KJP

Korean J Pain 2024;37(2):107-118
https://doi.org/10.3344/kjp.23326
pISSN 2005-9159, eISSN 2093-0569

Review Article

Current understanding of nociplastic pain

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ABSTRACT

Nociplastic pain by the "International Association for the Study of Pain" is defined as pain that arises from altered nociception despite no clear evidence of nociceptive or neuropathic pain. Augmented central nervous system pain and sensory processing with altered pain modulation are suggested to be the mechanism of nociplastic pain. Clinical criteria for possible nociplastic pain affecting somatic structures include chronic regional pain and evoked pain hypersensitivity including allodynia with after-sensation. In addition to possible nociplastic pain, clinical criteria for probable nociplastic pain are pain hypersensitivity in the region of pain to non-noxious stimuli and presence of comorbidity such as generalized symptoms with sleep disturbance, fatigue, or cognitive problems with hypersensitivity of special senses. Criteria for definitive nociplastic pain is not determined yet. Eight specific disorders related to central sensitization are suggested to be restless leg syndrome, chronic fatigue syndrome, fibromyalgia, temporomandibular disorder, migraine or tension headache, irritable bowel syndrome, multiple chemical sensitivities, and whiplash injury; non-specific emotional disorders related to central sensitization include anxiety or panic attack and depression. These central sensitization pain syndromes are overlapped to previous functional pain syndromes which are unlike organic pain syndromes and have emotional components. Therefore, nociplastic pain can be understood as chronic altered nociception related to central sensitization including both sensory components with nociceptive and/or neuropathic pain and emotional components. Nociplastic pain may be developed to explain unexplained chronic pain beyond tissue damage or pathology regardless of its origin from nociceptive, neuropathic, emotional, or mixed pain components.

Keywords: Central Nervous System Sensitization; Chronic Pain; Emotions; Hyperalgesia; Hypersensitivity; Neuralgia; Neuronal Plasticity; Nociception; Nociceptive Pain.

INTRODUCTION

Traditionally, pain can be divided into emotional and sensory components which originate from potential and actual tissue damage, respectively. The sensory component of pain is also divided into nociceptive and neuropathic pain. The International Association for the Study of Pain (IASP) has proposed the necessity of a new sensory component of pain in addition to nociceptive and neuropathic pain. Nociplastic (algopathic or nocipathic) pain is defined as pain that arises from altered nociception without clear evidence of nociceptive or neuropathic pain. It is different from idiopathic pain, pain of unknown origin. Nociception is defined as the neural process of encoding noxious stimuli, resulting in autonomic or behavioral changes [1–3].

Central nervous system (CNS) sensitization is the representative explanation for chronic non-specific pain

Received November 15, 2023; Revised December 28, 2023; Accepted January 9, 2024

Handling Editor: Francis S. Nahm

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without a clear origin of nociceptive input or enough tissue damage to explain the experienced pain severity, disability, and other symptoms. It is defined as an amplification of neural signaling within the CNS eliciting pain hypersensitivity. It is also defined as an increased responsiveness of nociceptive neurons in the CNS to their normal or subthreshold afferent input by the IASP [4].

Nociplastic pain describes not entirely nociceptive or neuropathic, but a mechanistic component of chronic pain with evoked pain by mechanical or thermal stimuli, pain hypersensitivity, and generalized symptoms. This concept of nociplastic pain has been developed from explaining pain mechanisms beyond tissue damage or pathology. The mechanisms of nociplastic pain is considered heterogeneous, affecting central or peripheral nervous systems. Pain hypersensitivity, allodynia, or painful aftersensation is suggested as neuronal sensitization [5].

This article reviews whether nociplastic pain is a third new separate category of sensory component, an intersectional sematic category of nociceptive and neuropathic pain of the sensory component or emotional component with/without unexplained pain, an emphasized emotional component based on the sensory component, or just a previous functional pain syndrome (FPS) or central sensitization.

MAIN BODY

1. Clinical criteria of nociplastic pain affecting somatic structures

The clinical criteria of nociplastic pain by the IASP include ① pain, ② evoked pain hypersensitivity, ③ pain hypersensitivity to touch, pressure, movement, or heat/cold, and ④ the presence of comorbidities. Possible nociplastic pain includes ① and ②; probable nociplastic pain includes all from ① to ④ (**Table 1**) [5,6].

