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REVIEW ARTICLE

NEUROPHYSIOLOGICAL STUDIES IN A STRATIFICATION OF CHRONIC PAIN SYNDROME – A NARRATIVE REVIEW

BADANIA NEUROFIZJOLOGICZNE W STRATYFIKACJI ZESPOŁU BÓLU PRZEWLEKŁEGO – PRZEGLĄD NARRACYJNY

Jędrzej Pepliński[1,A-B,D-F], Matylda Witkowska[1,B,D-E], Juliusz Huber[1,B,D-E]
[1]Department of Pathophysiology of Locomotor Organs, University of Medical Sciences in Poznan, Poland, Poland
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ABSTRACT
The latest definition of pain describes it as an unpleasant sensory and emotional experience associated with actual or potential tissue damage or resembling such damage. According to this definition, three subtypes of chronic pain are currently distinguished based on their underlying pathological mechanisms: nociceptive, neuropathic, and nociplastic. All three types share certain characteristic features, their symptoms may overlap, and co-occurrence is also possible. This makes diagnostic and treatment decisions difficult. This review provides a brief description of the most reliable tools for diagnosing and treating chronic pain and its sequelae, with a particular emphasis on neurophysiological research available in this field.

Keywords: neurophysiological diagnostics, chronic pain, stratification

STRESZCZENIE
Najnowsza definicja bólu opisuje go jako nieprzyjemne doznania zmysłowe i emocjonalne związane z rzeczywistym lub potencjalnym uszkodzeniem tkanki lub przypominające takie uszkodzenie. Wraz z tą definicją, wyróżnia się aktualnie trzy podtypy bólu przewlekłego na podstawie jego mechanizmu: nocyceptywny, neuropatyczny oraz nocyplastyczny. Wszystkie te trzy typy mają pewne charakterystyczne cechy, ich objawy mogą się nakładać na siebie, możliwe jest również zjawisko współwystępowania wymienionych typów. Podjęcie decyzji diagnostycznej i leczniczej jest z tego powodu znacznie utrudnione. Niniejszy przegląd zawiera krótki opis najbardziej wiarygodnych narzędzi do diagnozowania i leczenia bólu przewlekłego oraz jego następstw, ze szczególnym uwzględnieniem badań neurofizjologicznych dostępnych w tej dziedzinie.

Słowa kluczowe: diagnostyka neurofizjologiczna, ból przewlekły, stratyfikacja

Author responsible for correspondence:
Jędrzej Pepliński Department of Pathophysiology of Locomotor Organs, University of Medical Sciences in Poznan, Poland, 28 Czerwca 1956r. Nr 135/147, 61-545, Poznań, Poland,
Email: peplinski.jedrzej@gmail.com, Phone: 698949051
Jędrzej Pepliński – 0009-0000-9995-5090
Matylda Witkowska – 0009-0004-3016-4927
Juliusz Huber – 0000-0002-8671-0497

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Introduction

Pain definition

In 2020, pain was redefined as "An unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage." This definition requires further explanation, which is described in six points:

1. Pain is always a personal experience that is influenced to varying degrees by biological, psychological, and social factors.
2. Pain and nociception are different phenomena. Pain cannot be inferred solely as the consequence of activity in the sensory neurons.
3. Human learn the concept of pain through their life experiences.
4. A person's report of an experience as pain should be respected.
5. Although pain usually serves an adaptive role, it may have adverse effects on function and social and psychological well-being.
6. A verbal description is only one of several behaviors for expressing pain, and the inability to communicate does not negate the possibility that a human or a nonhuman animal experiences pain (Raja *et al.*, 2020).

