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Reward, motivation and emotion of pain and its relief

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Abstract

The experience of pain depends on interpretation of context and past experience that guide the choice of an immediate behavioral response and influence future decisions of actions to avoid harm. The aversive qualities of pain underlie its physiological role in learning and motivation. In this review, we highlight findings from human and animal investigations that suggest that both pain, and the relief of pain, are complex emotions that are comprised of feelings and their motivational consequences. Relief of aversive states, including pain, is rewarding. How relief of pain aversiveness occurs is not well understood. Termination of aversive states can directly provide relief as well as reinforce behaviors that result in avoidance of pain. Emerging preclinical data also suggests that relief may elicit a positive hedonic value that results from activation of neural cortical and mesolimbic brain circuits that may also motivate behavior. Brain circuits mediating the reward of pain relief, as well as relief-induced motivation are significantly impacted as pain becomes chronic. In chronic pain states, the negative motivational value of nociception may be increased while the value of the reward of pain relief may decrease. As a consequence, the impact of pain on these ancient, and conserved brain limbic circuits suggest a path forward for discovery of new pain therapies.

Keywords

chronic pain; mesolimbic dopamine circuit; nucleus accumbens; opioid signaling; cingulate cortex; hedonic response

Introduction: Qualities of pain and pain relief

Although pain is familiar to almost everyone, its precise definition continues to be elusive. Pain is most often viewed in the realm of somatosensation. However, this conceptualization is problematic as unlike most other sensations that are usually affectively neutral, pain has the additional quality of aversiveness. To focus only on aversive qualities is also problematic as there are many aversive conditions that are clearly recognized by humans as something other than pain. Fields has described the unique features of pain aversiveness as a quality of "algosity" [30]. The qualities that make pain unique, and immediately recognizable to humans, have been discussed since antiquity. Aristotle proclaimed the doctrine of the five

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senses (sight, hearing, smell, taste and touch) but did not include pain [23]. For the ancient Greek philosophers, pain was included with pleasure as "passions of the soul". While not technical, this definition was nevertheless elegant and meaningful. The recognition of pain and pleasure as opposites on a hedonic spectrum revealed an understanding that these two emotions provide motivations that guide our decisions for action selection, shaping the lives of organisms.

Pain is a call to action. Like hunger, thirst and desire for sleep, pain is a part of the body's survival systems that collectively are responsible for protecting the organism [25]. These primordial emotions, including pain, are characterized by a specific sensation that signals deviation from homeostasis and an intention to satisfy the need for homeostatic balance [22]. The sensation of pain generates an aversive state that demands a behavioral response (for pain, a motivation to seek relief). In contrast, relief of pain, and return to homeostatic balance is rewarding (see below). Because primordial emotions often signal that the very existence of the organism is threatened, they are ancient and encoded by phylogenetically conserved neural circuits consisting of afferent sensory pathways and areas of the brain including the thalamus, insula and cingulate cortex. These cortical regions have connections with the valuation/decision mesolimbic circuit, which integrates the information from multiple competing emotions and selects the behavioral action that offers the greatest benefit to the organism. The mesolimbic system also serves in learning the situations that lead to deviation or restoration of homeostasis and thus helps the organism to avoid aversive situations and find rewards.

Melzack and Casey first proposed the multidimensional model of pain in 1968 [55]. An important concept that emerged from this model was the partial separation of the affective and motivational features of pain from its sensory and discriminative qualities. Separation of these features also implied different anatomical substrates which were suggested to involve medial and lateral ascending pathways for affective/motivational and sensory/discriminative features, respectively [86]. Viewing pain as a human experience that involved the synthesis of sensory, affective and cognitive dimensions represented a momentous shift from unidimensional sensory models and underscored the distinction between pain and nociception and the lack of consistent relationship between pain and the state of the tissues. These concepts were based on clinical observation including, for example, the early studies by Beecher that soldiers in battle with serious wounds did not report feeling pain [11]. Such findings were explained, in part, by the gate control theory of pain proposed by Melzack and Wall in 1965 [54]. Melzack wrote that neural signals never enter the nervous system as a blank canvass. Rather, nociceptive signals are always subject to interpretation of meaning based on the present context and of past experience (i.e., learning and memories) [53]. Fields and colleagues have subsequently characterized descending bidirectional pain modulatory circuits that can enhance or diminish pain based on multiple factors including context, stress, expectation, and others ([31] for review). The role of these descending circuits in circumstances of competing motivations such as reward and threat have led to the the formulation of the motivational-decision model of pain [32] (see below).

