Review

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Spontaneous pain as a challenge of research and management in chronic pain

https://doi.org/10.1515/mr-2022-0007
Received May 4, 2022; accepted May 31, 2022;
published online June 28, 2022

Abstract: Spontaneous pain occurring without apparent external stimuli, is a significant complaint of individuals with chronic pain whose mechanisms, somewhat surprisingly, remain poorly understood. Over the past decades, neuroimaging studies start to reveal brain activities accompanying spontaneous pain. Meanwhile, a variety of animal models and behavioral tests have been established, including non-reflexive tests and free-choice tests, which have been shown to be effective in assessing spontaneous pain. For the spontaneous pain mechanisms, multiple lines of research mainly focus on three aspects: (1) sensitization of peripheral nociceptor receptors and ion channels, (2) spontaneous neuronal firing and abnormal activity patterns at the dorsal root ganglion and spinal cord level, (3) functional and structural alterations in the brain, particularly the limbic system and the medial pain pathway. Despite accumulating evidence revealing distinct neuronal mechanisms from evoked pain, we are still far from full understanding of spontaneous pain, leaving a big gap between bench and bedside for chronic pain treatment. A better understanding of the neural processes in chronic pain, with specific linkage as to which anatomical structures and molecules related to spontaneous pain perception and comorbidities, will greatly improve our ability to develop novel therapeutics.

Keywords: behavioral measurement; limbic system; primary sensitization; spontaneous pain.

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Introduction

Chronic pain is one of the most prevalent clinical situations and a serious medical, financial, and social burden [1]. For pain managements, opioids, first discovered and clinically applied over half a century ago, are still potent and efficacious drugs used for both acute and chronic pain conditions despite their common side effects such as tolerance and hyperalgesia [2–4]. Development novel painkillers and the optimization of pain managements are important goals in both preclinic and clinic studies. Unfortunately, the rapid accumulation of understanding on pain mechanisms is not followed by rapid success in discovering new analgesics [5].

Developing both pharmaceutical and non-pharmaceutical therapies for pain requires solid research models, especially animal models. When talking about pain mechanisms, we should make a clear distinction between reflexive pain and spontaneous pain, two distinct types of pain behaviors [6]. Reflexive pain is a basic physiological phenomenon that responding to the external sensory stimuli (nociceptive), in both physiological and pathological states. Due to the uniformity and convenience of assessment criteria, the monitoring of reflexive pain is currently the most widely used behavioral assessment feature for evaluating analgesia or hyperalgesia effects in animal pain models [7]. As a result, neurobiological mechanisms and drug development are also based on the conclusions obtained from reflexive pain behaviors. By contrast, spontaneous pain uniquely exists in pathological pain conditions and is the most frequent complaint from patients (see Box 1). In a study exploring the spectrum of sensory abnormalities among the 1,236 neuropathic pain patients, no more than one-third reported any thermal or mechanical somatosensory abnormality (with the frequency of most well below 25%), but 100% of these subjects reported spontaneous pain, usually burning or electric shock like [8]. However, for technical limitations, spontaneous pain behaviors are much less evaluated in animal research than reflexive pain. Thus, research on animal pain models may not be clinically relevant considering the distinction between spontaneous and reflexive pain.

In recent years, a significant rise in the interest on spontaneous pain has significantly boosted our understanding on this behavior [9–11]. In this review, we will summarize and discuss the current findings and future directions on the animal models, measurable methods, neurobiological mechanisms, comorbidities, and treatment strategies of spontaneous pain.

Box 1. What is spontaneous pain?
The standard definition of spontaneous pain is not given by the International Association for the Study of Pain. Similarly, the studies of spontaneous pain also go unheeded. Nevertheless, the impact of spontaneous pain on daily life cannot be ignored. "Spontaneous" means occurring without apparent external cause or trigger. In 2012, Bennett and Mogil et al. re-emphasized the term of spontaneous pain and pointed that might be temporally summated hypersensitivity (allodynia and hyperalgesia) from activities of daily life [12, 13]. In this review, we discuss the concept of "spontaneous pain" that is referred to the *symptomatology*, but rather the *etiology*. Based on different etiological mechanisms and pain models, ample evidence indicates that spontaneous pain has two major patterns of manifestation: ongoing pain and paroxysms pain. Ongoing pain is often described as burning pain. The factors trigger ongoing pain is not external but internal-inflammation and active receptors, and from human and animal studies, is thought to be dependent on C fibers [14]. Paroxysmal pain, or tonic pain is described as shooting pain or electric shock like and is thought to be dependent on Aβ and Aδ fibers [15].

Spontaneous pain: distinct from reflexive pain

Chronic pain is defined as "a persistent complaint of pain lasting for more than the usual period for recovery" [16]. Accumulated lines of evidence based on human brain imaging have revealed that chronic pain is not simply a sustained state of nociception, but rather an allostatic state established through gradually progressing plastic changes in the central nervous system [17, 18]. Central reorganization is a hallmark of chronic pain. Investigations using neuroimaging and electrophysiological approaches have further revealed the implication of broad brain areas. In early years, spontaneous pain is usually studied as a feature of chronic pain and substantially underappreciated.

