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Neuropathic Pain: From Mechanism to Clinical Application

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1. Introduction

A lesion or disease affecting the somatosensory system can cause a wide range of pathophysiologic symptoms including mild or severe chronic pain. Due to the diversity of etiologies giving rise to nervous system damage that generates neuropathic pain, it has become a ubiquitous health concern without respect for geographic or socioeconomic boundaries [1]. Within the developing world, infectious diseases [2-4] and trauma [5] are the most common sources of neuropathic pain syndromes. The developed world, in contrast, suffers more frequently from diabetic polyneuropathy (DPN) [6, 7], post herpetic neuralgia (PHN) from herpes zoster infections [8], and chemotherapy-induced peripheral neuropathy (CIPN) [9, 10]. There is relatively little epidemiological data regarding the prevalence of neuropathic pain within the general population, but a few estimates suggest it is around 7-8% [11, 12]. Despite the widespread occurrence of neuropathic pain, treatment options are limited and often ineffective, leaving many to live with the persistent agony and psychosocial burden associated with chronic pain [13, 14].

Neuropathic pain can present as on-going or spontaneous discomfort that occurs in the absence of any observable stimulus or a painful hypersensitivity to temperature and touch. This limits physical capabilities and impairs emotional well-being, often interfering with an individual's ability to earn a living or maintain healthy relationships. It is not surprising, therefore, that people with chronic pain have increased incidence of anxiety and depression and reduced scores in quantitative measures of health related quality of life [15].

Despite significant progress in chronic and neuropathic pain research, which has led to the discovery of several efficacious treatments in rodent models, pain management in humans

remains ineffective and insufficient [16]. The lack of translational efficiency may be due to inadequate animal models that do not faithfully recapitulate human disease or from biological differences between rodents and humans [16]. Whatever the cause, the translational gap necessitates a bridge between clinicians and basic researchers in order to move from the clinic to the laboratory and back into the clinic.

In an attempt to increase the efficacy of medical treatment for neuropathic pain, clinicians and researchers have been moving away from an etiology based classification towards one that is mechanism based. It is current practice to diagnose a person who presents with neuropathic pain according to the underlying etiology and lesion topography [17]. However, this does not translate to effective patient care as these classification criteria do not suggest efficacious treatment. A more apt diagnosis might include a description of symptoms and the underlying pathophysiology associated with those symptoms. This chapter attempts to define neuropathic pain at the cellular and molecular level, as seen by a laboratory scientist, and then describe how the manifestations of these pathophysiologic changes are observed in the clinic, as seen by a clinician. It will then discuss a merger of the two points of view and suggest how this can lead to better patient care through more effective treatment.

2. Definition of neuropathic pain

Neuropathic pain has been defined by the International Association for the Study of Pain (IASP) as “pain arising as the direct consequence of a lesion or disease affecting the somatosensory system” [18]. This is distinct from nociceptive pain – which signals tissue damage through an intact nervous system – in underlying pathophysiology, severity, and associated psychological comorbidities [13]. Individuals who suffer from neuropathic pain syndromes report pain of higher intensity and duration than individuals with non-neuropathic chronic pain and have significantly increased incidence of depression, anxiety, and sleep disorders [13, 19].

Any trauma to the somatosensory system appears to have the capacity to cause a neuropathic pain syndrome; yet the presence of any individual pathology does not guarantee the development of neuropathic pain, highlighting the importance of genetic and environmental factors as well as individual disease pathogenesis. To further complicate matters, individuals with seemingly identical diseases who both develop neuropathic pain may experience distinct abnormal sensory phenotypes. This may include a loss of sensory perception in some modalities and increased activity in others. Often a reduction in the perception of vibration and light touch is coupled with positive sensory symptoms such as paresthesia, dysesthesia, and pain [20]. Pain may manifest as either spontaneous, with a burning or shock-like quality, or as a hypersensitivity to mechanical or thermal stimuli [21]. This hypersensitivity takes two forms: allodynia, pain that is evoked from a normally non-painful stimulus, and hyperalgesia, an exaggerated pain response from a moderately painful stimulus. For a more extensive list of sensory signs and symptoms associated with neuropathic pain see Table 1. Ultimately, the path towards efficacious treatment of chronic pain will include a clear understanding of how certain pathophysiologic changes lead to specific sensory signs and symptoms. This will allow clinicians to translate

measurable sensory abnormalities into underlying pathology. With a clear view of mechanism, targeted treatment and individualized medicine become conceivable.

3. Anatomical overview of pain as a somatosensory modality

At the turn of the 20th century Charles Sherrington proposed the concept of pain-specific neural circuitry and deemed neurons within this circuit “nociceptors” [22]. This “specificity theory” of pain was competing for favor with the prevailing “pattern theory” which held that pain was encoded by the same low-threshold sensory nerve endings that transmit information about vibration and light touch through high frequency stimulation and central summation [23]. It is now clear, as Sherrington proposed that the sensation of pain is encoded by a unique set of peripheral and central neurons whose primary purpose is to alert the organism to a potentially dangerous situation.

The nociceptive system detects noxious stimuli (i.e. that are of a sufficient magnitude to cause bodily injury) and elicits appropriate avoidance behaviors. Detection begins with free nerve endings in the skin or viscera that carry specialized membrane receptors capable of converting high magnitude chemical, mechanical, or thermal energy into an electrical impulse. The impulse is carried from the periphery to the dorsal horn of the spinal cord where neurotransmitter release relays the activity to second order neurons. Here, signals from the periphery are integrated with information from descending sources that modulate nociceptive circuitry in a manner that is dependent on the environmental context. The sum of this exchange is carried by secondary projection neurons to supraspinal nuclei which interpret the signal and create the conscious perception of pain.

