PAIN

Brain circuits for pain and its treatment

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Pain is a multidimensional experience with sensory-discriminative, affective-motivational, and cognitive-evaluative components. Pain aversiveness is one principal cause of suffering for patients with chronic pain, motivating research and drug development efforts to investigate and modulate neural activity in the brain's circuits encoding pain unpleasantness. Here, we review progress in understanding the organization of emotion, motivation, cognition, and descending modulation circuits for pain perception. We describe the molecularly defined neuron types that collectively shape pain multidimensionality and its aversive quality. We also review how pharmacological, stimulation, neurofeedback, surgical, and cognitive-behavioral interventions alter activity in these circuits to relieve chronic pain.

INTRODUCTION

Chronic pain conditions are leading causes of disability and suffering

Chronic pain affects about 20% of the human population worldwide (*1*). Although chronic pain conditions do not directly cause death, they are major sources of disability and suffering. The Global Burden of Disease Study 2019 revealed that chronic low back pain was the single greatest cause of years lived with disability (YLDs) worldwide and that several other chronic pain conditions contribute as major sources of YLDs, including neck pain, migraine, osteoarthritis, other musculoskeletal disorders, and medication overuse headache (*2*, *3*). Furthermore, for patients affected by intractable conditions, the emotional burden associated with the prospect of living with daily pain and suffering can lead to mental disorders (*4*) and even suicide (*5*). In fact, chronic pain is considered both a symptom and a primary disease that brings about other illnesses such as depression (*6*, *7*). Because of this immense medical, economic, and social burden, achieving a better understanding of pain biology to develop targeted, novel, safe, and effective treatments has become a worldwide priority.

Pain mechanisms and treatment: peripheral divergence and central convergence

Most research and drug development efforts to discover effective analgesics focus on peripheral nervous system (PNS) and spinal mechanisms and targets. This strategy is motivated by the relative simplicity of this approach, given the pharmacological challenges associated with efficiently engaging brain targets without generating side effects, and the early description of a PNS cell type dedicated to generating pain, the primary afferent nociceptor (*8*). Successful identification of molecules either selectively expressed by nociceptors or that influence their function has been the main driver of analgesic drug development in recent decades (*9*), such as for ion channel transducers of the transient receptor potential channel family (TRP channels) (*10*, *11*). The recent resolution of dorsal root ganglion (DRG) neuron transcriptomes by RNA sequencing (*12*–*16*) and the discovery of additional potential drug targets, including in other DRG neuron types compared to nociceptors (for example, mechanosensory DRG neurons), as suggested by the role of the ion channel Piezo2 in mechanical allodynia (pain in response to light touch) (*17*, *18*), bring hope for the development of additional pain treatments targeting the PNS.

A complementary approach aims to identify analgesic targets that could directly act on the main concern of individuals living with pain—pain unpleasantness, suffering, and loss of control—by leveraging the latest knowledge of pain brain circuits. Indeed, peripheral nociception's cellular and molecular mechanisms are diverse and complex, corresponding to the function of the PNS to precisely detect, for each individual organ, a multitude of threatening environmental stimuli and/or internal dysfunctions. Notably, RNA sequencing studies also revealed dozens of DRG neuron types capable of generating pain (*12*–*16*); these studies and others have found that the mechanisms of function and molecular repertoires of these cells are dynamic and evolve considerably in an injury- and disease-specific manner as chronic pain develops. Considering a few common types of chronic pain conditions such as low back pain, osteoarthritic pain, migraine, cancer pain, or neuropathic pain (which on its own represents a broadly diverse group of conditions with diverse symptoms such as spontaneous pain and allodynia) illustrates that, for each condition, unique peripheral biological processes engage one or several distinct classes of molecularly defined primary afferent neurons to cause pain. Thus, the treatment of certain pain types by targeting nociceptors could prove exceptionally challenging, with each pain condition requiring specific research and drug development efforts, and the difficulty to faithfully model in animals some of the most prevalent human chronic pain conditions such as low back pain. Further complicating the targeting of peripheral biological processes for individual pain conditions is the growing recognition that these conditions frequently co-occur. This phenomenon, referred to as chronic overlapping pain conditions (COPCs), includes painful conditions such as temporomandibular disorder (TMD), fibromyalgia (FM), irritable bowel syndrome (IBS), vulvodynia, myalgic encephalomyelitis/chronic fatigue syndrome, interstitial cystitis/painful bladder syndrome, endometriosis, chronic tension-type headache, migraine headache, and chronic low back pain (*19*, *20*). Therefore, overcoming the

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emergent peripheral divergence of chronic pain mechanisms and COPCs represents an exciting challenge for the pain field (Fig. 1).

In contrast, after neurons of the trigeminal and spinal anterior/dorsal horn (DH) across all segmental levels process and transmit these diverse peripheral nociceptive signals to the brain, the brain's emotional circuits generate the unpleasant quality of pain across acute and chronic pain types, including COPCs. Thus, this convergent mechanistic organization of pain brain circuits, combined with the development of preclinical assays to interrogate the affective-motivational dimension of pain, provides an opportunity to develop treatments capable of limiting pain suffering and improving the quality of life of broad patient populations, regardless of their primary condition. In this review, we discuss the neural circuits that generate the emotional responses and negative affect during pain perception, and the therapeutic approaches that target these circuits to relieve pain suffering.

THE NEURAL BASIS OF PAIN

Pain multidimensional perceptions and behaviors

Pain is both a sensory and emotional experience. Philosophers have long debated how pain relates to the perception of noxious stimuli. Some argued that pain is the representation of a noxious object/event (representationalist approach, as for vision when we see an object), whereas others characterized pain as a feeling or experience with subjective properties (qualia) that are not necessarily related to that object/event (as is the case for referred pain) (*21*, *22*).

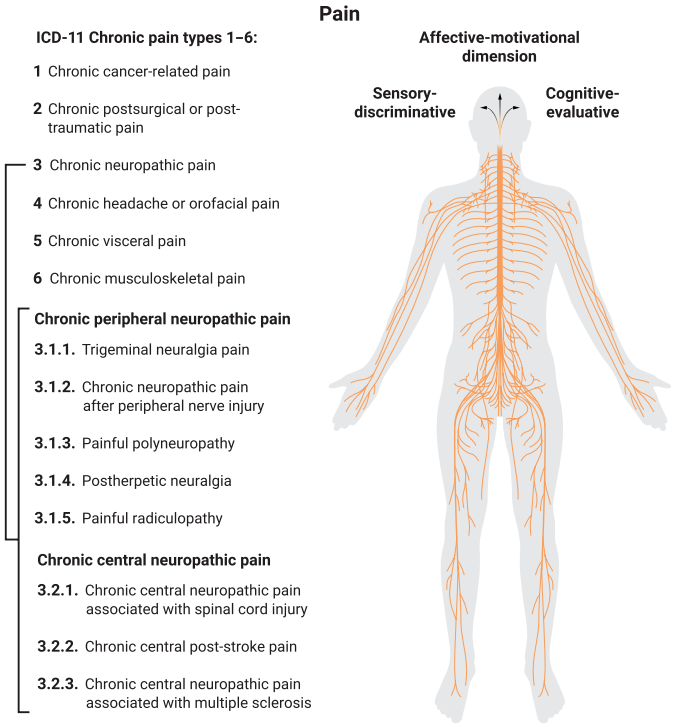

Fig. 1. Peripheral divergence and central convergence in pain mechanisms. The recent International Classification of Diseases (ICD-11) adopted by the World Health Organization describes chronic pain both as a primary disease and as a symptom of other illnesses, and divides it into six main categories. This figure illustrates the multitude of pain types (using neuropathic pain subtypes as an example) that can originate from various organs and tissues of the human body. In each case, nociception is initiated through a variety of complex cellular and molecular mechanisms. Acting on the common brain mechanisms that generate pain unpleasantness raises the possibility of treating chronic pain suffering across all pain categories at once.

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To reconcile these views, pain can be described as a complex multidimensional experience that includes sensory-discriminative, affective-motivational, and cognitive-evaluative components (*23*, *24*). Pain multidimensionality integrates (i) the somatosensory perception of the noxious object/event's features (such as location, temperature, and pressure), (ii) the encoding, within emotional and motivational circuits, of negative affect and the drive to halt the unpleasant percept, and (iii) an evaluation and modulation of pain experience by cognitive circuits. All three components are necessary to optimally select actions that limit exposure to noxious stimuli and pain experience.

As previously discussed for the field of emotions (*4*, *25*, *26*), understanding and treating pain affect require operational definitions that enable mechanistic studies. Pain includes both pre-cognitive physiological and behavioral responses (for example, withdrawal reflex and increase in heart and breathing rates) and cognitive processing of nociceptive information that leads to pain perception and affect; both are important for people living with chronic pain and can be defined and studied in animal models of pain (Fig. 2). First, primary afferent nociceptors [and, in the case of allodynia, non-nociceptive afferents (*27*)] engage motor and autonomic spinal/brainstem circuits to produce fast reflex responses, including withdrawal reflexes (Fig. 2A) (*28*). These stereotyped nocifensive responses, which persist in decerebrated animals (*29*, *30*), limit exposure to noxious stimuli and injury while nociceptive information is transmitted to and processed in the forebrain (*31*–*33*). The multidimensional pain perception is then generated and enables the selection of more complex adaptive behaviors. Specific behaviors are chosen from a panoply of possible nocifensive responses based on the features of the noxious event (sensory-discriminative component) and the expectation—derived from recalling previous experiences and an understanding of the context that led to and accompanies pain perception—that this action is the most likely to relieve pain unpleasantness and promote positive outcomes and survival (for example, attending, cooling down and putting a bandage on the affected body part in response to a mild burn injury; Fig. 2A). During this process, changes in pain perception and its context are continuously monitored and evaluated (cognitive-evaluative dimension). If the selected nocifensive behavior fails to relieve pain unpleasantness, another nocifensive behavior is selected (for example, planning a doctor visit to treat burn pain; Fig. 2A). In fact, in high-order species, conflicting needs can lead individuals not to engage in adaptive behaviors and instead to endure pain, when considering this action beneficial to achieve superiorly important or longer-term goals, at least when the pain condition is perceived as benign (for example, deciding not to go to the doctor and instead prioritizing participation in a work activity).