While the deconstruction of pain into multiple dimensions has been extraordinarily useful, the human experience of pain appears to require synthesis of all of these components

including affective, sensory and cognitive dimensions. Ploner and colleagues reported a patient with a stroke-induced lesion in the somatosensory cortex who could not identify the source of a nociceptive stimulus on the contralateral side but found it unpleasant [70]. However, the patient refused to identify the unpleasant nature of the stimulus as "pain", supporting both the partial dissociation between sensory and affective qualities of pain and the need to integrate these qualities to form the human experience. Fields has elegantly noted that while the affective dimension of pain is partially separable from its "sensory" qualities, pain affect is nevertheless tightly related to the degree of nociceptive inputs and can therefore be appropriately termed "sensory" as well. Evidence of partial dissociation of affective and sensory features of pain also emerge from cingulotomy studies where "pain" continues to be perceived but is considered no longer bothersome [18; 100; 101], as well as from imaging studies where pain unpleasantness can be modulated independently of sensory intensity, or where pain can be imagined [72]. Opiates are one of the most important classes of drugs to treat pain and produce their effects preferentially on modulation of affective, rather than sensory, dimensions of pain [65]. Navratilova and colleagues demonstrated that activation of cortical opioid receptors could selectively modulate pain aversiveness without influencing evoked reflexive measures in a preclinical model of chronic pain (52). This finding suggested the existence of distinct central mechanisms mediating affective qualities of pain. The aversive aspects of pain are the main complaint of patients. The unpleasant qualities of pain are essential in its physiological role to increase survival by promoting learning and influencing future decisions to avoid harm.

The neural mechanisms of appetitive learning have received considerable attention but our understanding of aversive learning remains limited. At present, very little is known about the mechanisms and neural circuitry that mediate aversiveness of pain. Neurons in the mesolimbic reward valuation network projecting from the ventral tegmental area to the nucleus accumbens have been implicated in both appetitive and aversive learning [17]. Thus, an unexpected reward increases phasic dopamine release while omission of an expected reward reduces phasic dopamine [75]. The difference between an expected and an actual outcome generates a prediction error that underlies reinforcement learning [84]. Roy and colleagues have elegantly described mechanisms by which responses of the brain to nociceptive inputs are influenced by learning using fMRI signals related to prediction errors [74]. They found that pain prediction errors were encoded in the periaqueductal gray (PAG), a part of the brain that is integral not only in ascending nociceptive signals but in descending pain modulation. The expected value-related input to the PAG arose from the ventromedial prefrontal cortex with relay of prediction error signals to prefrontal cortical regions that drive behavioral actions including orbitofrontal, anterior mid-cingulate and dorsomedial prefrontal cortices. Investigation of the affective qualities of pain and aversive learning using pre-clinical models that allow detailed investigation of the mediating circuits is in its earliest stages.

The human experience of pain is also influenced by other motivational, emotional and cognitive states ranging from basic physiological needs such as hunger or response to immediate threat to human rational thinking. Expectation of pain, or of pain relief, has been shown to dramatically alter not only the degree and quality of pain that is experienced, but also to increase or decrease the efficacy of even the most powerful opioids [15].

