Corticolimbic circuitry in the modulation of chronic pain and substance abuse

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ABSTRACT

The transition from acute to chronic pain is accompanied by increased engagement of emotional and motivational circuits. Adaptations within this corticolimbic circuitry contribute to the cellular and behavioral maladaptations associated with chronic pain. Central regions within the corticolimbic brain include the mesolimbic dopamine system, the amygdala, and the medial prefrontal cortex. The evidence reviewed herein supports the notion that chronic pain induces significant changes within these corticolimbic regions that contribute to the chronicity and intractability of pain. In addition, pain-induced changes in corticolimbic circuitry are poised to impact motivated behavior and reward responsiveness to environmental stimuli, and may modulate the addiction liability of drugs of abuse, such as opioids.

The French philosopher René Descartes (1596–1650) is credited for one of the earliest efforts to understand the physiological basis of the sensation of pain. Taking a dualist perspective between the body and mind, he described pain afferents in the skin as 'delicate threads' that form a direct and unmodifiable link to the brain (Descartes, 1664). However, even in Descartes' day, this simplistic view of pain processing was criticized for being unable to account for the complex and modifiable relationship between pain stimulus and perception. For example, Henry Beecher noted during the Second World War that badly wounded soldiers returning from battle complained little of their pain, and required much less morphine than civilians afflicted with similar injuries (Beecher, 1946). Conversely, cognitive and affective factors can amplify pain. For example, pain catastrophizing individuals, in which the pain-related threat is irrationally exaggerated, report greater pain and disability (Pulvers and Hood, 2013). We now appreciate that the sensation of pain is encoded by sensory, affective, and cognitive elements, and the interplay between these factors can amplify or diminish the perception and experience of pain.

Chronic pain is a disease state that is mechanistically distinct from acute pain (Tracey and Bushnell, 2009). It is defined as pain that persists beyond normal healing time, and thus lacks the acute warning function of physiological nociception (Treede et al., 2015). In fact, chronic pain can persist despite the lack of clear nociceptive inputs (Baliki et al., 2010), and thus evolves into a self-perpetuating disease

independent of the initiating stimulus. Of course, not all acute pain stimuli evolve into chronic pain conditions, and many studies have attempted to define the factors that contribute to the transition from acute to chronic pain.

Recent human imaging studies suggests adaptation in brain regions involved in emotional and motivated behavior (the corticolimbic circuitry) are particularly important in the transition from acute to chronic pain (Chang et al., 2017; Hashmi et al., 2013; Vachon-Presseau et al., 2016a). Alterations in corticolimbic circuitry may impact chronic pain in two ways. First, it may directly exacerbate the perception of pain, either through amplification of cortical and emotional circuitry or by interfering with endogenous pain control (Bushnell et al., 2013). Second, changes in corticolimbic function may impact the analgesic capacity or addiction liability of drugs, such as opioids, whose function is mediated by overlapping brain circuits. The latter point is supported by observations that repeated use of opioids or psychostimulants produce some behavioral and cellular modifications that are shared with chronic pain states. For example, chronic drug use is associated with allostatic changes in the brain that contribute to a negative affective state (Evans and Cahill, 2016). So, while initial drug use is driven largely by the euphoria associated with drugs of abuse (positive reinforcement), the desire to alleviate the negative consequences of withdrawal (negative reinforcement) may drive drug use in dependent states, much in the same way physical pain stimuli drive behaviors

related to pain relief (Koob, 2015). Moreover, both chronic pain and drug withdrawal are associated with anhedonia and depression driven by a hypofunction of brain circuits mediating reward and motivation (Elman and Borsook, 2016; Massaly et al., 2016; Shippenberg et al., 2007). While chronic pain and opioid addiction differ in many respects, an appreciation for the shared neural mechanisms between pain and reward processes may help enlighten our understanding of the chronic pain state and identify novel treatment strategies.

The ability to evaluate and respond to environmental cues predicting reward and aversion (such as pain) requires integration of sensory information with reward value, expectation, and memory. It also requires cognition to incorporate these inputs, and finally motor output to coordinate an appropriate response. Thus, the perception of pain and reward is a multidimensional experience that is a result of coordinated activity in regions that span the neuroaxis, from the brainstem to frontal lobes. To thoroughly review all relevant adaptations to these circuits in chronic pain would be outside the scope of this article. Rather, this review focuses on a subset of regions that are implicated in reward and motivated behavior, and in which there exists substantial evidence that these regions are also perturbed in chronic pain. The importance of these circuits to pain chronicity, analgesia, and addiction behavior will be discussed.

1. Mesolimbic dopamine system

The mesolimbic dopamine system is formed of dopamine cell bodies within the midbrain ventral tegmental area (VTA) and substantia nigra (SN) that send reciprocal projections throughout the limbic brain, including the striatum, amygdala, habenula, hippocampus, and prefrontal cortex (PFC) (Haber, 2014).

Based upon the observation that rewarding cues, including drugs of abuse and analgesia, stimulate the release of dopamine (Di Chiara and Imperato, 1988), the mesolimbic dopamine system has long been implicated in reward. However, it is now clear that dopamine, although crucial for reward processing, does not drive the hedonic experience of reward ("liking") but rather the instrumental behavior of reward-driven actions ("wanting") (Robinson and Berridge, 1993, for review, Berridge Kent and Kringelbach, 2015). Dopamine signaling is further nuanced by temporal factors, and can signal on short (phasic) and long (tonic) time scales (Floresco et al., 2003; Schultz, 2007). Phasic dopamine signals occur due to burst firing of dopamine neurons, usually following presentation of a salient cue, and signals on the millisecond time scale. Tonic dopamine is released from terminals in a spike-independent manner, and contributes to the background, steady-state level of extracellular dopamine. Importantly, phasic and tonic dopamine signaling have an inverse relationship, where increased tonic dopamine levels lead to reduced phasic dopamine signaling via autoreceptor-mediated inhibition (Benoit-Marand et al., 2001; Moquin and Michael, 2009).