In summary, possible nociplastic pain includes ① chronic pain over 3 months that is regional, multifocal, or widespread in distribution, solely resulting from neither nociceptive nor neuropathic mechanisms with

Table 1. Clinical criteria and grading for nociplastic pain affecting somatic structures [5,6]

1. Pain
① Chronic (over 3 mo)
② Regional (rather than discrete) distribution[a]
③ No evidence of nociceptive pain[b]
④ No evidence of neuropathic pain[b]
2. Evoked pain hypersensitivity phenomena in the region of pain (any one of the following)
① Static mechanical allodynia
② Dynamic mechanical allodynia
③ Heat or cold allodynia
④ Painful after-sensation reported following the assessment of any of the above alternatives
3. A history of pain hypersensitivity in the region of pain (any one of the following)
① Sensitivity of touch
② Sensitivity to pressure
③ Sensitivity to movement
④ Sensitivity to heat or cold
4. Presence of comorbidities (any one of the following)
① Increased sensitivity to sound, light, or odor
② Sleep disturbance with frequent nocturnal awakenings
③ Fatigue
④ Cognitive problems, such as difficulty to focus attention or memory disturbance
Possible nociplastic pain: 1 and 2[c]
Probable nociplastic pain: all (from 1 to 4)[c]

[a]Musculoskeletal pain is deep and regional, multifocal, or widespread (rather than cutaneous and discrete) in distribution. [b]The presence of a source of nociceptive or neuropathic pain does not exclude the concurrent nociplastic pain. The region of pain must be more widespread than that which can be explained by the identifiable pathology. [c]Definite nociplastic pain is difficult to be applied currently.

 https://doi.org/10.3344/kjp.23326

② evoked hypersensitivity in the region of the pain. In addition, probable nociplastic pain is considered if the presence of ③ pain hypersensitivity to touch, pressure, movement, or heat/cold and ④ comorbidities, such as sleep disturbance, fatigue, or cognitive problems, as well as hypersensitivity to various non-noxious stimuli, exist. However, the category of definitive nociplastic pain, unlike neuropathic pain, has not been established because no confirmatory test has been established.

Supposed pathophysiological mechanisms of nociplastic pain can be divided into supraspinal, spinal, and peripheral mechanisms. Supraspinal mechanisms include hypersensitivity to stimuli, hyperactivity between emotional areas and the secondary somatosensory cortex, hypoactivity between emotional areas in the brain, and increased pain provoking substance/decreased pain reducing substance. Spinal mechanisms include convergence, clustering, reorganization of the spinal cord for the pain source, decreased spinal inhibition, winding up, or summation, and immune system activation. In addition, peripheral mechanisms include increased sodium channels and sympatho-afferent coupling (**Table 2**) [2,7].

2. Differences between nociplastic pain and neuropathic pain

Neuropathic pain is defined by the IASP as pain caused by a lesion or disease of the somatosensory nervous system. Here, the somatosensory nervous system gathers information about the body *per se*, including visceral organs, rather than information about the external world, related to special senses for vision, hearing, or olfaction [1]. Therefore, neuropathic pain includes a lesion or disease arising from the general afferent nervous system, not from the special afferent nervous system. The great difference of neuropathic pain from nociplastic pain is the absence of increased sensitivity to sound, light, or odor. However, other comorbidities, such as insomnia due to pain, followed by fatigue and attention/memory disturbance, can also be found in patients with neuropathic pain.

If pain is the leading complaint, "possible neuropathic pain" is suspected when history of relevant neurological lesions or disease and plausible pain distribution neuroanatomically exist. From the physical examination, "probable neuropathic pain" is considered when pain is associated with sensory signs in the same neuroanatomi-

Table 2. Supposed pathophysiological mechanisms and clinical features of nociplastic pain [2,7]

Development of nociplastic pain	Pathophysiological mechanisms and clinical features
Supraspinal mechanisms	Hyper-responsiveness to pain stimuli
	Increased hyperactivity and connectivity between the medial prefrontal cortex and rostral, anterior cingulate cortex, and thalamus and the secondary somatosensory cortices
	Decreased hyperactivity and connectivity between the medial prefrontal cortex and rostral, anterior cingulate cortex, and the insula
	An increased concentration of substance P and glutamine level in the cerebrospinal fluid and inhibition of gamma aminobutyric acid transmission
	Changes in the size and shape of grey and white matter involved in pain
	Glial cell activation
Spinal mechanisms	Regional clustering and convergence of signals from different pain loci
	Spinal cord reorganization, amplified spinal reflex transmission
	Decreased spinal inhibition, winding up, and temporal summation
	Glial cell activation
	Immune system activation among other glial cells
Peripheral mechanisms	Proliferation of sodium channels
	Sympatho-afferent coupling
	Minor muscle pathology, such as changes in pH along with muscle fiber composition and trigger points
	Peripheral sensitization, such as expansion of receptive field, elevation of cytokine, and chemokine concentrations
	Hyperalgesia, dysesthesia, and allodynia
	Localized or diffused tenderness

Table 3. Grading system of neuropathic pain [8]

1. Possible neuropathic pain from the history (If the leading complain is pain)
① History of relevant neurological lesion or disease
② Pain distribution neuroanatomically plausible
2. Probable neuropathic pain from the physical examination
① Pain is associated with sensory signs in the same neuroanatomically plausible distribution
3. Definite neuropathic pain from the confirmatory test
① Diagnostic test confirming a lesion or disease of somatosensory nervous system explaining the pain

cally plausible distribution. From the confirmatory tests, "definite neuropathic pain" is considered if a confirmatory diagnostic test can be confirmed that a lesion or disease of the somatosensory nervous system can explain the pain (**Table 3**) [8].