Studies of the unique mechanisms of spontaneous pain (especially the differences from reflexive pain) originate from the neuroimaging observations of chronic pain patients by Apkarain and his colleagues in the 1990s [11, 19]. Interesting, they reveal distinct mechanisms between spontaneous pain and reflexive pain, despite some overlapping brain activation patterns. Spontaneous pain is associated preferentially with changes in the limbic system and the medial pain system, while reflexive pain relates more to the lateral pain system [20]. In knee osteoarthritis patients, knee pressure-evoked pain activates brain regions commonly observed for acute pain [11, 21], while ongoing spontaneous osteoarthritis pain engages medial prefrontal-limbic cortical areas [22]. Objective noxious stimulus intensity was inversely related to alpha (8–13 Hz) and beta (14–29 Hz) oscillations in sensorimotor areas, whereas subjective pain was positively related to neuronal oscillations at gamma (60–90 Hz) frequencies in the prefrontal cortex [23]. The prefrontal cortex plays an outstanding role in spontaneous pain. Functional magnetic resonance imaging (fMRI) studies of different chronic pain populations have shown that ongoing pain intensity is reflected by blood-oxygen level dependent (BOLD) signals in the medial prefrontal cortex [24, 25]. The dorsal medial prefrontal cortex (PFC) to insula connectivity can identify patients prone to persistent back pain [26]. Default mode network (DMN), which encompasses the PFC, to insula connectivity is associated with spontaneous pain in fibromyalgia patients [26]. In electroencephalogram (EEG) studies, prefrontal gamma oscillations also reflect ongoing pain intensity in chronic back pain patients [23].

Therefore, based on the brain imaging results from human, different brain regions were involved in the evoked pain and spontaneous pain, more broader brain regions were activated by allodynia pain, while the spontaneous pain were mainly associated with the affective and emotion areas [18, 19]. However, imaging studies mostly reveal correlation rather than causation. Animal experiments would prompt a better understand of mechanisms in spontaneous pain, so as development of targeted drugs and treatments.

Animal models and measures

To align available rodent models with clinically relevant forms of pain, we need to focus not only on their reflexive responses to external stimuli, but also on voluntary behaviors under unrestrained states. A major factor to keep in mind is that limitations in animal models of pain. Most animal literature relies on inflammatory and neuropathic pain, with the hindpaw as the implicated region [27]. Suitable models that mimic prevalent chronic pain conditions in

human, such as chronic back pain, trigeminal neuralgia, phantom limb pain and headache, are still lacking [9].

Another important factor is the measurements of spontaneous pain. Human self-ratings of pain using questionnaires or scales, though subjective, are quantitative and can be diversely adopted for the measurement of both experimental and clinical pain. While humans can address standardized questionnaires, and give defined ratings and detailed description for pain episodes with their occurrence and quality, we have to execute a series of surrogate measures and analyze comments of their wellbeing in rodent subjects [9]. In early years, there is a significant gap between the animal models used to study the etiological versus symptomatic aspects of the disease. Recently, researchers have built up the several measurable paradigms based on the affective component of pain and spontaneous behaviors, such as voluntary wheel running [28], home-cage monitoring [29], burrowing [30], passive avoidance [31], place preference [32] and facial expression analysis [33]. All these paradigms could be divided into two categories as follow (see Figure 1).

Non-reflexive tests are based on natural behaviors that reflect inner states. The observation of spontaneous lifting, licking, and flinching behaviors for the affected hindlimb is an easy and widely used method to assess spontaneous pain [34, 35]. Analyzing modifications of changes in the spontaneous posture have been demonstrated in many rodent models of peripheral never injury or inflammation, such as the spinal nerve injury (SNI) model in rats [36], the spinal nerve ligation (SNL) model in rats [37], the complete Freund's adjuvant (CFA) model in rats [10], and the monoarthritis model in rats [38]. Some laboratories have also evaluated spontaneous paw lifting behaviors in mouse cancer pain model [39]. However, no spontaneous posture changes are observed in rodents with chronic constriction nerve injury (CCI) model [40], suggesting that this method does not apply in all animal pain models.

