Pain serves to protect us from physical damage. But unlike physiologic pain, neuropathic pain does not originate from adequate stimulation of distal nerve endings. In neuropathic pain, the protective nature of pain gets lost. An initial event triggers activity driven changes in the periphery that lead to painful sensations. While the acute stimulus decays, persisting alterations in the peripheral nervous system continuously alert the whole body. As a consequence, the patient experiences...
nonpainful stimuli as painful (allodynia) and painful stimuli more painful (hyperalgesia). These symptoms can be accompanied by spontaneous pain, temperature sensitivity, numbness, tingling, or burning sensations (Treede et al., 2008).

Neuropathic pain represents a second-order consequence of nerve lesions or diseases affecting the nervous system. Macroscopic or microscopic lesions can result from trauma or surgery while chemotherapeutics can induce neuropathic pain as a consequence of their neurotoxicity (Polomano et al., 2001; Quasthoff & Hartung, 2002). Diseases in which neuropathic pain occurs as a secondary symptom are, for example, diabetes mellitus (Guy et al., 1985; reviewed in Boulton et al., 2005), the Guillain-Barré syndrome (Willison et al., 2016), channelopathies of hereditary origin (Yang et al., 2004), spinal muscular atrophy (SMA; Qu et al., 2019), and viral infections as herpes zoster (Sampathkumar et al., 2009), herpes simplex (Takasaki et al., 2000), or AIDS (De La Monte et al., 1988; Snider et al., 1983). The sensation of pain is highly subjective, hard to quantify, and, for this reason, difficult to diagnose. Reliable criteria for the diagnosis of neuropathic pain are the medical history of the patient concerning relevant lesions or diseases, the neuroanatomical plausibility of the pain distribution, and specialised questionnaires evaluating how the pain is experienced. Based on these criteria, a British group extrapolated from their data, collected in the United Kingdom, that the general prevalence of neuropathic pain is 8% (Torrance et al., 2006).

This review aims to give a widespread introduction into the field of neuropathic pain. The fundamental aspects of neuropathic pain research are introduced. Based on and guided along the anatomy of pain transmission, the established in vivo models, continuously developing in vitro models, and the assessment of evoked or spontaneous neuropathic pain in rodents are described. Hereinafter, pathological mechanisms and recent findings are presented. Subsequently, established clinical treatments and perspective therapeutic approaches are discussed and again back-linked to the anatomy. In view of the large number of research results, only selected publications will be discussed. Where appropriate, the reader is referred to more specific reviews, focusing on particular aspects.

2 | THE ANATOMICAL FUNDAMENTALS OF PAIN

The morphological correlate of the physiology underlying painful sensations is shown in Figure 1. The spinothalamic tract is the major ascending pathway responsible for the transmission of protopathic sensations. Besides pain, strong stimuli of pressure, touch, and changes in temperature are projected from the periphery to the brain. While the lateral spinothalamic tract carries information about pain, the anterior spinothalamic tract passes strong stimuli of pressure and touch. Sensory neurons which are able to sense painful stimuli are called nociceptors. This term is derived from the Latin word nocere—to hurt. Nociceptors, specialized receptors, and ion channels translate noxious stimuli into an electrical signal that can be transmitted along nerve fibres. Thinly myelinated A6 and unmyelinated C fibres are responsible for the transmission of nociceptive stimuli. Both types of fibres are composed of peripheral axons arising from the cell bodies of pseudounipolar neurons within the dorsal root ganglia (DRG). The central neurites of these cells synapse with glutamatergic multipolar second-order neurons within the dorsal horn of the spinal cord. To be more precise, painful stimuli are interconnected in the substantia gelatinsosa or lamina II of the grey matter dorsal horn. In a simplified conception, one can say that each segment of the spinal cord can be assigned to two DRGs, transmitting information from the right or left side of the body, respectively. Axons of the second-order neurons directly decussate through the white commissure to the contralateral ventral horn of the spinal cord and travel within the lateral spinothalamic tract towards the brain stem. Along this way, the fibres join the medial lemniscus and finally reach the thalamic nuclei in the diencephalon. The ventral posterolateral nucleus (VPL), serving as a switching station for the spinothalamic tract, shows a somatotopy. Each region of the body can be assigned to a specific area of the nucleus, arranged in the anteroposterior direction (Hong et al., 2011). Within the VPL, the information is passed onto a third-order neuron giving rise to an axon that travels into the primary somatosensory cortex of the somatotopically arranged postcentral gyrus of the telencephalon. Subsequently, further neurons in the postcentral gyrus are activated to forward and process the painful stimulus for an integrated perception (Bear et al., 2007; Blumenfeld, 2010; Trepel, 2017).

As depicted in Figure 1, the above-described ascending pathway is responsible for the transmission of nociceptive stimuli from the periphery into the central nervous system, leading to the perception of pain. This perception can be modulated centrally by descending sensory pathways which arise in the periaqueductal grey matter in the mid brain and the locus coeruleus in the rostral medulla oblongata. The periaqueductal grey matter receives input mainly from the telencephalic regions, like the prefrontal cortex, the amygdala, and the hypothalamus and it projects into the raphe nuclei within the rostral ventral medulla. Here, the descending glutamatergic neuron synapses with a serotonergic neuron which axon terminates in the dorsal horn. The second descending pathway arises in the locus coeruleus. The noradrenergic neuron likewise projects into the substantia gelatinosa of the spinal grey matter dorsal horn. Both pathways are able to modulate the transmission of painful stimuli between the first- and the second-order neuron of the lateral spinothalamic tract in a direct or indirect manner (Bear et al., 2007; Blumenfeld, 2010).
Pathways involved in the processing of painful stimuli. The ascending lateral spinothalamic tract is depicted in red, it originates from the substantia gelatinosa in the dorsal horn of the spinal cord synapses at diencephalic thalamic nuclei and finally projects into the telencephalic somatosensory cortex. The descending serotonergic projections from the raphe nuclei are influenced by projections from the periaqueductal grey that are depicted in green. The descending noradrenergic projections from the locus coeruleus are depicted in blue. Left from the spinal cord cross section, synaptic transmission within the spinal nucleus proprius is exemplary illustrated for all three pathways. (Inspired by Stieve & Kirsch, 1961)
The above-described pathways are well known and extensively explained in anatomical textbooks, as such they provide the basis for our understanding of pain mechanisms. However, recent studies were able to show the involvement of alternative fibres. They either originate or terminate in the dorsal horn of the spinal cord and participate in pain sensation. Liu et al. (2018), for example, described a feedback loop. Upon a stimulus, signals are propagated along fibres that originate in the somatosensory cortex and travel with the corticospinal tract into the dorsal horn of the spinal cord. In their target area, they are able to amplify the transmission of tactile information within the spinothalamic tract. Furthermore, there is evidence for central projections into the spinal cord that modulate pain sensation but differ from the well-known descending ones that originate from the periaqueductual grey matter and the locus coeruleus (see Section 2). Studies in the rat chronic nerve constriction injury model indicate that orexinergic projections from the lateral hypothalamus into the dorsal horn of the spinal cord contribute to pain modulation. Chemical stimulation of the lateral hypothalamus reduced allodynia and thermal hyperalgesia. The effect was revised by intrathecal application of orexin-1 and -2 receptor antagonists (Salehi et al., 2020). These examples demonstrate that new anatomical data will be highly valuable for an even deeper understanding and open also new insights for innovative therapeutic strategies in the future.

3 | ANIMAL MODELS

Taking into account the varying causes of neuropathic pain, different rodent animal models have been developed to investigate and understand the underlying pathologic mechanisms. As summarised in Table 1, the established models comprise nerve injury, chemotherapy-, and infection-induced neuropathic pain, or diabetic peripheral neuropathy. This review aims to focus on models emulating the most frequent causes of neuropathic pain. A more comprehensive review exclusively concentrating on animal models can be found elsewhere (Jaggi et al., 2011). The common phenotype of all different models should result in reproducible sensory deficits like allodynia, hyperalgesia, or spontaneous pain.

3.1 | Models of macroscopic or microscopic nerve lesions

Macroscopic or microscopic nerve lesions can, for example, result from an accident or a surgery and entail the development of neuropathic pain. The lesions most likely appear in the peripheral neurites of DRG neurons, the first-order neurons of the spinothalamic tract (see Section 2, Figure 1). Four of the most commonly used trauma models are the chronic constriction injury, the spared nerve injury, the spinal nerve ligation, and the partial sciatic nerve ligation model (less used animal models are comprehensively reviewed in Jaggi et al., 2011). The chronic constriction injury model and the spared nerve injury model both involve a lesion of the sciatic nerve. Chronic constriction injury can be induced by four loosely applied ligatures proximal to the trifurcation of the sciatic nerve, resulting in pain-like behaviour most likely resembling mechanical and thermal hyperalgesia, mechanical and cold allodynia, and possibly dysesthesia (Bennett & Xie, 1988; Gopalsamy et al., 2019). The circumscribed transection (axotomy) of the tibial or the fibular nerve, distal to the branching sural nerve, represents the spared nerve injury model (Bourquin et al., 2006; Decosterd & Woolf, 2000; Shields et al., 2003). The partial denervation leads to the development of mechanical and cold allodynia and mechanical hyperalgesia. A ligation of the lumbar spinal cord segment 5 (L5) spinal nerve or of the L5 and L6 spinal nerves can be performed to generate the spinal nerve ligation model (Ho Kim & Mo Chung, 1992; Xie et al., 2001; Ye et al., 2015). Thermal hyperalgesia, mechanical allodynia, and signs of dysesthesia can be observed in this animal model. The fourth model, a partial injury of the sciatic nerve, can be induced by a tight ligation of one-third to half of the sciatic nerve (Malmberg & Basbaum, 1998; Seltzer et al., 1990). The animals undergoing this procedure show mechanical and thermal allodynia and signs of dysesthesia. One common limitation and point of criticism of these nerve injury models is the reproducibility. The outcome highly depends on the surgical skills of the experimenter and the material used, for example, the suture material being inserted. The more accurate the surgery is performed, the more defined and reproducible is the introduced injury. The extent of the observed neuropathic pain might consequently differ. However, nerve injuries in humans induced by an accident or a surgery likewise show a high degree of variation. The different mouse and rat models (Table 1) and their varying outcome emulate the different clinical conditions and would therefore be a promising approach to identify common mechanisms of neuropathic pain following nerve injury.

3.2 | Chemotherapy-induced models

The neurotoxicity of chemotherapeutic agents can cause neuropathic pain, a frequent, dose-limiting and long-term complication of anticancer therapies. Based on the observed neurological symptoms, different animal models were developed to investigate the underlying mechanisms causing neuropathic pain. Chemotherapeutics with described neurotoxic effects can be categorised into four different chemical groups such as taxanes, platinum-based compounds, plant alkaloids, and proteasome inhibitors (reviewed in Farquhar-Smith, 2011).
The establishment of suitable experimental models mainly focuses on the drugs paclitaxel (Griffiths et al., 2018; Polomano et al., 2001; Smith et al., 2004), cisplatin, oxaliplatin (Authier et al., 2003a; Ling et al., 2007; Ta et al., 2009), vincristine (Authier et al., 2003b; Higuera & Luo, 2004; Kiguchi et al., 2008), and bortezomib (Carozzi et al., 2013; Duggett & Flatters, 2017) which are the most prominent members of the four chemical groups mentioned above. The animal models differ concerning the applied dose and the period of administration for each compound (Table 1). Consequently, signs of neuropathic pain differ in a dose-dependent manner, resembling the anticancer therapies in the clinic. Each model gives the opportunity to investigate the effect of a single chemotherapeutic on the nervous system. However, the dynamics of

