

Fifty years of pain research and clinical advances: highlights and key trends

Allan I. Basbaum^{a,*}, Troels S. Jensen^b, Francis J. Keefe^c

Abstract

This article highlights advances in basic science preclinical pain research, clinical research, and psychological research occurring over the 50 years since the International Association for the Study of Pain was founded. It presents important findings and key trends in these 3 areas of pain science: basic science preclinical research, clinical research, and psychological research.

Keywords: Animal models, Sensitization, Gate Control, Behavioral therapy, Psychometrics, Opiates

1. Introduction

Since its inception, the International Association for the Study of Pain (IASP) has aimed to foster high-quality pain research and management through a variety of approaches including its scientific publications (Pain and Pain Reports), books, guidelines, scientific meetings, and educational activities. This article highlights research and clinical advances occurring over the 50 years since IASP was founded. Given the need to be brief, we are unable to provide a comprehensive overview of the field. We apologize, in advance, to investigators whose work we fail to mention, omissions that, in fact, illustrate how productive the field has been over the past 50 years. We discuss important findings and key trends in 3 areas of pain science: basic science preclinical pain research, clinical research, and psychological research. As outlined elsewhere in this special issue of the journal,²⁰ many of these findings and trends have been significantly underpinned by several of the technological advances occurring over this period.

2. Highlights in basic science preclinical pain research

The past 50 years has seen many preclinical discoveries of the mechanisms that contribute to acute and chronic pain. Highlights include characterization of peripheral and central sensitization processes,^{3,19,53} transcriptomic analyses of primary sensory and dorsal horn neurons^{22,50} and nonneuronal cells,³² and the development of induced pluripotent stem cell (iPSC)-derived nociceptors.³³ Many of these analyses are also expanding in human tissue.⁴⁵ A particularly notable rodent highlight was discovery of the

spinoparabrachial pathway⁸ and its connections with forebrain regions that process pain affect.

The development of new animal models of inflammatory and neuropathic pain also provided important insights into chronic pain mechanisms.⁷ Although these models cannot replicate the clinical condition, they are critical surrogates for the study of novel therapies. Of note has been the development of more reliable, nonreflex-based methods to assess ongoing pain in preclinical settings, including conditioned place preference and aversion tests¹⁴ and the grimace scale.³⁴ Technological highlights include powerful optogenetic²⁷ and designer receptors exclusively activated by designer drugs (DREADDs⁴⁹)-based studies of pain generating and control circuits, as well the new ability to discover novel analgesics through in silico screening of millions of molecules against pain-relevant targets.^{5,17} Thanks to incredible advances in computer technology; single unit recording has been replaced by electrodes that monitor the activity of hundreds of neurons. Computational power has also greatly expanded the scope of genetic analyses and brain imaging.

It is of interest that neither the use of gabapentinoids nor serotonin–norepinephrine reuptake inhibitors for neuropathic pain resulted from initial preclinical studies. Rather, their assessment in preclinical studies occurred after their introduction in patients, to manage seizures and depression, respectively. Ziconotide is an exception,³⁶ but unfortunately, its clinical use is limited. However, 3 clinically translated highlights are especially noteworthy. First, the demonstration, initially in rats, that spinal morphine exerts a powerful analgesic action, with a therapeutic window much greater than after systemic administration.⁵⁵ Second, recognition of the parallels that characterize the preclinical phenomenon of diffuse noxious inhibitory controls and the features of conditioned pain modulation in patients. These parallels have mechanistic implications in the etiology of fibromyalgia, irritable bowel syndrome, temporomandibular disorder, and tension-type headache.⁴¹ And third, what is perhaps the most successful preclinical to clinical translation was the discovery of calcitonin gene-related peptide (CGRP), its expression in peptidergic nociceptors, and its potency as a vasodilator. Those discoveries provided the rationale for targeting CGRP in migraine^{39,42} with monoclonal antibodies against CGRP or with CGRP receptor blockers. Brain stimulation for chronic pain is now less common but did follow preclinical

Sponsorships or competing interests that may be relevant to content are disclosed at the end of this article.