The term chronic pain (CP) is a diagnosis of a pain condition that lasts or recurs for longer than 3 months, is often multifactorial, and is considered to be a biopsychosocial phenomenon [Treede *et al.,* 2019]. In the current research, CP is stratified into three subgroups based on the pain mechanism origin: nociceptive, neuropathic, and nociplastic (Figure 1). Nociplastic pain is currently standing as the biggest challenge in making a diagnosis and choosing the best therapy. In 2016 term "nociplastic pain" was first introduced in an article created by Kosek *et al.* (Kosek *et al.*, 2016), who challenged the then-current view that pain is either nociceptive from noxious input or stimulus resembling it, with a properly working somatosensory nervous system, or neuropathic, coming from demonstrable lesion or a disease of the nervous system. It was their team that had given us the current definition of nociplastic pain, accepted by International Association for the Study of Pain (IASP) in 2017, which is… "pain that arises from altered nociception despite no clear evidence of actual or threatened tissue damage causing the activation of peripheral nociceptors or evidence for disease or lesion of the somatosensory system causing the pain"… (Kosek *et al.,* 2016).

Another important aspect of this issue is the discussion whether this pain is primary, then this pain should be called a disease (e.g. complex regional pain syndrome, chronic primary headache pain), or is it secondary which would indicate that this pain is only a part of initial diagnosis (e.g. chronic neuropathic pain, chronic cancer-related pain (Treede *et al.,* 2019).

Significance of chronic pain

Chronic pain conditions present a significant global health burden as they affect approximately 10–30% of the worldwide population (Goldberg and McGee, 2011; Cohen, Vase and Hooten, 2021; Zimmer *et al.,* 2022). Notably, conditions such as fibromyalgia, complex regional pain syndrome, and chronic low back pain exemplify the diversity of chronic pain syndromes. Central sensitization is a critical mechanism underlying these conditions, characterized by an increased sensitivity of the central nervous system, which leads to abnormal pain perception and has been linked to neuroplastic changes in the brain.

Central sensitization in chronic pain

In recent years, central sensitization (CS) has attracted considerable attention in the scientific community, accounting for over 40% of related PubMed publications between 2019 and 2024 since its first description in 1982. Central sensitization is a state of hyperexcitability in central nervous system which results effect of aftersensation, increased process of temporal summation, secondary hyperalgesia which makes patient susceptible to feel pain from previously non-injured

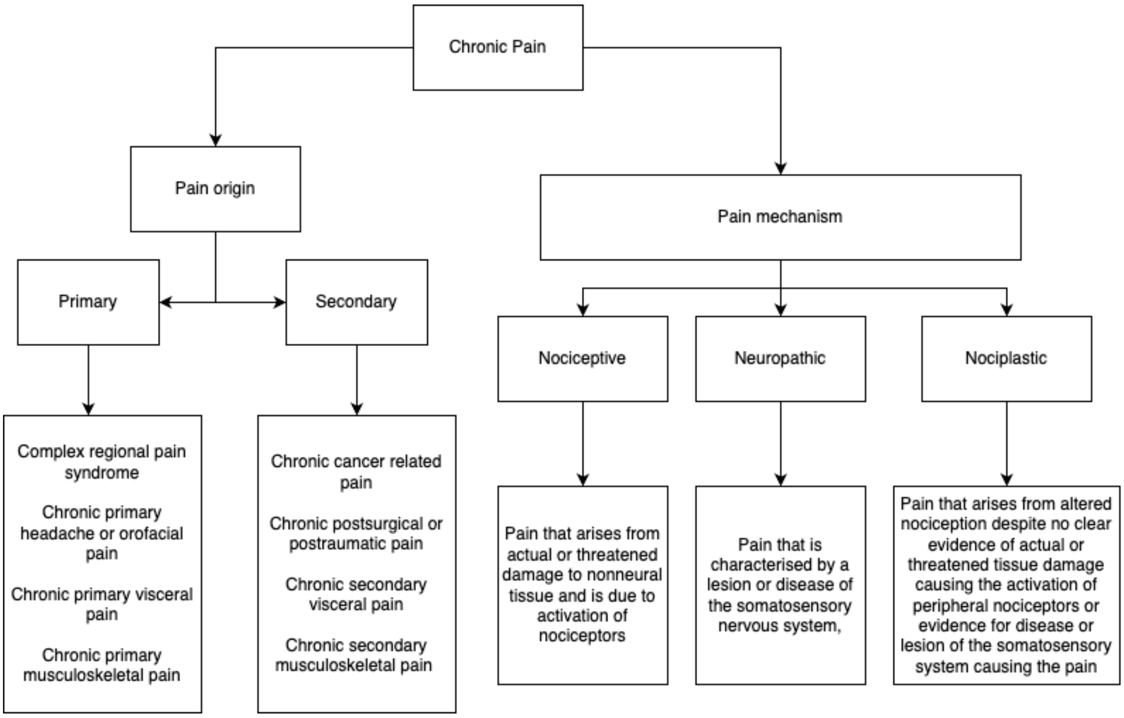

Figure 1. Pain stratification by its mechanism and by its origin.