The nociceptive circuit is not static, however; there is tremendous plasticity, from the periphery to the neocortex, which modulates the perception of pain to reflect the physiological needs of the organism and optimize survival. This is best understood by considering two examples of hypo- and hyper- sensitivity to pain: a time of war and an illness, respectively. Perceiving pain during a period of intense stress, such as wartime, would decrease chances of survival by increasing vulnerability to a more immediate threat. Conversely, in a low stress environment activation of the inflammatory response as a result of illness or injury sensitizes nociceptors leading to pain hypersensitivity, rest, and healing. Neuropathic pain, therefore, can be considered an inappropriate hijacking of inherent neuronal plasticity to promote hypersensitivity in contexts where it is not beneficial.

4. Peripheral nociceptors detect a noxious stimulus

Noxious stimuli are perceived by small diameter peripheral neurons whose free nerve endings are distributed throughout the body. These neurons are distinct from, although anatomically proximal to, the low threshold mechanoreceptors responsible for the perception of vibration and light touch. Both low and high threshold afferents are pseudounipolar neurons of the

dorsal root and trigeminal ganglion with peripheral terminals that extend into the skin/viscera and central terminals that extend into the gray matter of the spinal cord or trigeminal nucleus caudalis depending on whether they originated from the body or face, respectively. Low threshold afferents, or A β fibers, can be distinguished from nociceptors by biochemical and electrophysiological properties. A β neurons are large diameter, heavily myelinated, and fast conducting fibers, while nociceptors fall into one of two functionally distinct categories: lightly myelinated, medium diameter (1-5 μ m) A δ fibers that mediate a sharp, well localized “first” pain and unmyelinated, small diameter (0.2 – 1.5 μ m) C fibers that mediate a duller, anatomically diffuse “second” pain. Together with A α fibers (which will not be considered here) A β , A δ , and C fibers constitute the somatosensory system.

5. Membrane receptors capture energy and modulate excitability

As mentioned above, the purpose of these primary afferents is to detect noxious stimuli in the environment, for example a hot stove, or within the body as in an acidic or chemically unbalanced stomach. This requires the translation of chemical or high magnitude mechanical and thermal energy into an electrical impulse, a function carried out by a myriad of specialized receptors and ion channels (e.g. sodium and potassium channels, G-coupled protein receptors, receptor tyrosine kinases) that are embedded in the neuronal membrane. In addition to primary detection of the stimulus, these specialized receptors/ion channels also play an important role in nociceptive plasticity by regulating membrane excitability and dictating the magnitude of stimulus required to generate an action potential.

A major breakthrough in understanding how nociceptors detect environmental stimuli came with the discovery of the transient receptor potential (TRP) family of nonselective cation channels [24]. These membrane-bound receptors – for the first time – provided a substrate by which noxious energy could elicit neuronal depolarization. Each of the twenty-eight known TRP family members has a unique profile of activation that includes thermal and chemical stimuli [25]. The most well-characterized TRP channel, TRPV1, is activated by temperatures >42°C and the chemical compound capsaicin (the “hot” component of chili peppers) under normal physiological conditions [24]. In pathological states, TRPV1 has been implicated in pain hypersensitivity in models of inflammation, diabetic neuropathy [26, 27], partial nerve injury [28, 29], and chemotherapy-induced painful neuropathy [30]. Mechanistically, TRPV1 mediated hypersensitivity occurs as the result of changes in the expression, trafficking, and activation potential of TRPV1 following nerve injury [31]. Components of the inflammatory soup can modify TRPV1 by either direct allosteric modulation or indirect modification. For example, protons may bind directly to the extracellular domain, or stimulation of membrane bound receptor tyrosine kinases may trigger intracellular signaling cascades that result in phosphorylation of an intracellular domain. These physical modifications lead to altered activation kinetics and ultimately a lowered thermal or mechanical threshold for individual nociceptors (Figure 1) [31]. The behavioral correlate of a cellular lowering of threshold is hypersensitivity to thermal or mechanical stimuli i.e. allodynia and hyperalgesia.

In addition to hypersensitivity, individuals with neuropathic pain frequently experience ongoing spontaneous pain as a major source of discomfort and distress. Following trauma to the peripheral nerve, ectopic activity was observed in primary nociceptors in the periphery, suggesting this to be the major source of spontaneous pain [32]. In healthy individuals, a quiescent neuron will only generate an action potential when presented with a stimulus of sufficient magnitude to cause membrane depolarization. Following nerve injury, however, significant changes in ion channel expression, distribution, and kinetics lead to disruption of the homeostatic electric potential of the membrane resulting in oscillations and burst firing. This manifests as spontaneous pain that has a shooting or burning quality [31]. Three types of ion channels seem to mediate this effect: two-pore domain K^+ channels (TREK and TREK-2), voltage gated sodium channels (VGSC; i.e. $Na_v1.8$, $Na_v1.6$, $Na_v1.1$, $Na_v1.9$) and hyperpolarization-activated cyclic nucleotide-gated (HCN) channels (Figure 1) [31]. There is reasonable evidence to suggest that individual ion channels contribute to specific neuropathic pain symptoms; for example $Na_v1.8$ plays a role in cold-induced allodynia (for review see [33, 34]). The exact nature and extent of this relationship is unclear, but it provides an intriguing therapeutic possibility: unambiguous pharmacologic ion channel blockers to relieve individual sensory symptoms with minimal unintended effects allowing pain relief without global numbness.