Psychological manipulations of attention and distraction also alter pain, as does the emotional state, and even the religious beliefs of the subject [49; 88; 97]. Modulation of mood with pleasant and unpleasant odors has been demonstrated to positively or negatively influence emotional states resulting in reduced or increased pain [88]. Neuroimaging studies have found that these modulatory effects on pain are also reflected in altered activity in higher order pain related brain circuits [reviewed in 19; 35].

Assessment of ongoing pain in rodents

Mogil has suggested that a preclinical pain model is comprised of three basic components: the subjects, the assay, and the outcome measure [56]. Each component requires careful consideration in order to optimize potential translational value to the proposed human pain syndrome being modeled. Most preclinical studies of pain have emphasized output measures that rely on responses to evoked stimuli [56; 87]. While such stimuli engage the nociceptive pathway and are thought to accurately reflect nociceptive pain mechanisms, these reflexive responses do not capture the biologically relevant aversive qualities of pain. Reflexive behaviors can often be observed in decerebrated animals [98] and do not require learning [87], an essential feature of physiological pain. While the affective (unpleasant) quality of an evoked pain stimulus is essential in eliciting the reflexive withdrawal response, the response threshold has not easily allow mechanistic evaluation of affective qualities. Multiple approaches have and are being advanced to expand outcome measures that would better capture the affective (unpleasant) quality including, for example, place escape avoidance paradigms, ultrasonic vocalization, pain-suppressed behaviors and facial responsivity scales (see [40] for review). Efforts in this domain are often intended to assess pain without the need for an evoked reflexive withdrawal response. Most importantly, a lowered response threshold for an acutely applied stimulus can occur in the absence of ongoing pain. This can be seen, for example, in lightly sunburned skin in which a normally innocuous heat stimulus is felt as burning pain [16; 69]. Most clinically relevant pains have a tonic component that is not revealed by most currently used methods for pain assessment.

The presence of ongoing pain in animals without need for an evoked stimulus from the experimenter has been demonstrated using the conditioned place preference (CPP) learning paradigm that is based on the affective and motivational qualities of pain [41]. Because ongoing pain provides a*n ongoing* motivational drive to seek relief, preference for a context associated with relief of pain can be utilized as a measure of pain aversiveness [60]. Treatments that are clinically effective against ongoing pain in humans are effective in the CPP paradigm and the reverse is also true [41; 60; 61] providing support for this approach. CPP to pain relief was also demonstrated following axotomy of the sciatic nerve to elicit complete denervation of the hindpaw [26; 27] confirming the presence of an aversive state that likely reflects "spontaneous" neuropathic pain in this assay [71] and providing an important control that eliminated concerns of pain resulting from tactile stimulation during ambulation within the testing apparatus [71].

Relief of ongoing pain is rewarding

PET imaging studies have shown that placebo analgesia is associated with release of dopamine in brain areas associated with reward [77]. Human imaging has demonstrated that offset of an acute pain stimulus produces a positive BOLD signal in the nucleus accumbens, an area associated with reward-aversion processing in humans [8]. Navratilova and colleagues investigated whether pain relief produced direct activation of reward pathways using a preclinical model of post-operative pain (i.e., incisional injury of the hindpaw) in rats [61]. Following hindpaw incision, a context was paired with a peripheral nerve block and preference was assessed at multiple time points, exploiting the time-dependent nature of post-operative pain. Following surgery, humans demonstrate a period of strong ongoing pain that transitions to a longer-lasting state of tenderness in the injured area (i.e., hyperalgesia) [57]. Likewise, this model of incisional pain was shown to produce time-related ongoing pain [61]. Thus, CPP to peripheral nerve block was demonstrated one day but not four days after incisional injury. Only animals with injury demonstrated CPP suggesting that the relief of the aversive state induced by ongoing post-surgical pain is rewarding, consistent with the lack of intrinsic reward value of lidocaine.