tissues either directly or non-directly (e.g. not due to neuropathic pain from nerve root compression) and most commonly recognized an increased sensitivity to noxious stimuli (hyperalgesia) and increased sensitivity to non-noxious stimuli (allodynia) (Woolf, 2011). CS is currently strongly suspected to be a part of the nociplastic pain mechanism, while it is advocated not to use those words synonymously (Kosek *et al.*, 2021).

Controversies of diagnosing and treating the chronic pain

Chronic pain is a very well-studied topic and one that is very important. Having said that, despite this thorough research, there is still much more to be discovered. Moreover, new emerging concepts such as nociplastic pain complicate the classification of chronic pain syndromes, making it a necessity to further stratify pain and to redefine diagnostic criteria and treatments to properly match the specific needs of a patient. Current treatment and diagnosis methods often misdiagnose due to the complication and multifaceted character of this problem. This has led to controversies, including the concept of "Failed Back Surgery Syndrome" (FBSS), referring to patients whose symptoms persist or worsen following spinal surgery. FBSS is reported to be involved in 10–40% of patients (Inoue *et al.*, 2017; Sebaaly *et al.*, 2018). In recent years, this has seen a change with the term being replaced by Persistent Spinal Pain Syndrome and highlighting the importance of neuropathic pain mechanisms, which changes the patient's clinical picture where operation by itself can no longer bring full relief, and a multidisciplinary and holistic approach is needed for patient's individual needs (Miękisiak, 2023). Such an approach should be implemented routinely in clinical practice dealing with chronic pain patients. Realizing that pain is an inseparable part of everyday clinical practice, this knowledge should become standardized and spread among medical professionals as much as it is possible.

Neurophysiological diagnostic methods in the stratification of chronic pain or its pathological consequences

Methods of differential diagnosing chronic pain mechanisms are essential in making steady decisions when choosing treatment for a patient.

Neurophysiological examinations in the stratification of chronic pain syndrome encompass the study and assessment of neural mechanisms involved in pain transmission pathways. Figure 2 shows a simplified scheme of possible diagnostic tools. There are currently a few kinds of assessments that help by giving further insight into a patient's clinical health status. Quantitative sensory testing (QST), conditioned pain modulation (CPM), functional magnetic resonance imaging (fMRI), electromyography (EMG), nerve conduction studies (NCS), microneurography (mENG), electroencephalography (EEG), central sensitization inventory (CSI), sensory evoked potentials recordings (SEPs), laser evoked potentials recordings (LEPs) (Fillingim *et al.,* 2016; Shraim *et al.,* 2022), are just a few of the tools used in chronic pain research or its pathological consequences.

Electromyography is a method that allows the recording of motor units action potentials from the painful muscle. The non-invasive surface EMG (sEMG) mono- or unipolar recording evaluates the global activity of all motor units at muscle's rest or during the attempt of voluntary contraction. Needle EMG allows evaluation of the single motor unit potentials of the single myocytes, such as amplitude and duration, which, together with interference evaluation during the painful muscle's voluntary contraction, points to a more specific direction of diagnosis of a nervous system lesion or disorder. In studies of Wytrążek *et al.* (2015), they successfully assessed trigger points (TRPs), their pain threshold, and the activity of motor units in the neck and shoulder girdle muscles of young volunteers and applied palpation, algometry, and surface electromyography (EMG) for their detection. Trigger points evoked a moderate increase of resting EMG