The temporal logic of nociceptive behavior organization during acute pain perception, with pain-limiting reflexive behaviors exhibited first, followed by reflective and voluntary nocifensive behaviors, is largely conserved between humans and rodents (Fig. 2, A and B). These behaviors can be studied in detail in mice experiencing pain during the hotplate test, if this assay is used to comprehensively analyze mouse behavior (Fig. 2, B to D), rather than scoring only the latency for the first nocifensive reflex. In an opioid pharmacology

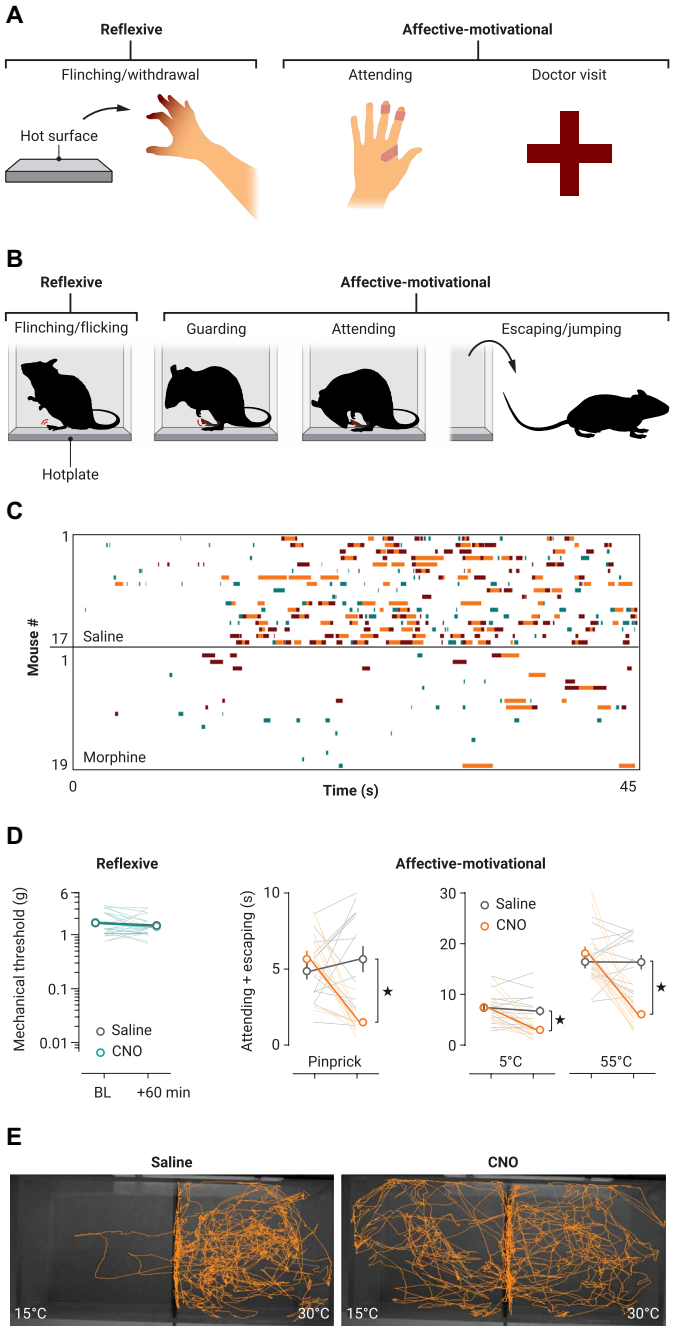

Fig. 2. Categorization of reflexive versus affective-motivational nocifensive behaviors to interrogate pain affect in rodents. (**A**) Examples of human responses to noxious stimulation, which include reflexive and affective-motivational behaviors. (**B**) Mouse responses to noxious stimulation, such as with the hotplate test, also include reflexive and affective-motivational behaviors like protective responses (such as guarding and licking of an affected paw) and escape seeking (for example, rearing and jumping). (**C**) Raster plots showing the nocifensive behavioral responses of individual mice in the hotplate assay and the reduction in both reflexive (green) and affective-motivational (orange, brown) pain behaviors after morphine administration. (**D**) In contrast to the effect of morphine (C), inhibition of nociceptive BLA neurons with hM4Di after injection of clozapine-*N*-oxide (CNO) reduces affective-motivational pain behaviors in the hotplate assay, but not reflexive withdrawal. (**E**) In a two-plate preference assay, CNO also decreases nerve injury-induced aversion to innocuous cool stimuli in the setting of neuropathic allodynia. Adapted from (*37*–*39*).

study that took advantage of single-, double-, and triple-knockout mice for opioid receptor subtypes, after opioid agonist administration intracerebroventricularly, only mu opioid receptor (μ or MOP receptor), but not delta opioid receptor (δ or DOP receptor), activation suppressed reflexive nocifensive withdrawal from noxious heat; however, activation of either μ or δ could result in antinociception if paw licking and jumping on the hotplate was measured to evaluate pain perception (*34*). Given the known differential expression of δ and μ receptors in the brain's pain pathways (*35*, *36*), these results suggested that distinct circuits (and molecules in these circuits) control different nocifensive behaviors during the hotplate pain experience. By annotating video recordings of mice exposed to noxious stimuli, raster plots can be generated to categorize and quantify the rapid and stereotyped reflexive paw withdrawal and flicks/flinches, versus the delayed, reflective, voluntary, and more variable behaviors aimed to minimize pain unpleasantness, which include attending to the affected paw (such as lifting, guarding, licking, and biting) and escape behaviors (searching for an escape route via exploration, rearing, and jumping; Fig. 2B) (*37*–*39*). Thus, each mouse displays a unique sequence of attending and escape behaviors (Fig. 2C), indicating that this method can also be used to study the mechanisms that underlie the idiosyncrasies of both the experience of pain and the expected efficacy of individual actions to provide pain relief. Given this variability, attending and escape behaviors can be grouped and labeled as affective-motivational behaviors (Fig. 2D). This categorization, which can be automated using deep learning approaches such as DeepLabCut or MoSeq, described elsewhere (*40*–*42*), complements other approaches such as conditioned place preference or avoidance paradigms (*43*, *44*), grimace scoring (*45*, *46*), and wheel running monitoring (*47*) to provide a more complete description of pain experience in nonverbal animals, which, combined with rigorous experimental design (*48*), may better predict the clinical efficacy of treatments than when relying solely on reflexive behavior–based measurements (*49*).

Brain circuits for pain experience (Fig. 3A)

Neuroimaging and neurophysiological studies in humans have shown that noxious stimuli elicit neural activation and connectivity patterns within and between numerous brain areas, including the somatosensory cortex, insular cortex (IC), various regions of the prefrontal cortex (PFC), anterior cingulate cortex (ACC), thalamus, periaqueductal gray (PAG), and cerebellum (*50*–*52*). Additional regions, including the basal ganglia, parabrachial complex, posterior cingulate, amygdala, hypothalamus, and supplementary motor area, show less consistent and more context-dependent responses to noxious stimuli. Earlier studies demonstrated a relatively consistent noxious stimuli–evoked response in some of these structures that correlated with the perceived intensity of pain, leading to the hypothesis of a specific network for pain perception, the "pain neuromatrix" (*50*, *51*). More recent evidence has refuted this hypothesis by challenging the notion that pain can be uniquely associated with a specific pattern of activated brain regions (*53*, *54*). Instead, it seems that pain perception engages brain regions that tend to coalesce in networks associated with the multidimensional components of pain experience and broader functionality related to multisensory integration, emotion regulation, general cognitive and attention processing, self-referential processing, and other functions (*55*, *56*). At the same time, a growing number of studies have used multivariate pattern analysis tools to capture, even within the same brain

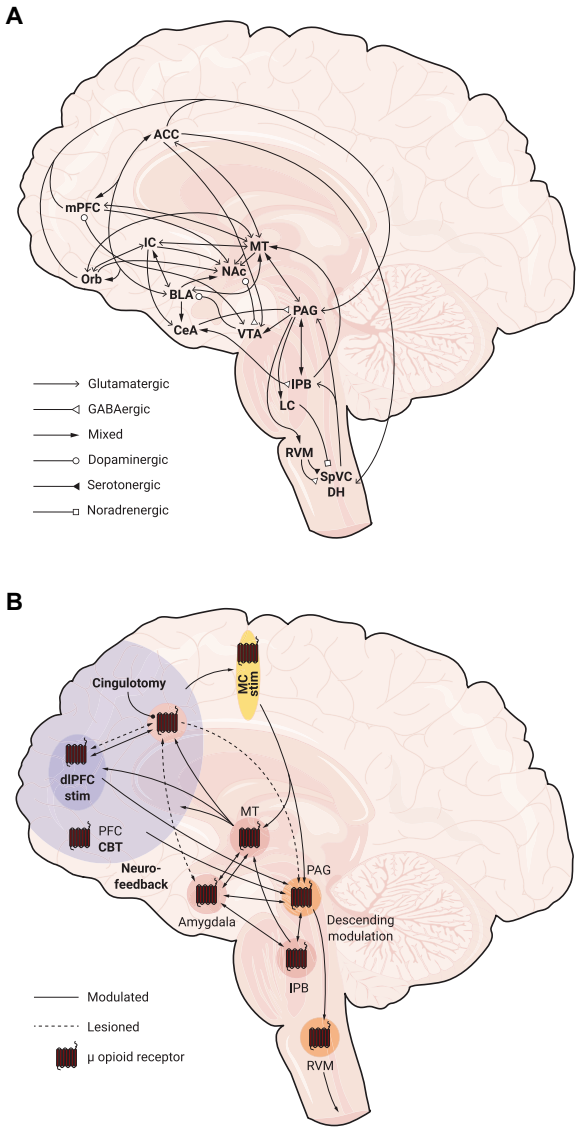

Fig. 3. Pain emotional and cognitive networks and treatments that can ameliorate chronic pain affect. (**A**) Primary afferent neurons synapse onto second-order neurons in the spinal dorsal horn (DH) or the trigeminal nucleus caudalis (SpVC). These neurons, in turn, project to the lateral parabrachial nucleus (lPB) and the periaqueductal gray (PAG), which then connect with the anterior cingulate, insular, and prefrontal cortices, medial thalamus, amygdala, nucleus accumbens, and hypothalamus to generate and modulate pain experience. Note, mixed arrows indicate glutamatergic and GABAergic pathways. (**B**) Prevalent treatments for pain commonly use opioid receptor signaling to induce a prominent action on pain affect circuits. Investigative treatments include motor cortex stimulation (MC stim), dlPFC stimulation (dlPFC stim), neurofeedback, and cognitive behavior therapy (CBT) that act on frontal cortex circuits to modulate pain. In severe cases of intractable pain, cingulotomy reduces chronic pain. Frontal cortex modulation is hypothesized to relieve pain through descending pain control in the PAG, but notable connections to the medial and intralaminar thalamus (MT) and to the parabrachial nucleus could also play a role. ACC, anterior cingulate cortex; BLA, basolateral amygdala; CeA, central amygdala; IC, insular cortex; mPFC, medial prefrontal cortex; NAc, nucleus accumbens; Orb, orbitofrontal cortex; RVM, rostromedial ventral medulla; VTA, ventral tegmental area.

regions, fine-grained differential activation patterns between the distinct components or modalities of pain experience, in healthy individuals versus patients with chronic pain (*57*–*60*). These studies have produced interesting findings; for example, although the amygdala is thought to critically contribute to the affective component of pain experience, these experiments found no specific role for this brain region in the encoding of thermal pain (*58*). Together, these findings suggest that the experience of pain involves numerous interconnected brain structures working together, whereas more domain-general features of the underlying experience may have distinct neural coding through more specific pathways. Pain research in animals offers unique opportunities because it allows characterization (for example, genes and proteins expressed, electrophysiological properties, and connectivity) and causal determination of the function of individual neurons in some of the regions described above. We describe here some of the rodent studies exemplifying the utility of this approach. Nevertheless, we should acknowledge the debate regarding the degree of neurophysiological and anatomical congruence between the rodent and human brain. For example, there are inconsistencies regarding the function and anatomy of the PFC subregions and thalamic nuclei across species (*61*–*63*).