| TABLE 1 Summary of animal models used in neuropathic pain research for introducing allodynia, hyperalgesia, or dysesthesia |
|---------------------------------------------------------------|
| **Model** | **Principle** | **Species** | **Introduced leading symptom** |
|---------------------------------------------------------------|
| **Trauma** | | | |
| Chronic constriction injury | Ligature of sciatic nerve | R, M | Hyperalgesia, allodynia, dysesthesia (Bennett & Xie, 1988; Gopalsamy et al., 2019) |
| Spared nerve injury | Axotomy of tibial and fibular nerve | R, M | Allodynia, mechanical hyperalgesia (Bourquin et al., 2006; Decosterd & Woolf, 2000; Shields et al., 2003) |
| Spinal nerve ligation | Ligation of L5 or L5/L6 spinal nerve | R, M | Thermal hyperalgesia, mechanical allodynia, dysesthesia (Ho Kim & Mo Chung, 1992; Ye et al., 2015) |
| Partial sciatic nerve ligation | Tight ligature around one-third to one-half of the sciatic nerve | R, M | Allodynia, dysesthesia (Malmberg & Basbaum, 1998; Seltzer et al., 1990) |
| **Chemotherapy** | | | |
| Paclitaxel-induced neuropathy | 4 intraperitoneal injections of 0.1–2.0 mg/kg on alternate days | R, M | Dose-dependent (Malmberg & Basbaum, 1998; Seltzer et al., 1990) |
| Cisplatin-induced neuropathy | Repeated intraperitoneal injections, cumulative dose of 15–23 mg/kg | R, M | Dose-dependent (Authier et al., 2003a; Ta et al., 2009) |
| Oxaliplatin-induced neuropathy | Repeated intraperitoneal injections, cumulative dose of 9–36 mg/kg | R, M | Dose-dependent (Ling et al., 2007; Ta et al., 2009) |
| Vincristine-induced neuropathy | 5–7 intraperitoneal injections of 50–150 µg/kg on alternate or consecutive days or infusion pump applying 30 µg/d/kg | R, M | Dose-dependent (Authier et al., 2003b; Higuera & Luo, 2004; Kiguchi et al., 2008) |
| Bortezomib-induced neuropathy | Repeated intraperitoneal injections, cumulative dose of 0.4–6.4 mg/kg | R, M | Dose-dependent (Carozzi et al., 2013; Duggett & Flatters, 2017) |
| **Virus** | | | |
| Herpes simplex virus type−1 | Intraplantar injection of virus | M | Hyperalgesia, allodynia (Takasaki et al., 2000) |
| Varicella zoster virus | Injection of infected allogenic cells (intraplantar/subcutaneous along spinal column) | R | Hyperalgesia, allodynia (Dalziel et al., 2004; Sadzot-Delvaux et al., 1990) |
| Human immunodeficiency virus | Delivery of envelop protein to sciatic nerve | R | Hyperalgesia, allodynia (Herzberg & Sagen, 2001) |
| **Diabetes** | | | |
| Alloxan-induced diabetes | Intraperitoneal injection | R, M | Hyperalgesia (Ahmadi et al., 2012; Lee et al., 1990) |
| Streptozocin-induced diabetes | Intraperitoneal injection | R, M | Mechanical hyperalgesia, allodynia (Ahlgren & Levine, 1993; Courteix et al., 1993; Murakami et al., 2013) |
| Goto-Kakizaki rat | Insulinopenia (18-month-old animals) | R | Mechanical allodynia (Goto et al., 1988; Murakawa et al., 2002) |
| Zucker diabetic fatty rat | Hyperglycemia (>1-month-old animals) | R | Hyperalgesia, allodynia (Brussee et al., 2008; Romanovsky et al., 2008) |

Abbreviations: M, mouse; R, rat.
combined treatment approaches, which are frequently used to treat cancer (reviewed in Kummar et al., 2010), are not well represented in the published animal models yet. Therefore, this aspect will be needed to be considered in future approaches analysing the chemotherapy-induced mechanisms underlying neuropathic pain.

3.3 | Viral infections

Apart from nerve injuries and neurotoxic drugs, there are a few known viral infections that impair the human peripheral nervous system and cause severe symptoms accompanying the primary disease. Various animal models were developed to understand how these infections can lead to neuropathic pain (Table 1). The used models are based on different infection routes. After an acute phase, the varicella zoster virus and the herpes simplex virus type 1 are able to cause a latent infection within the somatosensory ganglia of spinal and cranial nerves, respectively. Thereby, the first-order neurons of the primary disease. Various animal models were developed to study the processes underlying neuropathic pain associated changes in the peripheral nervous system and their treatment, for example, the application of local analgesics (Castel et al., 2017). On the basis of this knowledge, a porcine trauma model was established (Rice et al., 2018). The studies’ authors were able to show that the animals develop hyperalgesia (Ahlgren & Levine, 1993; Lee et al., 1990) and additional allodynia (Courteix et al., 1993). Neurological effects were also observed in the Zucker diabetic fatty (ZDF) rat strain, mimicking type 2 diabetes (Brussee et al., 2008; Romanovsky et al., 2008). The animals showed signs of hyperalgesia and allodynia, supporting the collected results of the chemical-induced diabetes models. Furthermore, unmyelinated and thinly myelinated fibre neuropathy was observed in the spontaneously diabetic Goto-Kakizaki rat strain (Goto et al., 1988; Murakawa et al., 2002), indicating an impairment of the first-order spinothalamic neurons (see Section 2).

The aetiologies of neuropathic pain are manifold. Hence, a multitude of animal models has been created to investigate the processes underlying neuropathic pain (Table 1). The observations in different models addressing the same aetiologies, however, show similar results. This, on the one hand, shows the validity and, on the other hand, hopefully allows the identification of common mechanisms in the future.

The significance of the insights gained from neuropathic pain research for the clinic, depends to a great extent on the translatability of the animal model used. The commonly used in vivo models are mainly established in rodents. However, different studies were able to show that nociceptive fibres of pigs and humans share essential characteristics that rodent fibres do not (reviewed in Obreja & Schmelz, 2010). These findings suggest pigs as a new and promising model organisms to study neuropathic pain-associated changes in the peripheral nervous system and their treatment, for example, the application of local analgesics (Castel et al., 2017). On the basis of this knowledge, a porcine trauma model was established (Rice et al., 2018). The animals developed a peripheral neuritis after loose ligatures were tied around the sciatic nerve. The observed findings correlate with those observed in humans, which underlines the importance of porcine models for future neuropathic pain research.

3.4 | Diabetes mellitus

Neuropathic pain is one major long-term complication of diabetes mellitus (Boulton et al., 2005). Appropriate models in mice and rat already exist due to diabetes research. The implications on the nervous system were investigated in a few of these models, for example, in the streptozocin- and alloxan-induced diabetic model (Ahlgren & Levine, 1993; Ahmadi et al., 2012; Courteix et al., 1993; Lee et al., 1990; Murakami et al., 2013). Both approaches are based on the toxic effect the applied compounds have on insulin-producing cells of the pancreas. The studies’ authors were able to show that the animals develop hyperalgesia (Ahlgren & Levine, 1993; Lee et al., 1990) and additional allodynia (Courteix et al., 1993). Neurological effects were also observed in the Zucker diabetic fatty (ZDF) rat strain, mimicking type 2 diabetes (Brussee et al., 2008; Romanovsky et al., 2008). The animals showed signs of hyperalgesia and allodynia, supporting the collected results of the chemical-induced diabetes models. Furthermore, unmyelinated and thinly myelinated fibre neuropathy was observed in the spontaneously diabetic Goto-Kakizaki rat strain (Goto et al., 1988; Murakawa et al., 2002), indicating an impairment of the first-order spinothalamic neurons (see Section 2).

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4 | Assessment of Neuropathic Pain in Animal Models

The following section comprises a short overview of different methods to detect neuropathic pain in rodent animal models, focusing on commonly used stimulus and nonstimulus evoked approaches (Table 2). More detailed reviews have, for example, recently been given by Turner et al. (2019) or Deuis et al. (2017). Neuropathic pain is difficult to assess in animals. The commonly performed in vivo analyses mainly evaluate stimulus-evoked pain-like behaviours, like withdrawal from the nociceptive stimulus, licking or shaking of the stimulated part of the animal’s body, and vocalisation. The
manual and mechanical von Frey test, for instance, can be used to evaluate mechanical allodynia (Chaplan et al., 1994; Ferrier et al., 2016). Thermal sensitivity can, for example, be addressed via the hot plate (Espejo & Mir, 1993), Hargreaves (Cheah et al., 2017; Hargreaves et al., 1988), or acetone test (Choi et al., 1994). Nocifensive behaviours can, for instance, be evaluated after intraplantar injection of chemicals like capsaicin (Sakurada et al., 1992) or formalin (Tjølsen et al., 1992). To a certain extent, the interpretation of the functional readouts may differ between laboratories and experimenters, due to the subjective nature of the observations.

Human patients do not only display an increased sensitivity or perceive nonpainful stimuli as painful but also report spontaneous or background pain sensations. This characteristic symptom, however, cannot be analysed with stimulation-evoked approaches in experimental research. In the last few years, different approaches were developed to address this issue in the animal models (reviewed in Tappe-Theodor & Kuner, 2014). The free choice thermal preference test, the conditioned place preference test, and the place escape avoidance test can be regarded as alternatives to established, stimulus-evoked approaches. The free choice thermal preference test allows the freely moving animal to choose between plates with different temperatures. The test can be used to assess cold hyperalgesia and allodynia (Duraku et al., 2014). The conditioned place preference test is a reward-based

| Method                        | Stimulus                                                                 | Observed behaviour                                      | Evaluated symptom                                                                 |
|-------------------------------|--------------------------------------------------------------------------|----------------------------------------------------------|-----------------------------------------------------------------------------------|
| **Stimulus-evoked**           |                                                                          |                                                          |                                                                                   |
| Von Frey Test                 | Manual or mechanical stimulation of the food pad with filaments of varying diameter | Paw withdrawal                                           | Mechanical allodynia (Chaplan et al., 1994; Ferrier et al., 2016)                  |
| Hot Plate Test                | Thermal stimulation at 48°C–55°C                                         | Paw licking, Paw withdrawal, jumping, freezing            | Thermal hyperalgesia (Espejo & Mir, 1993)                                          |
| Hargreaves Test               | Hind paw is exposed to a heat source (radiant or infrared)               | Paw withdrawal latency                                    | Thermal hyperalgesia (Cheah et al., 2017; Hargreaves et al., 1988)                 |
| Acetone Test                  | Application of acetone onto the plantar surface of the paw               | Paw withdrawal                                           | Cold allodynia (Choi et al., 1994)                                                 |
| Capsaicin Test                | Injection (s.c.) of capsaicin into dorsal surface of the hind paw        | Paw licking                                              | Hyperalgesia (Sakurada et al., 1992)                                               |
| Formalin Test                 | Injection (s.c.) of formalin into plantar surface of the paw             | Paw withdrawal, licking, biting, and shaking              | Hyperalgesia (Tjølsen et al., 1992)                                                |
| **Spontaneous**               |                                                                          |                                                          |                                                                                   |
| Free choice thermal preference Test | Differently temperature plates between the freely moving animal can choose | Frequency and length of stay                             | Cold hyperalgesia and allodynia (Duraku et al., 2014)                              |
| Conditioned place preference Test | Reward-based: animal is conditioned to the application of an analgesic in a multichambered system | Frequency and length of stay                             | Ongoing pain (He et al., 2012; King et al., 2009)                                  |
| Place escape avoidance Test   | Modified von Frey test, healthy and afflicted limb of the animal are stimulated at two distinct areas of the observation area | Frequency and length of stay                             | Motivational and affective aspects of neuropathic pain (Boyce-Rustay et al., 2010) |
| Grimace scale                 | Spontaneous facial expression of the rodent is observed                   | Orbital tightening, flattening of cheeks and nose, changes in position, orientation and shape of ears and orientation of whiskers | Non-stimulus evoked nociception (Akintola et al., 2017; Leung et al., 2019; Sperry et al., 2018) |
| Burrowing behaviour           | Spontaneous behaviour of the animal, observed in housing system          | Burrowing                                                | General discomfort possibly indicating pain (Leung et al., 2019)                    |
| Weight bearing                | Spontaneous behaviour of the animal, observed in housing system          | Weight bearing                                           | General discomfort possibly indicating pain (Tétreault et al., 2011)                 |
| Gait of the animal            | Spontaneous behaviour of the animal, observed in housing system          | Gait                                                     | General discomfort possibly indicating pain (Vrinten & Hamers, 2003)                |
method, able to give insights into ongoing pain in rat (King et al., 2009) and mouse (He et al., 2012). The animals are exposed to a multichambered system, where they receive an analgesic drug in one of the chambers during preconditioning. Afterwards, the preference behaviour of the freely moving animal can be evaluated. The place escape avoidance test addresses the motivational and affective aspects of neuropathic pain (Boyce-Rustay et al., 2010). The method is generally based on the von Frey test. The afflicted and a healthy limb of the animal are mechanically stimulated at two different areas of the testing field. The avoidance behaviour of the freely moving animal is evaluated.

In addition, methods solely based on the observation of the animal can be applied to assess spontaneous pain. The facial expressions of mice and rats provide information about their wellbeing. In particular, attention is paid on the orbital tightening, flattening of the cheeks and the nose, changes in the position, the orientation and the shape of the ears, and the orientation of the whiskers (Langford et al., 2010; Sotocina et al., 2011). The published grimace scales can be used to monitor and rank nonstimulus evoked nociception (Akinola et al., 2017; Leung et al., 2019; Sperry et al., 2018). The analysis of the burrowing behaviour (Leung et al., 2019), the weight bearing (Tétrault et al., 2011), the gait of the animal (Vrinten & Hamers, 2003), or automated systems additionally enabling to monitor the animals’ behaviour (Urban et al., 2011), can be used to support the collected data. However, it is important to consider that the altered behaviour does not strictly reflect pain in the animal but discomfort in general. Therefore, it must be interpreted carefully. Moreover, the methods cannot be applied to all animal models. If limb nerves are manipulated in an injury model, the weight bearing and the gait are very likely to be altered, independent of the pain the animal may additionally be experiencing.