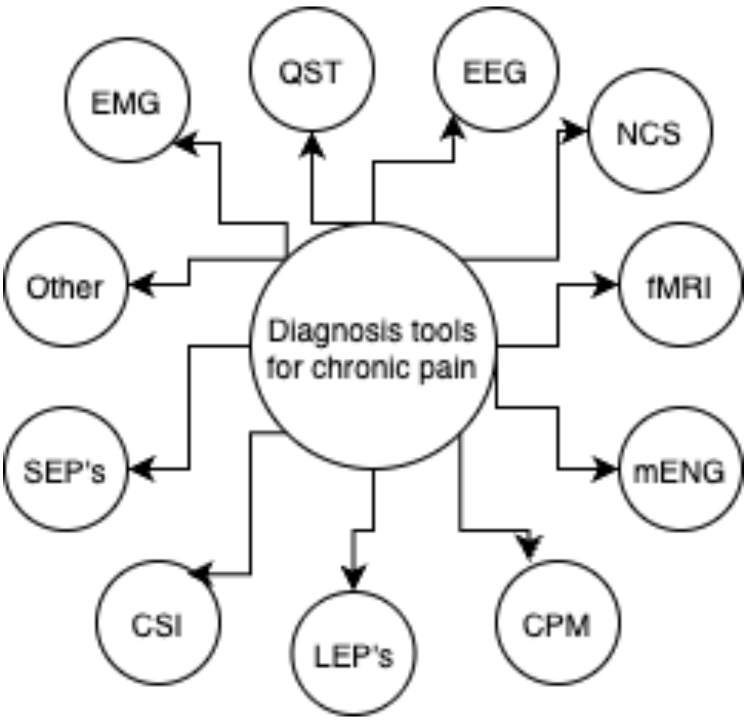

Figure 2. Possible tools for chronic pain evaluation or its pathological consequences. Abbreviations: EMG – electromyography, QST – quantitative sensory testing, EEG – electroencephalography, NCS – nerve conduction studies, fMRI – functional magnetic resonance imaging, mENG – microneurography, CPM – conditioned pain modulation, LEPs – laser evoked potentials, CSI – central sensitization inventory, SEPs – sensory evoked potentials recordings and recordings.

amplitude but with no evident changes in maximal voluntary contraction EMG recording. Moreover, Wytrążek *et al.* (2011) found that changes in muscle activity determine progression of clinical symptoms in patients with chronic spine-related muscle pain using both surface and needle EMG recordings; they revealed characteristic asynchronous discharges in muscles with TRPs. The results of EMG examinations point to a complexity of muscle pain that depends on progression of the myofascial syndrome. Using EMG, Huber *et al.* (2013) found positive correlations between increase in resting EMG amplitudes and high VAS scores of the painful muscle, as well as high-amplitude resting EMG recordings incidence and increased number of TRPs. Negative correlation was detected between amplitude in maximal contraction EMG and amplitude of resting EMG recordings. They concluded that dysfunction of trapezius muscle was most responsible for cervicogenic headache etiology.

Electroneurography allows practitioner to assess the functional state of neural conduction of impulses in nerve fibers where the electrical single or trains of stimuli are applied. There are different subtypes of nerve conduction studies (NCS), among others microneurography and sensory evoked potentials recording. Using NCS, non-nociceptive large myelinated Aβ-fibers can be evaluated; either in the orthodromic or antidromic studies. It also allows for examination of late responses where impulses are transmitted on the entire nerve H-reflex route, or with the reference to the trigeminal and facial nerves transmission the oligosynaptic Blink Reflex. Parameters of NCS allow for conclusions on damage to both motor and sensory fibers, either of an axonal and/or demyelinating origin. Examination of reflexes also enables an experienced examiner to deduce if there is damage to the central or peripheral nervous system (Leone and Truini, 2024). NCS study allows for verifying the neural transmission in small nociceptive Aδ fibres by studying the Nociceptive Withdrawal Reflex; elicited by electrical stimuli applied to a peripheral nerve, causing limb withdrawal at the spinal level. Hoffman Reflex and Blink Reflex have also been found to be abnormal in diseases in which patients often suffer from chronic pain (Al-Azzawi, Hamdan and Ali, 2008; Ge *et al.*, 2009).