Static and dynamic weight bearing of hindpaw is another objective measure employed in diverse pain models. In the CFA-induced inflammatory pain model, mice or rats exhibited significant changes in hindpaw weight distribution up to 21 days after inflammation [28, 41]. In the CCI model and the femoral cancer model in mice, abnormal distribution of weight bearing lasted for more than 28 days [41], and over 70 days has been found in an osteoarthritis rat model [42]. Recently, a reproducible and sensitive method reports that spontaneous pain could be accurately evaluated by the proportion of weight and the amount of time placed on each of mice's 4 limbs after induction of arthritis pain in one

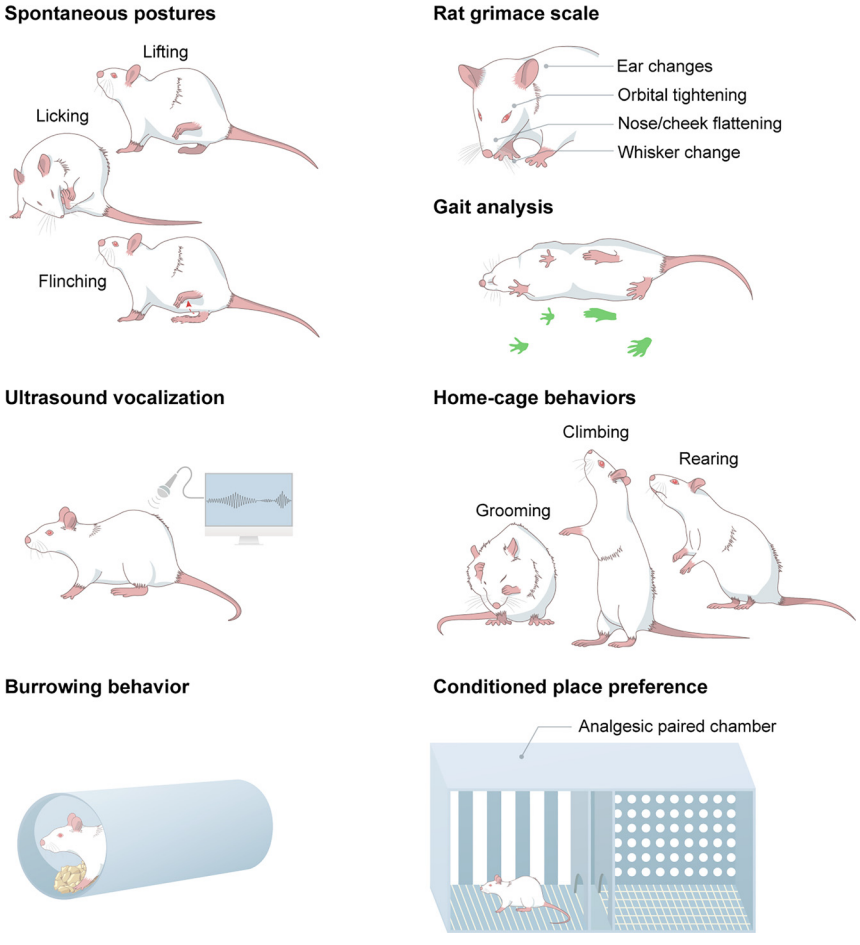

Figure 1: Behavioral measurements of spontaneous pain. Diagrams showing the typical behavioral tests of spontaneous pain, including spontaneous postures, ultrasound vocalization, burrowing behavior, rat grimace scale, gait analysis, home-cage behaviors, and conditioned place preference tests.

knee. Joint pain in these mouse models produces a significant increase in evoked pain responses and an alteration in weight bearing [43]. Systems for gait analysis are also used to detect the changes induced by spontaneous pain in rodent models [44, 45]. Recently, aberrant gait performance has been determined in a monoarthritis model in rats [46]. In the SNI model, changes of gait were detected and peaked just 1-day post-surgery and sustained shorter than the observed mechanical allodynia [40], leading to the assumption that the mechanisms of evoked pain and spontaneous pain are distinct. Again, however, several studies have found no significant correlation between weight bearing and nerve injury related models in rats [47]. Thus, although dynamic weight bearing has well application prospect, it still needs to be used with caution.

Like humans, mice or rats have been found in many studies to exhibit stereotyped facial expressions in response to salient events. Mogil and his colleagues develop the mouse grimace scale (MGS) [33] and rat grimace scale (RGS) [48] as a behavioral coding system to quantity the spontaneous pain. The method has been used in neuropathic, inflammatory, and fibromyalgia rodent models [33, 48, 49].

Except for the methods mentioned above, many studies have developed other methods to evaluate the level of spontaneous pain in rodents. For instance, ultrasound vocalization. Researchers record a period of vocalization from animal in an unspecific sound-free environment and then calculate to the intensity and duration of specific frequency-dependent cries to reflect the spontaneous pain [50, 51]. In addition, burrowing behaviors [30], home-cage behaviors (grooming, rearing, climbing, etc.) [29] and weight loss [52] are considered as signs for non-wellbeing due to spontaneous pain.

The advantage of non-reflexive tests is their unrestricted and longitudinal feature. Limited external factors would disturb the test performed in a familiar context considering the lack of additional intervention. However, a major disadvantage of these tests is their instability. Due to the fluctuating nature of spontaneous pain, the limited observation span could not cover the entire cycle of spontaneous pain. When the experiment timepoint drops into the trough or peak of behavioral oscillation, the detected level may decrease or increase in the following temporal window, respectively. Therefore, exploiting the full monitoring over the development and maintenance of chronic pain has been valued to be performed.