^a Department of Anatomy, University California San Francisco, San Francisco, CA, United States, ^b Danish Pain Research Center, Department of Clinical Medicine, Aarhus University Hospital, Aarhus N, Denmark, ^c Duke Pain Prevention and Treatment Research Program, Department of Psychiatry and Behavioral Sciences, Duke University Medical Center, Durham, NC, United States

*Corresponding author. Address: Department of Anatomy, University California San Francisco, CA 94158, United States. Tel.: 415-502-1399. E-mail address: allan.basbaum@ucsf.edu (A. I. Basbaum).

© 2023 International Association for the Study of Pain
<http://dx.doi.org/10.1097/j.pain.0000000000003058>

demonstrations of powerful descending control systems.⁴ For all of these translational successes, credit should not only go to the collaborative research of scientists and clinicians but also to the many volunteers who were participants in these studies.

The Nobel Prize awarded for the discovery of the transient receptor potential vanilloid 1 (TRPV1) and Piezo channels is unquestionably among the most memorable preclinical pain research highlights.³⁵ In addition, there remains a plethora of sensory neuron pain-relevant targets, including voltage-gated Na⁺, K⁺, and Ca⁺⁺ channels.³ Lidocaine, despite its therapeutic window limitations, is still the most effective way to block pain. For this reason, the clinical failure to date of drugs that target and block NaV1.7, loss of function of which leads to pain insensitivity,¹⁶ is disappointing. Nevertheless, the search continues for drugs to regulate NaV1.7 and other pain-relevant Na channels (eg, NaV1.8 and NaV1.9). The discovery of multiple opioid receptors³⁰ and endorphin subtypes²⁶ was also groundbreaking, but we still await translation of those findings to improved pain pharmacotherapy. Particularly disappointing is that we still lack a reliable laboratory or clinical biomarker for pain. Here is an important challenge for the new generation of basic and clinical pain researchers.

3. Highlights in clinical pain research

A cure for chronic pain has not been found; however, a number of milestones in clinical pain research have been seen in the past 50 years. Perhaps the most remarkable one has been the mutual exchange of knowledge and ideas between basic and clinical pain scientists. In the 1970s and 1980s, the pain field sparked with optimism. Basic science studies showed that stimulating brainstem opioid-linked circuits activate descending control systems that target the dorsal horn by the dorsolateral funiculus and suppress nociceptive processing.^{1,4} Opioids when administered intraspinally produced powerful analgesia⁵⁵ without sedation or affecting cognitive function. This observation had an immediate clinical impact on the management of acute preoperative and postoperative pain and certain types of cancer pain.¹⁰ However, the enthusiasm for opioids for chronic pain faded substantially with the increasing documentation of side effects associated with opioids. For postoperative pain, other multimodal pain strategies were introduced. These strategies not only improved pain management but also recovery after surgery, so-called fast track surgery.²⁹ In the 1990s, many clinical pain trials were performed with compounds, such as antidepressants and gabapentinoids developed for other conditions, but these showed meaningful clinical pain relief in mainly neuropathic types of pain.^{18,19}

Systematic reviews and meta-analysis became an important instrument for clinicians to understand what works and what does not work.³⁷ Following a number of negative clinical pain trials, where treatment efficacy was based solely on disease and type of pain, a completely new emphasis emerged, namely, a mechanism-based classification approach.⁵⁴ The key tenet in this approach was that a focus on specific small molecules targeting a specific mechanism may produce the relevant necessary and sufficient pain relief. Noted above is the success of CGRP receptor blockers and monoclonal antibodies to treat and even prevent migraine.^{39,42} Unfortunately, progress in the mechanism-based approach has been limited.

Brain imaging has shown that the complexity of the pain experience is mediated by a neuronal network connecting brain areas involved in sensory, emotional, and cognitive processes.¹³ Within the past 2 decades, genetic and genomic sequencing has contributed to understanding several Mendelian pain disorders.⁶

Genetic analysis, careful analysis of symptoms, and detailed sensory profiling of patients² with common pain conditions are areas being actively explored.