Cognitive flexibility and positive mood arise from a highly responsive phasic dopamine system (Ashby et al., 1999). Consequently, reduced phasic dopamine signaling is a hallmark of anhedonia (Romer Thomsen et al., 2015), and is exhibited in both drug dependent (i.e. Zhang et al., 2009) and chronic pain states (for review Taylor et al., 2016a). Given the high incidence of anhedonia and negative affect reported in the chronic pain population, it is possible that deficits in dopamine signaling contribute to some of these symptoms (for review Borsook et al., 2016; Rayner et al., 2016). Emerging evidence supports the hypothesis that chronic pain is characterized by a hypodopaminergic state. For example, fibromyalgia patients exhibited decreased VTA activation in response to pain and reward-predictive cues, as detected by functional magnetic resonance imaging (fMRI) (Loggia et al., 2014). Reduced spontaneous spiking of VTA neurons has been detected in an animal model of chronic pain (Ren et al., 2015). Moreover, several studies using in vivo recording of striatal dopamine release described significant reductions in evoked dopamine release in response to both

environmental (Ren et al., 2015) and opioid analgesics (Hipolito et al., 2015; Ozaki et al., 2002; Taylor et al., 2015). Importantly, treatment interventions that restore normal dopamine levels (i.e. L-DOPA) restore striatal function and improve pain behavior (Miller et al., 2015; Ren et al., 2015). However, a recent study has reported chronic pain leads to increased in dopaminergic firing, and further studies are warranted to unravel these conflicting reports (Zhang et al., 2017).

We have shown that brain-derived neurotrophic factor (BDNF) signaling driven by microglial activation in the VTA contributes to a loss in opioid-stimulated dopamine release in chronic pain (Taylor et al., 2015), a mechanism that is also exhibited in opioid dependent states (Taylor et al., 2016b). In fact, inflammation-driven hypodopaminergia is a characteristic of many conditions associated with anxiety-like conditions (Felger and Treadway, 2017), and may indicate a pivotal phenomenon driving the negative affective states of both chronic pain and drug withdrawal.

Chronic pain-induced alterations within the terminal regions of dopamine projections are also correlated with pain perception and aberrant reward behavior. Midbrain dopamine neurons projecting to the striatum synapse onto GABAergic medium spiny neurons (MSN), the major output neuron of the striatum. MSNs come in two flavors - the direct (dMSN) and indirect (iMSN), based on their basal ganglia projections and expression of dopamine G-protein coupled receptors (Gerfen et al., 1990). dMSNs express the G_s-coupled dopamine D1 receptor, and are activated by synaptic dopamine; iMSNs express the G_i-coupled dopamine D2 receptors are inhibited by dopamine. The reduced levels of synaptic dopamine in chronic pain have been shown to drive an increased excitability of the iMSNs, which are normally inhibited by dopamine, and this increase in activity contributes to tactile allodynia (Ren et al., 2015). Replacement of cellular dopamine levels with L-DOPA restored iMSN activity and alleviated pain behavior. A separate study has also described additional synaptic modifications on iMSNs, with chronic pain leading to a depression of excitatory synaptic transmission driven by galanin-dependent alteration in NMDA receptor stoichiometry (Schwartz et al., 2014). These studies suggest that the activity of D2-expressing iMSNs is selectively impacted in chronic pain. Human imaging studies provide further evidence that the indirect pathway of the striatum is critical for pain perception. In a positron emission tomography (PET) study of healthy controls, dopamine D2 receptor binding was positively associated with subjective ratings of sensory and affective qualities of pain in healthy controls (Scott et al., 2006). In chronic back pain patients, PET imaging revealed lower D2/D3 receptor activation in the striatum following a pain stimulus, and was associated with pain sensitivity and negative affect (Martikainen et al., 2015).

Pain-induced changes in the striatum are not restricted to basal ganglia projections, and cortical-striatal connections are also altered in chronic pain. In human fMRI studies, increased functional connectivity between the ventral striatum (nucleus accumbens, NAc) and prefrontal cortex predicted pain persistence (Baliki et al., 2012), and was associated with risky reward behavior (Berger et al., 2014). Interruption of NAc activity via lidocaine infusion in an animal model of chronic pain alleviated pain behavior (Chang et al., 2014). Thus, changes in striatal output, possibly mediated by altered dopamine efflux from midbrain terminals, contribute to pain behavior. However, it is unlikely that changes in mesolimbic dopamine circuitry are limited to nociceptive behaviors, and recent studies have begun to unravel the impact of hypodopaminergic signaling on motivated and reward behavior in the context of chronic pain.

As discussed previously, dopamine signaling is important for motivating approach or avoidance behavior following presentation of a salient stimulus, rather than the hedonic value. In this way, chronic pain induces behaviors indicative of a deficit in dopaminergic signaling. For example, when food rewards are easily available (i.e., under a fixed ratio operant responding task), there is no difference in reward consumption between chronic pain and control groups (Okun et al.,

2016; Schwartz et al., 2014). However, as the energy required to solicit a food reward increases (i.e. under a progressive ratio schedule), animals with chronic pain consume significantly less food than controls (Hipolito et al., 2015; Schwartz et al., 2014).

Additional studies have measured opioid seeking behavior in chronic pain (for review, Massaly et al., 2016). Interpreting these studies are complicated by the fact that opioids influence motivated behavior not only through their positive reinforcing effects (i.e. their euphoric attributes), but also through negative reinforcement via their analgesic properties. Nonetheless, several careful studies examining reward and motivated behavior in rodent models of chronic pain suggest deficit in opioid responding is driven by a hypo-responsive dopamine system. For example, opioids injected directly into the VTA fail to elicit a reward response in chronic pain (Taylor et al., 2015). Moreover, rodents self-administering opioids show a decreased in drug consumption at lower doses compared to controls (Hipolito et al., 2015; Lyness et al., 1989; Wade et al., 2013). Opioid self-administration in chronic pain escalates as the dose of opioid increases (Hipolito et al., 2015; Martin et al., 2007).

In addition to its role in motivated behavior, the mesolimbic dopamine system can also influence analgesia. Pain relief can indirectly influence corticolimbic circuitry via inhibition of ascending nociceptive inputs. For example, even peripherally or spinally restricted analgesia produces reward behavior, is self-administered, and evokes a striatal dopamine response when these treatments are applied in the context of pain (Martin et al., 2006; Navratilova et al., 2012). Most drugs of abuse that stimulate the dopamine system (including opioids and psychostimulants) also possess analgesic properties (Franklin, 1998). Moreover, morphine injected directly into the VTA is analgesic and lesioning the VTA impairs morphine analgesia (but not spinal anti-nociception) (Morgan and Franklin, 1990; Phillips and LePiane, 1980). Chronic pain has been shown to impair the ability of opioids to stimulate dopamine efflux in the nucleus accumbens, with both inflammatory and chronic pain conditions exhibiting reduced opioid-stimulated dopamine efflux (Hipolito et al., 2015; Taylor et al., 2015). Thus, deficits in dopamine signaling will not only contribute to motivational and mood deficits in chronic pain, but may also interfere with analgesic capacity of opioids.