In rodents, as is the case in primates, DH nociceptive projection neurons, which comprise distinct populations located predominantly in lamina I and, to a lesser extent, in deeper DH laminae [there are also, in fact, a number of nociceptive projection neurons in the intermediate and ventral horn that remain understudied (*64*–*66*)], directly transmit nociceptive information to several brain regions in the medulla [nucleus of the solitary tract (NTS), inferior olive, and reticular formation], pons [parabrachial nucleus (PB) and reticular formation], midbrain (PAG, superior colliculus, and reticular formation), and forebrain (thalamus), with the two most thoroughly studied outputs being the PB and thalamus. Activity in these ascending pathways elicits sensory-discriminative and affective-motivational pain perceptions and the array of autonomic physiological responses (for example, increase in breathing rate and grimace) and nocifensive voluntary behaviors (such as attending and escape) that characterize pain experience in most mammals. Regarding the sensory-discriminative aspect of pain, we recommend other readings that describe the function in the representation and discrimination of noxious stimuli of the lateral thalamus [ventral posteromedial (VPM), ventral posterolateral (VPL), and posterior (Po) nuclei], zona incerta (ZI), primary and secondary somatosensory cortices (S1 and S2), PFC, and posterior insular cortex (pIC) (*67*–*69*). In this translational review, we describe recent advances regarding the organization of brain circuits that shape the affective-motivational and cognitive-evaluative dimensions of pain.

Transmission of nociceptive information to the forebrain: spino-parabrachial-amygdalar and spino-thalamo-cortical circuits

Parabrachial nucleus

The PB receives diverse interoceptive and exteroceptive sensory information and plays a vital role in generating a wide array of autonomic responses, such as for pain, respiration, or thermoregulation (*70*–*72*). The lateral PB (lPB) has long been known to receive inputs from nociceptive projection neurons of the contra- and ipsilateral spinal cord (SC) DH and spinal trigeminal nucleus caudalis (SpVC; the neuroanatomical name for the trigeminal DH)

and, to a lesser extent, from neurons located in deeper spinal laminae (*73*–*75*). Recently, the identification of marker genes that define distinct populations of spino-parabrachial and lPB neurons enabled detailed studies of lPB connectivity and function in pain. DH projection neuron populations characterized by the expression of distinct molecular markers [*Tac1*, *Tac1r*, *Gpr83*, or *Phox2a* (*31*, *76*–*78*)] differentially innervate the external, dorsal, and superior (or internal) subdivisions of the lPB (lPBe,d,s/l), with the lPBe additionally receiving inputs from *Trpv1*$^+$ trigeminal ganglion nociceptors (*79*, *80*). Ablation of *Tac1*$^+$ DH projection neurons, which innervate the lPBs/i, abolishes paw licking and conditioned avoidance, but not reflexive nocifensive behaviors, in response to sustained noxious stimulation. Optogenetic stimulation in lPB of axon terminals either from *Tac1*$^+$ (*78*), *Tacr1*$^+$, or *Gpr83*$^+$ (*31*) DH projection neurons or from *Trpv1*$^+$ nociceptors (*80*) drove acute and conditioned avoidance. The nocifensive responses engaged after activation of these different pathways are, however, distinct; for example, stimulation of *Gpr83*$^+$ lPB inputs induced forward locomotion, whereas stimulation of *Tacr1*$^+$ lPB inputs caused backward locomotion and jumping (*31*). Interestingly, in the setting of facial pain induced by capsaicin injection, optogenetic silencing of *Trpv1*$^+$ nociceptor axon terminals in the lPB not only produced preference for the light-paired compartment in a real-time place preference assay but also diminished brisk head withdrawal after stimulation with a von Frey filament, suggesting an action both on pain affect and on reflexive withdrawal, presumably through descending control of nociception in the trigeminal DH (*80*). However, as is typical for optogenetically or chemogenetically driven place aversion or preference experiments in the pain field, although avoidance or preference indicates the aversive versus rewarding quality of the manipulation, whether the percept that motivates the animal's avoidance or preference behavior resembles experiencing authentic pain or analgesia, respectively, requires further clarification. This question can be resolved by comparing neural dynamics (*37*). Remarkably, low-intensity optogenetic stimulation of *Gpr83*$^+$ DH projection neurons, which predominantly receive input from primary afferent mechanosensory neurons and not *Trpv1*$^+$ nociceptors, can also, in contrast to the *Tac1r*$^+$ projection neuron population, promote place preference, suggesting a dual function in generating rewarding or aversive somatosensory experiences (*31*). This result also illustrates the importance of mimicking physiological firing patterns in optogenetic sufficiency experiments. Together, these studies support the idea that the lPB nociceptive circuits are essential for the expression of pain precognitive emotional physiological responses and behaviors. Furthermore, PB neurons integrate competitive signals that modulate pain, such as hunger, which inhibits nociception through inputs from hypothalamic agouti-related protein (*Agrp*$^+$)-expressing neurons and neuropeptide Y signaling in the PB (*81*).

Amygdala

Although the amygdala is prominently considered a key brain region involved in emotional experiences, research has shown that it plays a broader role, including processing and coding the biological value of various types of salient stimuli (*82*–*85*). Basic pain research on the amygdala first identified nociceptive neurons in the central amygdala (CeA), a predominantly gamma-aminobutyric acid–ergic (GABAergic) nucleus, and examined their physiological properties and connectivity, including with the lPB (*86*–*90*). These CeA GABAergic neurons include a distinct ensemble of neurons that are activated by general anesthesia and inhibit pain (*91*). Recent studies have begun to investigate distinct populations of lPB neurons, defined by expression of *Calca*, *Tac1*, *Nts1*, *Pdyn*, *Sst*, and/or *Tac1r* (*29*, *70*–*72*, *92*–*95*). Together, these studies suggest that lPB neurons that receive monosynaptic input from DH projection neurons transmit nociceptive information to the lateral subdivisions of the CeA (CeL) [and the laterocapsular subdivision (CeCL), often referred to as the "nociceptive amygdala"] through two populations of *Slc17a6*$^+$ (VGLUT2$^+$) neurons: (i) *Calca*$^+$ *Slc17a6*$^+$ lPBe neurons, via *Pdyn*$^+$ lPB neurons (*92*, *93*), and (ii) intralaminar (ILN) and midline thalamic (MThal) neurons, via *Tac1r*$^+$ lPB neurons (*94*, *95*). In addition to the CeA, ILN, and MThal, these molecularly defined populations of lPB neurons differentially project to the bed nucleus of the stria terminalis (BNST), ventromedial hypothalamus (VMH) and lateral hypothalamus/parasubthalamic nucleus, lateral and ventrolateral PAG (lPAG and vlPAG), superior colliculus, MThal, medial PFC (mPFC), and insular cortex (IC) (*29*, *93*–*96*). Functionally, silencing *Calca*$^+$ lPBe-to-CeA neurons with the light chain of tetanus toxin (TetTox) inhibited footshock-induced immediate locomotor response and nocifensive jump response in the hotplate test, without altering the latency for reflexive withdrawal from noxious heat or the force of mechanical stimuli necessary to elicit a withdrawal reflex (*92*). These findings indicate the necessity of *Calca*$^+$ lPBe-to-CeA neurons for innate escape behaviors after noxious stimulation, consistent with the essential function of the lPB for a variety of interoceptive and exteroceptive autonomic responses to threat (*71*). However, another study comparing the behavioral effects resulting from optogenetic stimulation of distinct lPB outputs found that activation of the lPBe-to-CeA pathway caused no substantial movement, whereas activation of either lPBd-to-VMH or lPBd-to-PAG neurons increased locomotion and jumping (*93*). Both studies provide evidence that the lPB-to-CeA circuit is necessary for aversive memories, albeit by manipulating different populations of neurons using dissimilar protocols: *Calca*$^+$ lPBe-to-CeA neurons in a footshock-based fear conditioning assay (*92*) or *Pdyn*$^+$ lPBd neurons in an intraplantar formalin-induced conditioned place avoidance assay (*93*). *Tac1r*$^+$ lPB neurons receive ipsi- and contralateral monosynaptic inputs from DH projection neurons and are activated in response to noxious stimuli (*95*). Chemogenetic activation of *Tac1r*$^+$ lPB neurons, which can disynaptically relay nociceptive information to the CeA, facilitated jumping in the hotplate test (*95*), as well as escape responses and nocifensive behaviors (for example, licking) in response to tail clip and after intraplantar injection of the TRPA1 agonist allyl isothiocyanate (AITC) (*95*) or formalin (*94*). Formalin-induced flinching (*94*) and the latency of the first nocifensive response on the hotplate (*95*) remained unaffected. Silencing of *Tac1r*$^+$ lPBs almost completely eliminated licking induced by tail clip or AITC (*95*). *Tac1*$^+$ lPB neurons include a subset of *Calca*$^+$ lPBe-to-CeA neurons, as well as a different population of neurons that project to the medullary reticular formation region (MdD), which contains forelimb premotor neurons (*29*). Remarkably, in the hotplate test, either chemogenetic or optogenetic stimulation of *Tac1*$^+$ lPB neurons resulted in immediate and repetitive jumping behavior and decreased licking. Complex CeA microcircuits, composed of multiple molecularly defined populations (such as *Sst*$^+$, *Pkcd*$^+$, and *Crh*$^+$) with distinct connectivity and functions (*97*–*101*), process nociceptive information, which is transmitted from the CeL to the medial subdivision (CeM), the major output region of the CeA, and then to