The development of more sophisticated outcome measures for pain beyond simple unidimensional pain scales may move us closer to identifying mechanisms underlying common pain disorders. Epidemiological pain research has great potential, not only for characterizing the prevalence of different types of pain but also their causes and how to prevent them.^{11,51} The new classification system for chronic pain⁴⁶ may generate new epidemiological data, similar to what has been seen in the field of headache.²³ Neuromodulation represents an interesting approach for both invasive and noninvasive electrical therapies for chronic pain.³¹ However, to rigorously test the effectiveness of these neuromodulation therapies, we need more high quality randomized controlled trials (RCTs).

4. Highlights in psychological pain research

In the early 1970s, psychological pain research was rapidly moving away from case studies rooted in psychodynamic formulations of chronic pain (ie, the notions of psychogenic pain or “pain prone patient”). Spurred on by developments in research and pain theory (ie, the gate control theory (Fig. 1) and behavioral and cognitive theories) and a growing recognition of the important role that biological, psychological, and social factors play in illness and disease (the biopsychosocial model), new assessment and treatment strategies emerged. Advances in psychometrics (multidimensional scaling) informed the development of the McGill Pain Questionnaire.³⁸ Psychophysical measures of sensory, affective, and other domains of pain are now used in many basic (pain threshold or tolerance measures; suprathreshold pain scaling) and applied (eg, quantitative sensory testing) research settings. The 1980s witnessed growth in the use of standardized psychological instruments and led to one of the most consistent, robust, and interesting findings in this area, ie, how much individuals experiencing pain vary in their psychological functioning. Early studies using the Minnesota Multiphasic Inventory found important individual personality differences and subgroups in chronic pain samples.^{9,43} We now know that such individual variations are apparent on most standardized psychological measures, eg, those assessing pain-related thoughts, beliefs, expectations, coping, or observed pain-related behaviors. Recent studies show that one can use smartphones and mobile devices to reliably capture within and across day variations in these domains.⁴⁴ This research can help clinicians better understand and explain variations in how their patients adjust to pain and can guide the tailoring of psychological treatments.

Psychological approaches now encompass a diverse array of empirically validated treatments. Fordyce pioneered a behavioral therapy approach based on operant conditioning.²¹ Early on, electromyographic (EMG) biofeedback (BFB) was found effective for tension headache. An important landmark study²⁴ found that changes in cognitions (self-efficacy), not changes in muscle tension (levels of EMG activity), explained the benefits of BFB for tension headache. Mitchell and White⁴⁰ were among of the first to develop and test a protocol for managing pain that taught patients cognitive and behavioral skills for managing pain (ie, cognitive-behavioral therapy [CBT]). Turk et al.⁴⁷ provided a comprehensive rationale and detailed description of CBT for chronic pain. Landmark studies demonstrated that CBT protocols could be tested using rigorous RCT methods,^{48,52} and numerous RCTs have now tested psychological pain-treatment protocols (eg, graded exposure, hypnosis, imagery, meditation, mindfulness training, acceptance and commitment therapy, and