2. Amygdala

The amygdala integrates sensory stimuli with affective valence, and plays a pivotal role in mediating the affective elements of pain. It is composed of two primary nuclei, the basolateral amygdala (BLA) and the central amygdala (CeA) that are thought to signal in a serial fashion (Wassum and Izquierdo, 2015). As such, inputs to the BLA are largely from sensory regions (thalamus, sensory cortices) with major outputs to the CeA, as well as the NAc, bed nucleus of the stria terminalis (BNST), PFC, and hippocampus. In this context, the CeA is primarily involved in mediating behavioral output (Janak and Tye, 2015). However, the CeA also receives direct sensory input by nociceptive afferents from the parabrachial nucleus (PBn) and contributes to the affective dimensions of pain (Braz et al., 2005). In chronic pain, synaptic transmission between the PBn and CeA is potentiated in persistent and chronic pain, and contributes to pain related anxiety (Nakao et al., 2012; Neugebauer et al., 2004). Genetic silencing of CGRP neurons from the PBn to the CeA blocked pain responses and memory formation, and optogenetic stimulation of this pathway produced defensive responses and a threat memory (Han et al., 2015; Zhang et al., 2014).

The BLA also sends projections to the NAc, which regulate dopamine efflux and modulate motivated behavior (Phillips et al., 2003). Alterations in BLA function is associated with the transition from acute to chronic pain. For example, a smaller amygdala volume predicted the transition to chronic pain in a human population (Vachon-Presseau et al., 2016b). In animal studies, decreased arborization of BLA cells were observed in chronic pain (Tajerian et al., 2014), and lesion of the BLA during early phase of chronic pain alleviated

mechanical allodynia (Li et al., 2013). As is seen in the mesolimbic dopamine system, inflammation plays a critical role in mediating many of the synaptic changes observed in the amygdala. For example, chronic pain induces microglial activation in the BLA (Taylor et al., 2016c), and local infusion of a TNF alpha neutralizing antibody reverses anxiety like behaviors in mice with persistent inflammatory pain (Chen et al., 2013). Additional research is needed to characterize the impact of altered BLA function on the reduced striatal dopamine function observed in chronic pain.

How changes in amygdala function contribute to reward behavior in a chronic pain state is a question that continues to be studied, but we can look to the drug addiction literature to provide some clues. Chronic drug use leads to altered BLA activity and insensitivity to reward devaluation (Schoenbaum and Setlow, 2005; Wassum and Izquierdo, 2015), and lesions of the BLA lead to increased reward seeking under punishment (Pelloux et al., 2013). There is some evidence that chronic pain patients may have similar impaired reward responding. For example, chronic pain patients show deficits in emotional decision making tasks, such as the Iowa Gambling Task (Apkarian et al., 2004). The mechanism in which BLA activity influences motivated behavior in the context of pain is an area that requires further study.

3. Medial prefrontal cortex

The medial prefrontal cortex (mPFC) is involved in sensory integration, decision making, and fear learning (Giustino and Maren, 2015). As such, it plays a vital role in affective and cognitive dimensions of pain. The mPFC is classified into distinct neuroanatomical subregions: the anterior cingulate cortex (ACC), the prelimbic cortex, and the infralimbic cortex. They form reciprocal excitatory connections to limbic regions such as the amygdala, NAc, and VTA (Heidbreder and Groenewegen, 2003; Hoover and Vertes, 2007). Like other cortical regions, the mPFC is further divided into medial-lateral layers I-VI, with layer V pyramidal neurons forming the primary excitatory output of the region. While acute pain stimuli activate the mPFC (Devoize et al., 2011; Felice et al., 2014; Nickel et al., 2017), this region undergoes both morphological and functional reorganization in chronic pain (Metz et al., 2009).

The infralimbic and prelimbic cortical subregions integrate sensory and limbic information and promote goal-directed behaviors through cortico-striatal connections. This is achieved, in part, by mPFC glutamatergic projections to the striatum and midbrain that modulate dopamine efflux (Del Arco and Mora, 2008; Jackson and Moghaddam, 2001). Thus, changes in prelimbic and/or infralimbic cortical activity may contribute to the altered dopamine signaling and motivated behavior, discussed above (Hipolito et al., 2015; Ren et al., 2015; Schwartz et al., 2014; Taylor et al., 2015).

Within the prelimbic cortex, persistent pain is associated with decreased metabolic activity (Thompson et al., 2014). More specifically, layer V pyramidal neurons showed reduced responses to excitatory glutamatergic inputs in chronic pain, and this was associated with decreased basal glutamate levels within the region (Kelly et al., 2016). A study using in vivo single unit recording demonstrated that the reduced prelimbic function was due to an increased feed-forward inhibition from BLA inputs (Ji and Neugebauer, 2011; Ji et al., 2010). Recently, impaired cholinergic modulation has also been shown to contribute to the decreased prelimbic cortical activity associated with chronic pain (Radzicki et al., 2017). Strategies that increase excitatory output or decrease inhibitory tone on prelimbic pyramidal neurons are effective for decreasing pain and anxiety related behaviors in chronic pain. For example, deactivation or activation of prelimbic pyramidal neurons promoted or decreased pain and anxiety, respectively (Lee et al., 2015; Wang et al., 2015). Conversely, optogenetic silencing of GABAergic interneurons within the prelimbic cortex decreased pain responses (Zhang et al., 2015). The analgesic and anxiolytic effects of prelimbic activation are driven by prelimbic-striatal projections, as

selective activation of prelimbic glutamatergic terminals in the NAc was sufficient to produce analgesic and anxiolytic effects (Lee et al., 2015).

Less has been studied regarding changes in infralimbic structure and function in chronic pain; however, information gleaned from the drug addiction literature may be relevant here. The prelimbic and infralimbic cortices can be distinguished based on their unique projection targets to the NAc core and shell, respectively (Sesack et al., 1989). The prelimbic-NAc core glutamatergic projections mediate learned associations between drug and environment, and drive cocaine relapse (Gipson et al., 2013; LaLumiere and Kalivas, 2008; Shen et al., 2011). In contrast, infralimbic projections to the NAc shell are thought to inhibit cocaine reinstatement and relapse (Peters et al., 2008). However, opioid-dependent reinstatement behaviors are mediated by different mPFC projections. While lesions of the *prelimbic*, but not *infralimbic* cortex, blocked cocaine reinstatement, lesions of the *infralimbic*, but not *prelimbic* cortex, blocked heroine reward and reinstatement (Bossert et al., 2011; Tzschentke and Schmidt, 1999). While the influence of the infralimbic versus prelimbic pathways on pain related behavior is still in its infancy, an initial study has found inactivation of prelimbic, but not infralimbic cortex, impaired acquisition and expression of formalin-induced conditioned place aversion (Jiang et al., 2014). This is perhaps surprising that chronic pain resembles psychostimulant, rather than opioid dependence, though may reflect the decreased excitatory output of the prelimbic region, described above. In any case, further research examining the impact of prelimbic and infralimbic cortical output on pain-related behavior is needed. In particular, studies incorporating goal-directed behavioral assays and contingent (rather than non-contingent) reinforcement is required to fully elucidate these processes.