brainstem structures such as the PAG (*99*, *102*) that mediate defensive behaviors. Physiological studies have demonstrated that calcitonin gene-related peptide (CGRP), which is encoded by *Calca*, facilitates *N*-methyl-D-aspartate (NMDA) receptor-mediated glutamatergic transmission at these lPB-to-CeL synapses (*103*), which show postsynaptic neuron type–specific (*Som*$^+$ versus *Crh*$^+$) alterations in synaptic transmission after sciatic nerve injury (SNI) (*104*). It is worth noting that *Pdyn*$^+$, *Sst*$^+$, and/or *Crh*$^+$ GABAergic CeA neurons project back to the lPB. This inhibitory pathway normally inhibits nocifensive behaviors; however, CeA-to-lPB inhibitory inputs are reduced after infraorbital nerve injury (*105*). A systematic comparison between the different lPB and CeA outputs, using the same silencing/activating tools and behavioral assays to interrogate distinct aspects of the pain experience, could further clarify the contributions of the lPBe-to-CeA and other lPB output circuits to pain. Optogenetic manipulation of the CeA and connected descending circuits in the lPAG and downstream reticular formation motor networks [the dorsal and ventral medullary reticular formation (MdD and MdV), sometimes called the magnocellular reticular nucleus (Mc)] can produce freezing/immobility and/or flight behaviors in the absence of noxious stimulus or conditioning (*106*). In the same study, the authors reported that optogenetic activation of *Slc17a6*$^+$ (VGLUT2$^+$) lPAG neurons increased withdrawal latency in the tail immersion test. In another study, photostimulation of *Pdyn*$^+$/*Penk*$^+$/*Slc17a6*$^+$ lPB neurons that project to the hypothalamus preoptic area (POA) could induce hypothermia, aversion, and suppression of locomotion (*107*). Disentangling effects on movement from those on nociception and pain experience may not be trivial. If changes in reflexive nocifensive responses after lPB, CeA, and lPAG neuron manipulations result from descending inhibition of nociception in the DH [presumably via the rostral ventromedial medulla (RVM)], one would expect to observe an antinociceptive effect that reduces not only withdrawal reflexes but also affective-motivational pain behaviors. Crucially, the maladaptive nocifensive responses observed when manipulating activity in lPB and CeA circuits (such as immediate and repetitive jumping upon *Tac1*$^+$ lPB neuron activation in the hotplate assay or absence of jumping when silencing *Calca*$^+$ lPBe-to-CeA neurons) illustrate the critical control function of cortical and subcortical structures. In these optogenetic and chemogenetic experiments, cortical and subcortical cognitive inputs are shunted during pain experience, resulting in failure to compute a wealth of information necessary to conceive plans (understanding current context, recalling memories from previous painful experiences, and formulating expectations) to select, among a wide variety of choices, the antinociceptive behaviors that are most likely to succeed, attempt them, and, in case of failure, adjust by selecting other behaviors (expectation violation and reformulation). Together, these results support the idea that lPB and CeA circuits mediate the expression of autonomic physiological effects and behaviors in response to noxious stimuli through connections with brainstem and hypothalamic effectors.

To be useful as a learning signal, the negative valence of acute (nociceptive) pain must be contextualized. Only then can an animal learn and thereby improve its ability to both avoid and respond to noxious stimuli in a context-specific manner to halt pain. For patients with chronic pain, the contextualization and constant evaluation of pain affect through cognitive circuits seem to drive emotional suffering and pain catastrophizing. Catastrophizing reflects maladaptive cognitions in response to actual or anticipated pain and has been associated with poor and deteriorating outcomes for people with chronic pain (*108*–*110*). A recent systematic review (*111*) in both healthy individuals and patients with chronic pain indicates that the brain regions most commonly linked to pain catastrophizing are those consistently active during pain processing and associated with the multidimensionality of pain, including the somatosensory cortex, thalamus, IC, ACC, and medial and dorsolateral PFC (dlPFC). The amygdala was also shown to play a role, although to a lesser extent. In healthy participants, during moderate pain, catastrophizing was negatively associated with neural activation in the amygdala (*112*). Compared to healthy controls, patients with chronic pain exhibited greater connectivity between the amygdala and a network of regions involved in cognitive processing, which was strongest in patients with the highest tendency to catastrophize (*113*). Moreover, patients showed decreased basolateral amygdala (BLA) connectivity to a network of regions involved in self-referential compared to healthy controls. Combatting this deleterious process is a major therapeutic goal. The BLA, unlike the CeA, is densely connected with cortical and subcortical cognitive circuits that process and contextualize affective information. Rodent studies have established that the BLA contains predominantly *Slc17a7*$^+$ (VGLUT1$^+$) pyramidal neurons that project to the CeA and the striatum, particularly to the nucleus accumbens (NAc) (*98*). Over the course of evolution, the size of the BLA versus the CeA within the amygdaloid complex markedly increased (*84*), evincing the critical importance of the BLA in human emotions and presumably in pain affect. However, considerably fewer rodent mechanistic studies have interrogated the contribution of BLA neurons to pain experience. Although footshock has been used extensively in the learning and memory field to investigate BLA function, the representation in the BLA of footshock and that of purely noxious stimuli considerably differ (*37*), presumably because the footshock generates activity in non-nociceptive primary afferents (such as mechanoreceptors and proprioceptors), producing an experience that is unquestionably aversive for the animal, but that does not precisely mimic pain experience. On the other hand, patient H.M., who had a temporal lobectomy that ablated most of the amygdala, including the BLA, but preserved the centromedial nucleus, could detect thermal noxious stimuli and report their intensity, but neither characterized them as painful nor showed motivation to avoid them (*114*, *115*). Recently, in vivo optical recordings of about 17,000 neurons in freely behaving mice encountering noxious stimuli, combined with the chemogenetic manipulation of BLA neurons active during pain, enabled the identification of a distinct neural ensemble of *CamkIIa*$^+$ *Rspo2*$^+$ BLA neurons that specifically encodes the negative affective valence of noxious stimuli across pain modalities (heat, cold, and mechanical) and is necessary for the behavioral manifestation of pain affect (*37*). Inhibition of this nociceptive ensemble using genetic tagging in TRAP mice and $G_{i/o}$ protein–coupled DREADDs (hM4Di) alleviated pain affective-motivational behaviors (attending and escape) without altering withdrawal reflexes, anxiety, or reward. Moreover, functional studies of this nociceptive ensemble revealed a causal neural basis for allodynia. Specifically, after peripheral nerve injury, innocuous stimuli begin to activate this nociceptive ensemble to drive dysfunctional perceptual changes associated with neuropathic pain, including aversion to light mechanical and cool stimuli, as reported in patients. Interestingly, this recoding phenomenon resembles that which occurs during fear conditioning, when the representation of the conditioned

stimulus (CS) becomes more similar to that of the unconditioned stimulus (US) (*116*), suggesting that pain chronification and associative learning share common BLA mechanisms, consistent with the view that aspects of the chronic pain disease state result from maladaptive plasticity in learning circuits. Neuroanatomical and electrophysiological studies have revealed the extensive connectivity of this nociceptive ensemble, including monosynaptic inputs from cortical areas such as the ACC and IC, MThal and hypothalamus, and projections to numerous regions such as the ACC, CeA, and NAc (*117*). In these pathways, altered activity in the BLA during chronic pain, including in arthritis pain models, results in enhanced feedforward inhibition both of mPFC pyramidal neurons, impairing decision-making, and of CeA and intercalated cell (ITC) masses (*101*, *118*), which are small clusters of tightly packed GABAergic neurons that receive BLA inputs and synapse onto CeA neurons.

Thalamus

In human functional magnetic resonance imaging (fMRI) studies, the thalamus is one of the brain regions most consistently activated by painful stimuli (*119*). The ILN and MThal, the latter of which includes the mediodorsal (MD) thalamus, are the major thalamic nuclei involved in pain affect and cognitive-evaluative processing of pain (*120*). As part of the dorsal thalamus, the ILN and MThal regions are composed almost entirely of *Slc17a6*$^+$ (VGLUT2$^+$) glutamatergic, excitatory neurons and are modulated by inhibitory neurons in the thalamic reticular nucleus and ZI. This region of the thalamus receives a confluence of nociceptive, arousal, and visceral information, notably not only from the *Tacr1*$^+$ neurons in the lPB (*94*), the NTS (*121*), and the PAG, but also from brainstem arousal nuclei like the pedunculopontine nucleus, locus coeruleus, and various parts of the reticular formation (*122*, *123*), as well as sparse inputs directly from the SC DH and SpVC (*124*). These diverse ascending signals are integrated with forebrain thalamo-amygdalar, thalamo-striatal, and thalamo-cortical loops (*125*–*127*). The ILN and MThal are composed of many small nuclei including the central medial (CM), parafascicular (Pf), central lateral (CL), reunions (Re), and submedius (Sm) (*119*). Sequencing data and axon morphology stratify the ILN and MThal neurons into two classes: The ILN and MThal nuclei excluding MD show similar RNA profiles, whereas the MD thalamus more closely resembles so-called higher-order processing thalamic nuclei like the posterior (Po) thalamus for somatosensation and the lateral posterior (LP) thalamus for vision (*128*). Each of the small nuclei in the ILN and MThal has distinct connections with the PFC (*122*, *123*, *129*, *130*), and some are known to play a specific role in processing pain affect (*126*, *131*, *132*). One well-studied example shows that the Sm nucleus, through its prime prefrontal partner, the ventrolateral orbitofrontal cortex (Orb), engages the vlPAG descending pain control circuits using opioid peptides, serotonin, dopamine, and glutamate (*131*). Furthermore, separate modulation of MD pathways to either the BLA or ACC was found to inversely modulate pain-related aversion (*127*). As a final example, a recent study showed that, when the CM nucleus is lesioned before nerve injury, mechanical hyperalgesia failed to develop, and revealed that the CM receives vlPAG inputs and sends outputs to excitatory neurons in the BLA that could mediate this effect (*132*). Although there is evidence for the specific roles of the ILN and MThal in acute and chronic pain, more emphasis must be placed on specific pathways to fully dissect the role of the thalamus in pain affect, particularly circuits connecting the ILN, BLA, and cortical hubs for pain affect such as the ACC and IC, which themselves have dense reciprocal connections with the BLA (*133*, *134*).

Cortical circuits involved in the affective-motivational and cognitive-evaluative dimensions of pain

The insular, anterior cingulate, and prefrontal cortices play important roles in mediating the cortical components of the affective-motivational and cognitive-evaluative aspects of pain experience. Human imaging studies performed during acute pain have specifically identified that the IC-to-PFC pathway is activated by discrimination of pain intensity, whereas the dlPFC is activated during spatial discrimination of pain (*135*).