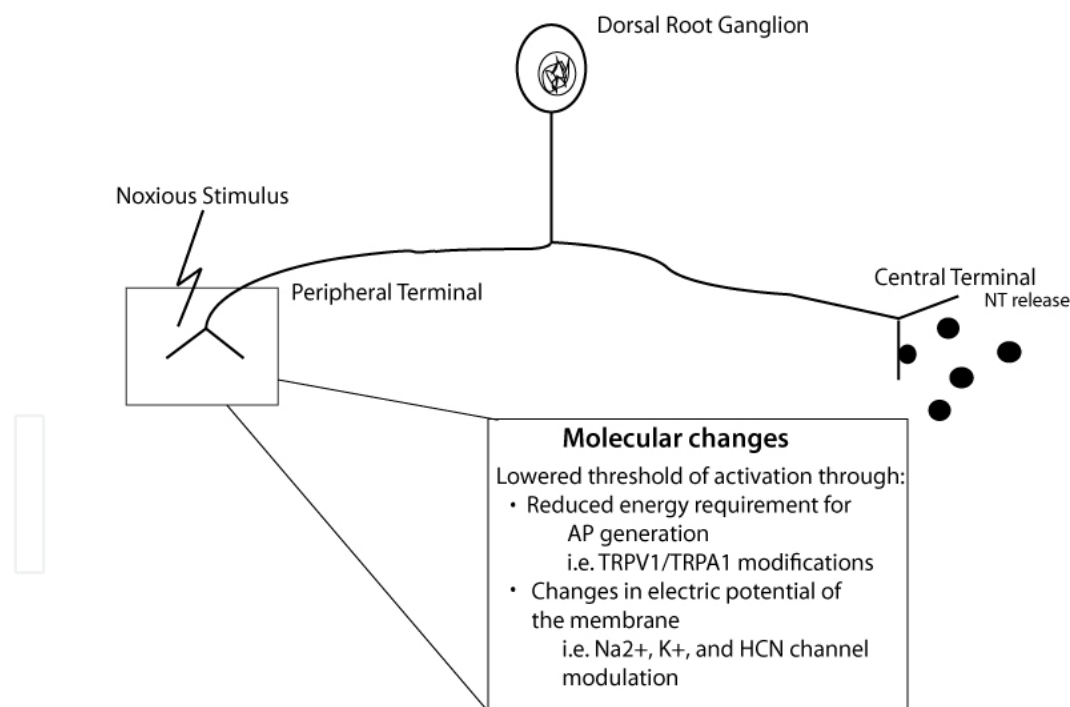


Figure 1. Pathophysiological changes associated with a primary afferent nociceptor. A pseudounipolar C-fiber detects a stimulus in the skin or viscera, and an action potential (AP) is propagated along the axon prompting neurotransmitter (NT) release from the central terminal. Following nerve injury, modulation and modification of molecular components can lead to painful hypersensitivity to stimuli as well as spontaneous or ongoing pain. For simplification we portray a unidirectional flow of information, but it's interesting to note that generation of an AP or NT release as well as the associated pathophysiological changes can occur at either terminal.

6. Pain circuits of the dorsal horn integrate information

A cross section of a spinal cord reveals morphologically and biochemically distinct layers of gray matter – Laminae of Rexed after the scientist who first described them – that integrate input from a variety of ascending and descending sources (Figure 2) [35]. Each layer forms a functional compartment containing a dense network of primary afferents, secondary projection neurons, descending fibers, and interneurons with unique patterns of connectivity. The most superficial layers of the dorsal horn, laminae I and II, receive peripheral input almost exclusively from A δ and C fibers while A β fibers innervate more medial laminae (III-IV)[36]. Lamina V contains wide dynamic range polymodal projection neurons that receive direct input from A δ and A β fibers as well as indirect input from C fibers [36]. Thus, it appears there is both anatomical segregation (laminae I-IV) and integration (laminae V) of painful and non-painful stimuli at the level of the spinal cord, providing the substrate for distinct pathophysiological mechanisms in the development of neuropathic pain.

It should be noted that primary afferents originating from the orofacial region project to the trigeminal nucleus caudalis of the medulla rather than the dorsal horn of the spinal cord [37]. Similar organization, function, and pathophysiological mechanisms are observed in both nuclei, so they will not be considered separately.

7. Central sensitization leads to painful hypersensitivity

Functional and structural changes of dorsal horn circuitry lead to pain hypersensitivity that is maintained independent of peripheral sensitization [38]. This central sensitization provides a mechanistic explanation for the sensory abnormalities that occur in both acute and chronic pain states, such as the expansion of hypersensitivity beyond the innervation territory of a lesion site, repeated stimulation of a constant magnitude leading to an increasing pain response, and pain outlasting a peripheral stimulus [39-41]. In healthy individuals, acute pain triggers central sensitization, but homeostatic sensitivity returns following clearance of the initial insult. In some individuals who develop neuropathic pain, genotype and environmental factors contribute to maintenance of central sensitization leading to spontaneous pain, hyperalgesia, and allodynia.

At the cellular level, potentiation or facilitation of synapses in the dorsal horn leads to central sensitization. The former is a type of homosynaptic strengthening whereby repeated neurotransmitter release from a primary nociceptor leads to post-synaptic molecular remodeling in second order neurons, ultimately reducing the quantity of neurotransmitter required to generate an action potential (i.e. hyperalgesia). This process resembles long term potentiation (LTP), the molecular correlate of learning and memory, differing in the time-scale of associated post-synaptic changes and several molecular components [42]. Like LTP, potentiation of nociceptors in the dorsal horn is dependent on the post-synaptic function of ionotropic glutamate receptors (N-Methyl-D-aspartic acid receptors; NMDAR) suggesting that this may be a viable target for treating centrally maintained neuropathic pain.