INTERNATIONAL ASSOCIATION FOR THE STUDY OF PAIN

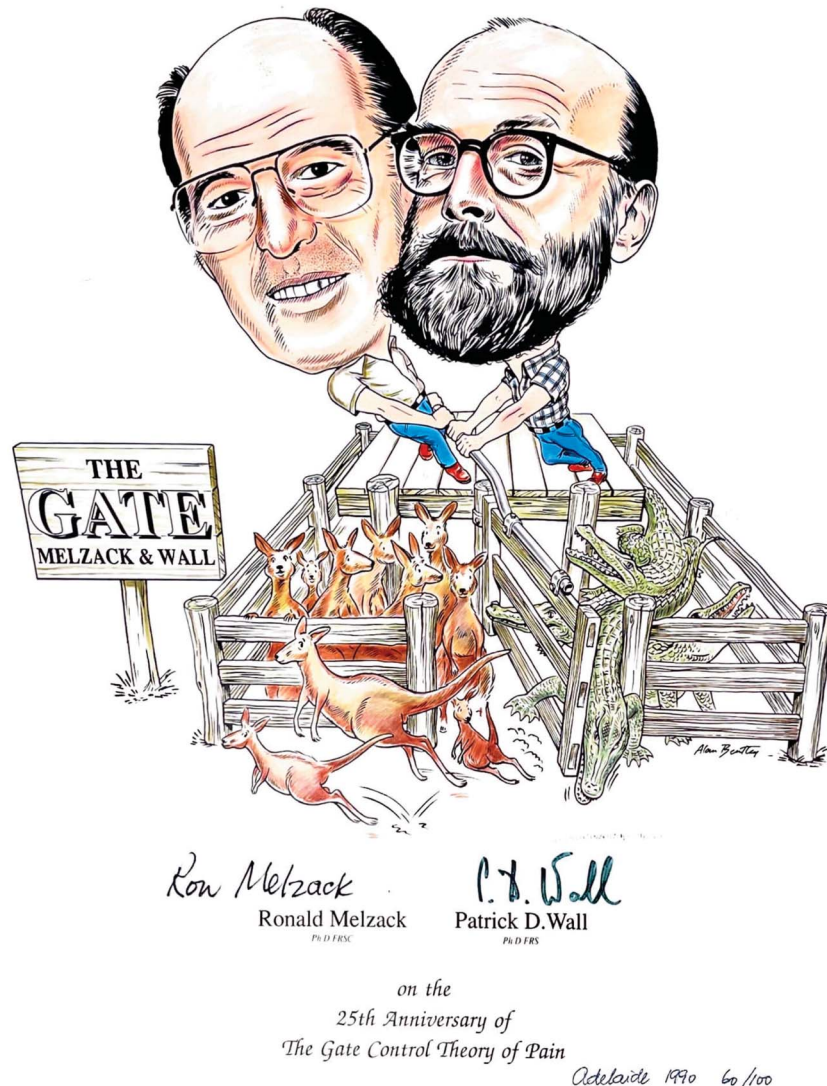


Figure 1. This IASP poster of the Gate Control Theory, presented in Adelaide at the 1990 World Congress on Pain, celebrated the 25th anniversary of the Ronald Melzack and Patrick D. Wall publication: Pain mechanisms: A new theory. *Science* 1965;150:971–9. The theory completely changed the way preclinical and clinical pain researchers addressed questions about the generation of acute and chronic pain and provided important insights into novel approaches to pharmacological, neuromodulatory, and psychological methods to pain management. Provided by Troels Jensen.

partner-assisted treatments). More RCTs testing the efficacy of combining psychological and medication treatments for pain are needed,^{25,28} given that this combination is used so often clinically. Recent interest in psychological treatments is not only due to growing evidence they may help in managing acute and persistent pain (eg, in children, older adults, and those having disease-related pain conditions) but also to the possibility that they may limit long-term use of opioids. The current focus on developing novel and disseminable strategies for enhancing access to psychological treatments is important. This could ensure that psychological treatments for pain are more readily available to the large population of individuals who may need and benefit from them.^{12,15}

5. Conclusions

Although the field of pain research and clinical practice has advanced considerably in the 50 years since the founding of IASP, it is clear that our understanding and ability to manage pain, in particular chronic pain, remain limited. We believe future advances in basic and applied pain science will provide a key pathway to the goal that we all share: reducing pain and pain-related suffering.

Conflict of interest statement

A.I.B. and colleagues have filed a patent for use of novel analgesics. The authors have no conflict of interest to declare.

Acknowledgements

Supported by: NIH NS R35 NS097306, DARPA-9691, Open Philanthropy (A.I.B.); NIH: 5UH3-AT009790; 239631/1-R01AG064947; 60062239/5R01-CA271220; 5R01-CA249959; 5R01-CA237892; 5R01-CA229425; 5UH3-AR077360-04; 5UH3-AG067493; 5R21-DA052729; U01-DK123813; 5UG3-NR019196 and Novo Nordisk Foundation NNF14OC0011633 (T.S.J.).