Free-choice tests reflect the level of spontaneous pain by means of rewarding system and conditioned training. Since built up by King et al. in 2009, conditioned place preference (CPP) has been considered the gold standard for measuring spontaneous pain in rodents [32]. In the initial study, the authors used a three-chamber system (two distinct side chambers with different visual, floor or odor cues and a middle neutral chamber). Animals were free to access to each chamber to set up preconditioning baseline. Spinal administration of analgesics was paired with one chamber. After conditioning, animals were permitted to shuttle across all chambers, and a preference for the analgesic-paired chamber was observed. The phenomenon indicates the existence of ongoing pain. The CPP method has been proved to work well in several chronic pain models, including SNI, CCI and CFA in rats [32, 53, 54], osteoarthritis in rats [55], and SNL in mice [56]. Beside the application of drugs [57], this measurement could also be used to evaluate the contribution of specific anatomical regions or neural pathways to analgesia when combined with opto- or chemo-genetic intervention [53, 58].

Coincidentally, place avoidance test utilizes the motivation that animals escape from noxious stimuli to avoid pain. The measures are subdivided into either real-time (RPA) or conditioned (CPA) aversion in freely moving rodents [31, 49, 59]. Similar to CPP, conditioned place aversion tests also use three-chamber device to pair conditioned training that the plantar stimulus is delivered on the injured paw, leading to avoidance of the location. Real-time place avoidance is employed to examine the immediate effects of regulating brain regions on avoidance or aversion that indicates the exacerbation of spontaneous pain in chronic pain models [31, 49]. This paradigm usually adopts two-chamber (occasionally three-chamber) or two-zone devices with free access to each area. When animals enter one assigned chamber/zone, the paired condition (like noxious stimulus, optogenetic stimulation) is applied which induces the avoidance. The other chamber/zone is paired with control stimulation.

The free-choice tests are stable and valuable paradigm with wide application. However, since the conditioning needs to be paired with the relevant analgesia strategies for several days, for example injection of painkillers, it could not be employed to evaluate spontaneous pain continuously, thus eliciting the first controversial issue. The second issue lies in the fact that the conditioned training requires animals to remember the relationship between the context and pain relief or aggravation. Thus, impaired memory functions, prominent comorbidity of chronic pain, could cause substantial confusion in explaining the failure of significant preference or avoidance to the invalidity of intervention. Finally, CPP experiments lack accurate quantitation and show substantial individual variations.

Challenges in studying spontaneous pain in rodents

Researchers hope to design short-duration tests with minimal efforts to observe significant changes in measurements. But considering the fluctuations of spontaneous pain

in humans, it is also important to design appropriate experiments to assess the longitudinal and periodic behavioral variations. Meanwhile, the establishment of observer-independent methodology should also be emphasized. Standardized and repeatable procedures are still lacking. The non-reflexive results, such as paw lifting, grooming and facial scoring, almost purely rely on the subjective qualitative and quantitative methods. But in recent years, with the application of machine learning techniques in neurobiology, it will be helpful to understand the objective readouts of spontaneous state of a rodent individual.

Subspinal pathological mechanism

Spontaneous pain can develop as a consequence of both primary afferents sensitization directly involved in the inflammatory or nerve injury processes, and sensitization of neuronal processing in the spinal cord (central sensitization) or higher centers. Previous studies have reported that abnormal spontaneous activity in individual sensory neurons is a common feature of many pain models and is a likely candidate for mediating spontaneous pain [60].

Primary afferents sensitization is caused by abnormal expression of nociceptors (ion channels and receptors) that contributes to hyperexcitability of primary sensory neurons, and is considered a fundamental mechanism of spontaneous pain [60–62]. Post-injury changes in the expression of ion channels and receptors lead to intrinsic changes in the membrane and discharge. For example, high-frequency spontaneous discharge has been documented in patients with painful neuromas and peripheral neuropathy [63, 64].