The ACC is located dorsal to the infralimbic and prelimbic cortices, and has been well implicated in mediating the cognitive and affective aspects of pain (Apkarian et al., 2005). This region receives nociceptive information from inputs originating from the thalamus, amygdala (particularly the CeA), and the primary sensory cortex (Eto et al., 2011; Shyu and Vogt, 2009; Vogt et al., 2003). In healthy individuals, acute pain stimuli activate the ACC, where it encodes affective, but not sensory, aspects of pain (Duerden and Albanese, 2013; Rainville et al., 1997). Lesions of the ACC attenuate the affective components of pain without impacting nociceptive behaviors (Gao et al., 2004; Johansen and Fields, 2004; Johansen et al., 2001; Qu et al., 2011). Unsurprisingly, given its involvement in acute pain processing, much has been described in this brain region in chronic pain. The reader is pointed to a recent review on this subject for a more thorough analysis of these changes (Bliss et al., 2016).

Briefly, unlike the prelimbic cortex that shows pain-induced inhibition, the ACC layer V pyramidal neurons exhibit increased intrinsic excitability in chronic pain (Blom et al., 2014; Koga et al., 2015). This increased excitability is due to potentiated glutamatergic signaling, as evidenced by increased presynaptic glutamate release and an enhancement of AMPA receptor signaling (Xu et al., 2008; Zhao et al., 2006). Inhibiting postsynaptic AMPA receptors was sufficient to blunt pain responses in a chronic pain state (Li et al., 2010; Wei et al., 2002). The increased ACC excitability is further modulated by forebrain serotonergic inputs (Santello and Nevian, 2015). Importantly, once established, the increased ACC activity occurs independently of primary afferent drive, as it persists in the presence of a peripheral nerve block (Wei and Zhuo, 2001).

Increased ACC activity in chronic pain may influence behavior in several ways. For one, ACC excitability in chronic pain mirrors what is observed in anxiety phenotypes (Kim et al., 2011; Osuch et al., 2000), and optogenetic stimulation of the ACC is sufficient to induce anxiety-like behaviors (Barthas et al., 2015). Thus, increases in ACC activity may certainly contribute to pain-induced anxiety. Moreover, the ACC is a region at the interface of pain and reward, and is involved in integrating costs and benefits when multiple competing relevant stimuli are encountered in the environment (Hillman and Bilkey, 2010). For example, an acute pain stimulus decreases the value of a monetary

reward, an effect that is accompanied by decreases ACC activity during reward anticipation (Talmi et al., 2009). Changes in ACC activity associated with chronic pain may alter reward responsivity in cost-benefit scenarios. For example, chronic pain-induced deficits in the BLA-ACC long term potentiation contribute to deficits in the rat gambling task (Cao et al., 2016). As discussed above, chronic pain patients also have deficits in emotional decision making tasks, a phenomenon likely mediated by coordinated inputs throughout the corticolimbic brain, including the ACC and amygdala.

4. Conclusions

The Cartesian dualist theory of pain, whereby the intensity of pain is directly proportional to the afferent input, inadequately encompasses the complexity of the pain experience. We now understand that in addition to sensory components, pain is mediated by emotional and cognitive circuits that can either amplify or diminish the pain experience.

The corticolimbic brain plays a central role in the affect and cognitive regulation of pain. There is now ample evidence, some of which is reviewed above, that supports the notion that chronic pain induces significant changes in corticolimbic circuitry that directly relate to the chronicity and intractability of this condition. In addition, pain-induced changes in corticolimbic circuitry are poised to impact motivated behavior and reward response to environmental stimuli, and may modulate the addiction liability of drugs of abuse, such as opioids. The question of opioid addiction liability in the chronic pain population is a topic that has received much scrutiny considering the current prescription opioid epidemic (Vowles et al., 2015). While delving into this topic is outside the scope of this review, the reader is pointed to several current reviews for further discussion (Brady et al., 2016; Franklin et al., 2014; Volkow and McLellan, 2016). In any case, additional studies examining the impact of chronic pain on reward and motivated behavior are warranted.

The implications of an aberrant corticolimbic circuitry extend beyond opioid addiction liability. As discussed above, a responsive reward system is required for full analgesic potency of many analgesic compounds, such as opioids. Thus, deficits in corticolimbic circuitry may interfere with pain management strategies. Moreover, deficits in corticolimbic function is associated with negative hedonic states, and may contribute to the co-morbid mood disorders that are prevalent within the chronic pain population (Elman et al., 2013). Strategies that restore function within this system could be effective means to alleviate these negative affective symptoms and/or improve the analgesic efficacy of opioid analgesics.

Acknowledgements

References

Apkarian, A.V., Bushnell, M.C., Treede, R.D., Zubieta, J.K., 2005. Human brain mechanisms of pain perception and regulation in health and disease. Eur. J. Pain 9, 463–484.

Apkarian, A.V., Sosa, Y., Krauss, B.R., Thomas, P.S., Fredrickson, B.E., Levy, R.E., et al., 2004. Chronic pain patients are impaired on an emotional decision-making task. Pain 108, 129–136.

Ashby, F.G., Isen, A.M., Turken, A.U., 1999. A neuropsychological theory of positive affect and its influence on cognition. Psychol. Rev. 106, 529–550.

Baliki, M.N., Geha, P.Y., Fields, H.L., Apkarian, A.V., 2010. Predicting value of pain and analgesia: nucleus accumbens response to noxious stimuli changes in the presence of chronic pain. Neuron 66, 149–160.

Baliki, M.N., Petre, B., Torbey, S., Herrmann, K.M., Huang, L., Schnitzer, T.J., et al., 2012. Corticostriatal functional connectivity predicts transition to chronic back pain. Nat. Neurosci. 15, 1117–1119.

Barthas, F., Sellmeijer, J., Hugel, S., Waltisperger, E., Barrot, M., Yalcin, I., 2015. The anterior cingulate cortex is a critical hub for pain-induced depression. Biol.

Psychiatry 77, 236–245.

Beecher, H.K., 1946. Pain in men wounded in battle. Ann. Surg. 123, 96–105.

Benoit-Marand, M., Borrelli, E., Gonon, F., 2001. Inhibition of dopamine release via presynpatic D2 receptors: time course and functional characteristics in vivo. J. Neurosci. 21 (23), 9134–9141.

Berger, S.E., Baria, A.T., Baliki, M.N., Mansour, A., Hermann, K.M., Torbey, S., et al., 2014. Risky monetary behavior in chronic back pain is associated with altered modular connectivity of the nucleus accumbens. BMC Res. Notes 7.

