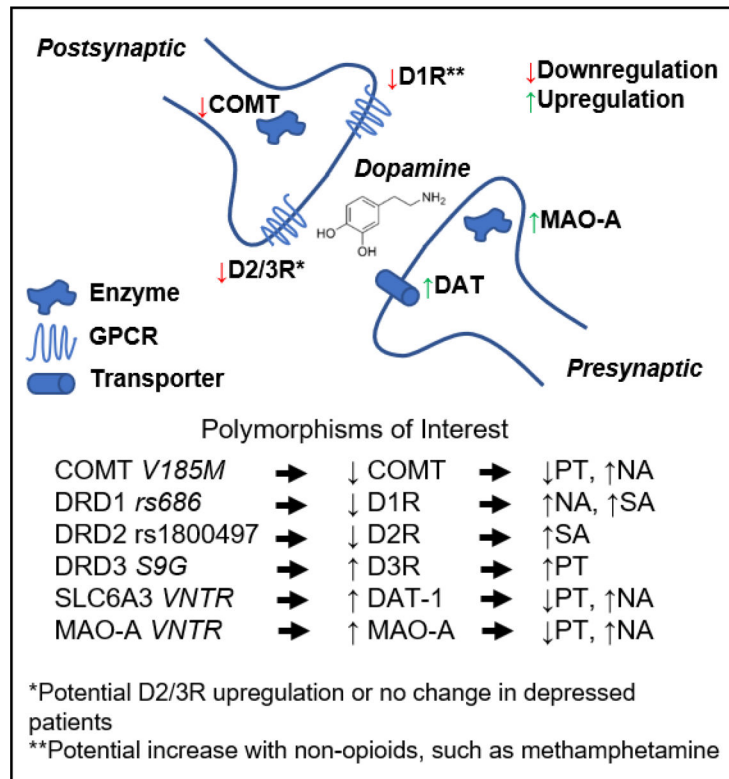
Figure 2:
Gene mutations underlying alterations in mesolimbic dopamine neurotransmission commonly encode proteins involved in dopamine synthesis, clearance, and release, as well as pre-synaptic reuptake and post-synaptic receptor binding. This representation shows examples of mutations altering the regulation of these genes, along with the respective abnormal affective phenotypes. COMT=catechol-O-methyltransferase; MAO-A=monoamine oxidase A; DAT=dopamine active transporter; D1/2/3R=dopamine receptor D1/2/3; PT=pain tolerance; NA=negative affect; SA=substance abuse risk

Table 1:

Summary of preclinical findings highlighting the role of different mesolimbic brain regions in the modulation of affective and sensory symptoms of chronic pain.

Brain Region	Pain Model	Intervention	Outcome	Reference
Nucleus Accumbens	Spared Nerve Injury	Optogenetic Activation (PFC-NAc core circuit)	Alleviated both mechanical and cold allodynia, reversed depression-like behaviors	115
		Chemogenetic Activation	Increased mechanical allodynia	115
		Chemogenetic Inhibition	Decreased mechanical allodynia	115
		Pharmacological blockade of calcium-permeable AMPA receptors	Increased depression-like behaviors	116
		Pharmacological activation of calcium-permeable AMPA receptors	Decreased depression-like behaviors	116
Prefrontal Cortex	Spared Nerve Injury	Electrophysiology (activation of mPFC-NAc circuit)	Increased excitatory postsynaptic potential, alleviated sensory hypersensitivity	117
		Optogenetic Activation	Alleviation of both mechanical and cold allodynia	117
		Optogenetic Inhibition	Increased nociceptive sensitivity and aversive responsiveness	118
Anterior Cingulate Cortex	Sciatic Nerve Cuff	Optogenetic Activation	Promoted depressive states	120
		In vivo electrophysiology	Increased firing rates and bursting activity coinciding with timepoints of development of anxiodepressive-like behaviors	120
Amygdala	Chronic Constriction Injury	Pharmacological inactivation of BLA and CeA Nuclei	Reversed hyperalgesia, allodynia and depressive-like behaviors	121
	Spared Nerve Injury	*In vivo* calcium imaging and optogenetics (Amygdala-NAc circuits)	No effect on nociceptive threshold, decreased affective pain symptoms	122