C-fiber nociceptors are thought to be highly associated with origin of spontaneous pain and have been extensively studied [10, 65]. Under normal condition, a large percentage of C-fiber nociceptors can be detected via their response to an electric shock but not a naturally noxious mechanical stimulus [66]. These nociceptors are activated by inflammation [67, 68]. Excitability in primary cutaneous C-nociceptors is significantly higher in patients with polyneuropathic pain [69] and small-fiber neuropathy [70], which contributes to spontaneous pain. In animal models, the amount of spontaneous paw lifting (a behavioral sign of spontaneous pain) is strongly correlated with the rate, but not percentage, of spontaneous firing in C-nociceptors with conducting fibers in neuropathic and inflammatory pain. TWIK-related potassium channel 2 (TREK2), a K^+ two-pore domain leak-channel (K2P), is selectively expressed in isolectin B4 positive ($IB4^+$) dorsal root ganglia (DRG) binding at C-nociceptors [14]. TREK2 has a hyperpolarizing influence on membrane potential of C-nociceptors of ≥10 mV, leading the limitation of C-nociceptor spontaneous firing rate, thus limiting inflammation-induced spontaneous pain behavior [71–73]. Moreover, decreased expression of TREK2 in the corresponding nerve fibers within the hindpaw skin, the tibial periosteum and the DRG neurons in bone cancer rats, contribute to the behavioral divergence of cancer-induced spontaneous pain [74]. Besides, demyelination of Aβ fibers and damage to Aδ fibers have also been confirmed to contribute to paroxysmal pain and abnormal sensations in carpal tunnel syndrome patients [15].

In clinic, patients often describe spontaneous pain as “burning”, indicating the involvement of thermal receptors [75]. In a masseter inflammation mice model, transient receptor potential cation channel subfamily V member 1 (TRPV1) contributes to spontaneous pain but not bite-evoked muscle pain, while TRPV1-expressing afferents and neurokinin 1 (NK-1) expressing second-order neurons commonly mediate both types of muscle pain. These 2 types of muscle pain are transmitted through a common nociceptive pathway. Spontaneous neuropathic pain and thermal hyperalgesia are mediated by TRPV1-positive fibers and spinal NK-1 positive ascending projections. In contrast, the large diameter dorsal column projection mediates nerve injury-induced tactile hypersensitivity, but does not contribute to spontaneous pain, indicating the similarities and differences between the spontaneous and evoked pain [76].

Central sensitization is due to changes intrinsic to the nociceptive neurons of the spinal dorsal horn, which clearly conduces pathological evoked pain [18, 77, 78]. But whether spontaneous discharges in the central nervous system directly arise from central sensitization independent from altered primary afferent inputs? There is still limited evidence for this question. Bennett et al. proposes a hypothesis that nerve injury may be accompanied by the death of primary afferent neurons under neuropathic pain and result in the degeneration of spinal terminal arbor and deafferentation of spinal cord dorsal horn neurons, thus developing the spontaneous discharge [12]. In a patient with a cauda equina lesion, spontaneous discharge has been recorded in deafferented dorsal horn neurons [79]. Shingles is known to kill dorsal root ganglion neurons and causes the degeneration of their intraspinal terminal arbors [80]. Postherpetic neuralgia patients have deafferented dorsal horn neurons and may have spontaneous discharge of central origin [12]. Except for spontaneous discharge, a new form of sensory neuron activity, spatially clustered sensory neurons sporadically firing together, is driven by norepinephrine released from sympathetic nerves in dorsal root ganglions and mediates spontaneous pain in mouse models of neuropathic pain [81].

Furthermore, microglia and astrocytes respond to increased inputs from the periphery by changing

morphology, proliferating, and releasing pro-nociceptive mediators such as adenosine triphosphate (ATP), cytokines and chemokines [82]. These gliotransmitters can sensitize neurons by activation of their cognate receptors thereby contributing to central sensitization underlying the generation of spontaneous pain. Liver X receptor β (LXRβ) is also involved in spontaneous pain. Deleting LXRβ enhances the expression of calcitonin gene-related peptide (CGRP), substance P (SP), and IB4 in the lamina I-II with more activated microglia and astrocytes in the spinal cord [83].

Symptom or syndrome? central re-organization in spontaneous pain

Given that reliable changed activities are observed within extensive brain regions in patients, research in animal models has gradually expanded. As mentioned above, most neuroimaging investigation is focused on the limbic system. Similar conclusions are also confirmed in animal studies. In temporomandibular joint pain rat model, increased clustering, node strength, network segregation, and activation of prefrontal-limbic pathways are observed in the group that develops persistent pain (spontaneous pain occurs only in the persistent pain group) [84]. Clustering and node strength show significant increases in persistent pain, particularly within the limbic system, and decrease when the pain resolves. In another rat pain model, a multiple single-unit study reveals that lateral (primary somatosensory cortex, ventral posterolateral thalamic nucleus) and medial pain (mediodorsal thalamic nucleus, anterior cingulate cortex) pathways differentially contribute to evoked pain and spontaneous pain behaviors [20].