The observed CPP following peripheral nerve block was also consistent with increased Fos expression in dopaminergic neurons in the ventral tegmental area and elevated tonic levels of dopamine in the nucleus accumbens detected one day but not four days after injury. Critically, the CPP resulting from peripheral nerve block was prevented by inactivation of the ventral tegmental area as well as blockade of dopaminergic receptors in the nucleus accumbens. The findings from relief of incisional pain with peripheral nerve block were extended to demonstrate the effectiveness of relief of ongoing pain with non-opioid treatments across multiple experimental pain conditions (i.e., nociceptive, inflammatory, neuropathic and cancer pain) (see [60] for review). For example, in an animal model of migraine-related pain resulting from application of inflammatory mediators to the dura mater of rats, anti-migraine drugs induced CPP as well as increased dopamine release in the nucleus accumbens shell [24]. Collectively, these studies demonstrated that activation of dopaminergic neurons in the ventral tegmental area and release of dopamine and activation of dopaminergic receptors in the nucleus accumbens mediates the reinforcing effect of pain relief. Importantly, CPP and nucleus accumbens dopamine release was demonstrated selectively in injured animals following pain relieving treatments that did not have intrinsic reward value in uninjured animals [60]. These findings were consistent with other studies suggesting that activation of the mesolimbic motivation/reward circuit contributes to both pain perception and pain relief. In a BOLD imaging study performed with healthy volunteers, the activity of the nucleus accumbens was decreased during onset of noxious thermal stimuli and was increased during offset of stimuli [6; 8]. Nucleus accumbens activity was also correlated with relief pleasantness associated with a cue signaling safety from pain [46].

Mechanisms of pain relief

Opioids are currently our most effective and widely used drugs for the treatment of moderate-to-severe pain. Multiple studies have demonstrated that opioid drugs have a

preferential effect on the affective qualities of pain. Consistent with their clinical efficacy, the anterior cingulate cortex (ACC) expresses high levels of opioid receptors in humans, as well as in rats [91]. PET imaging studies in humans have demonstrated the release of endogenous opioids in this cortical area during experimentally-induced pain as well as during placebo analgesia [77; 92]. A positive correlation between pain-induced endogenous opioid release in the ACC and reduced pain affect has been demonstrated [103]. Thus, release of endogenous opioids in the ACC is implicated both with pain and with pain relief. These human investigations suggested that the relief of pain aversiveness may ultimately be mediated by opioid signaling in the rostral ACC and subsequent activation of dopamine neurotransmission in the nucleus accumbens.

The ACC has previously been implicated in encoding the aversive features of pain [90]. Bushnell and colleagues used imaging techniques to demonstrate that the ACC, but not somatosensory cortex, is activated when unpleasantness of pain is increased with hypnotic suggestion [73]. In contrast, increasing sensory intensity of a noxious stimulus increased activity in both the somatosensory and anterior cingulate cortex, supporting the partial separation of affective and sensory features of pain. Johansen and colleagues used a conditioned place avoidance paradigm to demonstrate that lesion of the rostral anterior cingulate cortex (rACC) disrupted the aversive aspects of hindpaw formalin injection in rats without affecting evoked responses [38; 39]. Lesion of the rACC was similarly demonstrated to abolish CPP to pain relieving treatments in rats with spinal nerve ligation injury, without altering evoked responses [71]. These studies support the alteration of motivation from modulation of pain-induced aversiveness [71].

