Review

I feel! Therefore, I am. From Pain to Consciousness in DOC Patients.

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I Feel! Therefore, I Am. From Pain to Consciousness in DOC Patients

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Abstract: Pain assessment and management in patients with disorders of consciousness (DOC) is a challenging and important aspect of care, with implications for detecting consciousness and promoting recovery. This narrative review explores the role of pain in consciousness, the challenges of pain assessment and pharmacological treatment in DOC, and the implications of pain assessment for detecting changes in consciousness. The review discusses the Nociception Coma Scale and its revised version, which are used behavioral scales to assess pain in DOC patients, and the challenges and controversies surrounding the appropriate pharmacological treatment of pain in these patients. Moreover, we highlight recent evidence suggesting that an accurate pain assessment may predict changes in the level of consciousness in unresponsive wakefulness syndrome/vegetative state patients, underscoring the importance of ongoing pain management in these patients.

Keywords: pain; nociception; disorders of consciousness; consciousness

1. Introduction

Pain, a universal response to harmful stimuli, is a fundamental aspect of the evolutionary process in living organisms [1,2]. Our limited understanding of pain's development restricts our comprehension of its biology, and little is known about the relationships between pain-related states in animals and humans or the evolution of the processes required for these states. Pain is a complex, multidimensional experience essential for survival and adaptation, serving as a vital communication system between the body and the brain [3]. It alerts an organism to potential threats and prompts it to take appropriate action [4]. Investigations of cellular mechanisms and behavioral responses related to nociceptor activation, tissue injury, inflammation, and the environmental context of these responses are starting to reveal the evolution of mechanisms and behavior important for pain [2]. Consequently, pain has emerged as a universal response across diverse living beings, facilitating their ability to thrive and propagate their genetic material across generations [5,6].

2. Nociception is not pain

The term "noxious" originates from the Latin *noxius* ("hurtful, injurious"), *noxa* ("hurt, injury"), and *nocere* ("to hurt, injure"). The significance is applicable to both physical and emotional distress.

Nociception refers to the peripheral neurophysiological pathways within the sensory nervous system that detect and relay harmful stimuli (thermal, mechanical, chemical, or electrical) from the body to the spinal cord[3]. These biological signals mediate between external events and an organism's internal state, prompting reflexive behavior to protect the organism. This response can occur before and potentially without perception, making it an evolutionary trait found across species[2].

On the other hand, pain is a more conscious experience, often resulting from perceiving nociceptive information from external or internal sources[3]. The brain processes this information, making us consciously experience the stimulus as painful and considering its various characteristics.

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This then leads to complex behavioral expressions. Individual differences play a significant role in pain perception and reaction. Moreover, there is a complex relationship between these individual differences, cognitive processes, and the modulation of pain-related brain responses. Seminowics and Davis[7] used functional MRI (fMRI) to examine how a demanding cognitive task (Stroop) affects pain-related brain activity and vice versa. The study found that cognitive strategies can modulate pain-related brain regions, and different coping strategies may be related to behavioral subgroups in chronic pain patients.

Understanding the influence of cognitive strategies on pain-related brain activity not only sheds light on the complex interplay of mental and physical processes but also has implications for chronic pain management.

It was suggested that effective prevention and management approaches to chronic pain should consider the biological, psychological, socio-demographic, and lifestyle factors that influence and result from pain[8].

Phenomena like placebo analgesia or distraction-induced pain relief underscore the strong impact that cognitive functions and learning systems have on our perception of pain[9].

Again, studying the women's fears and attitudes to childbirth showed that it might influence the maternity care they receive and birth outcomes. Hines and colleagues [10] demonstrated that in a clustering classification, the women belonging to the “fearful” cluster had a negative birth experience compared to the women clustered as “self determines”. The comprehension of women's perspectives and their fear levels was helpful in assisting midwives and doctors in customizing their communication with women.

Pain research suggests that how individuals think and behave can influence how they perceive and respond to pain and that different subjects might react very differently to the same stimulus due to diverse sociocultural factors, cognitive beliefs, and expectations.

All these factors raise philosophical and ethical questions about our ability to truly comprehend another person's qualitative pain experience since the variability in pain perception and expression is influenced by numerous factors, including the person's physical state, cognitive thoughts, and cultural upbringing.

3. From nociception to pain

In the context of human or mammalian pain, several molecules and their receptors are implicated in nociception and pain perception. An example are the Acid-sensing ion channels (ASICs), membrane-bound receptors that mediate nociceptive responses to acids, playing a role in acid-induced pain perception in mammals [11,12]. They are expressed in mammalian mechanosensory neurons and are activated by low pH or protons[11].

Transient receptor potential (TRP) channels are another group of molecules involved in pain perception [13]. They are expressed in mammalian nociceptors and underpin thermal (heat) nociception and are responsible for detecting and transducing noxious thermal stimuli into electrical signals, playing a role in temperature-related pain perception in mammals[13].

Nociceptors are sensory neurons that respond to potentially damaging stimuli by sending signals to the spinal cord and brain[14].

Sherrington was the pioneer in defining the term "nociceptor" [15], which is the neural system that detects harmful stimuli. These harmful stimuli can include temperature extremes, mechanical shocks, and chemical threats that can potentially damage tissue.

Nociceptors are specialized nerve endings that primarily respond to harmful stimuli causing tissue damage. A significant number of nociceptors are polymodal, meaning they respond to a mix of these stimulus types. However, studies in rodents [16,17] have sparked a debate about the extent of polymodality, which may depend in part on whether the nociceptors innervate superficial or deep targets[18]. A subset of nociceptors, known as mechanically-insensitive or silent nociceptors, do not respond to any modalities in their natural state but only react to stimuli when inflammation is present. This demonstrates the ability of nociceptors to become more sensitive in disease states[19].