Neuropathic pain is defined as pain caused by a lesion or disease of the somatosensory nervous system. Complex regional pain syndrome (CRPS) is commonly defined as a neuropathic pain disorder presenting allodynia, hyperesthesia, sudomotor and vasomotor abnormalities, and motor/trophic changes. It can be divided into type I and II, defined by the absence or presence of nerve trauma, respectively. CRPS type I, with an absence of nerve injury, can thus exist with other musculoskeletal injuries, such as muscle, bone, joint, ligament, and/or tendon injuries. According to the grading system of neuropathic pain, CRPS type I has no relevant neurological lesion or disease, pain distribution, or sensory signs neuroanatomically plausible from the history, physical examination, and confirmatory test [8]. Therefore, a patient with CRPS type I does not have neuropathic pain, even though patients with CRPS type I have similar symptoms and signs to those with CRPS type II.

The spreading patterns of CRPS type I can be divided into 3 types. The contiguous spread type (19%) shows a gradual significant enlargement of the area affected initially. Independent spread type (70%) presents the appearance of CRPS type I in a distant and non-contiguous location with the initial site. Mirror-image spread pattern (11%) exhibits the appearance of symptoms on the opposite side of the area with a similar size to the initial presentation [9]. The spread of CRPS may show a contralateral (53%), ipsilateral (32%), or diagonal pattern. Contralateral and ipsilateral patterns of spread have no relation to secondary trauma, however the diagonal pattern of spread is usually triggered by a separate trauma. These patterns of spread indicate a spinal cord and/or supraspinal mechanism rather than systemic mechanisms [10].

Chronic neuropathic pain can be divided into peripheral and central neuropathic pain. Chronic peripheral neuropathic pain includes trigeminal neuralgia, peripheral nerve injury, painful polyneuropathy, postherpetic neuralgia, and painful radiculopathy. Chronic central neuropathic pain includes spinal cord injury, brain injury, post-stroke pain, and multiple sclerosis [11].

The IASP criteria for CRPS in 1994 can be summarized as an exclusive diagnosis for unexplained, disproportional, continuous pain, allodynia, or hyperalgesia with swelling, blood flow changes in the skin and sudomotor abnormalities related to preceding noxious events or immobilization [12].

CRPS is a regional and peripheral neuropathic pain. The Budapest clinical criteria for diagnosing CRPS includes ① continuing pain that is disproportionate to any inciting event, ② at least one symptom reported in at least three of four categories, ③ at least one sign at the time of evaluation in a least two of the four categories, and ④ no other diagnosis can better explain the symptoms and signs (**Table 4**) [13].

In summary, CRPS is defined as an exclusive diagnosis for disproportionate, continuing, regional pain with one of three or more of the corresponding categories of symptoms and one of the two or more of categories of signs. The criteria of CRPS do not include hypersensitivity to special senses, unlike nociplastic pain; however, insomnia due to pain followed by fatigue with cognitive dysfunction are frequently observed. Therefore, definitive nociplastic pain is also needed to demonstrate morphological or functional changes in the CNS which induces hypersensitivity to special senses.

3. Difference between nociplastic pain and FPS

FPS implies pain with related symptoms, suffering, and disabilities without clear structural or disease etiology. It is commonly combined with physiological, affective, and cognitive influences. Common FPS includes fibromyalgia, irritable bowel syndrome, functional gastrointestinal disorders, interstitial cystitis, and chronic fatigue syndrome/myalgic encephalomyelitis. Similar symptom

 https://doi.org/10.3344/kjp.23326

Table 4. Budapest criteria for diagnosing in complex regional pain syndrome [11]

1. Continuing pain, which is impropriate to any inciting event	
2. At least one symptom in three of the four following categories (report)	3. At least one sign in two or more of following categories (evidence)
Sensory: hyperesthesia and/or allodynia	Sensory: hyperesthesia (to pinprick) and/or allodynia (to light touch, deep somatic pressure, or joint movement)
Vasomotor: temperature asymmetry, skin color changes, or skin color asymmetry	Vasomotor: temperature asymmetry, skin color changes, or skin color asymmetry
Sudomotor: edema, sweating changes, or sweating asymmetry	Sudomotor: edema, sweating changes, or sweating asymmetry
Motor/trophic: decreased range of motion, motor dysfunction (weakness, tremor, or dystonia), or trophic changes (hair, nail, or skin)	Motor/trophic: decreased range of motion, motor dysfunction (weakness, tremor, or dystonia), or trophic changes (hair, nail, or skin)
4. There is no other diagnosis that better explains the signs and symptoms.	

clusters include somatoform disorder, somatization, functional somatic syndrome, bodily distress disorder, central sensitization syndrome, amplified pain syndrome, and primary pain disorder [14].