Consistent with the partial separation of affective and sensory features of pain, LaGraize et al., have shown that administration of morphine into the ACC of rats with experimental neuropathic pain, selectively decreases the affective/motivational measures of pain with no alteration of mechanical paw withdrawal threshold [42]. Similarly, ACC morphine treatment was sufficient to produce CPP and to elicit release of dopamine in the NAc only in injured rats [62]. The MOR in the ACC may thus represent a key target for relief of pain aversiveness. This conclusion is supported by the demonstration that the CPP, and NAc DA release, observed in rats with neuropathic or incisional injuries was required for the pain relieving effect of systemic morphine as well as non-opioid pain relieving treatments including spinal clonidine (α2 adrenergic agonist), systemic gabapentin or peripheral nerve block [62]. These findings provide a neural basis for the rewarding effects of pain relief by showing that they depend on opioidergic circuits in the ACC and downstream dopaminergic signaling in the NAc. Thus, endogenous opioidergic circuits within the ACC appear to be both necessary and sufficient for reward from pain relief. The role of endogenous opioid activity in pain relief has also been demonstrated by imaging studies in healthy volunteers. These investigations revealed positive correlation between brain activations in cortico-limbic regions evoked by painful stimulation and reductions in subjective pain reports from identical noxious stimulation during systemic opioid administration [95]. While this conclusion has been supported by current experimental data, non-opioid mechanisms may also be important. A recent study in humans of pain relief through mindfulness meditation showed a lack of dependence on endogenous opioids [102]. Future studies will be required

to determine the overall generality of opioid mechanisms as the major mediator of relief of pain aversiveness.

Relief as an emotion

The affective quality of relief from aversive states, including pain, is not well understood. Relief is a complex emotion that is difficult to associate with a clear affective valence. Studies in humans have suggested that relief may reflect the experience of a negative valence diminishing toward a neutral valence [33; 78]. Other studies, however, have suggested that relief may also be associated with increasing positive valence [46]. Becerra and Borsook reported that the offset of a noxious stimulus produced activation of the nucleus accumbens in human subjects [8; 9]. This observation was consistent with the findings of Leknes and colleagues who found that pain offset increases self-reported pleasantness and activates brain reward areas [45; 80]. Indeed, the same group in a study in which moderate pain was the best outcome compared to more intense pain, demonstrated a hedonic flip so that moderate pain was considered pleasurable [44]. Studies by Franklin and colleagues suggest that both decreased negative affect and increased positive affect may simultaneously contribute the emotion of relief [34]. Data demonstrating the release of endogenous opioids in the rACC with pain relief suggest that both positive and negative reinforcement learning participates in the motivation to seek relief.

Competing motivations: the motivation decision model

As noted above, descending modulation of nociceptive signals from the periphery is bidirectional based on interpretation of context, past experience, emotional and stress levels and other factors [89]. The output of the brain in producing modulation of nociceptive signals ultimately arises from the rostral ventromedial medulla (RVM) where OFF and ON cells that respectively mediate descending inhibition and facilitation have been identified [29]. The motivation-decision model of Fields has suggested a context dependent activation of these cells that guide the behavioral outcome of a nociceptive stimulus [32]. Thus, activation of nociceptors in a neutral setting elicits descending facilitation that focuses attention on pain with behavioral outcomes of recovery and healing. In the presence of competing motivations such as response to a threat or obtaining a food reward, conflict requires a neural cost-benefit computation and making a decision that leads to the best behavioral outcome for the organism. Thus, pain is suppressed when a more desirable outcome is advantageous, e.g., escape from a dangerous situation or obtaining a desired reward. By extension, the model also predicts that in situations when attending to pain is the most advantageous goal, conflicting rewards may be suppressed. Rewards such as food, pleasurable music or odors are known to suppress pain (see review in [47]). However, the impact of ongoing pain on the value of rewards is less understood.

Chronic pain and impact on reward circuits

Recently, research from Berridge laboratory, and others, have described rewards as a complex psychophysical construct composed of two main processes involving hedonic pleasure (i.e., “liking”) and motivation (i.e., “wanting”) to obtain rewards [20]. Hedonic

qualities are thought to be encoded primarily by the release of endogenous opioids in brain regions including the orbitofrontal cortex, the anterior cingulate cortex, the amygdala and the nucleus accumbens (NAc) while motivation to acquire rewards is mainly driven by dopamine signaling in the mesolimbic circuit [12–14; 67]. These areas overlap with brain circuits important for motivational and affective aspects of pain and pain relief [10; 47; 59], providing neural evidence for the interaction between pain and reward.