Microneurography is a very rarely used technique due to the fact that it requires putting a needle in a nerve fibre. It is very uncommon to meet this technique in the clinical practice; it is mostly used in a scientific studies. It brings, however, very interesting possibilities to examine directly C-fibers neural transmission, unachievable using standard NCS methodology (Ochoa *et al.*, 2005; Serra *et al.*, 2012).

Electroencephalography is a non-invasive neurophysiological method for recording electrical activity generated by neurons in the cerebral cortex, via surface electrodes placed on the scalp. It provides high temporal resolution data on brain dynamics, making it a valuable tool in both clinical diagnostics and cognitive neuroscience research. Similar to fMRI, it allows us to see changes in the part of the brain responsible for pain perception (Müller-Putz, 2020; Mussigmann, Bardel and Lefaucheur, 2022; Mathew *et al.*, 2024).

Laser-evoked potentials (LEP) are based on activation of nociceptors by a heat stimulus, giving activation of Aδ and C nociceptors in the most superficial skin layers; evoked potentials are then registered in the EEG systems (Truini *et al.*, 2004; Hüllemann *et al.*, 2017; Vecchio *et al.*, 2022). Laser-evoked potentials and neuropathic pain were found to be related to LEP amplitude changes and pain sensation (Truini *et al.*, 2004, 2008). This underscores the importance of neurophysiological evaluations in the clinical assessment and management of chronic pain syndromes.

Contemporary, EMG and ENG are being used for the diagnosis of neuropathic pain with one of the highest percentages of agreement among the experts, appropriately 79% and 69%. The highest score is taken by neurological testing of dermatomes and peripheral nerve distribution and imaging methods, with the same score of 86% (Shraim *et al.*, 2022).

Quantitative sensory testing is a set of tests that appraise the functioning of the sensory nervous system by means of measuring the threshold at which the patient reacts to various stimuli, such as heat, cold, pressure, electricity, or vibration. The additional effect measured using QST is the temporal summation; repeated stimuli of the same kind are delivered, and the appropriate patient's response is assessed, whether there is exaggeration in pain perception while the stimulus at the same level. It must be mentioned, that QST measuring the hyperalgesia in the painful body region may not specifically indicate central sensitization, since they can also reflect the peripheral sensitization, and the entire process of QST usually has an aspect of self-reported measures, making it only a partly objective method of diagnosis (Neblett *et al.,* 2024).

Conditioned pain modulation (CPM) is another tool that is used to diagnose changes in the somatosensory nervous system. An example of this process is easy to conduct. Firstly, one single painful stimulus is given, then the second one is given to a different part of the patient's body, and finally, the first one is repeated. In healthy the second stimulus should create an analgesic effect. However, this technique still requires further research and refinement before it can be established as a reliable diagnostic tool. Too many factors are unknown, for example, is the effect of CPM results of a specific neurotransmitter in a specific pathway? Do these pathways carry descending facilitatory or inhibitory impulses, or mixed? Until these questions and others remain, the CPM will only be a component of QST (Yarnitsky, 2010; Ramaswamy and Wodehouse, 2021).

The fMRI is used to detect the structural damage to the nervous system or changes in part of the nervous system associated with pain perception – pain matrix (e.g, increase of activity in insular cortex or decrease of brainstem regions which are responsible for descending analgesic mechanisms) (Iannetti and Mouraux, 2010; Jensen *et al.,* 2013; Sandström *et al.,* 2019; Fitzcharles *et al.,* 2021). Neuroimaging giving evidence of damage and/or disease to the nervous system was scored 78% in the aforementioned Delphi study.

The Central Sensitization Inventory is a questionnaire that is the most available form of a diagnosis for CS in patients; which is crucial for the diagnosis of nociplastic pain. A great setback of clinical questionnaires is that they are likewise to QST self-reported measures, which takes away their value as they lose objectivity (Schuttert *et al.,* 2021).

In all of those tests, there are limitations that cut their value. Part of them requires expensive and not commonly available technology, some require significant experience and expertise in evaluating the results, and most of those tests also have at least some sort of subjective part in them, either from the patient's or examiner's side. This significantly reduces the possibility of use for those tests in common clinical settings. This should put pressure on scientists to develop methods that will clearly show the pathomechanism taking place and in a process that will be commonly available. Given this complex interplay of factors contributing to chronic pain, a comprehensive approach to assessment and management is necessary to address the multifaceted nature of these conditions.