Similarly, facilitation also results in a lowered activation threshold in second order neurons, but distinct from potentiation, the molecular changes occur in a nearby dendritic spine rather than the spine receiving the nociceptive input. If the nearby dendritic spine is a silent partner of an $A\beta$ afferent, molecular changes that lower the threshold recruit this primary afferent into nociceptive circuitry resulting in the perception of pain from innocuous stimuli (i.e. allodynia).

In addition to heterosynaptic strengthening, phenotypic changes or dendritic sprouting of $A\beta$ fibers can lead to the incorporation of low threshold mechanoreceptors into pain circuitry.

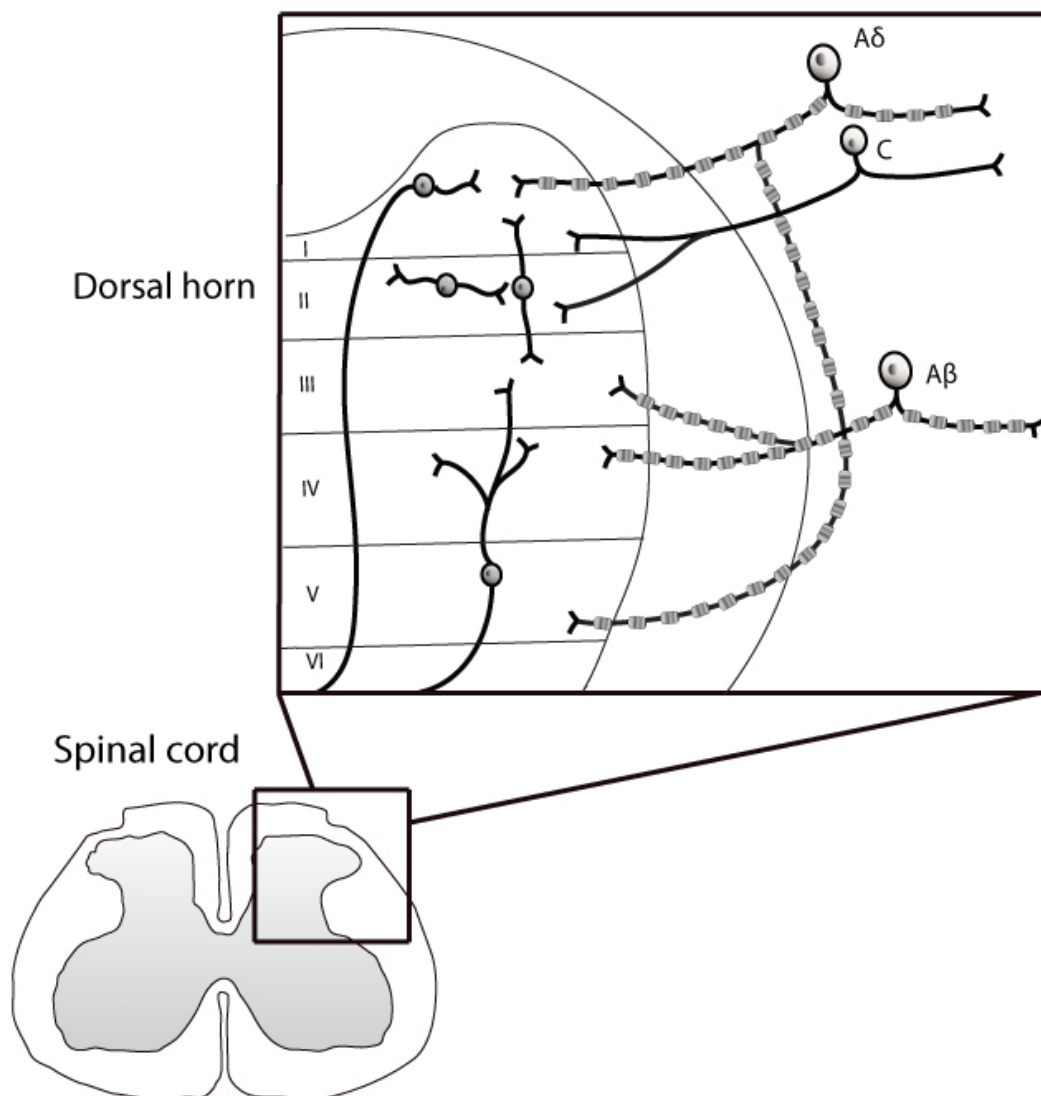


Figure 2. Neuronal architecture of the dorsal horn. Laminae (represented by numerals I-VI) are morphologically and functionally distinct layers within the gray matter of the spinal cord. Lamina I primarily contains large projection neurons that send processes up the spinal cord towards higher brain regions. Lamina II, in contrast, is more heavily populated with interneurons, many of which supply inhibitory signals to lamina I projection neurons. Lamina V contains wide dynamic range neurons that receive primary input from multiple sensory modalities. Peripheral afferents project to distinct laminae. While $A\delta$ and C fibers are associated with superficial laminae, $A\beta$ fibers project more medially. For a comprehensive review of dorsal horn circuitry see [36].

Two neuropeptides, substance P (SP) and calcitonin gene-related peptide (CGRP) are normally exclusively expressed by A δ and C fibers in the periphery. Following nerve injury, however, A β fibers begin to manufacture these neuropeptides [43]. Additionally, there is evidence to suggest that remodeling of A β dendritic arbors can create novel circuitry [44]. These changes all manifest as dynamic mechanical allodynia.