Article history:

Received 10 May 2023

Received in revised form 24 July 2023

Accepted 31 July 2023

References

- Akil H, Mayer DJ, Liebeskind JC. Antagonism of stimulation-produced analgesia by naloxone, a narcotic antagonist. *Science* 1976;191:961–2.
- Baron R, Förster M, Binder A. Subgrouping of patients with neuropathic pain according to pain-related sensory abnormalities: a first step to a stratified treatment approach. *Lancet Neurol* 2012;11:999–1005.
- Basbaum AI, Bautista DM, Scherrer G, Julius D. Cellular and molecular mechanisms of pain. *Cell* 2009;139:267–84.
- Basbaum AI, Fields HL. Endogenous pain control systems: brainstem spinal pathways and endorphin circuitry. *Annu Rev Neurosci* 1984;7:309–38.
- Bender BJ, Gahbauer S, Luttens A, Lyu J, Webb CM, Stein RM, Fink EA, Balius TE, Carlsson J, Irwin JJ, Shoichet BK. A practical guide to large-scale docking. *Nat Protoc* 2021;16:4799–832.
- Bennett DL, Clark AJ, Huang J, Waxman SG, Dib-Hajj SD. The role of voltage-gated sodium channels in pain signaling. *Physiol Rev* 2019;99:1079–151.
- Bennett GJ, Xie YK. A peripheral mononeuropathy in rat that produces disorders of pain sensation like those seen in man. *PAIN* 1988;33:87–107.
- Bernard JF, Bester H, Besson JM. Involvement of the spino-parabrachio-amygdaloid and -hypothalamic pathways in the autonomic and affective emotional aspects of pain. *Prog Brain Res* 1996;107:243–55.
- Bradley LA, Prokop CK, Margolis R, Gentry WD. Multivariate analyses of the MMPI profiles of low back pain patients. *J Behav Med* 1978;1:253–72.
- Cousins M, Mather L. Intrathecal and epidural administration of opioids. *Anesthesiology* 1984;61:276–310.
- Crombie IK, Davies HTO, Macrae WA. The epidemiology of chronic pain: time for new directions. *PAIN* 1994;57:1–3.
- Damall BD. Psychological treatment for chronic pain: improving access and integration. *Psychol Sci Public Int* 2021;22:45–51.
- Davis KD, Flor H, Greeley HT, Iannetti GD, Mackey S, Ploner M, Pustilnik A, Tracey I, Treede RD, Wager TD. Brain imaging tests for chronic pain: medical, legal and ethical issues and recommendations. *Nat Rev Neurol* 2017;13:624–38.
- De Felice M, Eyde N, Dodick D, Dussor GO, Ossipov MH, Fields HL, Porreca F. Capturing the aversive state of cephalic pain preclinically. *Ann Neurol* 2013;74:257–65.
- Eccleston C, Blyth FM, Dear BF, Fisher EA, Keefe FJ, Lynch ME, Palermo TM, Reid MC, Williams A. Managing patients with chronic pain during the COVID-19 outbreak: considerations for the rapid introduction of remotely supported (eHealth) pain management services. *PAIN* 2020;161:889–93.
- Emery EC, Luiz AP, Wood JN. Na_v1.7 and other voltage-gated sodium channels as drug targets for pain relief. *Expert Opin Ther Targets* 2016;20:975–83.
- Fink EA, Xu J, Hübner H, Braz JM, Seemann P, Avet C, Craik V, Weikert D, Schmidt MF, Webb CM, Tolmachova NA, Moroz YS, Huang XP, Kalyanaraman C, Gahbauer S, Chen G, Liu Z, Jacobson MP, Irwin JJ, Bouvier M, Du Y, Shoichet BK, Basbaum AI, Grmeyer P. Structure-based discovery of nonopioid analgesics acting through the α 2A-adrenergic receptor. *Science* 2022;377:eabn7065.
- Finnerup NB, Attal N, Haroutounian S, McNicol E, Baron R, Dworkin RH, Gilron I, Haanpaa M, Hansson P, Jensen TS, Kamerman PR, Lund K, Moore A, Raja SN, Rice AS, Rowbotham M, Sena E, Siddall P, Smith BH, Wallace M. Pharmacotherapy for neuropathic pain in adults: a systematic review and meta-analysis. *J Vasc Surg* 2015;62:1091–173.
- Finnerup NB, Kuner R, Jensen TS. Neuropathic pain: from mechanisms to treatment. *Physiol Rev* 2021;101:259–301.
- Flor H, Noguchi K, Treede R-D, Turk DC. The role of evolving concepts and new technologies and approaches in advancing pain research, management, and education since the establishment of the International Association for the Study of Pain. *PAIN* 2023;164:S16–S21.
- Fordyce WE, Fowler RS, Lehmann JF, Delateur BJ, Sand PL, Trieschmann RB. Operant conditioning in the treatment of chronic pain. *Arch Phys Med Rehabil* 1973;54:399–408.
- Häring M, Zeisel A, Hochgerner H, Rinwa P, Jakobsson JET, Lönnerberg P, La Manno G, Sharma N, Borgius L, Kiehn O, Lagerström MC, Linnarsson S, Ernfrors P. Neuronal atlas of the dorsal horn defines its architecture and links sensory input to transcriptional cell types. *Nat Neurosci* 2018;21:869–80.