Unlike the organic pain directly related to noxious stimuli, FPS lacks a well-defined cause and therapeutic target and connects with other common comorbidities, such as anxiety, depression, fatigue, and posttraumatic stress disorder [15].

1) Fibromyalgia

Fibromyalgia is considered a somatic FPS. Previous diagnostic criteria for fibromyalgia from the American College of Rheumatology (ACR) in 2010 included ① a widespread pain index (WPI) ≥ 7 and symptom severity scale score (SSSS) ≥ 5 or WPI 3–6 and SSSS ≥ 9, ② presence of symptoms at a similar level for at least 3 months, and ③ a disorder that could not otherwise explain the pain. ACR has been inserting SSSS while removing tenderness from the 1990 ACR criteria, focused on widespread pain with tenderness at 11 or more of the 18 tender point sites [16–18].

However, common musculoskeletal pain syndromes are developed and overlapped in these 19 regions: ① temporomandibular joint disorder or temporal muscle myofascial pain syndrome in left and right jaw, ② upper trapezius myofascial pain syndrome and tension headache in the neck, ③ referred pain from upper thoracic facet joint disorders in the chest, ④ referred pain from lower thoracic facet joint disorders in the abdomen, ⑤ referred pain from cervical or thoracic facet joint disorders in the upper back, ⑥ lumbar facet joint disorders or herniated nucleus pulposus in the lower back, ⑦ the subacromial and/or subdeltoid bursitis, impingement disorder, rotator cuff disorders, or frozen shoulder in both shoulder girdles, ⑧ medial and lateral epicondylitis in both arms, ⑨ brachioradialis myofascial pain syndrome in both forearms, ⑩ piriformis syndrome, iliopsoas muscle syndrome, and greater trochanteric bursitis in both buttocks, greater and lesser trochanters, and hips, ⑪ quadriceps myofascial pain syndrome, iliotibial band syndrome, and hamstrings myofascial pain syndrome in both thighs, and ⑫ Achilles tendinopathy, pes anserinus tendinopathy, and tennis leg in both legs.

These common musculoskeletal disorders should be treated prior to making a diagnosis of fibromyalgia that is an exclusive symptom cluster. Therefore, patients with both the common nociceptive somatic pain syndrome and generalized symptoms, such as fatigue, insomnia, or cognitive dysfunction may be misdiagnosed as having fibromyalgia with chronic widespread pain.

Currently, modified ACR criteria of fibromyalgia in 2016 were published: ① generalized pain, defined as pain in at least 4 of 5 regions, such as the left and right upper regions, left and right lower regions, and axial regions, ② chronic pain lasting over 3 months, ③ WPI ≥ 7 and SSSS ≥ 5 or WPI 4–6 and SSSS ≥ 9, and ④ an independent diagnosis with the presence of other clinically important illnesses. The WPI reassigned all of the previous 19 regions into the 5 regions (0–19). The SSSS includes fatigue, waking unrefreshed, and cognitive symptoms during the last week, counting from 0 (no symptom) to 1, 2, or 3 (mild, moderate, or severe symptom) (0–9). In addition, other bothersome symptoms, such as headaches, pain or cramps in the lower abdomen, or depression, during previous 6 months are given 0 or 1 point in absence or presence of each symptom (0–3). The fibromyalgia severity scale is the sum of the WPI and SSSS (**Table 5**) [19].

The Analgesic, Anesthetic, and Addiction Clinical Trial Translations Innovations Opportunities and Networks

Table 5. A new diagnostic criteria for fibromyalgia by the American College of Rheumatology (ACR) in 2016 [17]

Three of four conditions	
1. Widespread pain index (WPI) ≥ 7 and symptom severity scale score (SSSS) ≥ 5 or WPI 4–6 and SSSS ≥ 9 in last week	
WPI (0–19)	SSSS (0–12)
Region 1 (Left upper region)	Fatigue (0–3)
Left jaw	Wakening unrefreshed (0–3)
Left shoulder girdle	Cognitive symptoms (0–3)
Left arm	Other symptoms (0–3):
Left forearm	Headache (0–1)
Region 2 (Right upper region)	Abdominal pain (0–1)
Right jaw	Depression (0–1)
Right shoulder girdle	
Right arm	
Right forearm	
Region 3 (Left lower region)	
Left hip (Buttock and trochanter)	
Left thigh	
Left leg	
Region 4 (Right lower region)	
Right hip (Buttock and trochanter)	
Right thigh	
Right leg	
Region 5 (Axial region):	
Upper back	
Lower back	
Chest	
Abdomen	
Diagnosis of fibromyalgia: WPI ≥ 7 and SSSS ≥ 5 or WPI 4–6 and SSSS ≥ 9	
2. Presence of generalized pain, defined as pain at least 4 of 5 regions, excluding the jaw, chest, and abdominal pain	
3. Chronic pain over at least 3 mo	
4. Independent diagnosis even in the presence of other clinically illness	