In contrast to the gain-of-function changes that take place in A β fibers following injury, inhibitory descending and interneurons experience a sharp loss-of-function. This loss of inhibitory input releases the brake on neurotransmission and increases the excitatory current in the superficial dorsal horn [45]. Although there is evidence that excitotoxicity contributes to apoptotic loss of gamma-amino butyric acid (GABA)-ergic interneurons and descending inhibitory neurons of the rostroventral medulla [46, 47], it has been argued that injury-induced disinhibition is the result of attenuated efficacy of intact GABAergic interneurons that occurs independent of cell death [48-50]. Activation of microglia, resident macrophages of the nervous system, is a pathological hallmark of nervous system damage [51]. Release of brain-derived neurotrophic factor (BDNF) from activated microglia is necessary and sufficient to shift the anion reversal potential in lamina I projection neurons, reducing the effect of GABA in these neurons [52]. Specifically targeting BDNF or activated microglia may be a viable treatment for neuropathic pain.

8. Supraspinal nuclei interpret the signal

Activation of peripheral nociceptors elicits a complex behavioral response that allows an organism to avoid the noxious stimulus immediately (by moving away from the source) and in the future (by enhanced learning and memory). To carry out the sum of these behaviors the pain circuit recruits a large number of cortical and subcortical regions that manage a variety of aspects of cognition and perception. Prominent examples include areas of the brain associated with motivation/reward, learning/memory, and somatosensation (reviewed in [53]). Classically, pain in the brain has been described in terms of a particular pattern of activation referred to as the “pain matrix”. Areas of the matrix can be classified as belonging to one of two parallel pathways that control distinct aspects of pain: sensory discrimination (e.g. location, duration, and intensity) or affective/motivational (e.g. feelings of suffering and avoidance behaviors) [54, 55]. Increasing evidence gathered from rapidly evolving technology has suggested this description to be an oversimplification, however, as it applies uniquely to healthy individuals with experimentally induced acute pain [53]. Although useful, it is important for the future of pain research and treatment that we continue evaluate the current schematic, employing new technologies as they develop.

9. Decoding pain representation in the brain

Recent progress has expanded the current view of pain representation and encoding in the brain by utilizing functional magnetic resonance imaging (fMRI), MR spectroscopy, MR

morphometry, and diffusion tensor MRI. In a comprehensive review, Apkarian and colleagues summarize this recent progress and propose a model that includes a temporal, as well as a spatial, cerebral representation of pain [53]. They've suggested that in the context of acute thermal pain activity in the anterior insula, nucleus accumbens (NAc), and mid-cingulum peak prior to the conscious perception of pain, the "anticipation", while perception is distinctly correlated with peak activity in the anterior cingulate, mid- and posterior insula, and portions of the dorsal striatum. Lastly, as the stimulus is extinguished bringing about "relief" regions of the brainstem, in particular the periaqueductal grey (PAG), become active [53].

Another significant finding led to the disentanglement of the neural coding for two distinct dimensions of a stimulus: the objective magnitude of an applied stimulus and an individual's subjective perception of stimulus intensity. Again using fMRI in the context of acute thermal pain, Baliki et. al. suggest that actual stimulus intensity is encoded by large portions of the cingulate and insular cortices while specific subsections of each, namely the anterior portion of the cingulate and the posterior insula, correlate strongly with subjective perception [56]. Thus it appears that pain perception follows a similar processing stream as other sensory modalities (e.g. vision, hearing, olfaction) wherein information about subjective magnitude is extracted by specific regions of the insular cortex [53]. These findings are beginning to lay the foundation for a clear and accurate representation of spatiotemporal coding of pain in the brain, with the ultimate goal of correlating neural activity with distinct cognitive and behavioral functions.

10. Morphological and functional changes in the brain are associated with chronic pain

Chronic pain conditions are associated with vast functional and structural changes of the brain, when compared to healthy controls, but it is currently unclear which comes first: does chronic pain cause distortions of brain circuitry and anatomy or do cerebral abnormalities trigger and/or maintain the perception of chronic pain? Future studies will clarify these questions.

Brain abnormalities in chronic pain states include modification of brain activity patterns, localized decreases in gray matter volume, and circuitry rerouting [53]. Observation of overall brain activity patterns in a variety of chronic pain conditions has led to the discovery that spontaneous and evoked pain are uniquely represented in the brain [53]. Spontaneous pain associated with chronic back pain and PHN induce increased activity in the mPFC and amygdale while acute thermal pain and allodynia associated with PHN illicit larger responses in the thalamus and insula [53]. Similar activity patterns are observed in thermal and mechanical acute pain in healthy individuals and knee pain associated with osteoarthritis, all forms of evoked pain [53].

Chronic pain conditions are associated with localized reduction in gray matter volume, and the topography of gray matter volume reduction is dictated, at least in part, by the particular pathology. Chronic back pain, for example, is associated with a loss of bilateral dorsolateral prefrontal cortex and unilateral thalamic gray matter [57] while irritable bowel syndrome

displays a volume reduction in the insula and cingulate cortex [58]. In addition, gray matter atrophy has been suggested to occur in a variety of pain conditions including fibromyalgia, knee osteoarthritis, and headaches [59-66]. These changes appear to represent a form of plasticity as they are reversible when pain is effectively managed [63, 67, 68]. How or why individual pathologies result in distinct morphological distortions and what impact these changes have on individual pain perception remains to be determined.