- Headache Classification Committee of the International Headache Society (IHS) the international classification of headache disorders, 3rd edition. *Cephalalgia* 2018; 38:1–211.
- Holroyd KA, Nash JM, Pingel JD, Cordingley GE, Jerome A. A comparison of pharmacological (Amitriptyline HCL) and nonpharmacological (cognitive-behavioral) therapies for chronic tension headaches. *J Consult Clin Psychol* 1991;59:387–93.
- Holroyd KA, Penzien DB, Hursey KG, Tobin DL, Rogers L, Holm JE, Marcille PJ, Hall JR, Chila AG. Change mechanisms in EMG biofeedback training: cognitive changes underlying improvements in tension headache. *J Consult Clin Psychol* 1984;52:1039–53.
- Hughes J, Smith TW, Kosterlitz HW, Fothergill LA, Morgan BA, Morris HR. Identification of two related pentapeptides from the brain with potent opiate agonist activity. *Nature* 1975;258:577–9.
- Iyer SM, Vesuna S, Ramakrishnan C, Huynh K, Young S, Berndt A, Lee SY, Gorini CJ, Deisseroth K, Delp SL. Optogenetic and chemogenetic strategies for sustained inhibition of pain. *Sci Rep* 2016;6:30570.
- Keefe FJ, Shelby RA, Somers TJ, Varia I, Blazing M, Waters SJ, McKee D, Silva S, She L, Blumenthal JA, O'Connor J, Knowles V, Johnson P, Bradley L. Effects of coping skills training and sertraline in patients with non-cardiac chest pain: a randomized-controlled study. *PAIN* 2011;152:730–41.
- Kehlet H. Postoperative pain, analgesia, and recovery-bedfellows that cannot be ignored. *PAIN* 2018;159:S11–6.
- Kieffer BL, Evans CJ. Opioid receptors: from binding sites to visible molecules in vivo. *Neuropharmacology* 2009;56(suppl 1):205–12.
- Knotkova H, Hamani C, Sivanesan E, Le Beuffe MFE, Moon JY, Cohen SP, Huntoon MA. Neuromodulation for chronic pain. *Lancet* 2021;397:2111–24.
- Kuhn JA, Vainchtein ID, Braz J, Hamel K, Bernstein M, Craik V, Dahlgren MW, Ortiz-Carpena J, Molofsky AB, Molofsky AV, Basbaum AI. Regulatory T-cells inhibit microglia-induced pain hypersensitivity in female mice. *Elife* 2021;10:e69056.
- Labau JIR, Andelic M, Faber CG, Waxman SG, Lauria G, Dib-Hajj SD. Recent advances for using human induced-pluripotent stem cells as pain-in-a-dish models of neuropathic pain. *Exp Neurol* 2022;358:114223.
- Langford DJ, Bailey AL, Chanda ML, Clarke SE, Drummond TE, Echols S, Glick S, Ingrao J, Klassen-Ross T, Lacroix-Fralish ML, Matsumiya L, Sorge RE, Sotocinal SG, Tabaka JM, Wong D, van den Maagdenberg AM, Ferrari MD, Craig KD, Mogil JS. Coding of facial expressions of pain in the laboratory mouse. *Nat Methods* 2010;7:447–9.
- Ledford H, Callaway E. Medicine Nobel goes to scientists who discovered biology of senses. *Nature* 2021;598:246.
- Malmberg AB, Yaksh TL. Voltage-sensitive calcium channels in spinal nociceptive processing: blockade of N- and P-type channels inhibits formalin-induced nociception. *J Neurosci* 1994;14:4882–90.
- McQuay HJ, Moore RA. An evidence-based resource for pain relief. Oxford, United Kingdom: Oxford University Press, 1998.
- Melzack R. The McGill Pain Questionnaire: major properties and scoring methods. *PAIN* 1975;1:277–99.
- Messina R, Goadsby PJ. CGRP—a target for acute therapy in migraine: clinical data. *Cephalalgia* 2019;39:420–27.
- Mitchell KR, White RG. Behavioral self-management: an application to the problem of migraine headaches. *Behav Ther* 1977;8:213–21.
- Moont R, Pud D, Sprecher E, Sharvit G, Yarnitsky D. “Pain inhibits pain” mechanisms: is pain modulation simply due to distraction? *PAIN* 2010;150:113–20.
- Olesen J, Diener HC, Husstedt IW, Goadsby PJ, Hall D, Meier U, Pollentier S, Lesko LM. Calcitonin gene-related peptide receptor antagonist BIBN 4096 BS for the acute treatment of migraine. *N Engl J Med* 2004;350:1104–10.
- Sternbach R. Pain patients: traits and treatments. New York: Academic Press, 1974.
- Stone AA, Obbarius A, Junghaenel DU, Wen CKF, Schneider S. High resolution, field approaches for assessing pain: ecological momentary assessment. *PAIN* 2021;162:4–9.
- Tavares-Ferreira D, Shiers S, Ray PR, Wangzhou A, Jeevakumar V, Sankaranarayanan I, Cervantes AM, Reese JC, Chamesian A, Copits