On the other hand, the close monitoring of the animals still enables the detection of non-stimulus evoked nociception, an important characteristic of neuropathic pain in human patients. This is a clear advantage over afore mentioned methods evaluating stimulus evoked pain. However, the close monitoring of the animals is time consuming, requires specific training of the experimenter and most critical interpretation of the results. Hence, the discovery of a standardised biomarker would support the functional in vivo analysis of neuropathic pain in rodent animal models and would furthermore provide a sufficient readout of in vitro models in the future.

5 | CELLULAR MODELS

In order to complement the knowledge of molecular mechanisms underlying neuropathic pain and to reduce the number of animal experiments, in vitro models have been established and are being further developed. In the following, some different in vitro systems and personalised approaches will be described. Figure 2 summarises the concepts and illustrates the diversity of cell types, complex and innovative in vitro systems could be composed of.

The most frequently used cellular models include usage of established cell lines, for example, PC12 or SH-SY5Y cells and primary cultures, mostly derived from rodent DRGs (recently reviewed in Lehmann et al., 2020). However, efforts are being made to more closely emulate the condition in human patients and thereby increasing the translatability of the results. Human embryonic stem cells, for example, were successfully differentiated into peripheral sensory neurons. They provide a model system for the study of mechanisms initiated after chemotherapeutic treatment (Wheeler et al., 2015; Wing et al., 2017) or peripheral neuronal injury (Jones et al., 2018). Wainger et al. (2015) describe a similar approach, they derivated the nociceptive neurons from fibroblasts which were collected from human patients. The patient-derived cells could reduce the number of animal experiments, overcome the problem of inducing neuropathic pain in vitro and represent a possible basis for personalised medicine approaches in the future.

A very promising, recently published approach is based on a microfluidic platform. The device allows the experimenter to study the interaction between peripheral DRG and dorsal horn neurons, the first- and second-order neurons of the spinohalamic tract (Section 2). While the cell bodies are separated in different compartments of the device, the neurites can grow through small channels and reach the opposite compartment (Vysokov et al., 2019). Vysokov et al. focused their study on the evaluation of altered activity of voltage gated sodium channels after axotomy. However, the presented model would furthermore allow to investigate the impact of peripheral alterations on central neurons. From our overview, this would most sufficiently reflect the in vivo situation, therefore, allowing translatable research without the need for in vivo experiments and probably revealing new therapeutic concepts.

6 | PATHOGENIC MECHANISMS AND RECENT FINDINGS

The pathologic mechanisms leading to the development of neuropathic pain are manifold and poorly understood. Figure 3 gives an overview about some of the systemic triggers, as mentioned in the second paragraph of the introduction, and the cell types crucially involved in the development of neuropathic pain (see below). The neuropathic pain management predominantly starts after manifestation
FIGURE 2 Schematic illustration of a two-compartment microfluidic cell culture system. Such a platform could be of potential use for studying neuronal networking as well as neuronal-glia cellular interaction in the study of neuropathic pain cellular and molecular mechanisms. Neurite outgrowth can be directed towards the central microchannels, while the compartments could be filled with glia cells or first- and second-order neurons derived from different sources. Sources can be established cell lines primary animal cells or cells derived from patient derived stem cells in a more personalised concept.

FIGURE 3 Mechanisms leading to neuropathic pain are not yet fully understood. This schematic drawing summarizes the pathogenic mechanisms as detailed in Section 6. Systemic triggers, like underlying hereditary or infectious diseases (outer circle, see Section 1, second paragraph), are discussed to pave way for peripheral sensitization of first-order dorsal root ganglion neurons (top triangle), alterations in the circuitry of central structures involved into pain processing (right triangle), and modification in crosstalk and activity of glial and immunocompetent cells (left triangle).
of neuropathic pain and focuses on treating the symptoms. A better understanding of the underlying pathologic mechanisms is indispensable to ensure effective pain medication and to ultimately improve the patients’ life quality. Different alterations in the peripheral and central nervous system were discovered in structures that are involved in pain sensation. The following section will name some of the most frequently discussed molecular mechanisms, which can be linked to the anatomy, as the common thread of this review. More comprehensive reviews can be found elsewhere (Cohen & Mao, 2014; Colloca et al., 2017). To begin with, we present peripheral mechanisms which are postulated to promote the development of neuropathic pain (see Figure 4 for summary).

### 6.1 Peripheral sensitization

It is assumed that sensitisation is a key driver in the development of neuropathic pain. Multiple studies have shown that the sensory DRG neurons (Figure 3 top triangle), which represent the first station of the lateral spinothalamic tract (see Section 2) undergo different molecular processes leading to peripheral sensitisation. Voltage-gated ion channels of DRG neurons, which are able to regulate the electric membrane potential of the neuron, are likely to be involved. The predominantly expressed voltage-gated sodium channel in DRG neurons is NaV1.7 (Toledo-Aral et al., 1997). A few diseases of hereditary origin are known in which loss-of-function mutations of the channel lead to the inability to sense pain (Cox

![Figure 4](image-url)
et al., 2006). In contrast, gain-of-function mutations, found in inherited erythromelalgia patients, lead to the development of a chronic pain syndrome (Meents et al., 2019). Alternative splicing of NaV1.7 may even influence the disease onset (Choi et al., 2010). These findings underline the physiological importance of the ion channel for nociception.

Based on this knowledge, voltage-gated ion channels were investigated in different conditions associated with neuropathic pain (orange box in Figure 4). Besides NaV1.7, special focus was laid on NaV1.8, and NaV1.9. Following injury or chemotherapy, secretion of signal molecules may upregulate the expression of NaV1.7 in rats and humans, and cause an enhanced excitability (Chang et al., 2017; Sun et al., 2018). Other findings suggest that de novo expression of NaV1.8 is reduced in patients after peripheral nerve injury, while already present channels accumulate at the injury sites (Coward et al., 2000). Increased levels of the voltage-gated sodium channels NaV1.7 and NaV1.8 were furthermore detected in a mild severity mice model of SMA, showing mechanical allodynia, thermal allodynia, and hyperalgesia (Qu et al., 2019). Three of the studies mentioned above, were able to show that overexpression of voltage-gated sodium channels is accompanied by a reduced threshold potential of the cell (Chang et al., 2017; Qu et al., 2019; Sun et al., 2018). Due to the lowered threshold, minor stimuli may cause action potentials and consequently allodynia. Results of a clinical study, comprising oxaliplatin-treated patients with neuropathic pain symptoms, furthermore, suggest that the inactivation of voltage-gated sodium channels is delayed in these patients (Heide et al., 2018). The delayed inactivation of the channels causes a prolonged influx of positively charged sodium ions that might lead to hyperexcitability.

Interestingly, recently published studies identified gain-of-function mutations of voltage-gated sodium channels in patients with diabetes (Alsaloum et al., 2019; Blesneac et al., 2018). The described effects of altered sodium channels might even be enhanced by changes in the main energy producing pathways. In vivo application of the chemotherapeutic agent paclitaxel, for example, leads to decreased levels of adenosine triphosphate (ATP) in DRG neurons. Since ATP is crucial for transporting sodium out of the cell via the Na⁺/K⁺ ATPase, a dysfunction might lead to an accumulation of positively charged ions inside the cell (Duggett et al., 2017). Taken together, increased integration of sodium channels into the neuronal membrane, gain-of-function mutations, and low ATP levels lead to a higher membrane potential and thus aggravate the hyperexcitability, which can initially be caused by the altered function of the voltage-gated sodium channels (red box in Figure 4).

In contrast to other channel subtypes, there is some evidence that peripheral nerve injury causes downregulation of NaV1.9 (Dib-Hajj et al., 1998). This leads to the suggestion that NaV1.9 may not equally contribute to injury-induced neuropathic pain compared to NaV1.7 and NaV1.8. This hypothesis was supported by a study performed by Priest et al. (2005) who were not able to detect significant differences in a mouse injury model between wildtype mice and NaV1.9 knock out mice, regarding electrophysiology and thermal and mechanical sensitivity. However, differences in thermal sensitivity and spontaneous pain behaviour were observed regarding inflammatory pain (Priest et al., 2005). While the current review aims to give a brief overview about different mechanisms suggested to contribute to neuropathic pain, a comprehensive review about the role of voltage-gated sodium channels was, for instance, recently published by Bennett et al. (2019).

In addition to altered voltage-gated sodium channels, chloride ion levels were found to be affected in pain associated rat models of nerve trauma (see Section 3.1). Following chronic constriction injury, upregulation of the inwardly directed sodium-potassium-chloride cotransporter isoform 1 (NKCC1) could be detected. The increased integration of the transporter into the membrane presumably causes a higher chloride concentration in small and medium sized DRG neurons, including the nociceptive subpopulation of DRG neurons (Tan et al., 2020; dark blue box in Figure 4). Similar effects were observed in the dorsal horn after spinal cord injury in rat. Hasbargen et al. confirmed an upregulation of NKCC1, but where furthermore able to show a downregulation of the outwardly directed potassium-chloride cotransporter isoform 2 (KCC2; Hasbargen et al., 2010; light blue box in Figure 4). The increased chloride concentration may modulate the cell’s responsiveness to GABAergic inhibition. In contrast to other mechanisms that will be discussed below, it could additionally been shown that the downregulation of KCC2 and the functional consequences seems to be independent of sex (Mapplebeck et al., 2019).

The third type of voltage-gated channel associated with neuropathic pain, are calcium channels. Voltage-gated calcium channels, if integrated into the membrane of DRG neurons, become active during the initial depolarisation phase. The activation allows a calcium influx and thereby promotes the formation of an action potential. Upregulation of the auxiliary subunit α₂δ-1 has been found in first-order neurons of the DRG (Luo et al., 2001; Newton et al., 2001), of the trigeminal ganglion (Tachiya et al., 2018) and of second-order neurons of the spinal cord’s dorsal horn (Boroujerdi et al., 2008) after injury. The altered expression of the subunit is supposed to increase the frequency of the postsynaptic current, recorded in the dorsal horn of the spinal cord (Nguyen et al., 2009; Zhou & Luo, 2014; purple box in Figure 4; the underlying pathway is explained in Section 2). For further reading about the respective consequences of a potential increase in pain transmission, we would like to refer the reader to review articles exclusively discussing the role of the α₂δ-1 calcium channel subunit and the therapeutic aspects, for example given by Patel and Dickenson (Patel & Dickenson, 2016).
The major function of DRG neurons is to forward sensory information from the periphery to the central nervous system. Painful sensations, for example, are passed from the DRG neurons to the second-order neuron of the spinothalamic tract (see Section 2). However, studies proved the expression of the usually postsynaptic N-methyl-D-aspartate receptors (NMDARs) in the presynaptic primary sensory afferents (Liu et al., 1994). It is assumed that the excitatory receptors are quiescent under physiological conditions but integrate into the presynaptic membrane and become tonic active in individuals experiencing chronic neuropathic pain (Yan et al., 2013). The activated NMDARs could either cause a calcium influx in a direct manner or indirectly via stimulation of voltage-gated calcium channels. The resulting increase of calcium ions is assumed to trigger the spontaneous release of glutamate into the synaptic cleft in the absence of a stimulus (McGuinness et al., 2010). While the initial stimulus fades, ongoing synaptic transmission between the first and the second-order spinothalamic neuron could provoke the sensation of spontaneous pain (green box in Figure 4). However, in the recent years, this concept has not been explored further.

Peripheral sensitisation seems to involve enhanced excitation whereas central sensitisation most likely results from an imbalance between excitatory and inhibitory transmission. The imbalance leads to hyperexcitability of the affected somatosensory nerve (recently reviewed in Colloca et al., 2017). The Gate Control Theory postulated by Melzack and Wall involves inhibitory interneurons modulating the synaptic transmission from mechanoreceptive and nociceptive fibres to second-order spinothalamic neurons (Melzack & Wall, 1965; see Section 2). Through release of GABA or glycine, the interneurons, inter alia, prevent the transmission of two simultaneous stimuli which might otherwise lead to misinterpretation. Mice models of sciatic nerve injury revealed that increased levels of glutamate in the extracellular matrix presumably induce degeneration of GABAergic interneurons in the superficial dorsal horn, within four weeks after injury. While the peripheral nerves still retain their ability to regenerate after injuries, the significantly reduced regenerative potential of the central nervous system is likely to cause pain persistence. Therefore, the loss of inhibitory interneurons in the spinal cord might contribute to the transition from acute to chronic neuropathic pain (Inquimbert et al., 2018). This hypothesis was strongly supported by the results of Manion et al. who were able to show that transplantation of GABAergic interneurons can reduce neuropathic pain after spared nerve injury. The human induced pluripotent stem cell-derived transplants were delivered into the dorsal horn of the spinal cords’ lumbar enlargement of mice, after development of allodynia and thermal hyperalgesia. The symptoms were attenuated two weeks after transplantation, the effect lasted until the end of the experiment (2 months; Manion et al., 2020). Recently published expression data from the mouse spinal nerve ligation model indicate additional changes in neuronal signalling. Increased expression of voltage-gated calcium channels as well as of GABA and ionotropic glutamate receptors was shown in spinal cord tissue over a period of 4 weeks after nerve ligation injury (Yu et al., 2019).