Changes in brain circuitry have also been reported in patients with chronic back pain [69]. Baliki et. al. found that when an acute thermal stimulus is applied to the skin of healthy subjects, activity in the NAc at the end of the stimulus response cycle is strongly correlated with the insula. This is distinct from patients with chronic back pain where activity in the NAc is strongly correlated with the medial prefrontal cortex (mPFC) [69]. The resulting activity in the NAc is divergent as the phasic response observed in healthy subjects has been correlated to the prediction of reward while the activity pattern in chronic pain patients represents lack of reward or disappointment [69]. Although there is no difference in the reported perceived magnitude of the stimulus, this suggests that subconsciously chronic pain patients are disappointed when an acute pain stimulus is removed, begging the question, what are the resultant cognitive and behavior manifestations? This opens up the field to a series of questions considering the effects of subconscious components of brain activity on perception of pain and resultant behaviors.

11. Neuropathic pain diagnosis

Persistent pain is the single most common ailment that brings people to a primary care physician each year, accounting for approximately 40% of all visits [70]. Measurements of overall health-related quality of life, a multidimensional construct that takes into account physical, emotional, and social well-being, are depressed in chronic pain patients [15], and the resulting work absenteeism and elevated health care costs represent a substantial economical and societal burden [71-74]. Although effective management of chronic pain would certainly reduce this burden, treatment options are inadequate and often wrought with adverse health effects [15]. It is becoming increasingly clear that the path towards efficacious pain management is one of individualized medicine that stems from an understanding of the underlying pathophysiology and resultant sensory abnormalities [31, 75-77]. Although this may be the future of pain management, the current understanding of an individual "sensory phenotype" and dearth of clinical trials utilizing this perspective prevent immediate implementation. The following sections will highlight the current evidence based methods of diagnosing and treating neuropathic pain and suggest the future of research and clinical practice.

12. Clinical history

By definition, neuropathic pain indicates direct pathology of the nervous system while nociceptive pain is an indication of real or potential tissue damage. Due to the distinction in

pathophysiology, conventional treatments prescribed for nociceptive pain are not very effective in treating neuropathic pain and vice versa [78]. Therefore the first step towards meaningful pain relief is an accurate diagnosis.

Identifying neuropathic pain in a clinical setting begins with a thorough review of the patient's history through evaluation of previous medical records and verbal communication with the patient. Standardized screening tools such as the Leeds Assessment of Neuropathic Symptoms and Signs (LANSS) [79], the Douleur Neuropathique en 4 questions (DN4) [12], and painDETECT [13] can guide clinician through a series of questions aimed at indentifying possible neuropathic pain. In completing these questionnaires patients are asked to describe their pain in terms of quality (i.e. pricking, tingling, pins and needles, electric shocks/shooting, burning) and context (i.e. provoked by heat, cold, or pressure) [80]. In addition to verbal descriptors, the LANSS and DN4 also include a short bedside examination of sensory abnormalities. Although each screening tool is unique, they have similar sensitivity and specificity, between 80-85% for both parameters [80]. This suggests that approximately 1 in 5 patients who fit the criteria for neuropathic pain as determined by the screening tool and 20% of all individuals who've been evaluated are misdiagnosed. This reaffirms that careful clinical judgment is necessary to make an accurate diagnosis.

Additional information that is not included within the standardized questionnaires can also be useful in diagnosing neuropathic pain. Mapping pain topography allows the clinician to consider whether a lesion is anatomically logical, and descriptions of frequency (i.e. on-going, spontaneous) and intensity (e.g. mild, moderate, severe, excruciating or 1-10) can aid in identifying a potential mechanism [1].

13. Clinical examination

Evaluating sensory function in a bedside examination can be helpful in assessing neuropathic pain. Since a lesion of the nervous system will often manifest as decreased sensitivity in some sensory modalities and increased sensitivity in others, objectively measuring each sensory modality can aid in forming a diagnosis. Guided by the patient's history, the putative lesion innervation territory is tested while the contralateral side of the body serves as a control. Testing consists of touching the patient's skin with calibrated tools that elicit a response in a subset of peripheral neurons. For example, brushing the skin lightly will tests sensitivity of A β mechanoreceptors while a thermoroller will test heat sensitive C fibers [1]. For a list of bedside sensory tests see Table 1.

14. Pharmacological treatment of neuropathic pain

Treating neuropathic pain requires a multifaceted approach that aims to eliminate the underlying etiology, when possible, and manage the associated discomforts and emotional distress. Although in some cases it is possible to directly treat the cause of neuropathic pain,

for example surgery to alleviate a constricted nerve, it is more likely that the primary cause is untreatable, as is the case with singular traumatic events such as stroke and spinal cord injury and diseases like diabetes. When this is the case, symptom management and pain reduction become the primary focus. Unfortunately, in most cases complete elimination of pain is not a feasible endpoint; a pain reduction of 30% is considered to be efficacious [21]. Additionally, many pharmacological treatments require careful titration and tapering to prevent adverse effects and toxicity. This process may take several weeks to months, and ultimately the drug may be ineffective, necessitating another trial with a different medication. It is therefore necessary that both doctor and patient begin treatment with realistic expectations and goals.