Structural and functional changes in brain regions or pathways are not only the consequence, but also the cause of spontaneous pain. Persistent spontaneous pain disrupts ventral hippocampal CA1-infralimbic cortex (vCA1-IL) connectivity and decreases the secretion of brain-derived neurotropic factor (BDNF) in rats with peripheral inflammation. Genetic rescue of vCA1-IL dysfunction relieves spontaneous pain and accelerates overall pain recovery, demonstrating that this pathway specifically correlates with spontaneous pain [53]. Optogenetic activation of the central amygdala to lateral parabrachial pathway leads to the attenuation of ongoing pain-related behavior induced by formalin and CCI. Amygdalo-parabrachial pathway is a key regulator of spontaneous pain, and a novel target for pain relief [85]. In bee venom-induced inflammatory pain rat model, removing reactive oxygen species (ROS) in amygdala attenuates the spontaneous licking and lifting behaviors [86]. These results indicate the sufficiency and necessity of brain activities to spontaneous pain. By means of animal experiments (optogenetics, *in vivo/vitro* electrophysiological recording, etc.), manipulation and functional assessment of neurons and neural pathways are useful for further advancing spontaneous pain mechanisms.

Central organization is a vital pathological factor that causes spontaneous pain. Even though abundant literature have revealed brain activity changes accompanying spontaneous pain in past decades, mechanistic research in animal models verifying causal correlation is still lacking. Further investigation has to be considered in relation to the current findings. First, significant relationships between neuronal oscillations or BOLD signals and ratings of spontaneous pain are found for the spontaneous pain. But the responsible neuronal populations and the encoding patterns involved in spontaneous pain behaviors remain unknown. Second, pilot evidence suggests that along with the initial sensitization at the peripheral and spinal levels, spontaneous nociceptive information is transmitted to the brain and remodeled to form a "memory" of spontaneous pain, which is independent of peripheral afferents (see Box 2). Whether such a process exists and the underlying biological basis remains to be confirmed. Third, there is a dearth of research on the molecular mechanisms that could be potential therapeutic targets.

Box 2. Manifestation of spontaneous pain could be independent of inputs from peripheral and spinal levels.

In an unusual case report, a patient whose right leg was amputated suffered from spontaneous and touch-evoked phantom pain, as well as mechanical stump allodynia [87]. However, quantitative sensory testing revealed no abnormalities in touch and vibration senses or peripheral nociceptive C-fiber function (axon reflex vasodilatation and flare), but demonstrated considerable impairment of central spinothalamic systems. What causes phantom pain? The researchers performed a series of experiments and obtained the following results: sympathetic blocks did not change spontaneous and evoked pain; epidural and spinal anesthesia abolished evoked pain but had no effect on spontaneous phantom pain; extirpation of a neuroma of the sciatic nerve did not alter spontaneous and evoked pain. Based on these observations, we could conclude that activity in cutaneous C fibers and spinal nociceptive systems is not necessary to maintain central processes that account for painful sensations, especially spontaneous pain. The painful somatosensory memories may locate in the brain [87].

Comorbidity with other disorders

In clinic, when a patient presents with chronic pain (spontaneous pain as a main complaint), mental problems such as anxiety and depression often go undiagnosed [88–90]. Cognitive impairment also co-occurs with chronic pain [91]. There have been a wealth of studies and reviews on the comorbidity of chronic pain with emotional and cognitive impairments, which will not be described here but could be found elsewhere. We need to note that spontaneous pain is not unique for pain or injury related diseases. Hyperacusis in chronic pain is due to the neural interactions between auditory and nociceptive systems [92]. Nociceptive circuits become hypersensitive in ongoing pain; this spontaneous sensitivity spreads from the periphery to spinal neurons and higher centers in the brain, leading to hyperalgesia or spontaneous pain even in the absence of peripheral nociceptive input. This central sensitization may alter activity at sensory convergence points in the thalamus and brainstem centers such as the locus coeruleus, and give rise to hyperacusis in certain pain syndromes [92]. In Parkinson's disease (PD), pain threshold and pain tolerance tend to decrease as PD progresses, which can predispose to pain development [93]. Female gender, dyskinesia, medical conditions associated with painful symptoms, and postural abnormalities secondary to rigidity/bradykinesia may contribute to the appearance of spontaneous pain in predisposed subjects. Spontaneous pain is one of many complaints on initial examination of 845 patients with maxillary sinus carcinoma, in high relation to T-classification and direction of tumor spread [94]. A careful attention of spontaneous pain should be performed in order to diagnose malignant diseases as early as possible.

Therapy of spontaneous pain

Obviously, the development of therapies targeting spontaneous pain is meaningful. *Pharmacological treatments* remain the traditional management of spontaneous pain. Glucocorticosteroids are recommended to suppress inflammation and relieve spontaneous pain in patients with active rheumatoid arthritis [95]. The neuronal hyperexcitability and corresponding molecular changes in neuropathic pain have many features in common with the cellular changes in certain forms of epilepsy, which leads to the use of anticonvulsant drugs for treating spontaneous pain [96]. Carbamazepine [97], phenytoin [98], gabapentin [99] and lamotrigine [100] have been used in clinical trials and effective in painful diabetic neuropathy, paroxysmal attacks in trigeminal neuralgia, mixed neuropathies, post-herpetic neuralgia and post-stroke pain [101–103]. Other anticonvulsants, both new and old, are currently undergoing controlled clinical testing [96].