The IC is one of the brain regions most consistently activated in fMRI during pain (*56*, *136*) and while observing others in pain (*137*), and is the only cortical region that can be stimulated to induce pain experience (*138*). The anterior IC (aIC) and pIC receive visceral and nociceptive information through reciprocal connections with the PB, NTS, and ILN/MThal (*139*) and integrate this information with sensory and cognitive cues to generate internal and emotional states (*140*). The IC is thought to serve as a bridge for the exchange of pain affective and sensory-discriminative signals through reciprocal connections between the pIC, which connects to S1, S2, and lateral thalamus, and the aIC, which connects with the Orb, NAc, and ILN/MThal (*139*). Optogenetic inhibition of *CamkIIa*$^+$ neurons in the pIC of mice and transcranial magnetic stimulation (TMS) of the pIC in humans lead to enhanced a decrease in capsaicin-induced mechanical hypersensitivity and increased heat pain thresholds, respectively (*141*, *142*). Lesions of the pIC, but not of the ACC, prevent long-term mechanical hypersensitivity in sciatic nerve–injured mice (*143*). Together, these studies suggest that the pIC modulates the sensory-discriminative component of pain (*141*, *142*). In contrast, the aIC is thought to be important for pain affect and for its relief, including via μ opioid receptors (*144*, *145*). Injections of morphine into the aIC resulted in reduced nocifensive behaviors after hindpaw formalin injection (*144*).

Although the IC reciprocally connects to the BLA, these inputs display topographical patterns. The aIC preferentially targets excitatory outputs to the anterior BLA, the region preferentially associated with positive-valence neurons (*146*). In contrast, the pIC sends dense excitatory outputs to the posterior BLA, which is thought to be involved in negative valence processing. The entirety of the IC also sends excitatory projections to the CeA, which can drive descending circuits that mediate nocifensive behaviors. How these pathways encode pain affect and aversion during painful situations remains unexplored; however, conditioned taste aversion assays have implicated the necessity of the IC-to-amygdalar pathways (*133*, *147*). Activation of IC-to-BLA projection neurons during a pleasurable consumption (saccharin) induced aversion to an otherwise positive cue (*133*). These studies suggest an important role for these reciprocal IC-amygdalar connections in generating the negative valence of pain (*148*).

The ACC contributes to numerous functions related to cognition (such as attention or learning), socio-emotional processes (like reward or empathy), and somatosensation, and although it is undoubtedly engaged during pain, there remains an ongoing debate as to the precise nature of its contribution (*149*–*151*). The ACC described here is distinct from the more caudal midcingulate cortex (MCC); these cingulate regions contribute differently to nocifensive behaviors (*142*, *152*–*154*). In humans with ACC cingulotomies and

animal models involving lesions to the ACC, pain aversiveness is often diminished, with minimal impacts on executive, cognitive, or motor functions (*155*, *156*); however, this decrease in pain affect may be disorder- and/or context-specific, as shown by a case study in which a patient with schizoaffective disorder reported increased pain after cingulotomy (*157*). Structural changes have been observed in layer 2/3 (L2/3) of the ACC after induction of chronic pain in rodent models [recently reviewed here (*69*, *158*)]. After the development of chronic pain in mice with SNI, L5 pyramidal neurons in the ACC have increased dendritic integration due to a decrease in hyperpolarization-activated cyclic nucleotide-regulated (HCN) channels, which is reversed by the serotonergic agonist 5-HT_7 (*159*). A second study found HCN channel dysfunction in L2/3 pyramidal neurons in the ACC and mPFC developed after SNI in rats (*160*), further suggesting HCN channel function in the ACC changes during chronic pain.

Optogenetic activation of pyramidal neurons in the rodent ACC increases pain-related aversive behaviors. Optogenetic stimulation of pyramidal *CamkIIa*$^+$ ACC neurons abolishes ketamine-induced reductions in aversion to a pinprick-paired chamber in a conditioned place preference assay (*161*). Optogenetic inhibition of ACC neurons in rats with either chronic constriction of the trigeminal nerve or SNI resulted in a reduction of cold hypersensitivity, similar to what is observed after ACC lesion in rodents or cingulotomy in humans (*162*, *163*).

Bidirectional modulation of the ACC in the context of chronic pain can induce or abolish negative pain affect, resulting in secondary effects on mood, such as anxiodepressive phenotypes similar to those observed in patients with chronic pain. Lesions of the ACC abolish anxiodepressive-like behaviors in mice with SNI, including immobility during the forced swimming test and aberrant grooming behavior observed after splash (*143*). Conversely, optogenetic activation of predominantly *Thy1*$^+$ pyramidal neurons in L2/3 and L5 of the ACC induces anxiodepressive phenotypes in healthy mice, consistent with nerve-injured mice (*143*). Slice electrophysiology studies revealed presynaptic and postsynaptic long-term potentiation mechanisms in the ACC that have been associated with chronic pain and comorbid anxiety (*164*).

The ACC input and output circuits regulating pain affect are being explored in rodents using electrophysiology, calcium imaging, and manipulation of subcircuits with opto- and chemogenetics. Experiments examining the relationship between the ACC and MD thalamus show that noxious stimulus-evoked activity in acute and chronic pain states transmits through the MD thalamus before reaching the ACC and that lesioning the MD thalamus abolishes aberrant spiking in the ACC (*165*). This study reported that the MD thalamus inputs to ACC L2/3 are responsible for transmitting aberrant spiking activity to L5 neurons that, in turn, project to the BLA and dorsolateral PAG (dlPAG) as well as back to the MD thalamus (*127*, *165*, *166*). Optogenetic activation of the ACC-to-MD pathway was mildly aversive, as evidenced by a slight avoidance of the side paired with optogenetic stimulation in a place preference assay (*127*). In contrast, optogenetic activation of the ACC-to-BLA pathway reduces SNI-associated aversion for the optogenetic stimulation-paired chamber (*127*). fMRI studies in humans show ACC activation during pain or pain relief, as well as when observing another human in pain (*167*, *168*). A meta-analysis of fMRI during pain empathy consistently observed activation of the posterior ACC/anterior MCC border region and aIC and hypothesized an instrumental role for these two regions in empathy (*137*). Recent studies have shown that rodents likewise respond to social contagion with prosocial behaviors (*169*). Mice observing other mice with an acute inflammatory injury have decreased nocifensive thresholds; furthermore, this social transfer of pain is dependent on a pathway from the ACC to the NAc (*170*).

Although both the human and rodent PFC are similarly involved in decision-making, identification of reward, and executive functions, the rodent PFC differs in important ways from the human PFC. The most functionally analogous rodent structure to the human dlPFC lies within the rodent mPFC. Furthermore, the entire rodent PFC is agranular, whereas in humans, the mPFC, dlPFC, and most of Orb are granular (in other words, the mPFC and Orb lack a cortical L4 in rodents) (*171*–*173*). Although rodents might lack complex abstract thought, they show affective-motivational and cognitive-evaluative behaviors in response to painful stimuli not altogether dissimilar from those of humans (attending to injury, avoidance, etc.) (Fig. 2, A and B).

The mPFC, composed of the infralimbic (IL) and prelimbic (PL) cortical regions, and Orb are particularly well studied for their roles in Pavlovian and instrumental conditioning (*174*, *175*), both of which are driven by reward or punishment (for example, pain relief or pain). As previously discussed, the Orb receives input from the Sm nucleus of the ILN and receives notable inputs from the IC and ACC that create associations between pain and environmental cues conveyed from secondary somatosensory cortex or other higher-order sensory cortices (*176*). The Orb responds to a diverse set of nociceptive stimuli (cutaneous, visceral, and thermal) and can act on descending pain control through its direct output to the vlPAG (*131*).

The mPFC plays a key role in generating complex associations using working and long-term memory. A gradient has been observed from the ACC ventrally through the PL and IL that demonstrates the importance of the more dorsal ACC (dACC) and PL for memory retrieval, whereas the ventral IL is important for working memory (*177*). Mice with SNI exhibit altered mPFC-to-hippocampus oscillation patterns and decreased working memory (*178*). The PL and IL regions change distinctively during chronic pain. The PL had no change in density of FOS protein (an immediate early gene that reports recent neural activity) in mice observing a cagemate in pain; however, there was an increase in FOS expression after observing a stranger in pain (*179*). Acute blockade of the glucocorticoid stress response in the PL induces a social transfer of pain for stranger mice similar to that for cagemates, whereas injection of corticosterone in the PL reduces the social transfer of pain for cagemates (*179*). Inputs to the PL region from the ventral tegmental area (VTA) release dopamine, which induces antinociception in a mouse model of chronic pain by activating PL-to-dlPAG neurons (*180*). Bilateral lesions of the PL, but not IL, result in heat hypersensitivity and anxiety-like behaviors (*181*). Optogenetic inhibition of PL pyramidal *CamkIIa*$^+$ neurons induces anxiety-like behaviors, suggesting that the PL is involved in the regulation of social context and anxiety related to pain (*181*). The IL tends to show less distinctive changes during acute or chronic pain; however, BDNF protein decreases in the IL after peripheral inflammatory injury, and infusion of BDNF in the IL reverses inflammatory hypersensitivity (*182*). Further discussion of the distinct roles of the mPFC in chronic pain can be found elsewhere (*183*).

The PFC and ACC play critical roles in modulating pain experience based on the expectation of pain or pain relief. In humans, this

effect is often associated with the expectation of treatment. Human fMRI and positron emission tomography scans have paved the way to understanding the brain circuits underlying this phenomenon. Across the entire brain, fMRI studies have associated placebo analgesia, a phenomenon in which pain perception is shaped by expectation, with correlated activity in the PFC, ACC, hippocampus, PAG, pons, and cerebellum (*184*–*188*). Placebo analgesia in humans has recently been reviewed (*135*). Recent and ongoing work in rodents has used operant conditioning, which allows more precise circuit dissections to understand the precise pathways that mediate placebo or nocebo effects. For example, pairing opioids or aspirin with a CS cue showed that rodents can anticipate analgesia (*189*). Further work is needed to fully establish rodent models of placebo analgesia to take full advantage of the genetic and circuit dissection tools available.

PFC outputs to the PAG are believed to play a critical role in modulating pain by activating the descending pain control pathways from the PAG to the RVM and are discussed later in this review. Together, the PFC consolidates pain affective information and sensory features, evaluates motivational factors, and computes a course of action, effected through motor circuits, to halt or choose to endure pain.