Berridge Kent, C., Kringelbach, Morten L., 2015. Pleasure Systems in the Brain. Neuron 86, 646–664.

Bliss, T.V., Collingridge, G.L., Kaang, B.K., Zhuo, M., 2016. Synaptic plasticity in the anterior cingulate cortex in acute and chronic pain. Nat. Rev. Neurosci. 17, 485–496.

Blom, S.M., Pfister, J.P., Santello, M., Senn, W., Nevian, T., 2014. Nerve injury-induced neuropathic pain causes disinhibition of the anterior cingulate cortex. J. Neurosci. 34, 5754–5764.

Borsook, D., Linnman, C., Faria, V., Strassman, A.M., Becerra, L., Elman, I., 2016. Reward deficiency and anti-reward in pain chronification. Neurosci. Biobehav. Rev. 68, 282–297.

Bossert, J.M., Stern, A.L., Theberge, F.R., Cifani, C., Koya, E., Hope, B.T., et al., 2011. Ventral medial prefrontal cortex neuronal ensembles mediate context-induced relapse to heroin. Nat. Neurosci. 14, 420–422.

Brady, K.T., McCauley, J.L., Back, S.E., 2016. Prescription opioid misuse, abuse, and treatment in the United States: an update. Am. J. Psychiatry 173, 18–26.

Braz, J.M., Nassar, M.A., Wood, J.N., Basbaum, A.I., 2005. Parallel "pain" pathways arise from subpopulations of primary afferent nociceptor. Neuron 47, 787–793.

Bushnell, M.C., Ceko, M., Low, L.A., 2013. Cognitive and emotional control of pain and its disruption in chronic pain. Nat. Rev. Neurosci. 14, 502–511.

Cao, J.M., Wang, J., Mu, L., Poon, D.C., Li, Y., 2016. Impairment of decision making associated with disruption of phase-locking in the anterior cingulate cortex in viscerally hypersensitive rats. Exp. Neurol. 286, 21–31.

Chang, P.C., Centeno, M.V., Procissi, D., Baria, A., Apkarian, A.V., 2017. Brain activity for tactile allodynia: a longitudinal awake rat functional magnetic resonance imaging study tracking emergence of neuropathic pain. Pain 158, 488–497.

Chang, P.C., Pollema-Mays, S.L., Centeno, M.V., Procissi, D., Contini, M., Baria, A.T., et al., 2014. Role of nucleus accumbens in neuropathic pain: linked multi-scale evidence in the rat transitioning to neuropathic pain. Pain 155, 1128–1139.

Chen, J., Song, Y., Yang, J., Zhang, Y., Zhao, P., Zhu, X.J., et al., 2013. The contribution of TNF-alpha in the amygdala to anxiety in mice with persistent inflammatory pain. Neurosci. Lett. 541, 275–280.

Del Arco, A., Mora, F., 2008. Prefrontal cortex-nucleus accumbens interaction: in vivo modulation by dopamine and glutamate in the prefrontal cortex. Pharmacol. Biochem. Behav. 90, 226–235.

Descartes, R., 1664. L'homme de Rene Descartes (Treatise of Man). Harvard University Press.

Devoize, L., Alvarez, P., Monconduit, L., Dallel, R., 2011. Representation of dynamic mechanical allodynia in the ventral medial prefrontal cortex of trigeminal neuropathic rats. Eur. J. Pain 15, 676–682.

Di Chiara, G., Imperato, A., 1988. Drugs abused by humans preferentially increase synaptic dopamine concentrations in the mesolimbic system of freely moving rats. Proc. Natl. Acad. Sci. U. S. A. 85, 5274–5278.

Duerden, E.G., Albanese, M.C., 2013. Localization of pain-related brain activation: a meta-analysis of neuroimaging data. Hum. Brain Mapp. 34, 109–149.

Elman, I., Borsook, D., 2016. Common brain mechanisms of chronic pain and addiction. Neuron 89, 11–36.

Elman, I., Borsook, D., Volkow, N.D., 2013. Pain and suicidality: insights from reward and addiction neuroscience. Prog. Neurobiol. 109, 1–27.

Eto, K., Wake, H., Watanabe, M., Ishibashi, H., Noda, M., Yanagawa, Y., et al., 2011. Inter-regional contribution of enhanced activity of the primary somatosensory cortex to the anterior cingulate cortex accelerates chronic pain behavior. J. Neurosci. 31, 7631–7636.

Evans, C.J., Cahill, C.M., 2016. Neurobiology of opioid dependence in creating addiction vulnerability. F 1000Res. 5, 1–11.

Felger, J.C., Treadway, M.T., 2017. Inflammation effects on motivation and motor activity: role of dopamine. Neuropsychopharmacology 42, 216–241.

Felice, V.D., Gibney, S.M., Gosselin, R.D., Dinan, T.G., O'Mahony, S.M., Cryan, J.F., 2014. Differential activation of the prefrontal cortex and amygdala following psychological stress and colorectal distension in the maternally separated rat. Neuroscience 267, 252–262.

Floresco, S.B., West, A.R., Ash, B., Moore, H., Grace, A.A., 2003. Afferent modulation of dopamine neuron firing differentially regulates tonic and phasic dopamine transmission. Nat. Neurosci. 6, 968–973.

Franklin, G.M., American Academy of N, 2014. Opioids for chronic noncancer pain: a position paper of the American Academy of Neurology. Neurology 83, 1277–1284.

Franklin, K.B., 1998. Analgesia and abuse potential: an accidental association or a common substrate? Pharmacol. Biochem. Behav. 59, 993–1002.

Gao, Y.J., Ren, W.H., Zhang, Y.Q., Zhao, Z.Q., 2004. Contributions of the anterior cingulate cortex and amygdala to pain - and fear-conditioned place avoidance in rats. Pain 110, 343–353.

Gerfen, C.R., Engber, T.M., Mahan, L.C., Susel, Z., Chase, T.N., Monsma Jr., F.J., et al., 1990. D1 and D2 dopamine receptor-regulated gene expression of striatonigral and striatopallidal neurons. Science 250, 1429–1432.

Gipson, C.D., Kupchik, Y.M., Shen, H., Reissner, K.J., Thomas, C.A., Kalivas, P.W., 2013. Relapse induced by cues predicting cocaine depends on rapid, transient synaptic potentiation. Neuron 77, 867–872.

Giustino, T.F., Maren, S., 2015. The role of the medial prefrontal cortex in the conditioning and extinction of fear. Front. Behav. Neurosci. 9, 298.

Haber, S.N., 2014. The place of dopamine in the cortico-basal ganglia circuit. Neuroscience 282, 248–257.