CGRP is believed to contribute to trigeminal nerve hypersensitivity in migraine [104]. Peripherally administered CGRP can act in a light-independent manner to produce spontaneous pain in mice, which is blocked by pre-administration of a monoclonal anti-CGRP-blocking antibody, but fail or partly fail to be blocked by meloxicam (a nonsteroidal anti-inflammatory drug) or sumatriptan (an antimigraine drug) [105]. The results herald the potential of therapeutic antibodies that block the actions of CGRP or its receptor to prevent spontaneous pain in migraine. Gamma-aminobutyric acid (GABA) system also plays the key role in modulating central pain [106]. GABA-A agonists, such as propofol [107], sodium amytal [108] execute dramatic reduction of spontaneous pain in clinical research.

New targets for analgesic therapy include sensory proteins in nociceptive nerve endings, such as activating TRPV and acid sensing ion channels, and inhibitory opioid and cannabinoid receptors [109]. Therapeutic targets are also found among the axonal channels that set membrane potential and modulate discharge frequency such as voltage sensitive sodium channels and various potassium channels, such as ralfinamide [110] and lidocaine [111].

Non-pharmacological treatments are potentially novel implemented intervention for the treatment of spontaneous pain from a series of case reports. Spinal cord stimulation (SCS) is known to be an effective treatment for a range of neuropathic pain conditions. A study reports that areas and intensity of spontaneous neuropathic pain are reduced during treatment and most domains also improve with SCS treatment [112]. Heterotopic noxious conditioning stimulation (HNCS) reduces the intensity of spontaneous pain, but not of allodynia in painful peripheral neuropathy [113]. Occipital nerve blocks have been reported in the management of post-dural puncture headache and spontaneous intracranial hypotension headache, including corticosteroids blockers and pulsed radiofrequency treatment [114]. In addition, pulsed radiofrequency ablation is also a viable treatment option which could be used for long-term relief of intractable spontaneous residual limb pain and phantom limb pain [115]. Repetitive transcranial magnetic stimulation (rTMS) is applied for neuropathic pain relief, especially in patients with refractory pain, via increasing the levels of BDNF, tumor necrosis factor alpha (TNF-α), and interleukin-10 (IL-10) in the PFC [116]. The alterations induced by rTMS on neurochemical parameters may contribute to the analgesic effect presented.

The use of olfactory ensheathing cells for dorsal root repair via acute transplantation, could exert an anti-nociceptive effect by modification of inflammation and astrogliosis, without affecting injury-induced central reorganization and afferent sprouting [117]. Water-soluble titanium microparticle-permeated tape have a good effect on relieving the temporomandibular disorder-related spontaneous pain and limitation of daily functions [118]. Spontaneous fibromyalgia pain pattern can be reproduced by mechanical stimulation of active myofascial trigger points located in different muscles, suggesting that fibromyalgia pain is largely composed of pain arising from muscle pain and spasm. Targeting active myofascial trigger points and related perpetuating factors may be an important strategy in fibromyalgia spontaneous pain control [119].

Despite significant gains in knowledge around spontaneous pain in this field, research from animal models has not yet resulted in emergence of novel pain therapeutics. Attempts for treating spontaneous pain, as mentioned, are almost pure application of traditional analgesic drugs or treatments. It is essential to bridge the gap between bench and bedside. Based on the literature, novel therapy may be developed in two aspects: designing drugs or exploiting gene therapy aiming at the pathological changes of receptors and ion channels, or finding brain biomarkers of spontaneous pain, as they constitute potential targets for pain diagnosis and treatment using approaches such as neurofeedback and neurostimulation.

Conclusion and future directions

As seen from the studies presented in this review, the past years have yielded a growing number of studies trying to understand the mechanisms of the spontaneous pain. Clinical studies provide epidemiological and neuroimaging data, whereas pre-clinical studies are crucial for divulging cause-effect relations. With advances in animal research, more disease models and behavioral assessments have been established to more closely mimic clinical conditions. Meanwhile, our understanding of the mechanisms underlying the development of spontaneous pain remains limited. Referring to classic chronic pain mechanisms, recent advances highlight three aspects: peripheral sensitization, spinal sensitization and central reorganization, which are corroborated by anatomical and functional studies (see Figure 2). Mechanistic distinctions of spontaneous pain and evoked pain is a topic