(ACTTION) public-private partnership with the U.S. Food and Drug Administration (FDA) and the American Pain Society (APS) made the ACTTION-APS Pain Taxonomy (AAPT) to develop a diagnostic system for chronic pain disorders [20]. The AAPT divided the body into 9 regions of defined multi-site pain, similar to the 2010 criteria instead of the chronic widespread pain of 1990 criteria: head, right and left arms, chest, abdomen, upper back and spine, lower back and spine including both buttocks, and right and left legs.

Genetic factors include family history of first-degree relatives being 8.5 times more likely to have fibromyalgia than rheumatoid arthritis. Polymorphisms in catechol-O-methyl transferase genes are believed to be related to the tenderness of fibromyalgia. Functional magnetic resonance imaging (fMRI) in patients with fibromyalgia shows an increased response to stimuli in the insula and anterior cingulate cortex where the processing and perception of unpleasant nociceptive signals are involved. They also show grey matter reduction in morphometric analysis according to stress, pain, or cognitive function, which can explain the flare-up to these stimuli [21].

Therefore, fibromyalgia, a somatic FPS, includes SSSS, such as fatigue, wakening unrefreshed, cognitive symptoms, and other symptoms (headache, abdominal pain, and depression). The WPI is not only based on nociceptive or neuropathic pain, but also on pain in at least 4 of 5 regions, excluding jaw, chest, and abdominal pain. The emotional pain component in chronic somatic pain is revealed in the insula and anterior cingulate cortex from fMRI.

2) Irritable bowel syndrome

Irritable bowel syndrome is considered a visceral FPS. The Rome III diagnostic criteria for irritable bowel syndrome is recurrent abdominal pain or discomfort at least 3 days/month in the last 3 months and 2 or more of the following: ① improvement with defecation, ② onset associated with a change in stool frequency, or ③ onset associated with a change in stool form [21]. It can be divided into diarrhea-predominant and constipation-predominant types, more common in men and women, respectively.

The National Institute for Health and Care Excellence in 2017 provided diagnosis and management guidelines for irritable bowel syndrome [22]. Three major symptoms should be present for at least 6 months: ① abdominal pain or discomfort, ② bloating, and ③ a change in bowel habits. Therefore, abdominal pain or discomfort that is either relieved by defecation or associated with altered bowel frequency or stool form. Other symptoms accompanied by at least 2 of 4 include ① altered stool passage, ② abdominal bloating, distension, tension, or hardness, ③ symptoms made worse by eating, and ④ passage of mucus. Diagnostic tests to exclude other diagnoses include ① complete blood cell count, ② erythrocyte sedimentation rate or plasma viscosity, ③ C-reactive protein, and ④ antibody testing for celiac disease (endomysial antibodies or tissue transglutaminase). In addition, treatment includes laxatives, antimotility agent, or tricyclic antidepressants. Other symptoms, such as lethargy, nausea, backache, and bladder symptoms, may support the diagnosis.

Potential specific targets include serotonin transport and G-protein polymorphism. Altered activation in the insula, dorsal anterior cingulate cortex, and prefrontal cortex is observed in response to intestinal stimulation [21].

Therefore, irritable bowel syndrome includes visceral nociceptive pain improved by defecation and change of stool frequency or form. In addition, other symptoms, such as lethargy, nausea, backache, or bladder symptoms, may be present. As with fibromyalgia, the emotional pain component is also revealed in the insula, dorsal anterior cingulate cortex, and prefrontal cortex in fMRI.

In conclusion, functional pain syndromes, including fibromyalgia and irritable bowel syndrome, show pain and comorbidities without evoked hypersensitivity or pain hypersensitivities to touch, pressure, movement, or heat/cold.

4. Difference between predominant central sensitization pain and nociplastic pain

Central sensitization has at least four characteristics: ① allodynia, ② hyperalgesia, ③ expansion of receptive field, and ④ unusually prolonged pain after removal of a stimulus. Proposed mechanisms for central sensitization include dysregulation in both ascending and descending CNS pain pathways due to physical trauma and sustained pain impulses and chronic release of pro-inflammatory cytokines from the immune system. Non-central sensitization is supposed to be related to hypothalamus-pituitary-adrenal stress axis dysfunction [23].