The loss of GABAergic interneurons and the increased expression of GABA receptor Gabrb3, detected in the spinal cord, are not necessarily contradictory. Other cell types may attempt to compensate the lack of inhibition to restore the balance within the neuronal network. Data on expression profiles of single cells would be helpful to determine the specific population that undergoes upregulation of Gabrb3.

### 6.2 Plasticity of central pain circuits

As indicated in Figure 3, right triangle, the sensation of neuropathic pain is caused by pathologic changes in afferent pathways. However, alterations of central descending pathways involved in pain modulation seem to also contribute. The major descending pathways, contributing to pain modulation, are explained in Section 2 and Figure 1. Findings from different studies indicate that increased activity of noradrenergic neurons in the locus coeruleus (Brightwell & Taylor, 2009) and of neurons and glia cells in the periaqueductal grey matter (Ni et al., 2016; Samineni et al., 2017) might be involved in the development and maintenance of neuropathic pain. The projections of both areas terminate in the dorsal horn of the spinal cord and are able to modulate the transmission of painful stimuli from the first to the second-order spinothalamic neuron (see Section 2, Figure 1). The periaqueductal grey mainly receives afferents from the prefrontal cortex, the amygdala and the hypothalamus. Huang et al. (2019) were able to identify an afferent pathway in mice, projecting from the basolateral amygdala via the prefrontal cortex to the periaqueductal grey. This linear circuit was found to be strengthened after peripheral nerve injury, resulting in a reduced release of serotonin in the dorsal horn of the spinal cord. The inhibition of pain transmission through the lateral spinothalamic tract is therefore compromised. The linear projection from the amygdala to the prefrontal cortex would hence be a putative target for neuropathic pain medication. The influence of the amygdala on neuropathic pain is additionally supported by a recently published study. With a sophisticated chemogenic manipulation approach, the authors were able to demonstrate that inhibition of the basolateral amygdala reduces pain affective-motivational behaviours in mice, like escaping or attending behaviour (Corder et al., 2019).

### 6.3 Glial and immunocompetent cells

For years, it has been assumed that glial cells mainly provide a structural and nutritional function in the nervous system.
However, it became increasingly evident that the functions of glial cells are much more diverse. Concerning neuropathic pain, special emphasis is laid on the communication among glial cells and between glial and neuronal cells. This crosstalk might be modulated in the condition of neuropathic pain. As indicated in the left triangle of Figure 3, both, peripheral as well as central glia cells appear to be important in this context. Satellite glial cells, for example, which concentrically surround the soma of DRG neurons, show increased expression of the glial fibrillary acid protein (GFAP) and chemotherapy-induced altered coupling. The communication among these peripheral glia cells via gap junctions is enhanced after in vivo application of the chemotherapeutics oxaliplatin or paclitaxel (Poulsen et al., 2015; Warwick & Hanani, 2013). It has furthermore been found that proinflammatory cytokines such as interleukin 1β (IL-1β), IL-6, and tumor necrosis factor alpha (TNFα) are upregulated in central and peripheral glial cells, following spinal cord injury or chemotherapy. In contrast, anti-inflammatory cytokines such as IL-4 and IL-10 are downregulated. The increased release of pro-inflammatory cytokines might lead to hyperexcitability (Brandolini et al., 2019; Davies et al., 2007; Vallejo et al., 2010). Taken together, these findings suggest gap junction-forming glycoproteins, like pannexin1, and inhibitors of inflammatory pathways as putative therapeutic targets to address neuropathic pain (Brandolini et al., 2019; Hanstein et al., 2016).

Astrocytes are assumed to modulate pain signalling in the dorsal horn of the spinal cord under physiological conditions. Interferon alpha (IFN-α), which is produced by astrocytes, could inhibit the release of glutamate and substance P. This might reduce synaptic transmission between the first- and second-order neuron of the spinothalamic tract (Liu et al., 2016; see Section 2, Figure 1). Several studies support the hypothesis that astrocytes are furthermore involved in pain signalling under pathological conditions. For example, intrathecal injection of TNF-α-activated astrocytes was shown to produce mechanical allodynia in mice (Gao et al., 2010). Menetski et al. (2007) additionally discovered that the overexpression of chemokine ligand 2 (CCL2) in astrocytes results in thermal hyperalgesia and induces nocifensive behaviours in a mouse ligation injury model.

The predominantly active central glial cell type seems to change during pain chronification. Recruitment of microglia was found during the acute phase, whereas astrocytes become active if the pain persists (Raghavendra et al., 2003). Microglia hold a special position among the glial cells. In contrast to all other types of glial cells, which are derivatives of the ectodermal neural plate, microglia originate from the mesoderm. They are referred to as the resident immune cells of the central nervous system, constantly surveying their environment. It has been shown that peripheral nerve injuries induce microglia activation (recently reviewed in Inoue & Tsuda, 2018).

Apart from microglia, other immunocompetent cells might as well be involved in the pathophysiology of neuropathic pain (Figure 3, left triangle). Signalling between immune cells and neurons might contribute to chronic pain hypersensitivity. In the periphery, macrophages were found to be involved in the development and maintenance of mechanical hypersensitivity. Their targeted depletion leads to a significant reduction of the pain-related behaviour in a mouse injury model that was introduced by spinal nerve ligation (Yu et al., 2020). Peng et al. (2016) proposed a synergistic mechanism. Their data suggest that spinal microglia and recruited peripheral monocytes, together, promote the development of mechanical allodynia and thermal hyperalgesia and contribute to the chronification of neuropathic pain. Furthermore, there is evidence that the neuropathic pain-inducing chemotherapeutic agent vincristine may alter the integrity of the blood-spinal cord barrier, which is formed by astrocytes. Consecutively, peripheral monocytes could infiltrate the spinal cord through the battered barrier and release pro-nociceptive factors. This mechanism might be involved in the development of acute mechanical hypersensitivity (Montague-Cardoso et al., 2020). On the other hand, studies by Sorge et al. (2011, 2015) highlighted sex-specific differences regarding the types of immunocompetent cells contributing to mechanical allodynia after spared nerve injury. They were able to show that mainly T cells are recruited into the spinal cord after traumatic nerve injury in female mice, whereas microglial cells dominate in male mice. Interestingly, there is some indication that the described sex differences only occur if the pain persists and do not occur during the acute phase (Inoue & Tsuda, 2018). Nevertheless, the proposed sex-dependence of neuroinflammation suggests that therapeutic strategies addressing the immune system may need to be adapted to the patient’s gender or hormone status.

### 7 Therapeutic Approaches

Neuropathic pain is the result of numerous nerve-affecting mechanisms like trauma, infectious diseases, or accompanying symptoms of other diseases. According to the diversity of causes and underlying molecular mechanisms of neuropathic pain, the therapeutic recommendations are manifold. This impedes the establishment of a generally successful, above all standardised therapy. The frequently used pharmaceuticals are divided into first-, second-, and third-/fourth-line treatments. In the following section, we aim to give a brief overview of established therapeutic approaches, to complete the introduction into the research field of neuropathic pain along its anatomical basis. More comprehensive reviews, solely focusing on the therapy of neuropathic pain, can be found elsewhere (e.g., Attal, 2019; Cavalli et al., 2019; Moisset et al., 2020). This section does
not include recent, more experimental approaches of neuropathic pain therapy. Hence, we would like to refer the reader to other reviews, for example, discussing stem cell technologies (Liu et al., 2020), electrical stimulation of peripheral nerves (Nayak & Banik, 2018), the spinal cord (Dones & Levi, 2018), or selected areas of the brain (Farrell et al., 2018) and the application of immunoglobulin (Chang & Park, 2020).

### 7.1 First-line recommendations

The recommended first-line drugs, showing a strong evidence for their use, include tricyclic antidepressants, serotonin reuptake inhibitors, noradrenaline reuptake inhibitors, and gabapentinoids. Chronic neuropathic pain and depressions are commonly thought to interact with each other. The application of antidepressants can consequently improve the patients’ quality of life. But the mechanisms underlying the alleviation of neuropathic pain, following the application of antidepressants, still have to be investigated. Serotonin-noradrenaline reuptake inhibitors (e.g., Duloxetine or Venlafaxine) increase the noradrenaline concentration in the spinal cord and could therefore possibly promote pathways that reduce the pain transmission in the spinal cord (Nakajima et al., 2012; see Section 2 for descending, pain-modulating pathways). A study from Alba-Delgado et al. (2012) furthermore indicates that serotonin-noradrenergic reuptake inhibitors promote the activation of the locus coeruleus in response to nociceptive stimulation (Alba-Delgado et al., 2012). Painful stimuli are likely to be attenuated by an increase of noradrenaline release from the respective neurons into the dorsal horn of the spinal cord.

The anticonvulsant gabapentinoids, gabapentin and pregabalin, are antagonists of the α2δ-1 subunits of voltage-gated calcium channels which are expressed in DRG neurons, the first-order neurons of the spinothalamic tract (see Sections 2 and 6.1, Figure 2). They are able to inhibit the influx of calcium ions into the cell and thereby modulate neurotransmission. This mechanism of action is suggested to also decrease the hyperexcitability caused by neuropathic pain, discussed in Section 6.1 (recently reviewed in Alles et al., 2020). Kopel and Browner (2020) suggest the administration of pregabalin to patients which do not respond to gabapentin treatment. The presented case report describes a male patient who developed neuropathic pain from postherpetic neuralgia. After failure of the initial therapeutic intervention with gabapentin, pregabalin was able to reduce the pain associated symptoms. The individual example suggests that if patients do not response to a drug, different substances of the same class should be tested. Only afterwards a drug with another mode of action should probably be chosen.

### 7.2 Second- and third-line recommendations

Lidocaine is applied as a second-line treatment for peripheral neuropathic pain, while other topical agents like capsaicin and botulinum toxin A were recently recommended second and third line (Attal, 2019; Moisset et al., 2020). However, the evidence base for their use is either weak or inconclusive. Lidocaine, which is a commonly used local anaesthetic, acts as an antagonist of sodium-channels. An ion-channel expressed in DRG neurons, the first-order neurons of the spinothalamic tract (see Sections 2 and 6.1). The topical application of lidocaine patches leads to a moderate pain relief (Binder et al., 2009). Consequently, patients with a sodium channel-related mechanism of neuropathic pain show a better response to lidocaine (Demant et al., 2015). The natural compound capsaicin is an agonist of the transient receptor potential vanilloid subtype 1 (TRPV1), an ion channel that is stimulated by chemical or thermal stimuli. Capsaicin can be topically applied as an ointment or plaster, leading to moderate pain relief. The capsaicin-mediated desensitisation or hypoalgesia is caused by a reversible degeneration of epidermal nerve fibres (Nolano et al., 1999). Botulinum toxin A is a bacteria-derived, neurotoxic protein which is primarily known for its effect on cholinergic neuronal transmission. A few studies were able to show that a single administration might reduce peripheral neuropathic pain (Attal et al., 2016), for example, postherpetic neuralgia (Apalla et al., 2013), trigeminal neuralgia (Zhang et al., 2017), and spinal cord injury (Han et al., 2016). Hence, the off-label use of Botulinum toxin A is recommended third line (Attal, 2019; Moisset et al., 2020).

Besides topical agents, some systemically applied agents are administered as second-line treatment too. Tramadol, for instance, acts as a noradrenalin reuptake inhibitor and additionally enhances the release of serotonin. The data currently available, do, however, not provide sufficient evidence for the use of tramadol in neuropathic pain (Boureau et al., 2003; Norrbrink & Lundeberg, 2009). The long-term application of tramadol as an opioid, furthermore, holds the risk of abuse or overdosing by the patient and should thus be pre-scribed with caution. The same applies to stronger opioids like oxycodone and morphine. Therefore, they are recommended as third-line treatment (Attal et al., 2002; Watson et al., 2003; Wu et al., 2008). Stronger opioids are only applied if the patient shows no response to reasonable alternatives. Furthermore, there are occasional studies reporting the use of other, off-label-used pharmaceutics.