Chronic pain changes the behavioral goals shifting the focus away from other motivations toward achieving homeostatic equilibrium (i.e., relief). The tonic long-lasting motivational shift could result in time-dependent adaptive changes in motivational circuits contributing to pain chronification [2]. Consistent with this, brain neuroimaging studies in patients with chronic conditions including back pain, neuropathic pain, fibromyalgia, irritable bowel syndrome, headache, complex regional pain syndrome (CRPS) and osteoarthritis have demonstrated functional, anatomical (structural) or molecular changes. For example, widespread abnormalities were identified in grey matter density [37; 52], in the connectivity of the white matter [37], as well as in glutamate, opioid and dopamine neurotransmission (see [3; 85] for review).

Many of the brain changes observed in chronic pain patients involve regions encoding affective, emotional and motivational contexts. Baliki and colleagues observed that at the offset of an acute thermal stimulation, brain responses in the NAc differed between healthy subjects and patients with chronic back pain [6]. In normal subjects, a positive phasic nucleus accumbens signal at pain offset reflected prediction of reward associated with relief of pain. In contrast, a negative NAc signal was found in patients, consistent with return of attention to their ongoing chronic pain at the termination of acute stimulus. The magnitude of nucleus accumbens activity at the stimulus offset positively correlated with the subject's ratings of ongoing back pain. These findings suggest that the motivational value of acute pain offset may be distorted in chronic pain conditions.

Furthermore, Baliki and colleagues monitored fMRI responses in patients with back pain over several years. These investigations identified that the strength of functional connectivity between NAc and PFC predicted whether the patient will recover, or will transition to chronic pain [7] and suggest that as pain becomes chronic, pain perception may shift from sensory to emotional brain regions [6]. Interestingly, similar abnormalities in prefrontal and mesolimbic regions were also observed in rats several months after experimental neuropathic pain [79]. Such observations suggest that anatomical and functional changes in reward/motivation and learning circuits may lead to the co-morbid emotional and cognitive disorders often observed in chronic pain patients [4; 5].

Impact of chronic pain on motivational and hedonic components of reward

Despite the overwhelming evidence of overlapping neurocircuitry for pain and pleasure, and documented abnormalities in these regions in chronic pain states, data demonstrating hedonic or motivational deficits in chronic pain patients are scarce. Comprehensive evaluations of the impact of chronic pain on reward deficits in humans are difficult and the outcomes have been variable. For example, a study in patients with chronic low back pain

(CLBP) did not find altered ratings of pleasure or aversion to sweet, salty, or bitter tastants [82]. However, a different study in CLBP patients detected a small, but significant, decrease in pleasure from high fat pudding, although no change was found in response to sweet solutions [36]. In a recent questionnaire-based study, patients with chronic pain reported reduced reward responsiveness [28]. Other investigations in patients with neuropathic pain demonstrated diminished desire to participate in activities, suggesting possible deficits in motivation, but contributions of pain-related decreased physical mobility could not be ruled out [51; 63]. It should be pointed out, however, that these outcomes in patients may be influenced for example by medications, thus direct causal link between pain and reward deficits remains unclear.

Studies in rodent models of inflammatory or neuropathic pain show diminished rewards from intracranial self-stimulation or from morphine [43; 64]. However, there are conflicting reports on the effects of pain on natural food rewards, including sucrose preference, with some studies demonstrating decreased sucrose consumption [1; 48; 50; 81; 93; 99] while others show no change [66; 76; 94]. A study by Schwartz and colleagues used mice with sciatic nerve injury-induced neuropathic pain or CFA-induced inflammation and demonstrated that even though injured animals showed no deficits in sucrose preference, they displayed decreased motivation for food reward in a progressive ratio operant responding task [76]. Moreover, the authors showed that decreased motivation during chronic pain required galanin-mediated synaptic modifications in the nucleus accumbens.