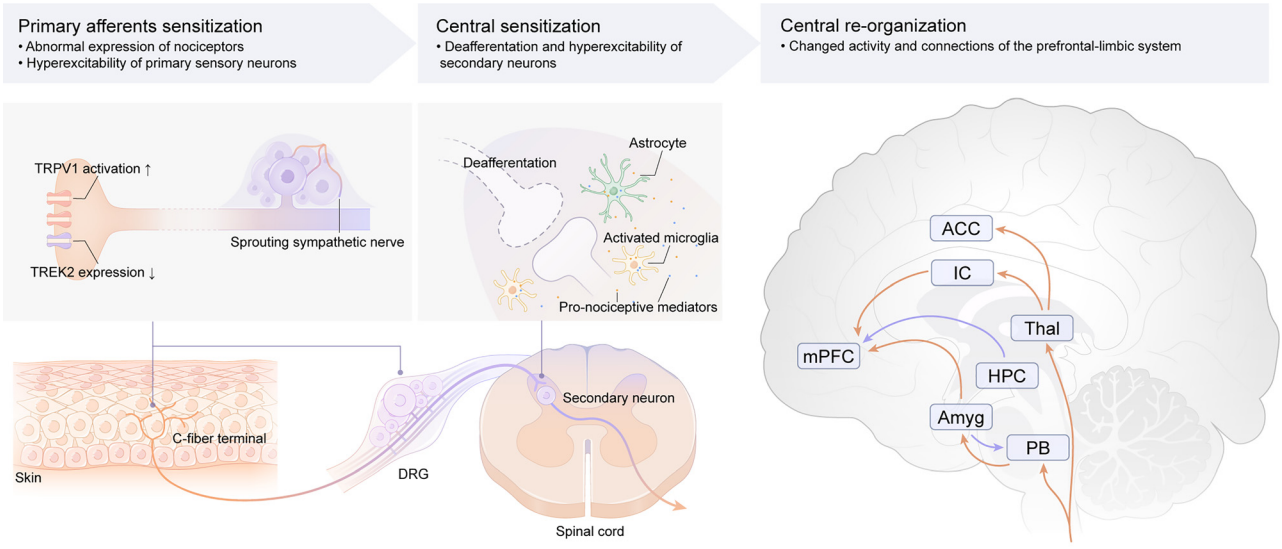

Figure 2: Neural mechanisms of spontaneous pain. Spontaneous pain can be developed as a consequence of primary afferents sensitization, central sensitization and central reorganization. Primary afferents sensitization results from abnormal expression and activity of nociceptor (TRPV1, TREK2, etc.) and sympathetic sprouting, manifesting hyperexcitability of primary sensory neurons. Pro-nociceptive mediators (ATP, cytokines, etc.) released from astrocytes and microglia contribute to central sensitization, which is independent from primary afferents sensitization. Neural imaging studies in humans and manipulation of brain regions in animals have demonstrated changes in neural activity and connections of distributed brain regions, especially the prefrontal-limbic system (arrows in purple indicate decreased connection). mPFC, medial prefrontal cortex; ACC, anterior cingulate cortex; IC, insular cortex; Thal, thalamus; HPC, hippocampus; Amyg, amygdala; PB, parabrachial nuclei. DRG, dorsal root ganglia; TRPV1, transient receptor potential cation channel subfamily V member 1; TREK2, TWIK-related potassium channel 2.

of interest in the field, which is reflected at behavioral, neuronal circuit, cellular and molecular levels. In addition, characteristics of a specific pain model such as species, age, sex, type, and duration of pain should be taken into consideration when discussing the pathological mechanisms (see Box 3).

However, further studies are needed to search for indicative biomarkers in order to identify candidates for early diagnosis and intervention of developing spontaneous pain. Finally, forthcoming efforts devoted to exposing the underlying cellular and molecular mechanisms of spontaneous pain should direct to novel therapeutic advancements for prevention and alleviation of the negative consequences of these conditions.

Box 3. Standing questions and goals.

(1) How to establish spontaneous pain assessment methods and animal models that more closely simulate clinical spontaneous pain.
(2) If spontaneous pain is "stored" in the brain as a "memory", which brain regions and neuronal populations participate in the process?
(3) In the brain, how do neurons encode and regulate spontaneous pain behaviors?
(4) From the peripheral to the central nervous systems, are specific molecules involved in the formation and maintenance of spontaneous pain?
(5) What are the neurobiological mechanisms of spontaneous pain and its comorbidity with other diseases?
(6) How to develop new drugs and therapies aiming at spontaneous pain?

Acknowledgments: We thank members of You Wan and Ming Yi labs for technical support and helpful suggestions. Longyu Ma was supported in part by the Postdoctoral Fellowship of Peking-Tsinghua Center for Life Sciences.
Research funding: This work was supported by the National Natural Science Foundation of China (31872774, 82101303, 81974166, 81821092), Beijing Natural Science Foundation (7202083, 5182013), the Interdisciplinary Medicine Seed Fund of Peking University (BMU2018MX011) and China Postdoctoral Science Foundation (2020M670061). Funders have no role in research design, discussion, and explanation.
Author contributions: Longyu Ma, Ming Yi and You Wan wrote the paper; Shuting Liu designed and finished the figures. All authors read and confirmed the manuscript. All authors have accepted responsibility for the entire content of this manuscript and approved its submission.
Competing interests: Authors state no conflict of interest.
Ethical approval: The local Institutional Review Board deemed the study exempt from review.

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