Various studies and case reports have been published, reporting the clinical outcome of different therapeutic strategies addressing neuropathic pain. The applied drugs differ considerably in their efficiency and the described effects
could mainly be observed in small subsets of patients. What is still missing is a satisfying therapeutic approach that successfully addresses a larger number of patients suffering from neuropathic pain.

8 | PERSPECTIVES AND RECENT CONCEPTS

The sensation of pain requires the awareness and interpretation of a physical stimulus as well as an adequate behavioural response. However, due to, for example, central modulation, emotions and personal experience, the perception must not reflect the amplitude or frequency of the stimulus. Data from different magnetic resonance imaging studies support the hypothesis that emotions and personal experiences contribute to the perception of neuropathic pain. Patients experiencing neuropathic pain do not only show alterations in brain regions associated with sensorimotor functions, but also in regions related to memory, emotion and behaviour. The grey matter volume of patients with postherpetic neuralgia was observed to be increased in the parahippocampal gyrus, whereas decreased in the medial frontal gyrus and the insula lobes (Liu et al., 2019). These findings provide new options for the development of therapies that alternate from conventional pain medication.

As mentioned above, the pharmaceutical inhibition of the basolateral amygdala by Corder et al. (2019) resulted in a reduction in pain affective-motivational behaviour in mice. However, the authors were able to show that the nociceptive stimulus was still perceived. This means that the animal still experienced pain but without the psychological implications like avoidance behaviour, as induced by projections from the amygdala. Juarez-Salinas et al. (2019) for example demonstrated that transplantation of inhibitory interneuron progenitor cells into the anterior cingulate gyrus can modify pain aversive behaviour. In a chemotherapy-induced neuropathic pain model, the transplantation of these cells significantly alleviated pain aversiveness in male mice (Juarez-Salinas et al., 2019). The anterior cingulate cortex can consequently be regarded as another key player in the affective-emotional component of neuropathic pain. Dopaminergic and glutamatergic projections of the anterior cingulate cortex were found to modulate long-term nociception in a rat trauma model (López-Avila et al., 2004). Liu, Shu, et al. (2020) were able to show the effects of dopamine receptor activation in a mouse model of trigeminal neuropathic pain. The activation of the dopamine receptor D2 alleviates neuropathic pain symptoms, 14 days after trauma induction. The activation of the dopamine receptor D1, however, enhanced painful sensations during the whole observation period. The central lateral nucleus of the thalamus is another central structure which may be a potential target for the therapy of neuropathic pain. Projections from the spinothalamic tract (see Section 2, Figure 1) to the central lateral nucleus are involved in motivational-affective responses to pain (reviewed in Sengul & Watson, 2015). A clinical study conducted with a very small cohort indicates that Gamma Knife central lateral thalamotomy may reduce neuropathic pain in patients suffering from trigeminal neuralgia (Frazini et al., 2020). Taken together, these findings could serve as a good starting point for an alternative treatment of neuropathic pain.

9 | CONCLUSION

Neuropathic pain is a life altering complication of a trauma or disease of the somatosensory system. Neuropathic pain, pursuant to projections, affects approximately 8% of the population worldwide (Torrance et al., 2006). Various changes have been described that can be connected to neuropathic pain. The alterations range from general to specific. A decrease of the grey matter volume in the cross-sectional areas of the spinal cord (Eaton et al., 2001) and in the primary somatosensory cortex (Selvarajah et al., 2014) was, for instance, found in diabetic peripheral neuropathy patients. Specific alterations on the molecular level, for instance, include the changes in the expression pattern of ion channels and receptors (Blesneac et al., 2018; Chang et al., 2017; Inquimbert et al., 2018; Meents et al., 2019; Sun et al., 2018; Yan et al., 2013).

The different in vivo models presented in this review, are able to reflect the divers’ origins of neuropathic pain observed in humans. The assessment of neuropathic pain, however, proves to remain rather difficult. Neuropathic pain is not only characterised by allodynia and hyperalgesia, the patients additionally report spontaneous pain. The evaluation of non-stimulus evoked nociception in the animal requires regular handling of the animals and skilled experimenter. When regarding the presented mechanisms that are suggested to contribute to the pathology, it becomes clear that the common thread is still missing. This has a direct impact on the success of the applied therapeutics. It would be desirable to dispose of satisfactory drugs that are able to relieve the pain in a large number of patients.

From our overview, a targeted search for common molecular markers in suitable in vitro models could offer insights into the mechanisms underlying neuropathic pain. The discovery of standardised biomarkers would complete functional in vivo studies and would hence facilitate the evaluation of novel compounds.

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The authors declare that they have no conflict of interest.

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SK and KHT conceived the review and performed the literature research. SK wrote the first draft of the manuscript. All authors contributed to the revision and approved the final draft of the manuscript.

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ORCID
Svenja Kankowski https://orcid.org/0000-0003-0387-3184
Claudia Grothe https://orcid.org/0000-0002-4683-0769
Kirsten Haastert-Talini https://orcid.org/0000-0003-2502-8969

REFERENCES
Ahlgren S. C., & Levine J. D. (1993). Mechanical hyperalgesia in streptozotocin-diabetic rats. *Neuroscience*, 52(4), 1049–1055. http://dx.doi.org/10.1016/0366-4522(93)90551-p
Ahmadi, S., Ebrahimi, S. S., Oryan, S., & Rafieenia, F. (2012). Blockades of ATP-sensitive potassium channels and L-type calcium channels improve analgesic effect of morphine in alloxan-induced diabetic mice. *Pathophysiology*, 19, 171–177. https://doi.org/10.1016/j.pathophys.2012.04.007
Akintola, T., Raver, C., Studlack, P., Uddin, O., Masri, R., & Keller, A. (2017). The grimace scale reliably assesses chronic pain in a rodent model of trigeminal neuropathic pain. *Neurobiology of Pain*, 2, 13–17. https://doi.org/10.1016/j.neu pain.2017.10.001
Alba-Delgado, C., Mico, J. A., Sánchez-Blázquez, P., & Berrocoso, E. (2012). Analgesic antidepressants promote the responsiveness of locus coeruleus neurons to noxious stimulation: Implications for neuropathic pain. *Pain*, 153. https://doi.org/10.1016/j.pain.2012.03.034
Alles, S. R. A., Cain, S. M., & Snutch, T. P. (2020). Pregabalin as a pain therapeutic: Beyond calcium channels. *Frontiers in Cellular Neuroscience*, 14. https://doi.org/10.3389/fncel.2020.00083
Apalla, Z., Sotiriou, E., Lallas, A., Lazaridou, E., & Ioannides, D. (2013). Botulinum toxin A in postherpetic neuralgia. *The Clinical Journal of Pain*, 29(10), 857–864. http://dx.doi.org/10.1097/AJP.0b013e31827a2742
Attal, N. (2019). Pharmacological treatments of neuropathic pain: The latest recommendations. *Revue Neurologique*, 175, 46–50. https://doi.org/10.1016/j.neuro.2018.08.005
Attal, N., de Andrade, D. C., Adam, F., Ranoux, D., Teixeira, M. J., Galhardoni, R., Raicher, I., Üçeyler, N., Sommer, C., & Bouhassira, D. (2016). Safety and efficacy of repeated injections of botulinum toxin A in peripheral neuropathic pain (BOTNEP): A randomised, double-blind, placebo-controlled trial. *The Lancet Neurology*, 15(6), 555–565. http://dx.doi.org/10.1016/s1474-4422(16)00017-x
Attal, N., Guirmand, F., Brasseur, L., Gaude, V., Chauvin, M., & Bouhassira, D. (2002). Effects of IV morphine in central pain: A randomized placebo-controlled study. *Neurology*, 58(4), 554–563. http://dx.doi.org/10.1212/wnl.58.4.554
Authier, N., Gillet, J.-P., Flialip, J., Eschalier, A., & Couadore, F. (2003a). An animal model of nociceptive peripheral neuropathy following repeated cisplatin injections. *Experimental Neurology*, 182(1), 12–20. https://doi.org/10.1016/S0014-4886(03)00003-7
Authier, N., Gillet, J.-P., Flialip, J., Eschalier, A., Couadore, F. (2003b). A new animal model of vincristine-induced nociceptive peripheral neuropathy. *Neurotoxicology*, 24(6), 797–805. http://dx.doi.org/10.1016/s0161-813x(03)00043-3
Bear, M. F., Connors, B. W., & Paradiso, M. A. (2007). *Neuroscience: Exploring the brain* (Chapter 12, pp. 408–421). Lippincott Williams & Wilkins.
Bennett, D. L., Clark, A. J., Huang, J., Waxman, S. G., & Dib-Hajj, S. D. (2019). The role of voltage-gated sodium channels in pain signaling. *Physiological Reviews*, 99, 1079–1151. https://doi.org/10.1152/physrev.00052.2017
Bennett, G. J., & Xie, Y. K. (1988). A peripheral mononeuropathy in rat that produces disorders of pain sensation like those seen in man. *Pain*, 33, 87–107. https://doi.org/10.1016/0304-3959(88)90209-6
Binder, A., Bruxelle, J., Rogers, P., Hans, G., Böl, I., & Baron, R. (2009). Topical 5% lidocaine (lignocaine) medicated plaster treatment for post-herpetic neuralgia. *Clinical Drug Investigation*, 29, 393–408. https://doi.org/10.2165/00440011-200929060-00003
Blesnec, I., Themistocleous, A. C., Fratter, C., Conrad, L. J., Ramirez, J. D., Cox, J. J., Tesfaye, S., Shillo, P. R., Rice, A. S. C., Tucker, S. J., & Bennett, D. L. H. (2018). Rare NaV1.7 variants associated with painful diabetic peripheral neuropathy. *Pain*, 159(3), 469–480. http://dx.doi.org/10.1097/j.pain.0000000000001116
Blumenfeld, H. (2010). *Neuroanatomy through clinical cases*. Sinauer Associates, Chapter 7 (pp. 276–287).
Boroujerdi, A., Kim, H. K., Lyu, Y. S., Kim, D. S., Figueroa, K. W., Chung, J. M., & Luo, D. Z. (2008). Injury discharges regulate calcium channel alpha-2-delta-1 subunit upregulation in the dorsal horn that contributes to initiation of neuropathic pain. *Pain*, 139(2), 358–366. http://dx.doi.org/10.1016/j.pain.2008.05.004
Boulton, A. J. M., Vinik, A. I., Arezzo, J. C., Bril, V., Feldman, E. L., Freeman, R., Malik, R. A., Maser, R. E., Sosenko, J. M., & Ziegler, D. (2005). Diabetic neuropathies. *Diabetes Care*, 28(4), 956–962. https://doi.org/10.2337/diacare.28.4.956
Boureau, F., Legallicier, P., & Kabir-Ahmad, M. (2003). Tramadol in post-herpetic neuralgia: A randomized, double-blind, placebo-controlled trial. *Pain*, 104, 323–331. https://doi.org/10.1016/s0304-3959(03)00020-4
Bourquin, A.-F., Süveges, M., Pertin, M., Gilliard, N., Sardy, S., Davison, A. C., Spahn, D. R., & Decosterd, I. (2006). Assessment and analysis of mechanical allodynia-like behavior induced by spared nerve injury (SNI) in the mouse. *Pain*, 122(1), 14e1–14e14. https://doi.org/10.1016/j.pain.2005.10.036
Boyce-Rustay, J. M., Zhong, C., Kohnken, R., Baker, S. J., Simler, G. H., Wensink, E. J., Decker, M. W., & Honore, P. (2010). Comparison of mechanical allodynia and the affective component of inflammatory pain in rats. *Neuropharmacology*, 58, 537–543. https://doi.org/10.1016/j.neuropharm.2009.08.008
Brandolini, L., Castelli, V., Atramini, A., Giorgio, C., Bianchini, G., Russo, R., De Caro, C., D’Angelo, M., Catanesi, M., Benedetti, E., Giordano, A., Cimini, A., & Allegretti, M. (2019). DF2726A, a new IL-8 signalling inhibitor, is able to counteract chemotherapy-induced neuropathic pain. *Scientific Reports*, 9(1). http://dx.doi.org/10.1038/s41598-019-48231-z
Brightwell, J. J., & Taylor, B. K. (2009). Noradrenergic neurons in the locus coeruleus contribute to neuropathic pain. *Neuroscience*, 160(1), 174–185. https://doi.org/10.1016/j.neuroscience.2009.02.023
Brussee, V., Guo, G., Dong, Y., Cheng, C., Martinez, J. A., Smith, D., Glazner, G. W., Fernyhough, P., & Zochodne, D. W. (2008). Distal degenerative sensory neuropathy in a long-term Type 2 diabetes rat model. *Diabetes*, 57, 1664–1673. https://doi.org/10.2373/dib07-1737