Central sensitization inventory includes part A (total score 0–100 from 25 items by 5 degrees from 0 to 4 by the patient) and part B (8 specific disorders with 2 non-specific disorders diagnosed by the doctor). Part A includes 5 subcategories: ① physical symptoms, ② emotional distress, ③ headache/jaw symptoms, ④ urological symptoms, and ⑤ other unclassified symptoms. A higher total score shows higher symptoms of central sensitization. Part B includes 8 specific disorders which are related to central sensitization and 2 non-specific disorders, such as anxiety/pain attacks and depression. Patients with fibromyalgia, compared to normal control patients, showed a higher total central sensitization inventory score (average 58.2 > 28.4); however, patients with chronic widespread pain without fibromyalgia and chronic low back pain did not show any difference with normal control patients (**Table 6**) [23].

Central sensitization also shows ① a disproportionate pain experience to the nature and extent of injury or pathology, ② diffuse pain distribution, such as a symmetric pain pattern, pain varying in location unrelated to the presumed source of nociception or non-segmental pain distribution, wide-spread pain, and/or allodynia/hyperalgesia outside the segmental area of primary nociception, and ③ hypersensitivity of senses unrelated to the musculoskeletal system. Additional signs and symptoms may be observed such as numbness, muscle weakness, cognitive deficits, insomnia, inconsistent clinical examination findings, phantom swelling sensation with enhancement or diminishment, altered perception of an affected body part, impaired tactile location, phantom stiffness, and dyskinesthesia [24].

Non-neuropathic central sensitization pain shows 5 different characteristics from neuropathic pain: ① no history of a lesion or disease of the nervous system, ② no established medical cause for pain, ③ neuroanatomically illogical pain, such as segmental pain unrelated to the

Table 6. Central sensitization inventory in 2012 [20]

	Symptom inventory by patients	Never (0), Rarely (1), Sometimes (2), Often (3), or Always (4)	
Physical symptoms			
1	Muscle ache and stiffness		
2	Necessity of help in performing daily activity		
3	Very easily tiredness during active physical activity		
4	Generalized pain on the whole body		
5	Insomnia		
6	Muscle tension in the neck and shoulder		
7	Uncomforting and restlessness of the legs during sleep at night		
Emotional distress			
1	Anxiety attack		
2	Difficult concentration		
3	Aggravation of physical symptoms from stress		
4	Feeling sad or depression		
5	Low energy		
6	Poor memory		
7	Trauma as child		
Headache/jaw symptoms			
1	Grinding and clenching teeth		
2	Sensitivity to bright lights		
3	Headaches		
4	Jaw pain		
5	Feeling dizzy and nauseated from certain smells		
Urological symptoms			
1	Bladder discomfort and/or burning pain on voiding		
2	Voiding frequency		
3	Pelvic pain		
Unclassified symptoms			
1	Unrefreshed wakening		
2	Diarrhea and/or constipation		
3	Skin problems, such as dryness, itching, or rashes		
Total (100)			
Disorders diagnosed by physicians		Yes or No	Year diagnosed
Specific disorders			
1	Restless leg syndrome		
2	Chronic fatigue syndrome		
3	Fibromyalgia		
4	Temporomandibular joint disorder		
5	Migraine or tension headache		
6	Irritable bowel syndrome		
7	Multiple chemical sensitivities		
8	Neck injury, including whiplash injury		
Non-specific disorders			
9	Anxiety or panic attacks		
10	Depression		

primary source of nociception, ④ vague and dull pain, not likely burning, shooting, or pricking pain, and ⑤ illogical sensory dysfunction with numerous hyperalgesias at unrelated segmental sites [24].

Central sensitization of musculoskeletal pain is determined by a disproportionate pain experience with ① diffuse pain distribution (bilateral, widespread, or neuroanatomically illogical pain distribution) and/or allodynia/hyperalgesia or ② a central sensitization inventory score ≥ 40/100 [24].

Central sensitization is commonly found in restless leg syndrome, chronic fatigue syndrome, temporomandibular disorders, tension headache, migraine, fibromyalgia, irritable bowel syndrome, and multiple chemical sensitization. The suggested treatment is centrally-acting medications, selective serotonin and norepinephrine reuptake inhibitors, gabapentinoid anticonvulsants, and N-methyl-D-aspartic acid receptor antagonists [24].