Midbrain circuits for reward and aversion, and the motivation-decision model of pain

Pain is aversive, whereas pain relief is rewarding. The motivation to avoid pain and seek pain relief is generated through dopaminergic VTA and substantia nigra compacta (SNc) outputs, particularly to the NAc (mesolimbic dopaminergic system) (*190*). Human fMRI studies have revealed the involvement of the VTA and NAc both during pain and when anticipating pain or its relief, as well as altered functionality during chronic pain (*191*–*197*), consistent with the dual function of the VTA-to-NAc pathway in processing both rewarding and aversive stimuli. Rodent studies have shown NAc responses analogous to those in humans during pain onset and offset (*198*) and have enabled investigation of the anatomy and function of discrete VTA and NAc cell types and circuits in aversion and reward (*190*, *199*–*203*). For example, in a mouse model of nerve injury–induced neuropathic pain, increased excitability of NAc indirect pathway medium spiny projection neurons (MSNs) increased mechanical allodynia (*204*). In a rat model of migraine, vlPAG inputs to the VTA are required to generate conditioned place avoidance (*205*, *206*). Remarkably, dysfunction in the mesolimbic dopaminergic system during chronic pain also involves non-neuronal cells, including activated microglia in the VTA that can alter dopamine release in the NAc (*207*). In addition, the decreased motivational drive that can accompany chronic pain has been associated with galanin receptor 1–induced depression of excitatory synaptic transmission in NAc indirect pathway MSNs (*208*). Inhibition of κ opioid receptor signaling in the NAc using the selective antagonist NorBNI or chemogenetic inhibition of NAc dynorphin-expressing (*Pdyn*$^+$) MSNs restored normal motivation in a model of chronic inflammatory pain (*209*). Note that alongside this mesolimbic dopaminergic pathway, which mediates learning and anticipation of pain, the mesocortical dopamine system entrains the relative reward value (*190*), both systems defining the aversiveness of the situation and urgency to respond during pain. Crucially, pain aversiveness is often perceived in the context of other conflicting goals; cortical inputs to the NAc resolve these motivational conflicts and implement action decisions based on predictions (*210*, *211*). Glutamatergic projections from the ACC, IL, and PL regions to the NAc and VTA regulate approach-avoidance behaviors (*212*–*214*). Chemogenetic inhibition and optogenetic excitation of the IL-to-NAc pathway revealed an essential role for determining the approach-avoid balance in response to a pain-predictive cue (*212*). Pairing chemogenetic inhibition of either the ACC-to-NAc and ACC-to-VTA (*214*) or PL-to-NAc (*213*) projections with a chamber in a conditioned place paradigm led to chamber preference in chronic injury rats, but not controls. The importance of reward circuits and motivation in the context of pain has been thoroughly reviewed elsewhere (*192*, *210*, *211*, *215*, *216*).

Descending circuits for pain modulation

Activity in forebrain and midbrain circuits can profoundly influence nociception at the spinal level through direct cortico-spinal connections or medullary relays (*217*–*222*). For example, ACC neuron axon terminals, which can be observed in the SC DH, facilitate spinal excitatory transmission and behavioral hypersensitivity (*223*). Furthermore, neurons of the somatosensory cortex also innervate the DH, control tactile sensitivity, and contribute to tactile allodynia during neuropathic pain (*224*). The PAG critically contributes to descending pain modulation by integrating forebrain and midbrain inputs and, through neurons located predominantly in its lateral and ventral quadrants (vlPAG), by engaging distinct populations of RVM neurons that project to the DH and facilitate or inhibit nociception. Three populations of nociceptive RVM neurons have been defined: (i) On-cells show a burst in firing rate before a nociceptive withdrawal reflex and facilitate pain; (ii) off-cells fire tonically, pause during withdrawal reflexes, and inhibit pain; and (iii) neutral cells show no alteration in firing pattern during a nociceptive reflex, and their role remains less well understood (*218*, *219*, *225*). Recent studies have begun to elucidate the molecular identity of some of these RVM-to-SC neurons, their connectivity, and modulatory function in distinct pain modalities (*218*, *226*). A population of dual GABAergic and enkephalinergic (*Penk*$^+$) RVM-to-SC neurons reduces behavioral sensitivity to both heat and mechanical stimuli (*227*). In contrast, another population of GABAergic, but Penk-negative, RVM-to-SC neurons facilitates mechanical pain by inhibiting spinal GABAergic and enkephalinergic (*Penk*$^+$) neurons that normally presynaptically inhibit mechanosensitive primary afferent DRG neurons via $GABA_A$ and opioid receptors located on their central terminals (*228*). These RVM-to-SC neurons express the μ opioid receptor and represent a class of RVM on-cells. Alternatively, RVM neurons can modulate nociception by synapsing directly onto the central terminals of nociceptors and controlling their release of glutamate. Thus, RVM-to-SC serotonergic neurons release serotonin (5-HT) onto 5-HT3A- and TRPV1-expressing nociceptors, which sensitizes TRPV1 and causes hyperalgesia (*229*). In addition to GABA and 5-HT, another neurotransmitter, noradrenaline (NA) from the locus coeruleus (LC), critically contributes to descending pain modulation. Remarkably, activation of LC neurons that project to the SC inhibits nociception and can relieve neuropathic pain, whereas activating forebrain-projecting LC neurons increases spontaneous pain (*230*). This engagement of LC neurons for descending antinociception may depend on phospholipase Cβ4 (PLCβ4) signaling in PAG-to-LC neurons (*231*). These descending pain control systems show considerable sexual dimorphism (*232*), as well as modulation by

additional antinociceptive and pronociceptive endogenous molecules and drugs such as hormones, neuropeptides, cannabinoids, and nicotine (*233*–*237*). Last, note that the vlPAG also contains ascending pain modulatory neurons; a recent study described a class of vlPAG/dorsal raphe nucleus dopamine antinociceptive neurons that project to the BNST (*238*). Remarkably, this cell population shows sexual dimorphism; its optogenetic activation inhibited nocifensive behaviors resulting from inflammatory pain in male, but not female, mice.

MANIPULATING THE BRAIN'S AFFECTIVE PATHWAYS TO PROVIDE PAIN RELIEF (FIG. 3B)

Pharmacology (opioids)

Long-term opioid use is associated with harmful side effects, as well as risk of misuse, abuse, and opioid use disorder (*239*). However, clinical experience suggests that, in a subgroup of patients with chronic pain, stable doses of opioids can provide durable pain relief with limited side effects. This section focuses on opioids because long-standing evidence indicates a direct action on affective-motivational and cognitive-evaluative networks (*240*, *241*). Furthermore, the identification of the μ opioid receptor as the molecular target of clinical opioids like morphine (*242*) has enabled detailed mechanistic studies of neurotransmission modulation by opioids (*243*–*245*), including in affective circuits. Both clinical and rodent studies support the idea that opioids preferentially decrease the affective component of pain (*246*–*248*). For example, moderate activation of μ opioid receptors with a low dose of the biased and partial agonist PZM21 reduced affective-motivational nocifensive behaviors, without altering reflexive withdrawal from noxious stimuli in rodents (*39*). These features separate opioids from other common analgesic drugs that limit the production of pronociceptive mediators [for example, non-steroidal anti-inflammatory drugs (NSAIDs) (*249*)] or affect the function of primary afferent nociceptors (including sodium channel or calcium channel blockers such as lidocaine and ziconotide, respectively) or for which the molecular and circuit mechanisms of action remain unclear (such as gabapentinoids, anticonvulsants, and antidepressants). For example, activation of the gabapentin receptor α2δ-1, in addition to its effects on ion channels (*250*, *251*), can promote excitatory synaptogenesis in response to thrombospondin released by astrocytes in the SC DH (*252*, *253*). Gabapentin blocks this synaptogenesis mechanism, which may contribute to central sensitization during chronic neuropathic pain. However, it remains unclear whether gabapentinoids also influence remodeling of brain synapses of the pain affect circuitry via the same mechanisms to produce pain relief (*254*).

At the circuit level, μ opioid receptor distribution is prominent in emotional and cognitive brain circuits (*255*). The study of these opioidergic circuits has been facilitated by the generation of mutant mouse lines in which individual opioid receptor or peptide genes have been either targeted to express fluorescent receptors or DNA recombinases or flanked by loxP sites for conditional deletion experiments (*117*, *228*, *256*–*262*). Remarkably, μ opioid receptor–expressing neurons are found in lPB, ILN/MThal, and PAG, the three major output regions by which nociceptive DH projection neurons connect with emotional and cognitive circuits (*35*, *36*, *257*, *263*, *264*).

In the lPB, μ opioid receptors are expressed by *Calca*$^+$ lPBe neurons, in which μ receptor activation decreases glutamate release onto CeL neurons. In the dorsomedial/midline thalamus (dMT), μ receptors are present in thalamo-cortical (ACC), thalamo-striatal [dorsomedial striatum (DMS)], and thalamo-amygdalar (CeL and BA) circuits. In the dMT, including the paraventricular (PVT) and paratenial (PT) thalamic nuclei, μ receptor activation decreases glutamatergic transmission between dMT neurons and basal amygdala (BA) and CeL amygdala neurons, resulting in an overall reduction in feedforward activation of CeM neurons (*265*). μ receptors are also expressed by several classes of amygdalar neurons: by some BLA neurons (*266*) and, more abundantly, by ITC masses and populations of CeA GABAergic neurons, including *Cck*$^+$ neurons and neurons that project to the PAG, in which μ receptors regulate both the flow of information within the amygdaloid complex through G protein-coupled inwardly rectifying K+ (GIRK)-mediated hyperpolarization and the release of GABA in downstream targets (*36*, *267*–*270*). Note that μ receptor expression in the PVT might also mediate the expression of opioid withdrawal symptoms and aversive memory through a PVT-to-NAc circuit (*271*). A recent study demonstrated that μ opioid receptor$^+$ dMT neurons project to the dorsomedial, rather than the ventral, region of the striatum, where they synapse onto MSNs that receive convergent, μ opioid receptor–negative [although, see also (*272*)] input from ACC pyramidal neurons. Interestingly, these μ opioid receptor$^+$ thalamo-striatal neurons also project back onto L5 ACC pyramidal neurons, and μ opioid receptor agonists can presynaptically decrease glutamate release onto both DMS MSNs and L5 ACC pyramidal neurons. The latter synaptic mechanism of function of μ opioid receptors may contribute to the antinociceptive effect of intracerebral ACC morphine injections on the affective component of pain, without influencing withdrawal reflexes (*247*, *273*). Because glutamatergic thalamic μ opioid receptor$^+$ neurons predominantly express VGLUT2, these synaptic mechanisms could underlie the reduced opioid antinociception in mice with a conditional deletion of μ receptors in *Slc17a6*$^+$ neurons (*274*). However, aside from regulating excitability and transmitter release, including via several forms of synaptic plasticity in multiple types of pyramidal neurons, such as in the mPFC and insula (*126*, *272*), μ receptors are also thought to be expressed by multiple populations of GABAergic cortical interneurons such as *Lamp5*$^+$, *Sst*$^+$, *Vip*$^+$, and *Pvalb*$^+$ neurons (*275*). Precise genetic strategies may be required to resolve the contribution of these distinct populations of cortical μ opioid receptor-expressing neurons to opioid analgesia. Although intracerebral injection of μ opioid receptor agonist into the vlPAG has long been known to produce antinociception (*276*), the identity and connectivity of μ opioid receptor–expressing neurons in the vlPAG remain less well understood (*218*). We know, however, that these vlPAG neurons regulate the activity of several classes of spinally projecting neurons in the RVM, including μ receptor–expressing on-cells (*217*–*222*, *227*, *228*, *277*). Identifying the precise contribution to these different processes of the molecularly and pharmacologically diverse types of receptors activated by morphine-like opioids represents an exciting challenge (*278*–*282*).