Carozzi, V. A., Renn, C. L., Bardini, M., Fazio, G., Chiorazzi, A., Meregalli, C., Oggoni, N., Shanks, K., Quattu, M., Serra, M. P., Sala, B., Cavalletti, G., & Dorsey, S. G. (2013). Bortezomib-induced painful peripheral neuropathy: An electrophysiological, behavioral, morphological and mechanistic study in the mouse. *PLoS One*, 8, e72995. https://doi.org/10.1371/journal.pone.0072995

Castel, D., Sabbag, I., & Meilin, S. (2017). The effect of local/topical analgesics on incisional pain in a pig model. *Journal of Pain Research*, 10, 2169–2175. http://dx.doi.org/10.2147/jpr.s144949

Chaplan, S. R., Bach, F. W., Pogrel, J. W., Chung, J. M., & Yaksh, T. L. (1994). Quantitative assessment of tactile allodynia in the rat paw. *Journal of Neuroscience Methods*, 53(1), 55–63. http://dx.doi.org/10.1016/0165-0270(94)90144-9

Cheah, M., Fawcett, J. W., & Andrews, M. R. (2017). Assessment of thermal pain sensation in rats and mice using the hargreaves test. *Bio-protocol*, 7(16). http://dx.doi.org/10.21769/bioprotoc.2506

Choi, Y., Yoon, Y. W., Na, H. S., Kim, S. H., & Chung, J. M. (1994). Behavioral signs of ongoing pain and cold allodynia in a rat model of neuropathic pain. *Pain*, 59(3), 369–376. http://dx.doi.org/10.1016/0304-3959(94)90023-x

Cohen, S. P., & Mao, J. (2014). Neuropathic pain: Mechanisms and their clinical implications. *BMJ*, 348, f7656. https://doi.org/10.1136/bmj.f7656

Colloca, L., Ludman, T., Bouhassira, D., Baron, R., Dickenson, A. H., Yarnitsky, D., Freeman, R., Truini, A., Attal, N., Finnerup, N. B., Eccleston, C., Kalso, E., Bennett, D. L., Dworkin, R. H., & Raja, S. N. (2017). Neuropathic pain. *Nature Reviews Disease Primers*, 3, 17002. http://dx.doi.org/10.1038/nrdp.2017.2

Corder, G., Ahanonu, B., Grewe, B. F., Wang, D., Schnitzer, M. J., & Scherrer, G. (2019). An amygdalar neural ensemble that encodes the unpleasantness of pain. *Science*, 363, 276–281. https://doi.org/10.1126/science.aap8586

Courteix, C., Eschalier, A., & Lavarenne, J. (1993). Streptozocin-induced diabetic rats: Behavioural evidence for a model of chronic pain. *Pain*, 53, 81–88. https://doi.org/10.1016/0304-3959(93)90059-X

Coward, K., Plumptre, C., Facer, P., Birch, R., Carlstedt, T., Tate, S., Boutroun, C., & Anand, P. (2000). Immunolocalization of SNS/PN3 and NaNSNS2 sodium channels in human pain states. *Pain*, 85, 41–50. https://doi.org/10.1016/s0304-3959(99)00251-1

Cox, J. J., Reimann, F., Nicholas, A. K., Thornton, G., Roberts, E., Springell, K., Karbani, G., Jafari, H., Mannan, J., Raashid, Y., Al-Gazali, L., Hamamy, H., Valente, E. M., Gorman, S., Williams, R., McHale, D. P., Wood, J. N., Gribble, F. M., & Woods, C. G. (2006). An SCN9A channelopathy causes congenital inability to experience pain. *Nature*, 444, 894–898. https://doi.org/10.1038/nature05413

Dalziel, R. G., Bingham, S., Sutton, D., Grant, D., Champion, J. M., Dennis, S. A., Quinn, J. P., Bountra, C., & Mark, M. A. (2004). Allodynia in rats infected with varicella zoster virus – A small animal model for post-herpetic neuralgia. *Brain Research Reviews*, 46(2), 234–242. https://doi.org/10.1016/j.brainresrev.2004.07.008

Davies, A. L., Hayes, K. C., & Dekaban, G. A. (2007). Clinical correlates of elevated serum concentrations of cytokines and autoantibodies in patients with spinal cord injury. *Archives of Physical Medicine and Rehabilitation*, 88, 1384–1393. https://doi.org/10.1016/j.apmr.2007.08.004

De La Monte, S. M., Gabuzda, D. H., Ho, D. D., Brown, R. H., Hedley-Whyte, E. T., Schooley, R. T., Hirsch, M. S., & Bhan, A. K. (1988). Peripheral neuropathy in the acquired immunodeficiency syndrome. *Annals of Neurology*, 23(5), 485–492. https://doi.org/10.1002/ana.410230510

Decosterd, I., & Woolf, C. J. (2000). Spared nerve injury: An animal model of persistent peripheral neuropathic pain. *Pain*, 87, 149–158. https://doi.org/10.1016/s0304-3959(00)00276-1

Demant, D. T., Lund, K., Finnerup, N. B., Vollert, J., Maier, C., Segerdahl, M. S., Jensen, T. S., & Sindrup, S. H. (2015). Pain relief with lidocaine 5% patch in localized peripheral neuropathic pain in relation to pain phenotype: A randomised, double-blind, and placebo-controlled, phenotype panel study. *Pain*, 156(11), 2234–2244. https://doi.org/10.1097/j.pain.0000000000002266

Deuis, J. R., Dvorakova, L. S., & Vetter, I. (2017). Methods used to evaluate pain behaviors in rodents. *Frontiers in Molecular Neuroscience*, 10. https://doi.org/10.3389/fnmol.2017.00284

Dib-Hajj, S. D., Tyrrell, L., Black, J. A., & Waxman, S. G. (1998). A neuronal model of bortezomib-induced painful neuropathy. *Proceedings of the National Academy of Sciences of the United States of America*, 95(15), 8963–8968. https://doi.org/10.1073/pnas.95.15.8963

Dones, I., & Levi, V. (2018). Spinal cord stimulation for neuropathic pain: Current trends and future applications. *Brain Sciences*, 8, 138. https://doi.org/10.3390/brainsci8080138

Duggett, N. A., & Flatters, S. J. L. (2017). Characterization of a rat model of bortezomib-induced painful neuropathy. *British Journal of Pharmacology*, 174, 4812–4825. https://doi.org/10.1111/bph.14063

Duggett, N. A., Griffiths, L. A., & Flatters, S. J. L. (2017). Paclitaxel-induced painful neuropathy is associated with changes in mitochondrial bioenergetics, glycolysis, and an energy deficit in dorsal root ganglia neurons. *Brain Research*, 174, 17–28. https://doi.org/10.1016/j.brainres.2004.07.008

Duraku, L. S., Niehof, S. P., Misirli, Y., Everaers, M., Hoendervangers, S., Holstege, J., Boele, H.-J. J., Koekkoek, S. K. E., Smits, E. S., Selles, R. W., & Walbyeem, E. T. (2014). Rotterdam advanced multiple plate: A novel method to measure cold hyperalgesia and allodynia in freely behaving rodents. *Journal of Neuroscience Methods*, 224, 1–12. http://dx.doi.org/10.1016/j.jneumeth.2013.12.006
Eaton, S. E. M., Harris, N. D., Rajbandhari, S. M., Greenwood, P., Wilkinson, I. D., Ward, J. D., Griffiths, P. D., & Tesfaye, S. (2001). Spinal-cord involvement in diabetic peripheral neuropathy. The Lancet, 358(9275), 35–36. http://dx.doi.org/10.1016/s0140-6736(00)05288-5

Espeso, E. F., & Mir, D. (1993). Structure of the rat's behaviour in the hot plate test. Behavioural Brain Research, 56(2), 171–176. http://dx.doi.org/10.1016/0166-4328(93)90035-o

Farquhar-Smith, P. (2011). Chemotherapy-induced neuropathic pain. Current Opinion in Supportive & Palliative Care, 5(1), 1–7. http://dx.doi.org/10.1097/sop.0b013e23283429cc

Farrell, S. M., Green, A., & Aziz, T. (2018). The current state of deep brain stimulation for chronic pain and its context in other forms of neuromodulation. Brain Sciences, 8(8), 158. https://doi.org/10.3390/brainsci8080158

Ferrier, J., Marchand, F., & Balayssac, D. (2016). Assessment of mechanical allodynia in rats using the electronic von Frey test. BIO-PROTOCOL, 6(18). http://dx.doi.org/10.21769/bioprotoc.1933

Fraznini, A., Attuati, L., Zaed, I., Moosa, S., Stravato, A., Navarria, P., Gopalsamy, B., Sambasevam, Y., Zulazmi, N. A., Chia, J. S. M., Farquhar-Smith, P. (2020). Gamma Knife central lateral thalamotomy for the treatment of neuropathic pain produced by segmental spinal cord involvement: In vivo evidence for slowed sodium channel inactivation. Clinical Neurophysiology, 129, 694–706. https://doi.org/10.1016/j.clinph.2017.11.015

Herzberg, U., & Sagen, J. (2001). Peripheral nerve exposure to HIV viral envelope protein gp120 induces neuropathic pain and spinal gliosis. Journal of Neuroimmunology, 116, 29–39. https://doi.org/10.1016/S0165-5728(01)00288-0

Higuera, E. S., & Luo, Z. D. (2004). A rat pain model of vincristine-induced neuropathy. Pain Research: Methods and Protocols, 99, 91–98. https://doi.org/10.1385/1-59259-770-x:255

Hong, J. H., Kwon, H. G., & Jang, S. H. (2011). Probabilistic somatotopy of the spinothalamic pathway at the ventroposterolateral nucleus of the thalamus in the human brain. American Journal of Neuroradiology, 32(7), 1358–1362. https://doi.org/10.3174/ajnr.A2497

Ho Kim, S., & Mo Chung, J. (1992). An experimental model for peripheral neuropathy produced by segmental spinal nerve ligation in the rat. Pain, 50(3), 355–363. http://dx.doi.org/10.1016/0304-3959(92)90041-9

Huang, J., Gadotti, V. M., Chen, L., Souza, I. A., Huang, S., Wang, D., Ramakrishnan, C., Deisseroth, K., Zhang, Z., & Zamponi, G. W. (2019). A neuronal circuit for activating descending modulation of neuropathic pain. Nature Neuroscience, 22(10), 1659–1668. https://doi.org/10.1038/s41593-019-0481-5

Inoue, K., & Tsuda, M. (2018). Microglia in neuropathic pain: Cellular and molecular mechanisms and therapeutic potential. Nature Reviews Neurology, 19, 138–152. https://doi.org/10.1038/nrrn.2018.2

Inquimbert, P., Moll, M., Latremoliere, A., Tong, C.-K., Whang, J., Sheehan, G. F., Smith, B. M., Korb, E., Athié, M. C. P., Babanjii, O., Ghasemlou, N., Yanagawa, Y., Allis, C. D., Hof, P. R., & Scholz, J. (2018). NMDA receptor activation underlies the loss of spinal dorsal horn neurons and the transition to persistent pain after peripheral nerve injury. Cell Reports, 23(9), 2678–2689. https://doi.org/10.1016/j.celrep.2018.04.107

Jaggi, A. S., Jain, V., & Singh, N. (2011). Animal models of neuropathic pain. Fundamental & Clinical Pharmacology, 25, 1–28. https://doi.org/10.1111/j.1472-8206.2009.00801.x

Jones, I., Yelhekar, T. D., Wiberg, R., Kingham, P. J., Johansson, S., Wiberg, M., & Carlsson, L. (2018). Development and validation of an in vitro model system to study peripheral sensory neuron development and injury. Scientific Reports, 8(1). http://dx.doi.org/10.1038/s41598-018-34280-3

Juarez-Salinas, D. L., Braz, J. M., Elin, A., Gee, S., Sohal, V., & Basbaum, A. I. (2019). GABAergic cell transplants in the anterior cingulate cortex reduce neuropathic pain aversiveness. Brain, https://doi.org/10.1093/brain/awv203

Kiguuchi, N., Maeda, T., Kobayashi, Y., & Kishioka, S. (2008). Up-regulation of tumor necrosis factor-alpha in spinal cord contributes to vincristine-induced mechanical allodynia in mice. Neuroscience Letters, 445, 140–143. https://doi.org/10.1016/j.neulet.2008.09.009

Hargreaves, K., Dubner, R., Brown, F., Flores, C., & Joris, J. (1988). A new and sensitive method for measuring thermal nociception in cutaneous hyperalgesia. Pain, 32, 77–88. https://doi.org/10.1016/0304-3959(88)90026-7

Hasbargen, T., Ahmed, M. M., Miranpuri, G., Li, L., Kahle, K. T., Resnick, D., & Sun, D. (2010). Role of NKCC1 and KCC2 in the development of chronic neuropathic pain following spinal cord injury. Annals of the New York Academy of Sciences, 1198, 168–172. https://doi.org/10.1111/j.1749-6632.2010.05462.x