- BA, Dougherty PM, Gereau RW IV, Burton MD, Dussor G, Price TJ. Spatial transcriptomics of dorsal root ganglia identifies molecular signatures of human nociceptors. *Sci Transl Med* 2022;14:eabj8186.
- [46] Treede RD, Rief W, Barke A, Aziz Q, Bennett MI, Benoliel R, Cohen M, Evers S, Finnerup NB, First MB, Giamberardino MA, Kaasa S, Korwisi B, Kosek E, Lavand'homme P, Nicholas M, Perrot S, Scholz J, Schug S, Smith BH, Svensson P, Vlaeyen JWS, Wang SJ. Chronic pain as a symptom or a disease: the IASP classification of chronic pain for the International Classification of Diseases (ICD-11). *PAIN* 2019;160:19–27.
- [47] Turk DC, Meichenbaum D, Genest M. Pain and behavioral medicine: a cognitive-behavioral perspective. New York: Guilford, 1983.
- [48] Turner JA. Comparison of group progressive-relaxation training and cognitive-behavioral group therapy for chronic low back pain. *J Consult Clin Psychol* 1982;50:757–65.
- [49] Urban DJ, Roth BL. DREADDs (designer receptors exclusively activated by designer drugs): chemogenetic tools with therapeutic utility. *Annu Rev Pharmacol Toxicol* 2015;55:399–417.
- [50] Usoskin D, Furlan A, Islam S, Abdo H, Lönnnerberg P, Lou D, Hjerling-Leffler J, Haeggström J, Kharchenko O, Kharchenko PV, Linnarsson S, Erfors P. Unbiased classification of sensory neuron types by large-scale single-cell RNA sequencing. *Nat Neurosci* 2015;18:145–53.
- [51] Von Korff M, Dworkin SF, Le Resche L, Kruger A. An epidemiologic comparison of pain complaints. *PAIN* 1988;32:173–83.
- [52] Williams AC dC, Richardson PH, Nicholas MK, Pither CE, Harding VR, Ridout KL, Ralphs JA, Richardson IH, Justins DM, Chamberlain JH. Inpatient vs. outpatient pain management: results of a randomised controlled trial. *PAIN* 1996;66:13–22.
- [53] Woolf CJ. Evidence for a central component of post-injury pain hypersensitivity. *Nature* 1983;306:686–8.
- [54] Woolf CJ, Bennett GJ, Doherty M, Dubner R, Kidd B, Koltzenburg M, Lipton R, Loeser JD, Payne R, Torebjork E. Towards a mechanism-based classification of pain? *PAIN* 1998;77:227–9.
- [55] Yaksh TL, Rudy TA. Analgesia mediated by a direct spinal action of narcotics. *Science* 1976;192:1357–8.