Han, S., Soleiman, M.T., Soden, M.E., Zweifel, L.S., Palmiter, R.D., 2015. Elucidating an affective pain circuit that creates a threat memory. Cell 162, 363–374.

Hashmi, J.A., Baliki, M.N., Huang, L., Baria, A.T., Torbey, S., Hermann, K.M., et al., 2013. Shape shifting pain: chronification of back pain shifts brain representation from nociceptive to emotional circuits. Brain 136, 2751–2768.

Heidbreder, C.A., Groenewegen, H.J., 2003. The medial prefrontal cortex in the rat: evidence for a dorso-ventral distinction based upon functional and anatomical characteristics. Neurosci. Biobehav. Rev. 27, 555–579.

Hillman, K.L., Bilkey, D.K., 2010. Neurons in the rat anterior cingulate cortex dynamically encode cost-benefit in a spatial decision-making task. J. Neurosci. 30, 7705–7713.

Hipolito, L., Wilson-Poe, A., Campos-Jurado, Y., Zhong, E., Gonzalez-Romero, J., Virag, L., et al., 2015. Inflammatory pain promotes increased opioid self-administration: role of dysregulated ventral tegmental area mu opioid receptors. J. Neurosci. 35, 12217–12231.

Hoover, W.B., Vertes, R.P., 2007. Anatomical analysis of afferent projections to the medial prefrontal cortex in the rat. Brain Struct. Funct. 212, 149–179.

Jackson, M.E., Moghaddam, B., 2001. Amygdala regulation of nucleus accumbens dopamine output is governed by the prefrontal cortex. J. Neurosci. 21, 676–681.

Janak, P.H., Tye, K.M., 2015. From circuits to behaviour in the amygdala. Nature 517, 284–292.

Ji, G., Neugebauer, V., 2011. Pain-related deactivation of medial prefrontal cortical neurons involves mGluR1 and GABA (A) receptors. J. Neurophysiol. 106, 2642–2652.

Ji, G., Sun, H., Fu, Y., Li, Z., Pais-Vieira, M., Galhardo, V., et al., 2010. Cognitive impairment in pain through amygdala-driven prefrontal cortical deactivation. J. Neurosci. 30, 5451–5464.

Jiang, Z.C., Pan, Q., Zheng, C., Deng, X.F., Wang, J.Y., Luo, F., 2014. Inactivation of the prelimbic rather than infralimbic cortex impairs acquisition and expression of formalin-induced conditioned place avoidance. Neurosci. Lett. 569, 89–93.

Johansen, J.P., Fields, H.L., 2004. Glutamatergic activation of anterior cingulate cortex produces an aversive teaching signal. Nat. Neurosci. 7, 398–403.

Johansen, J.P., Fields, H.L., Manning, B.H., 2001. The affective component of pain in rodents: direct evidence for a contribution of the anterior cingulate cortex. Proc. Natl. Acad. Sci. U. S. A. 98, 8077–8082.

Kelly, C.J., Huang, M., Meltzer, H., Martina, M., 2016. Reduced glutamatergic currents and dendritic branching of layer 5 pyramidal cells contribute to medial prefrontal cortex deactivation in a rat model of neuropathic pain. Front. Cell. Neurosci. 10, 133.

Kim, S.S., Wang, H., Li, X.Y., Chen, T., Mercaldo, V., Descalzi, G., et al., 2011. Neurabin in the anterior cingulate cortex regulates anxiety-like behavior in adult mice. Mol. Brain 4, 6.

Koga, K., Descalzi, G., Chen, T., Ko, H.G., Lu, J., Li, S., et al., 2015. Coexistence of two forms of LTP in ACC provides a synaptic mechanism for the interactions between anxiety and chronic pain. Neuron 85, 377–389.

Koob, G.F., 2015. The dark side of emotion: the addiction perspective. Eur. J. Pharmacol. 753, 73–87.

LaLumiere, R.T., Kalivas, P.W., 2008. Glutamate release in the nucleus accumbens core is necessary for heroin seeking. J. Neurosci. 28, 3170–3177.

Lee, M., Manders, T.R., Eberle, S.E., Su, C., D'Amour, J., Yang, R., et al., 2015. Activation of corticostriatal circuitry relieves chronic neuropathic pain. J. Neurosci. 35, 5247–5259.

Li, X.Y., Ko, H.G., Chen, T., Descalzi, G., Koga, K., Wang, H., et al., 2010. Alleviating neuropathic pain hypersensitivity by inhibiting PKMzeta in the anterior cingulate cortex. Science 330, 1400–1404.

Li, Z., Wang, J., Chen, L., Zhang, M., Wan, Y., 2013. Basolateral amygdala lesion inhibits the development of pain chronicity in neuropathic pain rats. PLoS One 8, e70921.

Loggia, M.L., Berna, C., Kim, J., Cahalan, C.M., Gollub, R.L., Wasan, A.D., et al., 2014. Disrupted brain circuitry for pain-related reward/punishment in fibromyalgia. Arthritis Rheum. 66, 203–212.

Lyness, W.H., Smith, F.L., Heavner, J.E., Iacono, C.U., Garvin, R.D., 1989. Morphine self-administration in the rat during adjuvant-induced arthritis. Life Sci. 45, 2217–2224.

Martikainen, I.K., Nuechterlein, E.B., Pecina, M., Love, T.M., Cummiford, C.M., Green, C.R., et al., 2015. Chronic back pain is associated with alterations in dopamine neurotransmission in the ventral striatum. J. Neurosci. 35, 9957–9965.

Martin, T.J., Kim, S.A., Buechler, N.L., Porreca, F., Eisenach, J.C., 2007. Opioid self-administration in the nerve-injured rat: relevance of antiallodynic effects to drug consumption and effects of intrathecal analgesics. Anesthesiology 106, 312–322.

Martin, T.J., Kim, S.A., Eisenach, J.C., 2006. Clonidine maintains intrathecal self-administration in rats following spinal nerve ligation. Pain 125, 257–263.

Massaly, N., Moron, J.A., Al-Hasani, R., 2016. A trigger for opioid misuse: chronic pain and stress dysregulate the mesolimbic pathway and kappa opioid system. Front. Neurosci. 10, 480.

Metz, A.E., Yau, H.J., Centeno, M.V., Apkarian, A.V., Martina, M., 2009. Morphological and functional reorganization of rat medial prefrontal cortex in neuropathic pain. Proc. Natl. Acad. Sci. U. S. A. 106, 2423–2428.

Miller, L.L., Leitl, M.D., Banks, M.L., Blough, B.E., Negus, S.S., 2015. Effects of the triple monoamine uptake inhibitor amitifadine on pain-related depression of behavior and mesolimbic dopamine release in rats. Pain 156, 175–184.