He, Y., Tian, X., Hu, X., Porreca, F., & Wang, Z. J. (2012). Negative reinforcement reveals non-evoked ongoing pain in mice with tissue or nerve injury. The Journal of Pain, 13, 598–607. https://doi.org/10.1016/j.jpain.2012.03.011

Heide, R., Bostock, H., Ventzel, L., Grafe, P., Bergmans, J., Fuglsang-Frederiksen, A., Finnerup, N. B., & Tankisi, H. (2018). Axonal excitability changes and acute symptoms of oxaliplatin treatment: In vivo evidence for slowed sodium channel inactivation. Clinical Neurophysiology, 129, 694–706. https://doi.org/10.1016/j.clinph.2017.11.015

Kankowski et al.
King, T., Vera-Portocarrero, L., Gutierrez, T., Vanderah, T. W., Dussor, G., Lai, J., Fields, H. L., & Porreca, F. (2009). Unmasking the tonic-aversive state in neuropathic pain. *Nature Neuroscience*, 12, 1364–1366. https://doi.org/10.1038/nn.2407

Kopel, J., & Brower, G. L. (2020). Effectiveness of pregabalin as a secondary treatment for neuropathic pain from postherpetic neuralgia. *Procedures (Baylor University. Medical Center)*, 33, 469–470. https://doi.org/10.1080/08999828.2020.1767461

Kummar, S., Chen, H. X., Wright, J., Holbeck, S., Millin, M. D., Tomaszewski, J., Zweibel, J., Collins, J., & Doroshow, J. H. (2010). Utilizing targeted cancer therapeutic agents in combination: Novel approaches and urgent requirements. *Nature Reviews Drug Discovery*, 9, 843–856. https://doi.org/10.1038/ndr3216

Langford, D. J., Bailey, A. L., Chanda, M. L., Clarke, S. E., Drummond, T. E., Echsols, S., Glick, S., Ingrao, J., Klassen-Ross, T., LaCroix-Echols, S., Glick, S., Ingrao, J., Klassen-Ross, T., LaCroix-Tommasi, M., Ling, B., Authier, N., Balayssac, D., Eschalier, A., & Coudore, F. (2020). Stem cells in the treatment induced peripheral neuropathy (CIPN) in vitro: Prospects and anatomical correlates. *Brain, Behavior, and Immunity*, 95, 563–574. https://doi.org/10.1016/j.bbi.2019.10.018

Lee, J. H., Cox, D. J., Mook, D. G., & McCarty, R. C. (1990). Effect of hyperglycemia on pain threshold in alloxan-diabetic rats. *Pain*, 40, 105–107. https://doi.org/10.1016/0304-3959(90)91057-P

Lee, J. H., Vera- Portocarrero, L., Gutierrez, T., Vanderah, T. W., Dussor, G., Lai, J., Fields, H. L., & Porreca, F. (2009). Unmasking the tonic-aversive state in neuropathic pain. *Nature Neuroscience*, 12, 1364–1366. https://doi.org/10.1038/nn.2407

Liu, C.-C., Gao, Y.-J., Luo, H., Berta, T., Xu, Z.-Z., Ji, R.-R., & Tan, L.-H., Wang, H., Sheng, M., Jan, L. Y., Jan, Y. N., & Basbaum, A. I. (1994). Evidence for presynaptic N-methyl-D-aspartate autoreceptors in the spinal cord dorsal horn. *Proceedings of the National Academy of Sciences of the United States of America*, 91, 8383–8387. https://doi.org/10.1073/pnas.91.18.8383

Liu, J., Gu, L., Huang, Q., Hong, S., Zeng, X., Zhang, D., Zhou, F., & Jiang, J. (2019). Altered gray matter volume in patients with herpes zoster and postherpetic neuralgia. *Journal of Pain Research*, 12, 605–616. https://doi.org/10.2147/jpr.s183561

Liu, M., Li, K., Wang, Y., Zhao, G., & Jiang, J. (2020). Stem cells in the treatment of neuropathic pain: Research progress of mechanism. *Stem Cells International*, 2020. https://doi.org/10.1155/2020/8861251

Liu, S., Shu, H., Crawford, J., Ma, Y., Li, C., & Tao, F. (2020). Optogenetic activation of dopamine receptor D1 and D2 neurons in anterior cingulate cortex differentially modulates trigeminal neuropathic pain. *Molecular Neurobiology*, 57, 4060–4068. https://doi.org/10.1007/s12035-020-02020-2

Liu, Y., Latremoliere, A., Li, X., Zhang, Z., Chen, M., Wang, X., Fang, C., Zhu, J., Alexandre, C., Gao, Z., Chen, B., Ding, X., Zhou, J.-Y., Zhang, Y., Chen, C., Wang, K. H., Woolf, C. J., & He, Z. (2018). Touch and tactile neuropathic pain sensitivity are set by cortico-spinal projections. *Nature*, 561, 547–550. https://doi.org/10.1038/s41586-018-0155-2

López-Avila, A., Coffeen, U., Ortega-Legasi, M. J., del Ángel, R., & Pellicer, F. (2004). Dopamine and NMDA systems modulate long-term nociception in the rat anterior cingulate cortex. *Pain*, 111, 136–143. https://doi.org/10.1016/j.pain.2004.06.010

Luo, Z. D., Chaplin, S. R., Higuera, E. S., Sorkin, L. S., Stauderman, K. A., Williams, M. E., & Yakh, T. L. (2001). Uregulation of dorsal root ganglion (alpha)2(delta) calcium channel subunit and its correlation with allodynia in spinal nerve-injured rats. *Journal of Neuroscience*, 21, 1868–1875. https://doi.org/10.1523/jneurosci.21-06-01868.2001

Malmberg, A. B., & Basbaum, A. I. (1998). Partial sciatic nerve injury in the mouse as a model of neuropathic pain: Behavioral and neuroanatomical correlates. *Pain*, 76, 215–222. https://doi.org/10.1016/s0304-3959(98)00045-1

Manion, J., Khung, T., Harney, D., Littleboy, J. B., Ruan, T., Loo, L., Costigan, M., Larance, M., Caron, L., & Neely, G. G. (2020). Human induced pluripotent stem cell-derived GABAergic interneuron transplants attenuate neuropathic pain. *Pain*, 161, 379–387. https://doi.org/10.1097/j.pain.000000000001733

Maplebeck, J. C. S., Lorenzo, L.-E., Lee, K. Y., Gauthier, C., Muley, M. M., De Koninck, Y., Prescott, S. A., & Salter, M. W. (2019). Chloride dysregulation through downregulation of KCC2 mediates neuropathic pain in both sexes. *Cell Reports*, 28, 590–596.e4. https://doi.org/10.1016/j.celrep.2019.06.059

McGuiness, L., Taylor, C., Taylor, R. D. T., Yau, C., Langenhau, T., Hart, M. L., Christian, H., Tynan, P. W., Donnelly, P., & Emptage, N. J. (2010). Presynaptic NMDARs in the hippocampus facilitate transmitter release at theta frequency. *Neuron*, 68, 1109–1127. https://doi.org/10.1016/j.neuron.2010.11.023

Meents, J. E., Bressan, E., Sontag, S., Foerster, A., Hautvast, P., Rösseler, C., Hampl, M., Schüler, H., Goetzke, R., Le, T. K. C., Kleggetveit, I. P., Le Cann, K., Kerth, C., Rush, A. M., Rogers, M., Kohl, Z., Schmelz, M., Wagner, W., Jorm, E., … Lampert, A. (2019). The role of Nav1.7 in human nociceptors: Insights from human induced pluripotent stem cell-derived sensory neurons of erythro-melanoglia patients. *Pain*, 160, 1327–1341. https://doi.org/10.1097/j.jpain.000000000001511

Melzack, R., & Wall, P. D. (1965). Pain mechanisms: A new theory. *Science*, 150, 971–978. https://doi.org/10.1126/science.150.3699.971

Menetski, J., Mistry, S., Lu, M., Mudgett, J. S., Ransohoff, R. M., DeMartino, J. A., Macintyre, D. E., & Abbadie, C. (2007). Mice overexpressing chemokine ligand 2 (CCL2) in astrocytes display enhanced nociceptive responses. *Neuroscience*, 149, 706–714. https://doi.org/10.1016/j.neuroscience.2007.08.014

Moisset, X., Bouhassira, D., Avez Couturier, J., Alchaar, H., Conradi, S., Delmotte, M. H., Lanteri-Minet, M., Lefaucheur, J. P., Mick, G., Piano, V., Pickering, G., Piquet, E., Regis, C., Salvat, E., & Attal, N. (2020). Pharmacological and non-pharmacological treatments for neuropathic pain: Systematic review and French recommendations. *Revue Neurologique*, 176, 325–352. https://doi.org/10.1016/j.neuro.2020.01.361

Montague-Cardoso, K., Pitcher, T., Chisolm, K., Salera, G., Lindstrom, E., Hewitt, E., Solito, E., & Malcangio, M. (2020). Changes in vascular permeability in the spinal cord contribute to chemotherapy-induced neuropathic pain. *Brain, Behavior, and Immunity*, 83, 248–259. https://doi.org/10.1016/j.bbi.2019.10.018
Nadakuditi, K. B., & Monceaux, M. E. (2018). Development of sensory
neuropathy in streptozotocin-induced diabetic mice. *Brain and Behavior, 3*, 35–41. https://doi.org/10.1002/brb3.111
Murakami, Y., Zhang, W., Pierson, C. R., Brismar, T., Östenson, C.-
G., Efendic, S., & Sima, A. A. F. (2002). Impaired glucose tolerance
and insulinopenia in the GK-rat causes peripheral neuropathy. *Diabetes/Metabolism Research and Reviews, 18*, 473–483. https://
doi.org/10.1002/dmr.326
Nakajima, K., Obata, H., Iriuchijima, N., & Saito, S. (2012). An increase
in spinal cord noradrenaline is a major contributor to the antihyper-
algesic effect of antidepressants after peripheral nerve injury in the
rat. *Pain, 153*, 990–997. https://doi.org/10.1016/j.pain.2012.01.029
Nayak, R., & Banik, R. K. (2018). Current innovations in peripheral
nerve stimulation. *Pain Research and Treatment, 2018*, 9091216. https://doi.org/10.1155/2018/9091216
Newton, R. A., Bingham, S., Case, P. C., Sanger, G. J., & Lawson, S. N.
(2001). Dorsal root ganglion neurons show increased expression of the
calcium channel alpha2delta-1 subunit following partial sciatic
nerve injury. *Brain Research. Molecular Brain Research*, 94, 50–61. https://doi.org/10.1016/S0929-493X(01)00188-7
Nguyen, D., Deng, P., Matthews, E. A., Kim, D. S., Feng, G., Dickenson, A. H., Xu, Z. C., & Luo, Z. D. (2009). Enhanced pre-
synaptic glutamate release in deep-dorsal horn contributes to cal-
cium channel alpha-2-delta-1 protein-mediated spinal sensitization
and behavioral hypersensitivity. *Molecular Pain, 5*, 6. https://doi.
org/10.1186/1744-8069-5-6
Ni, H.-D., Yao, M., Huang, B., Xu, L.-S., Zheng, Y., Chu, Y.-X., Wang,
H.-Q., Liu, M.-J., Xu, S.-J., & Li, H.-B. (2016). Glial activation in
glia in peripheral neuropathy. *Neuropharmacology, 102*, 9382–9387. https://doi.org/10.1016/j.neuropharm.2015.05.009
Poulten, J., Warwick, R., Duroux, M., Hanani, M., & Gazerani, P.
(2015). Oxaliplatin enhances gap junction-mediated coupling in cell
cultures of mouse trigeminal ganglia. *Nature, 336*, https://doi.
or/10.1038/nj.ejccr.2015.05.009
Priest, B. T., Murphy, B. A., Lindia, J. A., Diaz, C., Abbadie, C.,
Ritter, A. M., Liberator, P., Iyer, L. M., Kash, S. F., Kohler, M. G., Kaczorowski, G. J., MacIntyre, D. E., & Martin, W. J. (2005).
Contribution of the tetrodotoxin-resistant voltage-gated sodium
channel Nav1.9 to sensory transmission and nociceptive behavior. *Proceedings of the National Academy of Sciences of the United
States of America, 102*, 9382–9387. https://doi.org/10.1073
pnas.0501549102
Qu, R., Yao, F., Zhang, X., Gao, Y., Liu, T., & Hua, Y. (2019). SMN
deficiency causes pain hypersensitivity in a mild SMA mouse model
through enhancing excitability of nociceptive dorsal root ganglion
neurons. *Scientific Reports, 9*, 6493. https://doi.org/10.1038/s4159
8-019-43053-5
Quasthoff, S., & Hartung, H. P. (2002). Chemotherapy-induced per-
ipheral neuropathy. *Journal of Neurology, 249*, 9–17. https://doi.
or/10.1007/pl00007853
Raghavendra, V., Tanga, F., & DeLeo, J. A. (2003). Inhibition of microg-
lial activation attenuates the development but not existing hyper-
sensitivity in a rat model of neuropathy. *Journal of Pharmacology
and Experimental Therapeutics, 306*, 624. https://doi.org/10.1124/
jp.et.103.052407
Rice, F. L., Castel, D., Ruggiero, E., Dockum, M., Houk, G., Sabbag, L.,
Albrecht, P. J., & Melin, S. (2018). Human-like cutaneous neuro-
pathologies associated with a porcine model of peripheral neuritis:
A translational platform for neuropathic pain. *Neuropathol Pain, 5*,
100021. https://doi.org/10.1016/j.nypai.2018.07.002
Romanovsky, D., Walker, J. C., & Dobretsov, M. (2008). Pressure pain
precedes development of type 2 disease in Zucker rat model of dia-
betes. *Neuroscience Letters, 445*, 220–223. https://doi.org/10.1016/j.
neulet.2008.08.087
Sadzot-Delvaux, C., Merville-Louis, M. P., Delree, P., Marc, P.,
Piette, J., Moonen, G., & Rentier, B. (1990). An in vivo model of
varicella-zoster virus latent infection of dorsal root ganglia.*Journal of
Neuroscience Research, 26*, 83–89. https://doi.org/10.1002/jnr.
490260110
Sakurada, T., Katsumata, K., Tan-No, K., Sakurada, S., & Kisara, K.
(2012). The capsaicin test in mice for evaluating tachykinin an-
tagonts in the spinal cord. *Neuropharmacology, 31*, 1279–1285.
https://doi.org/10.1016/j.neuropharm.2012.07.002
Salehi, S., Kashfi, K., Manabeji, H., & Haghiparast, A. (2020). Chemical
stimulation of the lateral hypothalamus induces antiallodynic and
anti-thermal hyperalgesic effects in animal model of neuropathic pain:
Involvement of orexin receptors in the spinal cord. *Brain Research*,
1732, 146674. https://doi.org/10.1016/j.brainres.2020.146674
Samimi, S., Pourmokhtar, T. R., & Eshaghi, S. (2017). Neurovascular
pain-induced enhancement of spontaneous and pain-
evoked neuronal activity in the periaqueductal gray that is attenu-
ated by gabapentin. *Pain, 158*, 1241–1253. https://doi.org/10.1097/j.
pain.0000000000009095
Sampathkumar, P., Drage, L. A., & Martin, D. P. (2009). Herpes zoster
(shingles) and Postherpetic neuralgia. *Mayo Clinic Proceedings, 84*,
274–280. https://doi.org/10.4065/mcp.2009.3.274
Seltzer, Z.-E., Dubner, R., & Shir, Y. (1990). A novel behav-
ioral model of neuropathic pain disorders produced in rats
by partial sciatic nerve injury. *Pain, 43*, 205–218. https://doi.
or/10.1016/0304-3959(90)91074-S
Selvarajah, D., Wilkinson, I. D., Maxwell, M., Davies, J., Sankar, A., Boland, E., Gandhi, R., Tracey, I., & Tesfaye, S. (2014). Magnetic resonance neuroimaging study of brain structural differences in diabetic peripheral neuropathy. *Diabetes Care, 37*, 1681–1688. https://doi.org/10.2337/dc13-2610