We used a facial reactivity score in rats to investigate the influence of chronic neuropathic pain on hedonic responses to food rewards independently from motivation [66]. Sweet or bitter liquid solutions were passively delivered via intraoral catheters to rats 21 days after spinal nerve ligation or sham surgery and “liking/disliking” responses were scored according to a facial reactivity scale. Neuropathic rats did not differ from sham controls in either “liking” or “disliking” reactions, suggesting no differences in perceived hedonic value of sweet or bitter tastants. The possibility that hedonic deficits could be detected by other approaches, or would be observed at later time points following injury requires further study.

Possible motivational deficits during acute and chronic pain was investigated using fixed- and progressive-ratio response paradigms of sucrose pellet presentation in rats with transient inflammatory or chronic neuropathic pain [66]. Assessment of response acquisition and break points under the progressive ratio schedule revealed no differences between sham and SNL rats for up to 120 days post-injury. However, rats with inflammation showed decrements in lever pressing and break points on post-CFA days 1 and 2 that normalized by day 4, consistent with transient ongoing pain. Thus, while acute, ongoing inflammatory pain may transiently reduce reward motivation, influences of chronic neuropathic pain on hedonic or motivational responses to food rewards could not be detected [66]. Whether, and how, chronic pain may influence the value of other natural rewards remains to be determined. However, these findings suggest that adaptations that allow normal reward responding to food, regardless of chronic pain, may be of evolutionary benefit to promote survival.

Pain in discovery research

Pain discovery research has largely focused on modulation of behavioral responses to noxious stimuli through interventions aimed at modulation of transduction, transmission, or central amplification of neural signals [68]. Pain relieving actions of blockade of nociceptive input arising from the periphery is clinically validated (e.g., local anesthetics), however this is not always possible in patients [96]. Additionally, inhibition of the physiological function of pain can be dangerous and can lead to bodily harm as seen in patients with congenital insensitivity to pain [21; 58]. Pain relief, however, can also be achieved by selective modulation of pain affect (e.g., placebo, hypnotic suggestion, attention/distraction, neurostimulation)[72; 83; 88]. Importantly, the demonstration that opioids preferentially act in the brain to selectively modulate pain affect (52) suggests opportunities for novel mechanisms to engage brain circuits for pain relief. Thus, relief of pain is often managed clinically largely through modulation of pain affect.

Currently, the contribution of preclinical studies to the discovery of pain therapies focus primarily on reduction of one dimension (intensity). This approach does not reflect how pain is managed clinically or fit with current understanding of pain relief as a multidimensional and emotional experience. Preclinical discovery strategies might be improved by including assessments of affective/motivational aspects of pain at behavioral, and brain circuit levels. As the motivational and emotional neural circuits engaged in relief are phylogenetically ancient, and highly conserved across species, effective pain relief, regardless of the site and the molecular target, must be reflected in opioid and dopamine activity in motivation/aversion circuits. Activity analyses within these circuits may thus serve as a novel readout of efficacy with high likelihood of translational relevance that could increase chances of clinical success.

Conclusions

Knowledge of circuits that underlie pain affect remains rudimentary. However, it now appears that pain, and pain relief, may be reflected by activation of opioidergic and dopaminergic cortico-limbic circuits. Clinical impression suggests that the effectiveness of pain relieving treatments may change in patients with increased chronicity of pain. Consistent with this, neuroimaging studies provide evidence of anatomical and neurological changes in these circuits in the setting of chronic pain in which there may be sustained nociceptive drive for very long times, even decades. Maladaptive changes in reward and valuation circuits could represent a "pain memory" so that motivational decisions are skewed toward increasing the magnitude and cost of nociceptive inputs while diminishing the value and benefit of pain relief. Increased mechanistic studies in preclinical models of the intersection between pain, chronic pain and reward and motivation circuits may offer new approaches for improvement of therapy.

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