Note that the expression patterns of δ and κ opioid receptors in pain circuits profoundly differ from that of μ receptors (*36*, *255*, *257*, *259*, *283*, *284*), consistent with the divergent properties of their selective agonists. For example, in the cortex, δ receptors are predominantly expressed by *Pvalb*$^+$ (PV) inhibitory interneurons rather than by thalamic μ-expressing glutamatergic inputs to the ACC, where δ enhances the glutamatergic, excitatory input from the MThal to the pyramidal neurons in the ACC by disinhibiting local

feed-forward inhibition mediated by *Pvalb*$^+$ interneurons (*126*). Note that these PV inhibitory interneurons represent the class of cortical and hippocampal neurons that abundantly coexpresses δ and μ receptors, a rare feature in the nervous system (*36*, *257*, *275*, *283*–*285*). In the amygdala, δ receptors are predominantly found in the BLA, on the soma and axon terminals (*258*), in contrast to μ receptor distribution in ITC and CeA neurons. κ receptors are also present in affective and valence circuits, but generally in different cell types compared to μ, consistent with the diverging properties of their selective agonists (*209*, *286*, *287*). Last, although μ opioid receptors are expressed by nociceptors and spinal projection neurons (*36*, *283*), conditional deletion studies suggest that μ receptors in nociceptors are dispensable for morphine analgesia [(*38*); however, see also (*288*)].

Stimulation

The first documented use of stimulation intended specifically to alleviate chronic pain was performed in the 1960s, targeting deep brain electrical stimulation (DBS) to the thalamus (*185*). In the 1980s, TMS was developed as an alternative to electrical stimulation (ES) (*289*). TMS uses magnetic induction to generate macroscopic electrical currents in the brain (*289*). A shift from invasive to noninvasive forms of stimulation like TMS has made stimulation and modulation of brain circuits available to a broader patient group. Today, TMS and transcranial direct current stimulation (tDCS) are the most commonly used methods for noninvasive modulation of brain circuits to alleviate chronic pain (*290*).

How do TMS, ES, and tDCS work?

ES and TMS drive action potential firing by exciting neurons and passing axons and backfiring input terminals at the site of stimulation (*291*). In contrast, tDCS is less temporally and spatially specific than ES and TMS and acts by hyperpolarizing the resting membrane potential, making the anode region more excitable and the cathode less (*292*). Studies in human subjects and animal models both show that high-frequency stimulus trains excite the target more efficiently than low-frequency trains (*293*–*297*). Theta burst stimulation, a TMS protocol commonly used for cortical stimulation, uses three pulse bursts delivered at high frequency (for example, 50 Hz), repeated every 200 ms (5 Hz) (*293*). Theta burst protocols are a compromise aimed to capture the advantages of high-frequency stimulation while limiting the risk of inducing seizures (*294*, *298*). Examination of fMRI interleaved between TMS pulse trains shows a stimulus target volume of 5 to 10 cm^3 (*299*). In vivo voltage dye imaging in cat cortex found a progressive rise in excitation at the targeted region throughout a 10-Hz electrical stimulus train (*300*), supporting previous slice electrophysiology studies that had similarly concluded that high-frequency stimulation in cortical tissue preferentially activates excitatory neurons (*301*). Furthermore, a recent calcium imaging study in mice showed that excitatory neurons in L2/3 activate in response to specific stimulation frequencies, similar to visual cortical neurons tuned to a specific direction of drifting grating stimuli (*296*). Although our understanding of the biophysics underlying brain stimulation is evolving, many important questions remain to be explored.

MCS for pain relief and as a model for understanding TMS and tDCS

The motor cortex (MC) is a common target of studies attempting to determine the neurobiology of cortical stimulation. MC stimulation (MCS) results in motor activity that enables confirmation of correct targeting. The muscle end-plate potential (MEP), which can be performed in humans and in animal models, enables examination of resting motor threshold, amplitude of stimulus-evoked responses, and long-term changes in muscle tone (*299*, *302*). Performing MCS with MEP as the readout reveals long-term changes in MC excitability after stimulation (*303*, *304*).

MCS was first used to reduce chronic pain in 1991, when Tsubokawa and colleagues (*305*) implanted electrodes into the primary MC of patients with refractory central pain. Nine of 12 patients described their pain relief as good or excellent on the days when stimulation occurred, and 8 of these patients continued the therapy with reduced chronic pain after 1 year of treatment (*305*). In the intervening 30 years, hundreds of patients have received MCS. A meta-analysis across studies reported that 64% of patients experienced a favorable response after MCS and 45 to 75% of patients reported a decrease of at least 5 points on a 0 to 10 visual analog scale (VAS) of pain intensity (*297*). Furthermore, case studies applying MCS to patients with severe, otherwise untreatable, pain showed remarkable pain relief (*295*, *305*, *306*).

The mechanisms underlying MCS efficacy remain poorly understood. fMRI imaging in human subjects identified MCS-induced hotspots of activity in descending pain control regions that correlated with suppression of acute secondary hyperalgesia (*307*). Intracranial injection of GABAergic or glycinergic antagonists into the PAG of SNI rats before MCS prevented MCS-induced antinociception, providing further evidence for the involvement of descending pain control (*308*). In contrast, MCS increased the density of FOS$^+$ neurons in the ACC and BLA, and lesions of the aIC enhanced MCS-induced antinociception in a chronic pain rat model (*309*–*311*), together suggesting that pain affective circuits are involved in MCS analgesia as well.

Noninvasive targeting of pain-related brain regions

In addition to MC, noninvasive brain stimulation has been targeted to many pain-related brain areas with the intention of reducing chronic pain, including the ACC, IC, somatosensory cortex, and dlPFC, with varying degrees of success (*312*). Stimulation of S1 and/or S2 has been found to modulate perception of sensory features of pain without providing the clinically necessary reduction in pain affect (*313*–*315*). In contrast, a study using noninvasive stimulation of the ACC or IC in patients with central chronic pain found that neither target evoked a measurable effect on chronic pain scores in patients, although the ACC stimulation decreased anxiety and the IC stimulation increased heat pain thresholds (*141*). The most promising alternative, to the MC for noninvasive stimulation is the dlPFC, the stimulation of which reduces acute pain in healthy volunteers and decreases chronic pain scores in patients (*290*, *316*–*318*).

DBS for chronic pain relief

Many regions critical for pain processing are difficult to effectively stimulate noninvasively. The ACC, VP thalamus, and PAG have all been identified as promising DBS targets for reducing chronic pain; the literature for these methods has recently been reviewed (*319*).

Neurofeedback

Given the crucial role of the brain in the experience of pain and its modulation, researchers have hypothesized that direct manipulation of one or more brain regions could enhance pain modulatory systems and thereby reduce the underlying central nervous system (CNS) abnormalities associated with chronic pain. In addition to the pharmacological, direct stimulation (TMS, DBS, and tDCS), and surgical techniques discussed in this review, researchers have

developed neurofeedback techniques that teach individuals to self-regulate brain functionality. Neurofeedback is a noninvasive therapy that directly targets brain activity and/or connectivity patterns and uses either electroencephalograph (EEG) recordings or fMRI signals to provide individuals with real-time visual and/or auditory feedback reflective of the targeted brain functionality (*320*, *321*).

EEG neurofeedback is used more frequently than fMRI because of its greater accessibility and lower cost. Typically, EEG neurofeedback targets a change in a specific oscillatory bandwidth, most often the alpha band (8 to 13 Hz) (*322*). In contrast to EEG neurofeedback, fMRI neurofeedback measures and feeds back information from specific brain regions or networks using fMRI's higher spatial resolution. The lower temporal resolution of fMRI seems to benefit the learning of self-regulating brain functionality.

An example from one of the earliest studies of fMRI neurofeedback fed back brain signals from the dACC (*323*). In healthy volunteers given an evoked thermal stimulus, neurofeedback training led to increased control over brain activity and an associated increase in control over pain intensity. In a single training session, patients with chronic pain noted reduced pain that correlated with the degree of brain control over the dACC. Similarly, Guan *et al.* (*324*) modulated the rostral ACC (rACC) in a group of patients with postherpetic neuralgia (PHN). Patients learned to modulate their rACC signal and their pain perception. Using an fMRI-to-EEG amygdala fingerprint, Goldway *et al.* (*325*) conducted a neurofeedback trial in which they taught patients with FM to modulate their own amygdalar activity using a single EEG channel. Patients demonstrated improvements in objective measures of sleep and follow-up improvements in pain, demonstrating the benefit of this approach combining fMRI and EEG neurofeedback (*325*).

More recently, Zhang *et al.* (*326*) illustrated the potential of implicit learning strategies to modulate pain. Specifically, they used real-time decoded fMRI signals from the IC integrated into a closed-loop feedback control system and found that decoding the brain patterns without the participant's volitional control leads to adaptive changes in the brain. These results demonstrate the need to account for these adaptive changes in the design of future systems intended to direct brain control. Although neurofeedback using fMRI and EEG is a promising avenue for therapeutic interventions, researchers must still identify the optimal brain targets, patterns, frequency bands, and networks for manipulation; demonstrate that neurofeedback training leads to learning; ensure that neurofeedback leads to measurable changes in behavior (examples include pain relief, coping, pain catastrophizing, and fear avoidance); and develop appropriate controls and clinical trial designs (*327*, *328*). For additional information on neurofeedback in the context of pain, we direct the reader to the following reviews (*320*, *321*, *329*).

Cognitive behavioral therapy

Cognitive behavioral therapy (CBT) is a psychotherapeutic treatment encompassing a set of techniques and approaches, ranging from structured psychotherapies to self-help materials, that helps individuals learn to identify and change destructive and/or disturbing thought patterns that may negatively influence behavior and emotions (*330*–*333*). Key processes for pain management include relaxation training, cognitive restructuring, and exposure techniques. In addition to pain, CBT is used to treat a wide variety of mental health conditions including addiction (*334*, *335*), anxiety (*336*, *337*), depression (*338*, *339*), and personality disorders (*340*). It has also proved helpful for patients with chronic pain (*340*, *341*).