Sengul, G., & Watson, C. (2015). Chapter 8 – Ascending and descending pathways in the spinal cord. *The rat nervous system* (pp. 115–130; 4th ed.). https://doi.org/10.1007/B978-0-12-374245-2_20008-5

Shields, S. D., Eckert, W. A., & Basbaum, A. I. (2003). Spared nerve injury model of neuropathic pain in the mouse: A behavioral and anatomic analysis. *The Journal of Pain, 4*, 465–470. https://doi.org/10.1067/mjp.2003.73881-8

Smith, S. B., Crager, S. E., & Mogil, J. S. (2004). Paclitaxel-induced neuropathic hypersensitivity in mice: Responses in 10 imbed mouse strains. *Life Sciences, 74*, 2593–2604. https://doi.org/10.1016/j.lfs.2004.01.002

Snider, W. D., Simpson, D. M., Nielsen, S., Gold, W. M. J., Metzoka, C. E., & Posner, J. B. (1983). Neurological complications of acquired immune deficiency syndrome: Analysis of 50 patients. *Annals of Neurology, 14*, 403–418. https://doi.org/10.1002/ana.410140404

Sorge, R. E., Lacroix-Fralish, M. L., Tuttle, A. H., Sotocinal, S. G., Austin, J. S., Ritchie, J., Chanda, M. L., Graham, A. C., Topham, L., Beggs, S., Salter, M. W., & Mogil, J. S. (2011). Spinal cord toll-like receptor 4 mediates inflammatory and neuropathic hypersensitivity in male but not female mice. *Journal of Neuroscience, 31*, 15450–15454. https://doi.org/10.1523/jneurosci.3859-11.2011

Sorge, R. E., Mapplebeck, J. C. S., Rosen, S., Beggs, S., Taves, S., Alexander, J. K., Martin, L. J., Austin, J.-S., Sotocinal, S. G., Chen, D., Yang, M., Shi, X. Q., Huang, H., Pillon, N. J., Bilan, P. J., Tu, Y., Klip, A., Ji, R.-R., Zhang, J., … Mogil, S. (2015). Different immune cells mediate mechanical pain hypersensitivity in male and female mice. *Nature Neuroscience, 18*, 1081–1083. https://doi.org/10.1038/nn.4053

Sotocinal, S. G., Sorge, R. E., Zaloum, A., Tuttle, A. H., Martin, L. J., Wieskopf, J. S., Mapplebeck, J. C., Wei, P., Zhan, S., Zhang, S., McDougall, J. J., King, O. D., & Mogil, J. S. (2011). The rat grimace scale: A partially automated method for quantifying pain in the laboratory rat via facial expressions. *Molecular Pain, 7*. https://doi.org/10.1186/1744-8069-7-55

Sperry, M. M., Yu, Y.-H., Welch, R. L., Granquist, E. J., & Winkelstein, B. A. (2018). Grading facial expression is a sensitive means to detect grimace differences in orofacial pain in a rat model. *Scientific Reports, 8*, 13894. https://doi.org/10.1038/s41598-018-32297-2

Stephen G. (2019). A gain-of-function sodium channel β2-subunit mutation in painful diabetic neuropathy. *Diabetes Care, 42*, 3742–3748. https://doi.org/10.2337/dc19-0124

Stieve, H., & Kirsche, W. (1961). *Zeichenvorlagen für die Vorlesung über Nervensystem und Sinnesorgane des Menschen*. VEB Gustav Fischer Verlag.

Sun, J., Li, N., Duan, G., Liu, Y., Guo, S., Wang, C., Zhu, C., & Zhang, X. (2018). Increased Nav1.7 expression in the dorsal root ganglion contributes to pain hypersensitivity after plantar incision in rats. *Molecular Pain, 14*. https://doi.org/10.1186/s12940-018-02833-6

Ta, L. E., Low, P. A., & Windebank, A. J. (2009). Mice with ciscplatin and oxaliplatin-induced painful neuropathy develop distinctive early responses to thermal stimuli. *Molecular Pain, 5*, 1744–8069-1745-1749. https://doi.org/10.1186/1744-8069-5-9

Tachiya, D., Satoh, T., & Ichikawa, H. (2018). Nerve injury increases the expression of alpha-2-delta-1 subunit of L-type calcium channel in sensory neurons of rat spinal and trigeminal nerves. *Annals of Neurosciences*, 24, 191–200. https://doi.org/10.1159/000477604
Wainger, B. J., Buttermore, E. D., Oliveira, J. T., Melin, C., Lee, S., Saber, W. A., Wang, A. I., Ichida, J. K., Chiu, I. M., Barrett, L., Huebner, E. A., Bilgin, C., Tsujimoto, N., Brenneis, C., Kapur, K., Rubin, L. L., Eggan, K., & Woolf, C. J. (2015). Modeling pain in vitro using nociceptor neurons reprogrammed from fibroblasts. *Nature Neuroscience, 18*, 17–24. https://doi.org/10.1038/nn.3886

Warwick, R. A., & Hanani, M. (2013). The contribution of satellite glial cells to chemotherapy-induced neuropathic pain. *European Journal of Pain, 17*, 571–580. https://doi.org/10.1002/j.1532-2149.2012.00219.x

Watson, P. C. N., Moulin, D., Watt-Watson, J., Gordon, A., & Eisenhoffer, J. (2003). Controlled-release oxycodone relieves neuropathic pain: A randomized controlled trial in painful diabetic neuropathy. *Pain, 105*, 71–78. https://doi.org/10.1016/s0304-3959(03)00160-x

Wheeler, H. E., Wing, C., Delaney, S. M., Krause, M., Wheeler, H. E., & Dolan, M. E. (2015). Modeling chemotherapeutic neurotoxicity with human induced pluripotent stem cell-derived neuronal cells. *PLoS One, 10*, e0118020. https://doi.org/10.1371/journal.pone.0118020

Willison, H. J., Jacobs, B. C., & Van Doorn, P. A. (2016). Guillain-Barré syndrome. *The Lancet, 388*, 717–727. https://doi.org/10.1016/S0140-6736(16)00339-1

Wing, C., Komatsu, M., Delaney, S. M., Krause, M., Wheeler, H. E., & Dolan, M. E. (2017). Application of stem cell derived neuronal cells to evaluate neurotoxic chemotherapy. *Stem Cell Research, 22*, 79–88. https://doi.org/10.1016/j.scr.2017.06.006

Wu, C. L., Agarwal, S., Tella, P. K., Klick, B., Clark, M. R., Haythornthwaite, J. A., Max, M. B., & Raja, S. N. (2008). Morphine versus mexiletine for treatment of postamputation pain. A Randomized, Placebo-controlled, Crossover Trial. *Anesthesiology: The Journal of the American Society of Anesthesiologists, 109*(2), 289–296. https://doi.org/10.1097/ALN.0b013e31817f4523

Xie, J., Park, S. K., Chung, K., & Chung, J. M. (2001). The effect of lumbar sympathectomy in the spinal nerve ligation model of neuropathic pain. *The Journal of Pain, 2*, 270–278. https://doi.org/10.1054/jpai.2001.24559

Yan, X., Jiang, E., Gao, M., & Weng, H.-R. (2013). Endogenous activation of presynaptic NMDA receptors enhances glutamate release from the primary afferents in the spinal dorsal horn in a rat model of neuropathic pain. *The Journal of Physiology, 591*, 2001–2019. https://doi.org/10.1113/jphysiol.2012.250522

Yang, Y., Wang, Y., Li, S., Xu, Z., Li, H., Ma, L., Fan, J., Bu, D., Liu, B., Fan, Z., Wu, G., Jin, J., Ding, B., Zhu, X., & Shen, Y. (2004). Mutations in SCN9A, encoding a sodium channel alpha subunit, in patients with primary erythermalgia. *Journal of Medical Genetics, 41*, 171. https://doi.org/10.1136/jmg.2003.012153

Ye, G.-L., Savelieva, K. V., Vogel, P., Baker, K. B., Mason, L., Lanthorn, T. H., & Rajan, I. (2015). Ligation of mouse L4 and L5 spinal nerves produces robust allodynia without major motor function deficit. *Behavioural Brain Research, 276*, 99–110. https://doi.org/10.1016/j.bbr.2014.04.039

Yu, H., Zhang, P., Chen, Y.-R., Wang, Y.-J., Lin, X.-Y., Li, X.-Y., & Chen, G. (2019). Temporal changes of spinal transcriptomic profiles in mice with spinal nerve ligation. *Frontiers in Neuroscience, 13*, https://doi.org/10.3389/fnins.2019.01357

Yu, X., Liu, H., Hamel, K. A., Morvan, M. G., Yu, S., Leff, J., Guan, Z., Braz, J. M., & Basbaum, A. I. (2020). Dorsal root ganglion macrophages contribute to both the initiation and persistence of neuropathic pain. *Nature Communications, 11*, 264. https://doi.org/10.1038/s41467-019-13839-2

Zhang, H., Lian, Y., Xie, N., Chen, C., & Zheng, Y. (2017). Single-dose botulinum toxin type a compared with repeated-dose for treatment of trigeminal neuralgia: A pilot study. *J Headache Pain, 18*(1), 81. https://doi.org/10.1186/s10194-017-0793-3

Zhou, C., & Luo, Z. D. (2014). Electrophysiological characterization of spinal neuron sensitization by elevated calcium channel alpha-2-delta-1 subunit protein. *European Journal of Pain, 18*(5), 649–658. https://doi.org/10.1002/j.1532-2149.2013.00416.x

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