Central sensitization is defined as an amplification of neuronal signaling within the CNS that elicits pain hypersensitivity or an increased responsiveness of nociceptive neurons in the CNS to their normal or subthreshold afferent input. Its clinical features include spreading of pain, pain hypersensitivity, sensitivity to touch, movement, pressure, or heat/cold. It is one of the major underlying mechanisms of nociplastic pain. Nociplastic pain is a pain phenotype associated with many features of central sensitization. Central sensitization is also a key underlying mechanism of neuropathic pain. Cognitive-emotional factors play a major role in any pain experience and contribute to a sensitized CNS in patients with chronic pain. Common similarities of both central sensitization and inflammation in the human body are a kind of homeostatic mechanism which works as an adaptive process in the short term, but as a maladaptive process in the long term. They share multiple biomarkers without a single gold standard for measurement and become a key mechanism for various clinical disorders. Therefore, central sensitization is considered an umbrella term. Regarding central sensitization as an important mechanism in chronic pain syndromes produces a paradigm shift from treating damaged tissue-targeted treatment to a normalization of CNS functioning [25].

Nociplastic pain is asserted to be a third mechanistic pain descriptor or pain phenotype in addition to nociceptive and neuropathic pain. However, central sensitization becomes the major underlying mechanism of not only nociplastic pain but also neuropathic pain.

5. Difference between nociplastic pain and psychogenic pain

It is commonly accepted that emotional components of pain, such as anxiety, depression, and/or pain panic, become evident during the chronification of pain, especially in coexistence of neuropathic pain or extensive actual tissue damage (resulting in nociceptive pain). Diagnostic criteria of psychogenic pain include ① unclear onset and poorly localized pain, ② changes of pain intensity according to the patient's mood, ③ pain relief by antidepressants and sedatives, ④ insomnia, and ⑤ association with neurotic disorders or personality disorders [26].

Psychogenic pain is linked to emotional conflict or psychosocial problems rather than nociceptive or neuropathic pain. Excitation of nociceptors is mediated by retrograde activation resulting from sympathetic efferents or reflex muscle tension [27]. Psychogenic pain exhibits pain and comorbidities, such as insomnia; however, it does not present evoked pain and hypersensitivity to special senses, touch, pressure, movement, or heat/cold [26].

6. Summary of similarity and dissimilarity between nociplastic pain and other painful disorders

From the criteria of nociplastic pain, possible nociplastic pain is suspected from chronic regional pain over 3 months without clear evidence of nociceptive or neuropathic pain and allodynia with painful after-sensation. Probable nociplastic pain should be added to hypersensitivity to touch, pressure, movement, or heat/cold stimuli and comorbidities with hypersensitivity to special senses [5,6].

Neuropathic pain is defined as pain caused by a lesion or disease of the somatosensory nervous system, including visceral organs [1]. Possible, probable, and definite neuropathic pain is considered when there are relevant neurological lesions or diseases, plausible neuroanatomical pain distribution from the history, sensory signs from the physical examination, and confirmatory diagnostic examination [8]. CRPS type I cannot be found relevant to neurologic lesions or diseases. CRPS, especially type II, a neuropathic pain syndrome, is defined as excessive chronic pain (more than expected, compared to actual tissue damage) with sensory, vasomotor, sudomotor edema, and motor/trophic symptoms (3/4 or more) and signs (2/4 or more) when there is no other exclusive diagnosis that explains the above symptoms and signs [13]. Neuropathic pain fulfills all the criteria of probable nociplastic pain, except hypersensitivity to special senses. In

Table 7. Criteria of nociplastic pain and comparison of similarity/dissimilarity with other painful disorders

Nociplastic pain	Possible (① + ②)	① Pain ② Evoked hypersensitivity in the region of pain	
	Probable (All from ① to ④)	③ Pain hypersensitivity to touch, pressure, movement, or heat/cold ④ Presence of comorbidities	
Other painful disorders		Similarities	Dissimilarities
Neuropathic pain : From the history, physical examination, and confirmatory test, pain should originate from a lesion or disease of the somatosensory nervous system, including visceral organs		All from ① to ④	Absence of hypersensitivity to special senses, such as sound, light, or odor Presence of definite confirmatory test for neuropathic pain in the somatosensory system
Functional pain syndrome	Fibromyalgia : WPI ≥ 7 and SSSS ≥ 5 or WPI 4–6 and SSSS ≥ 9 Irritable bowel syndrome : recurrent abdominal pain or discomfort with ① improvement with defecation, ② onset associated with a change in stool frequency, or ③ onset associated with a change in stool form	① and ④	② and ③
Central sensitization pain : allodynia, hyperalgesia, expansion of receptive field, and prolonged pain after removal of a stimulus		All from ① to ④	None
Psychogenic pain : ① unclear onset and poorly localized pain, ② changes of pain intensity according to patients' mood, ③ pain relief by antidepressants and sedatives, ④ insomnia, and ⑤ association with neurotic disorders or personality disorders		① + ④	② + ③

WPI: widespread pain index, SSS: symptom severity scale score.

addition, there is no definite confirmatory diagnostic tool for nociplastic pain.

FPS, including fibromyalgia and irritable bowel syndrome, present pain and comorbidities, without evoked hypersensitivity or pain hypersensitivities to touch, pressure, movement, or heat/cold.