Signs and Symptoms	Bedside Test	Pathological Response
<i>Abnormal Sensations</i>		
Hypoesthesia	Touch skin with cotton swab or gauze	Reduced sensation
Hypoalgesia	Prick skin with pin	Reduced sensation
Paraesthesia	Reported – grade intensity 1-10	
<i>Spontaneous Pain</i>		
Shooting	Reported – grade intensity 1-10	
Ongoing	Reported – grade intensity 1-10	
<i>Evoked Pain</i>		
Allodynia/Hyperalgesia		
Cold	Touch skin object <20°C	Painful, burning sensation
Heat	Touch skin object >40°C	Painful, burning sensation
Dynamic Mechanical	Move object (cotton swab or gauze) along skin	Sharp burning superficial pain in putative lesion territory as well as unaffected area
Punctate Mechanical	Pinprick with sharp object	Sharp burning superficial pain in putative lesion territory as well as unaffected area
Static Mechanical	Apply gentle pressure to skin	Dull pain in putative lesion territory as well as unaffected area
Temporal Summation	Pinprick with sharp object at 3s intervals for 30s	Sharp pain with increasing intensity

Table 1. A list of bedside tests used to identify signs and symptoms that are suggestive of neuropathic pain.

Recently, the Neuropathic Pain Special Interest Group (NeuPSIG) of the International Association for the Study of Pain reviewed the evidence-based guidelines for the pharmacological treatment of neuropathic pain and made recommendations that take into account clinical efficacy, adverse effects, effects on health related quality of life, convenience, and cost [81]. These findings as well as more recent evidence are reviewed here.

First-line medications for the treatment of neuropathic pain are those that have proven efficacy in randomized clinical trials (RCTs) and are consistent with pooled clinical observations [81]. These include antidepressants, calcium channel ligands, and topical lidocaine [15]. Tricyclic antidepressants (TCAs) have demonstrated efficacy in treating neuropathic pain with positive results in RCTs for central post-stroke pain, PHN, painful diabetic and non-diabetic polyneuropathy, and post-mastectomy pain syndrome [82]. However they do not seem to be effective in treating painful HIV-neuropathy or CIPN [82]. Duloxetine and venlafaxine, two selective serotonin norepinephrine reuptake inhibitors (SSNRIs), have been found to be effective in DPN and both DPN and painful polyneuropathies, respectively [81]. Adverse effects associated with TCAs and SSNRIs are relatively mild and can be mitigated by a slow titration beginning with a low dose [81].

Gabapentin and pregabalin have also demonstrated efficacy in several neuropathic pain conditions including DPN and PHN [81, 82]. Both drugs exert their effects by inhibiting neurotransmitter release through binding of the $\alpha_2\text{-}\delta$ subunit of presynaptic calcium channels [83]. Adverse effects and efficacy of gabapentin and pregabalin are similar; however pregabalin may provide more rapid analgesia due to straightforward dosing determined by linear pharmacokinetic [78]. Topical lidocaine (5% patch or gel) has significantly reduced allodynia associated with PHN and other neuropathic pain syndromes in several RCTs [81, 82]. With no reported systemic adverse effects and mild skin irritation as the only concern, lidocaine is an appropriate choice for treating localized peripheral neuropathic pain.

In the event that first line medications, alone or in combination, are not effective at achieving adequate pain relief, second line medications may be considered. These include opioid analgesics and tramadol, pharmaceuticals which have proven efficacy in RCTs but are associated with significant adverse effects that warrant cautious prescription [15]. Although opioid analgesics are effective pain relievers in several types of neuropathic pain [81, 82, 84], they are associated with misuse or abuse, hypogonadism, constipation, nausea, and immunological changes [15]. Because many of these side effects can be mitigated by a low dose, careful titration, and short term use, opiates are an appropriate choice for treating acute or episodic neuropathic pain [81]. Careful consideration should be given when prescribing opiates to patients who have a personal or family history of drug or alcohol abuse, and additional monitoring to ensure appropriate use may be necessary.

Tramadol, a weak opioid μ -receptor agonist and serotonin and norepinephrine reuptake inhibitor (SNRI), is more effective than placebo but less effective than strong opioid μ -receptor agonists (e.g. morphine and oxycodone) in treating neuropathic pain [82]. Although the risk is considerably less than opioid analgesics, tramadol is also associated with abuse [81]. A rare but potentially fatal serotonin syndrome has been described, and tramadol may increase the likelihood of seizures or interact with other medications [15].

Recent clinical trials have considered additional intervention strategies with possible utility in treating neuropathic pain, although their efficacy remains to be determined. Treatments include botulinum toxin for PHN and postoperative allodynia [85,86], high concentration capsaicin patch for the treatment of PHN and painful HIV neuropathy [15], and lacosamide, an antiepileptic drug with suggested efficacy in treating DPN [87-89]. There is also accumulating evidence that

intravenous Ca^{2+} and Mg^{2+} may be effective at preventing CIPN caused a commonly used chemotherapeutic, oxaliplatin, without attenuating its antineoplastic efficacy [9].

15. Non-pharmacological treatment of neuropathic pain

The use of alternative and complementary medicine is on the rise, particularly in the United States [90]. Although anecdotal evidence abounds, there are relatively few RCTs supporting the use of such therapies. It is important in considering these treatments, however, that the lack of evidence is not read as evidence of lacking efficacy. The scarcity of well controlled, robust clinical trials considering non-pharmacological treatments of chronic pain makes it difficult to recommend or dismiss these alternative treatments. A few studies have examined the use of acupuncture, herbal therapy, massage, hypnosis, and biofeedback on easing chronic pain but have yielded mixed results (for a review see [90]). The difficulty in standardizing treatment, inherent to these multi-faceted approaches, is a major obstacle in drawing reliable conclusions. Additionally, small sample sizes and lack of obvious controls are also significant barriers. Despite these hurdles, which obscure evidence-based conclusions, non-pharmacological treatments are often prescribed in conjunction with evidence-based recommendations due to low risk of accompanying adverse effects.