Moquin, K.F., Michael, A.C., 2009. Tonic autoinhibition contributes to the heterogeneity of evoked dopamine release in the rat striatum. J. Neurochem. 110 (5), 1491–1501.

Morgan, M.J., Franklin, K.B., 1990. 6-Hydroxydopamine lesions of the ventral tegmentum abolish D-amphetamine and morphine analgesia in the formalin test but not the tail flick test. Brain Res. 519, 144–149.

Nakao, A., Takahashi, Y., Nagase, M., Ikeda, R., Kato, F., 2012. Role of capsaicin-sensitive C-fiber afferents in neuropathic pain-induced synaptic potentiation in the nociceptive amygdala. Mol. Pain 8, 51.

Navratilova, E., Xie, J.Y., Okun, A., Qu, C., Eyde, N., Ci, S., et al., 2012. Pain relief produces negative reinforcement through activation of mesolimbic reward-valuation circuitry. Proc. Natl. Acad. Sci. U. S. A. 109, 20709–20713.

Neugebauer, V., Li, W., Bird, G.C., Han, J.S., 2004. The amygdala and persistent pain. Neuroscientist 10, 221–234.

Nickel, M.M., May, E.S., Tiemann, L., Schmidt, P., Postorino, M., Ta Dinh, S., et al., 2017. Brain oscillations differentially encode noxious stimulus intensity and pain intensity. NeuroImage 148, 141–147.

Okun, A., McKinzie, D.L., Witkin, J.M., Remeniuk, B., Husein, O., Gleason, S.D., et al., 2016. Hedonic and motivational responses to food reward are unchanged in rats with neuropathic pain. Pain 157 (12), 2731–2738.

Osuch, E.A., Ketter, T.A., Kimbrell, T.A., George, M.S., Benson, B.E., Willis, M.W., et al., 2000. Regional cerebral metabolism associated with anxiety symptoms in affective disorder patients. Biol. Psychiatry 48, 1020–1023.

Ozaki, S., Narita, M., Narita, M., Iino, M., Sugita, J., Matsumura, Y., et al., 2002. Suppresion of the morphine-induced rewarding effect in the rat with neuropathic pain: implication of the reduction in mu-opioid receptor functions in the ventral tegmental area. J. Neurochem. 82, 1192–1198.

Pelloux, Y., Murray, J.E., Everitt, B.J., 2013. Differential roles of the prefrontal cortical subregions and basolateral amygdala in compulsive cocaine seeking and relapse after voluntary abstinence in rats. Eur. J. Neurosci. 38, 3018–3026.

Peters, J., LaLumiere, R.T., Kalivas, P.W., 2008. Infralimbic prefrontal cortex is responsible for inhibiting cocaine seeking in extinguished rats. J. Neurosci. 28, 6046–6053.

Phillips, A.G., Ahn, S., Howland, J.G., 2003. Amygdalar control of the mesocorticolimbic dopamine system: parallel pathways to motivated behavior. Neurosci. Biobehav. Rev. 27, 543–554.

Phillips, A.G., LePiane, F.G., 1980. Reinforcing effects of morphine microinjection into the ventral tegmental area. Pharmacol. Biochem. Behav. 12, 965–968.

Pulvers, K., Hood, A., 2013. The role of positive traits and pain catastrophizing in pain perception. Curr. Pain Headache Rep. 17, 330.

Qu, C., King, T., Okun, A., Lai, J., Fields, H.L., Porreca, F., 2011. Lesion of the rostral anterior cingulate cortex eliminates the aversiveness of spontaneous neuropathic pain following partial or complete axotomy. Pain 152, 1641–1648.

Radzicki, D., Pollema-Mays, S.L., Sanz-Clemente, A., Martina, M., 2017. Loss of M1 receptor dependent cholinergic excitation contributes to mPFC deactivation in neuropathic pain. J. Neurosci (in press).

Rainville, P., Duncan, G.H., Price, D.D., Carrier, B., Bushnell, M.C., 1997. Pain affect encoded in human anterior cingulate but not somatosensory cortex. Science 277, 968–971.

Rayner, L., Hotopf, M., Petkova, H., Matcham, F., Simpson, A., McCracken, L.M., 2016. Depression in patients with chronic pain attending a specialised pain treatment centre: prevalence and impact on health care costs. Pain 157, 1472–1479.

Ren, W., Centeno, M.V., Berger, S., Wu, Y., Na, X., Liu, X., et al., 2015. The indirect pathway of the nucleus accumbens shell amplifies neuropathic pain. Nat. Neurosci. 19 (2), 220–222.

Robinson, T.E., Berridge, K.C., 1993. The neural basis of drug craving: an incentive-sensitization theory of addiction. Brain Res. Brain Res. Rev. 18 (3), 247–291.

Romer Thomsen, K., Whybrow, P.C., Kringelbach, M.L., 2015. Reconceptualizing anhedonia: novel perspectives on balancing the pleasure networks in the human brain. Front. Behav. Neurosci. 9, 49.

Santello, M., Nevian, T., 2015. Dysfunction of cortical dendritic integration in neuropathic pain reversed by serotoninergic neuromodulation. Neuron 86, 233–246.

Schoenbaum, G., Setlow, B., 2005. Cocaine makes actions insensitive to outcomes but not extinction: implications for altered orbitofrontal-amygdalar function. Cereb. Cortex 15, 1162–1169.

Schultz, W., 2007. Multiple dopamine functions at different time courses. Annu. Rev. Neurosci. 30, 259–288.

Schwartz, N., Temkin, P., Jurado, S., Lim, B.K., Heifets, B.D., Polepalli, J.S., et al., 2014. Decreased motivation during chronic pain requires long-term depression in the nucleus accumbens. Science 345, 535–542.

Scott, D.J., Heitzeg, M.M., Koeppe, R.A., Stohler, C.S., Zubieta, J.K., 2006. Variations in the human pain stress experience mediated by ventral and dorsal basal ganglia dopamine activity. J. Neurosci. 26, 10789–10795.

Sesack, S.R., Deutch, A.Y., Roth, R.H., Bunney, B.S., 1989. Topographical organization of the efferent projections of the medial prefrontal cortex in the rat: an anterograde tract-tracing study with *Phaseolus vulgaris* leucoagglutinin. J. Comp. Neurol. 290, 213–242.

Shen, H., Moussawi, K., Zhou, W., Toda, S., Kalivas, P.W., 2011. Heroin relapse requires long-term potentiation-like plasticity mediated by NMDA2b-containing receptors. Proc. Natl. Acad. Sci. U. S. A. 108, 19407–19412.

Shippenberg, T.S., Zapata, A., Chefer, V.I., 2007. Dynorphin and the pathophysiology of drug addiction. Pharmacol. Ther. 116, 306–321.