Psychogenic pain presents pain and comorbidities, such as insomnia, however, does not present evoked pain and hypersensitivity to special senses, touch, pressure, movement, or heat/cold [26].

In summary, the clinical criteria of nociplastic pain show similarities or dissimilarities from other existing painful disorders, such as neuropathic pain, FPS, and psychogenic pain; however, central sensitization pain becomes the standard for explaining nociplastic pain. Therefore, nociplastic pain meets the criteria to fulfill the symptom inventory of central sensitization pain [22]. Nociplastic pain seems to be a pain phenotype associated with features of central sensitization [25] (**Table 7**, **Fig. 1**).

CONCLUSIONS

The category of nociplastic pain may be developed for further understanding unexplained chronic pain beyond actual tissue damage. Criteria for possible nociplastic pain include chronic regional pain, originating from not only sensory pain components, such as nociceptive or neuropathic pain, but also evoked pain including allodynia and painful after-sensation. For the confirmation of probable nociplastic pain, pain hypersensitivity to various stimuli and comorbidities with increased special senses should be added to these 2 criteria for possible nociplastic pain.

However, the previous classification of pain, divided into sensory components with nociceptive and/or neuropathic pain and emotional components with anxiety, depression, and/or pain panic, is also sufficient to explain chronification of pain. Chronic pain usually has extensive actual tissue damage and/or neuropathic pain, and emotional components must be noticeable during

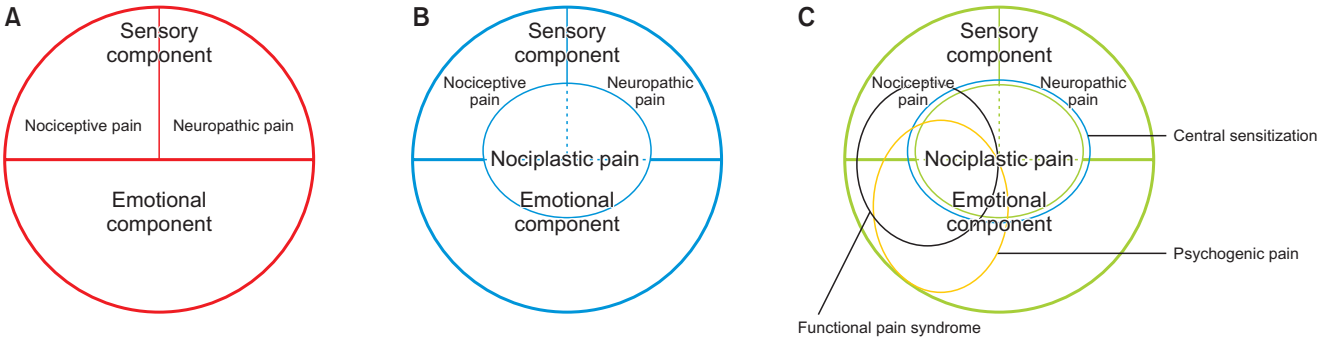

Fig. 1. Current concept of nociplastic pain. (A) Traditional pain consists of sensory (nociceptive and neuropathic pain) and emotional components (anxiety, depression, and pain panic), originating from actual and potential tissue damages, respectively. (B) Nociplastic pain is chronic pain with altered nociception, originating from entirely neither nociceptive nor neuropathic pain, along with emotional components. (C) According to the criteria of nociplastic pain, central sensitization (blue circle) becomes a basic mechanism for explanation of nociplastic pain. Functional pain syndrome (black circle) shows nociceptive pain (rather than neuropathic pain) based on emotional component. Psychogenic pain (orange circle) shows pain, depends on emotional status, and responds to antipsychotics, antidepressants, or anxiolytics.

the chronification of pain. Correctable somatic nociceptive pain should be attended to immediately; neuropathic pain should be addressed using anticonvulsants and antidepressants appropriately; emotional components of pain should also be properly controlled using anxiolytics, antidepressants, and antipsychotics.

Still, it is better to understand nociplastic pain as a term used for better understanding unexplained chronic pain from combined supraspinal, spinal, and peripheral mechanisms, rather than as a third new category of nociceptive and neuropathic pain of sensory components or as a third category of pain in addition to sensory and emotional components.

DATA AVAILABILITY

Data sharing is not applicable to this article as no datasets were generated or analyzed for this paper.

CONFLICT OF INTEREST

Kyung-Hoon Kim is an editorial board member of the Korean Journal of Pain; however, he has not been involved in the peer reviewer selection, evaluation, or decision process of this article. No other potential conflict of interest relevant to this article was reported.

FUNDING

This study was supported by a 2-year research grant from Pusan National University from 2023 to 2024.

AUTHOR CONTRIBUTIONS

Yeong-Min Yoo: Data curation; Kyung-Hoon Kim: Writing/manuscript preparation.

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