Although we refer here and below to CBT (and its neural correlates) as a singular therapy, it represents a family of psychological treatments that has evolved over time. The first generation of CBT applied learning principles intended to change overt behavior. Classic CBT (second generation) was introduced in the late 1970s and focuses on the role of maladaptive thought processes in emotion, behavior, and pain. More recently, a third generation of CBT places more emphasis on themes such as acceptance, mindfulness, values, metacognition, and interpersonal relationships, giving rise to therapies such as acceptance and commitment therapy, mindfulness-based cognitive therapy, and several others. This section will focus on classic CBT and review its neural correlates.

CBT draws on cognitive and behavioral strategies to improve pain-related functioning and help patients cope with pain (*341*). After CBT treatment, patients with chronic pain report reduced pain, distress, nocebo hyperalgesia, and pain catastrophizing, as well as improvement of their daily functioning (*342*–*344*). CBT-induced pain relief is highly variable between patients, and the improvement correlates strongly with the patient's attitude: Distressed patients who see their pain as an uncontrollable and highly negative life event benefit less, whereas patients with low perceived disability and high orientation toward self-management during CBT treatment benefit more (*342*, *343*). These observations support the hypothesis that the outcomes of multidisciplinary pain treatment correlate with the individual patient's cognitions and coping responses (*343*).

Although CBT continues to be widely used for pain management, the neural mechanisms that mediate analgesia during CBT remain unclear. Human functional neuroimaging studies dominate CBT research related to pain perception. Given the relatively limited literature investigating brain activation changes during CBT treatment in patients with pain, it is helpful to first understand how CBT impacts an individual's psychological state to affect pain processing. Studies examining the effects of distraction on pain processing found that pain-evoked activity in several cortical areas, like the S1, IC, and ACC, is stronger when an individual focuses on pain than when distracted (*345*–*347*). Neuroimaging studies evaluating the effects of emotional states on pain processing found that negative emotional states alter pain-evoked cortical activation in several brain regions, but most consistently in the ACC (*345*, *347*, *348*). Placebo administration has been shown to increase activity in the ACC, PAG, and cerebellum but decrease activity in the S1 and IC (*349*–*351*).

Studies have demonstrated that, for individuals with chronic pain, CBT generates both functional and structural changes in the brain. One of the first studies on chronic pain found that CBT treatment increased pain-evoked activity in the lateral PFC, which subsequently increased its connectivity with the thalamus, compared to controls (*352*). This lateral PFC region contributes to semantic processing and cognitive control, both of which are associated with exposure and cognitive restructuring therapies. Similarly, large brain networks involved in sensorimotor, self-referential, and cognitive control show altered connectivity patterns in patients with chronic pain compared to controls, which return to baseline after CBT (*353*–*355*). These connectivity changes also occurred in healthy controls when receiving CBT-based training to cope with evoked pain (*356*). In another study in patients with chronic pain, CBT led to increased gray matter volume in multiple regions

associated with pain processing, such as the dlPFC, ACC, and S1, some of which correlated with decreased pain catastrophizing (*357*).

A few studies have shown evidence that CBT generally affects neural function in pain networks. Biofeedback relaxation activates the ACC, basal ganglia, S1, inferior parietal cortex, and cerebellar vermis (*358*). Similarly, progressive muscle relaxation, one type of CBT, gradually decreases activity in the superior frontal gyrus (SFG), inferior frontal gyrus (IFG), and posterior cingulate cortex (PCC) (*359*), suggesting that CBT may activate endogenous pain descending modulatory systems. Last, the efficiency of CBT for the treatment of other mental diseases such as anxiety and depression (*68*, *360*) may suggest that the nociceptive neurons within CBT-responsive cognitive and emotional circuits are polymodal neurons that control other functions beyond pain, such as attention and mood.

Finally, researchers have identified that different cognitive strategies to modulate pain evoke distinct brain activity patterns. For example, during focused attention, brain activity localizes to the pre- and postcentral gyrus (the primary motor and somatosensory cortices, respectively), middle occipital gyrus, and inferior parietal lobe, whereas reappraisal of the pain (imaging the painful stimulus alternating between harmful or nonharmful) engaged the thalamus, amygdala, ventral lateral PFC, MCC, and parahippocampal gyrus (*361*). The postcentral gyrus was the only area that overlapped in activation during both strategies. In a more recent study, researchers investigated three distinct pain modulation strategies: (i) non-imaginal distraction by counting backward in steps of seven, (ii) imaginal distraction by imagining a safe place, and (iii) reinterpretation of the pain valence (reappraisal) (*362*). They also identified strategy-dependent activations. Reappraisal and the imaginal distraction (safe place) primarily engaged the anterior insula, whereas the non-imaginal distraction task activated primarily the central operculum. The tasks involving distraction from pain (counting and safe place) modulated activity in the PCC. Together, these findings and others suggest that combining specific strategies with targeted brain stimulation or neurofeedback enhances treatment efficacy.

Surgery

First used in 1962, cingulotomy (lesioning of the ACC or the cingulum bundle white matter) has long been an option for decreasing chronic pain unpleasantness in patients who fail to respond to other interventions (*185*, *363*). In this initial study, 16 patients suffering from debilitating chronic pain were selected for unilateral or bilateral cingulotomies (*363*). The authors classified pain relief as poor, fair, good, or excellent, finding that 12 of the 16 patients experienced good or excellent pain relief and 11 of 16 showed decreases in comorbid psychiatric disorders (*363*). The authors further noted that pain relief was observed immediately after the cingulotomy was performed, while the patient was still in the operating room (*363*). Although use of this technique has decreased in recent years in favor of nondestructive alternatives, a recent meta-analysis comparing data from 11 articles that included 224 patients concluded that, across all studies, more than 60% of patients reported substantial pain relief at least 1 year after the intervention (*364*). In this meta-analysis, the few side effects noted included, in <5% of patients, transient postoperative confusion and/or seizures (*364*). However, a case study of a patient with schizoaffective disorder found that cingulotomy increased pain, the opposite of the expected effect (*157*). Last, note that a number of other surgical procedures are used to treat pain (*365*).

CONCLUSION

Although pharmacotherapy, brain stimulation, neurofeedback, CBT, and surgical protocols used to treat pain continue to improve, research regarding the brain circuits and neuron types that mediate pain affect in animal models is revealing a wealth of candidate molecular targets to develop innovative analgesic drugs that could selectively dampen the unpleasantness of pain, without altering nociception in the circuits that underlie other necessary aspects of pain experience, such as withdrawal reflexes and the sensory-discriminative dimension of pain.

Cell type–specific multiomics is revolutionizing our understanding of neuronal diversity by revealing the molecular content of individual neurons within circuits. In the pain field, single-cell/nucleus RNA sequencing (*366*) can now generate, from each of a subject's nociceptive neurons, comprehensive catalogs of expressed genes that encode proteins with inhibitory functions and potential analgesic capabilities, enabling precision pain medicine. Similarly, although this review focuses on circuits, molecules in non-neuronal cells such as microglia could be targeted for the treatment of pain (*367*, *368*). Optically recording the activity of molecularly defined nociceptive neurons in freely moving mice experiencing chronic pain and administered with candidate analgesics can be used as a screening approach that relies on the normalization of both affective-motivational behaviors and pathological neural codes associated with pain chronification in the amygdala (*37*) and connected regions including the ACC, IC, ILN, MThal, and lPB (*148*). For example, with agonists of neuromodulatory receptors such as inhibitory $G_{i/o}$ protein-coupled receptors ($G_{i/o}$ GPCRs), individualized drug dosage could reduce patients' pain unpleasantness while preserving both withdrawal reflexes and the sensory-discriminative dimension of pain. Such pain asymbolia-like treatments would not only rescue the well-being and function of patients with chronic pain, but also maintain sufficient nociceptive functions necessary to sense and withdraw from noxious stimuli unrelated to their chronic pain condition, a substantial challenge when targeting primary afferent nociceptors or spinal networks and their ascending circuits. As a proof of principle, expressing and activating $G_{i/o}$ protein-coupled DREADDs (hM4Di) (*369*) in BLA nociceptive neurons of mice alleviated pain affective-motivational behaviors across pain modalities (acute heat, cold and mechanical pain, and chronic neuropathic pain) without altering withdrawal reflexes, anxiety, or reward (*37*); one would expect that activating $G_{i/o}$ GPCRs natively expressed in these neurons to have the same effect. Alternatively, by resolving the molecular repertoires both of the μ opioid receptor–expressing neuron types that modulate emotional and cognitive pain circuits to dampen pain affect during opioid analgesia and of the μ opioid receptor–expressing neuron types responsible for deleterious effects such as addiction and opioid-induced respiratory depression, researchers could potentially develop better opioid therapies that mimic the effect of morphine on nociceptive neurons and/or adjuvant therapeutics that oppose deleterious opioid signaling in reward and breathing circuits.

In conclusion, these neural circuit discoveries and translational endeavors, supported by outstanding efforts such as the National Institutes of Health (NIH) Brain Research Through Advancing Innovative Neurotechnologies (BRAIN) (*370*) and Helping to End Addiction Long-term (HEAL) (*371*, *372*) Initiatives and its Preclinical Screening Platform for Pain (PSPP) (*373*), provide an unprecedented opportunity to end the dual public health crises of chronic

pain and opioid use disorders. To fulfill this goal, we will need to use these discoveries to develop better biomarkers to facilitate the development of non-addictive pain therapies. Objective biomarkers can indicate that a therapeutic intervention has reached its central target, predict the response to the therapy, enhance the quality of the clinical trial by allowing clustering of patients by presumed responsiveness, and improve monitoring of safety and efficacy over time. Frameworks for developing and validating neuroimaging-based biomarkers and composite biomarkers have been put forward (*374*, *375*). Programs like the NIH HEAL Initiative are stimulating considerable research efforts to advance the development and translation of biomarkers to yield targeted, safe, and effective therapies for pain.

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Acknowledgments: We thank J. Blair for editing the manuscript. We regret that we could not cite numerous important studies given the reference number limit and broad scope of this review article. We encourage readers to also consider the references in the articles we could cite. **Funding:** The authors' research on the circuits for pain and its treatment is supported by NIH grants (S.M.) R61NS11865, R01NS109450, K24NS126781, (N.M.L.) F32DE030003, (G.S.) R01DA044481, R01NS106301, and R21DA049241. G.S. is a New York Stem Cell Foundation – Robertson Investigator. **Competing interests:** G.S. is a cofounder of Epiodyne, a drug discovery company, an inventor on a patent application related to imaging of neural dynamics to discover analgesics, and a member of the NIH PSPP Preclinical Screening Platform for Pain External Consulting Board.

Submitted 7 July 2021
Accepted 22 October 2021
Published 10 November 2021
10.1126/scitranslmed.abj7360

Science Translational Medicine

Brain circuits for pain and its treatment

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Sci. Transl. Med., 13 (619), eabj7360. • DOI: 10.1126/scitranslmed.abj7360

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