Shyu, B.C., Vogt, B.A., 2009. Short-term synaptic plasticity in the nociceptive thalamic-anterior cingulate pathway. Mol. Pain 5, 51.

Tajerian, M., Leu, D., Zou, Y., Sahbaie, P., Li, W., Kham, H., et al., 2014. Brain neuroplastic changes accompany anxiety and memory deficits in a model of complex regional pain syndrome. Anesthesiology 121, 1–14.

Talmi, D., Dayan, P., Kiebel, S.J., Frith, C.D., Dolan, R.J., 2009. How humans integrate the prospects of pain and reward during choice. J. Neurosci. 29, 14617–14626.

Taylor, A.M., Becker, S., Schweinhardt, P., Cahill, C., 2016a. Mesolimbic dopamine signaling in acute and chronic pain: implications for motivation, analgesia, and addiction. Pain 157, 1194–1198.

Taylor, A.M., Castonguay, A., Ghogha, A., Vayssiere, P., Pradhan, A.A., Xue, L., et al., 2016b. Neuroimmune regulation of GABAergic neurons within the ventral tegmental area during withdrawal from chronic morphine. Neuropsychopharmacology 41, 949–959.

Taylor, A.M., Castonguay, A., Taylor, A.J., Murphy, N.P., Ghogha, A., Cook, C., et al., 2015. Microglia disrupt mesolimbic reward circuitry in chronic pain. J. Neurosci. 35, 8442–8450.

Taylor, A.M., Mehrabani, S., Liu, S., Taylor, A.J., Cahill, C.M., 2016c. Topography of microglial activation in sensory - and affect-related brain regions in chronic pain. J. Neurosci. Res (in press).

Thompson, S.J., Millecamps, M., Aliaga, A., Seminowicz, D.A., Low, L.A., Bedell, B.J., et al., 2014. Metabolic brain activity suggestive of persistent pain in a rat model of neuropathic pain. NeuroImage 91, 344–352.

Tracey, I., Bushnell, M.C., 2009. How neuroimaging studies have challenged us to rethink: is chronic pain a disease? J. Pain 10, 1113–1120.

Treede, R.D., Rief, W., Barke, A., Aziz, Q., Bennett, M.I., Benoliel, R., et al., 2015. A classification of chronic pain for ICD-11. Pain 156, 1003–1007.

Tzschentke, T.M., Schmidt, W.J., 1999. Functional heterogeneity of the rat medial prefrontal cortex: effects of discrete subarea-specific lesions on drug-induced conditioned place preference and behavioural sensitization. Eur. J. Neurosci. 11, 4099–4109.

Vachon-Presseau, E., Centeno, M.V., Ren, W., Berger, S.E., Tetreault, P., Ghantous, M., et al., 2016a. The emotional brain as a predictor and amplifier of chronic pain. J. Dent. Res. 95, 605–612.

Vachon-Presseau, E., Tetreault, P., Petre, B., Huang, L., Berger, S.E., Torbey, S., et al., 2016b. Corticolimbic anatomical characteristics predetermine risk for chronic pain. Brain 139, 1958–1970.

Vogt, B.A., Berger, G.R., Derbyshire, S.W., 2003. Structural and functional dichotomy of human midcingulate cortex. Eur. J. Neurosci. 18, 3134–3144.

Volkow, N.D., McLellan, A.T., 2016. Opioid abuse in chronic pain–misconceptions and mitigation strategies. N. Engl. J. Med. 374, 1253–1263.

Vowles, K.E., McEntee, M.L., Julnes, P.S., Frohe, T., Ney, J.P., van der Goes, D.N., 2015. Rates of opioid misuse, abuse, and addiction in chronic pain: a systematic review and data synthesis. Pain 156, 569–576.

Wade, C.L., Krumenacher, P., Kitto, K.F., Peterson, C.D., Wilcox, G.L., Fairbanks, C.A., 2013. Effect of chronic pain on fentanyl self-administration in mice. PLoS One 8, E79239.

Wang, G.Q., Cen, C., Li, C., Cao, S., Wang, N., Zhou, Z., et al., 2015. Deactivation of excitatory neurons in the prelimbic cortex via Cdk5 promotes pain sensation and anxiety. Nat. Commun. 6, 7660.

Wassum, K.M., Izquierdo, A., 2015. The basolateral amygdala in reward learning and addiction. Neurosci. Biobehav. Rev. 57, 271–283.

Wei, F., Qiu, C.S., Kim, S.J., Muglia, L., Maas, J.W., Pineda, V.V., et al., 2002. Genetic elimination of behavioral sensitization in mice lacking calmodulin-stimulated adenylyl cyclases. Neuron 36, 713–726.

Wei, F., Zhuo, M., 2001. Potentiation of sensory responses in the anterior cingulate cortex following digit amputation in the anaesthetised rat. J. Physiol. 532, 823–833.

Xu, H., Wu, L.J., Wang, H., Zhang, X., Vadakkan, K.I., Kim, S.S., et al., 2008. Presynaptic and postsynaptic amplifications of neuropathic pain in the anterior cingulate cortex. J. Neurosci. 28, 7445–7453.

Zhang, Y., Picetti, R., Butelman, E.R., Schlussman, S.D., Ho, A., Kreek, M.J., 2009. Behavioral and neurochemical changes induced by oxycodone differ between adolescent and adult mice. Neuropsychopharmacology 34, 912–922.

Zhang, Z., Gadotti, V.M., Chen, L., Souza, I.A., Stemkowski, P.L., Zamponi, G.W., 2015. Role of prelimbic GABAergic circuits in sensory and emotional aspects of neuropathic pain. Cell Rep. 12, 752–759.

Zhang, Z., Tao, W., Hou, Y.Y., Wang, W., Lu, Y.G., Pan, Z.Z., 2014. Persistent pain facilitates response to morphine reward by downregulation of central amygdala GABAergic function. Neuropsychopharmacology 39, 2263–2271.

Zhang, Z., Quan, Y.L., Li, C., Liu, D., Wang, L., Wang, W.Y., Liu, M.J., Liu, H., Zhang, S., Guo, X.Y., Yang, J.X., Ding, H.L., Koo, J.W., Mouzon, E., Deisseroth, K., Nestler, E.J., Zachariou, V., Han, M.H., Cao, J.L., 2017. Brain-Derived neurotrophic factor in the mesolimbic reward circuitry mediates nociception in chronic neuropathic pain. Biol Psychiatry in press.

Zhao, M.G., Ko, S.W., Wu, L.J., Toyoda, H., Xu, H., Quan, J., et al., 2006. Enhanced presynaptic neurotransmitter release in the anterior cingulate cortex of mice with chronic pain. J. Neurosci. 26, 8923–8930.