Neuromodulation treatment-based possibilities

Chronic pain syndromes are complex conditions that necessitate a multidisciplinary approach to treatment. Traditional management strategies, including pharmacological interventions and surgical options, frequently fall short for a significant subset of patients, prompting the exploration of other techniques as alternative therapies. Neuromodulation therapies encompass a range of methods aimed at altering nerve activity to achieve therapeutic outcomes. Neurostimulation by means of electrical or magnetic stimuli has already been in use for decades, and at the same time, it still brings the same controversies as it evoked before (Zyss, 2008; Megía

García *et al.*, 2019; Johnson *et al.*, 2022). Even though they have been in a medical environment for such a long time, new approaches are still being developed (Bosi *et al.*, 2013; Lin *et al.*, 2020; Gilmore *et al.*, 2023; Arhos *et al.*, 2024).

Promising ways of neuromodulation for managing chronic pain are new therapies, for example, transcutaneous vagus nerve stimulation, which modulates activity of the autonomic nervous system (Hilz, 2022), or trans-spinal focused ultrasound, which potentially reduces windup activity associated with small nociceptive nerve fibers (Song *et al.*, 2025). These studies are usually either low-grade, short-term, or conducted on animal models. It shows future potential in the research of neuromodulation modalities for patients with chronic pain.

A key aspect of effective treatment lies in the meticulous evaluation of patients, taking into account various individual factors, including psychological components, previous treatment responses, and specific underlying pathologies. This holistic evaluation is critical as it informs the clinician's decisions regarding the most appropriate neurostimulation techniques, whether non-invasive or more invasive options like motor cortex stimulation or deep brain stimulation (Guzzi *et al.*, 2024). Older treatments are also being re-evaluated for their mechanisms since new mechanisms are coming into light (Luckey, Adcock and Vanneste, 2023). At the current stage of knowledge, especially in the light of research on the effectiveness of TENS electrotherapy, it is difficult to judge the validity of the "pain gate control" theory by Melzack and Wall. Understanding precise mechanisms of these therapies would help predict outcomes regarding patients' responses and sooner decide if there is a need for more invasive treatments, thereby enhancing the personalization of care strategies (Woolf, 2022; Luckey, Adcock and Vanneste, 2023).

Mindfulness-based interventions and cognitive behavioral therapy also represent significant modalities in the management of chronic pain. These approaches focus on enhancing present-moment awareness and modifying cognitive patterns, respectively, to help patients manage their pain experiences better, with neuroimaging studies suggesting that these benefits may be linked to changes in brain connectivity associated with pain processing (Luckey, Adcock and Vanneste, 2023; Vase, Wager and Eccleston, 2025).

Despite the promise shown by these therapeutic modalities, challenges remain in establishing their long-term effectiveness and cost-effectiveness, particularly for neuromodulation techniques. There is a notable lack of comprehensive high-quality studies that thoroughly evaluate the economic implications of these treatments.

Therefore, while the potential of neuromodulation and psychological therapies in treating chronic pain is increasingly recognized, ongoing research and evaluation are necessary to refine these approaches and ensure they meet the diverse needs of patients. This continuous exploration is vital not only for optimizing patient outcomes but also for advancing the field of pain management as a whole.

Conclusions

This review covers only the tip of the iceberg in terms of precise mechanisms in which different types of pain are diagnosed, how they are differentiated during the diagnosis process, and treatment possibilities. To conclude this article, a set of questions should be asked that are crucial to verify whenever dealing with a patient suffering from chronic pain.

- Is this a primary or secondary pain?
- Does this pain mechanism result from nociceptive input, from lesion of the somatosensory nervous system, or neither of them?
- Whether there are indicators of central sensitization?
- Whether there is one, two, or three pain mechanisms taking place?
- What type of diagnosis tool is best for him based on suspected pain mechanisms?

- What type of therapy should be applied, and what other medical professionals should work with this patient to achieve the best results as soon as possible?

Addressing these questions may help clarify the clinical decision-making process within the complex and often fragmented landscape of chronic pain management.

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