Deep brain stimulation, a neurosurgical technique by which an implanted electrode delivers controlled electrical impulses to targeted brain regions, has demonstrated some efficacy in treating chronic pain but is not routinely employed due to a high risk-to-benefit ratio [91]. Targeting the periventricular/periaqueductal gray, internal capsule, and sensory thalamus has demonstrated efficacy in various pain conditions [91], but not all types of chronic pain are responsive. An intriguing new target, the NAc, has recently emerged as a potential site for deep brain stimulation as it has demonstrated efficacy in a case study of post-stroke pain [92]. As studies of pain processing in the brain have suggested, the pattern of activity in the NAc is divergent in nociceptive and chronic pain representation, validating this structure as a possible therapeutic target [69].

Another type of electro-stimulation device is emerging as a promising therapeutic tool for the treatment of neuropathic pain [93, 94]. Delivering repeated pulses of electrical stimulation trans-cutaneously, termed Scrambler therapy, has demonstrated some efficacy with lasting effects in CIPN [94], postsurgical pain, PHN, and spinal canal stenosis [93]. With few adverse effects and low associated risk, this may be a viable alternative to pharmacological treatment.

16. The future of neuropathic pain management correlating symptoms to mechanism

Limited efficacy of current pain treatment options has necessitated a revaluation of the standard classification of neuropathic pain in clinical practice [17] [31, 75-77]. It has been suggested that within etiology based neuropathic pain syndromes there are distinct subgroups

of patients who experience similar “symptom constellations” representing distinct pathophysiological mechanisms [95]. Furthermore, these symptom constellations can be seen, albeit in different proportions, across neuropathic pain syndromes, suggesting that the same underlying mechanism can cause neuropathic pain within and apart from the initiating etiology. Hypothetically, with this understanding comes an approach of targeted treatment that aims to identify the pathophysiological mechanism and specifically inhibit, block, or enhance the offending molecules. To implement this type of treatment will require a more intimate understanding of the mechanisms of neuropathic pain and the corresponding symptom manifestations. As this becomes defined, specific treatments can begin to emerge, and clinical trials can test the efficacy of this approach. See Table 2 for examples.

Signs and Symptoms	Example Mechanisms	Targeted Treatment
<i>Spontaneous Pain</i>		
Shooting	Ectopic impulse generation, Na ²⁺ channel dysregulation	Selective Na ²⁺ channel blocker
Ongoing	Inflammation in nerve root, central sensitization (potentiation), disinhibition	Cytokine antagonists, Calcium channel blocker, NMDA receptor antagonist
<i>Evoked Pain</i>		
Allodynia/Hyperalgesia		
Cold	Modulation of TRPM8 or Na ²⁺ channels in peripheral nociceptors	TRPM8 receptor antagonist, Selective Na ²⁺ channel blocker
Heat	Modulation of TRPV1 in peripheral nociceptors	TRPV1 receptor antagonist
Dynamic Mechanical	Central sensitization (potentiation and facilitation), disinhibition	Ca ²⁺ channel blocker, NMDA receptor antagonist
Punctate Mechanical	Central sensitization (potentiation and facilitation), disinhibition	Ca ²⁺ channel blocker, NMDA receptor antagonist
Static Mechanical	Modulation of unknown mechanoreceptors in peripheral nociceptors, TRPA1	?
Temporal Summation	Central sensitization	Ca ²⁺ channel blocker, NMDA receptor antagonist

Table 2. Hypothetical examples of how signs and symptoms obtained in a bedside examination might indicate underlying pathophysiological mechanism. Once a putative mechanism has been established there is a potential for selective and specifically targeted treatments to be applied. For a comprehensive review see [21].

17. Genetic and environmental determinants of pain susceptibility

A major challenge in treating neuropathic pain is the heterogeneity of disease pathogenesis within an individual etiological classification. Patients with seemingly identical diseases may experience completely different neuropathic pain phenotypes, possibly due to genetic and environmental variation. A holistic approach to treating neuropathic pain, therefore, will require identification of risk or determinant factors that may play a role in neuropathic pain severity, progression, duration, or presentation.

Although there are major obstacles to studying the genetics of pain in humans, a few potential biomarkers have been identified [96]. A candidate gene association study, which compares allele frequencies between cohorts of patients with and without a particular trait, has yielded evidence that a polymorphism in catechol-O-methyltransferase (COMT) is associated with temporomandibular joint disorder [97, 98]. Other similar studies have identified alleles for the μ -opioid receptor 1 (OPRM1) [99] and the melanocortin-1 receptor (MCR1) [100] as potential determinants of sensitivity to opioid induced analgesia. A separate approach to identifying genetic determinants of pain biology uses rodent models and has also yielded promising results. Using this method, Tegeder et. al. identified a haplotype for the enzyme GTP cyclohydrolase 1 (GCH1), the rate limiting enzyme in the synthesis of tetrahydrobiopterin (BH4) [101]. BH4 is an important cofactor in the synthesis of serotonin, catecholamines, and all nitric oxide synthases [101] and plays a role in the development of chronic pain [96].

18. Conclusion

Neuropathic pain is a major source of physical and mental disability worldwide. It is associated with severe societal and individual psychosocial burden and will continue to be a major health concern until more effective treatments emerge. One of the biggest barriers to successful management of neuropathic pain has been the lack of understanding in the underlying pathophysiology that produces a pain phenotype. To that end, significant progress has been made in basic science research. From the discovery of the nociceptor and individual ion channel transducers to the mapping of pain representation in the brain, a foundational understanding has been laid. As we continue to build on this foundation, it is essential that strong communication exists between the laboratory and the clinic in order to ensure effective translation. With optimism we suggest that this could lead to better patient care and lessen the worldwide impact of neuropathic pain.

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