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In mammals, nociceptors are classified into two types: small myelinated A-delta fibers and smaller unmyelinated C fibers[20] (Table 1). These nociceptors are present in both peripheral tissues [20] and deep tissues or viscera [21,22] and have lower conduction velocity than A-fibre. Electrophysiological and anatomical studies have characterized different types of nociceptors in mammals, including C fibers that are sensitive to mechanical stimuli, thermal stimuli, or both [23]. Some C fibers, known as "silent" C fibers, are only activated by heat when sensitized [23]. Cutaneous fibers in mammals are primarily nociceptive, while a smaller proportion serves touch and pressure functions[24,25]. This indicates that the mammalian nociception system can discriminate between different types of noxious stimuli to generate appropriate responses and avoid tissue damage.

Aδ-mechanonociceptors are fast-conducting fibers [26] that are believed to transmit initial pain signals [27]. These fibers have higher mechanical thresholds compared to touch fibers and some of them are also responsive to cold temperatures. Some Aδ-fibers innervate the epithelial layer and are activated by noxious stimuli. A distinct group of Aβ-nociceptors, which are heavily myelinated, are specialized in detecting high-threshold mechanical stimuli. These neurons have faster conduction velocities compared to Aδ-fibers and are not highly responsive to low-intensity brush stimuli[28].

C fibers, on the other hand, are thought to underlie long-lasting pain perception. Aδ stimulation is associated with pricking pain, while C fiber activation is associated with pressing and dull pain[29]. Approximately one-third of C fibers in mammals are polymodal, meaning they respond to mechanical, thermal, and chemical stimuli [30].

Table 1. Nerve Fiber Characteristics and Associated Pain.

Nerve Fiber	*Conduction Speed*	*Diameter*	*Myelination*	*Type of Pain*	*Pain Characteristics*
A-Delta	Fast (5-30 m/s)	Medium (2-5 micrometers)	Myelinated	Acute pain	Sharp, pricking, or stabbing pain is often associated with acute injuries. Felt immediately following an injury and is usually localized to the area of injury. It can be described as "fast pain."
A-Beta	Very fast (33-75 m/s)	Large (5-20 micrometers)	Myelinated	Typically not associated with pain	Generally responsible for transmitting non-painful stimuli such as touch, pressure, and proprioception. However, in nerve injury or disease cases, they may become involved in transmitting pain signals.
C Fibers	Slow (0.5-2 m/s)	Small (0.4-1.2 micrometers)	Unmyelinated	Chronic pain	Dull, throbbing, aching, or burning pain is typically associated with chronic conditions. Felt a short while after an injury and can be widespread. Can be described as "slow pain".

Nociceptors play a crucial role in encoding stimulus modality, intensity, and duration, transmitting this information to the central nervous system and facilitating nocifensive withdrawal responses[3].

Nociceptors extend their central axons from the tissues they innervate to second-order neurons located in either the trigeminal subnucleus caudalis or the dorsal horn of the spinal cord. In the spinal cord, A-fibers establish connections with neurons in laminae I, II, and V, while C-fibers form synapses in laminae I and II before undergoing modulation and/or transmission to the brain[14,26]

In healthy systems, the process of detecting harmful stimuli starts with afferent activation. When the signal is strong enough, it results in a complex pain perception that includes both discriminative and affective components.

4. Pain and Homeostasis

Pain plays a crucial role in maintaining overall health and well-being by promoting homeostasis, which helps the body maintain a stable internal environment in response to changing external conditions [31]. When an organism experiences pain, homeostasis is disrupted, creating an unpleasant state. In response to injury or inflammation, pain signals trigger physiological responses

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such as immune activation, tissue repair, and endorphin release [32]. These responses work together to promote healing, mitigate further damage, and reduce the experience of pain.

Acute pain is a defensive mechanism that signals an immediate and active threat, but this definition does not fully encompass chronic pain, which persists even in the absence of an active threat or cause. Chronic pain is now recognized as a disease by itself [33].

Homeostatic dysregulation is a cornerstone of diverse neural disorders, particularly chronic pain, which is a major health problem worldwide.

5. Pain and role of the insula

The insula seems to have a basic role in homeostatic regulation. Craig described a somatotropic order in pain ascending pathways terminating at the insular cortex in a homunculus-like representation of the body [34]. The insula receives inputs from the sympathetic and parasympathetic systems and from pain pathways, transmitting them to other cortical areas. The afferent information are anatomically structured and proceeds in their integration and stabilization from the posterior to the anterior insula [35]. The integration of these information contribute to the homeostatic response and give insight into the role of the anterior insula in awareness [36].

The insula is also connected to the anterior cingulate cortex (ACC) and the amygdala. The first is an important cortical area connected with the prefrontal cortex and involved in consciousness and behavior. The second brain area is also connected to ACC and is responsible for fear responses [37].

The interaction between the insula, ACC, and amygdala contributes to reaching homeostasis, where the activation of the insula occurs when an event, i.e., an afferent stimulus, causes a perturbation of the normal homeostatic condition [38].

The destabilization caused by the new input may be recognized as pain, which becomes the emotion that contributes to homeostasis.

6. Pain and Pain Matrix

Pain is usually defined as an unpleasant sensory and emotional experience associated with actual or potential tissue damage [39]. At the same time, it involves cognitive and affective dimensions that modulate the perception and expression of pain [40]. On the other hand, consciousness is a multifaceted phenomenon encompassing different levels and aspects of awareness, such as wakefulness, attention, self-awareness, and declarative memory [41].

The interaction between pain and consciousness has been explored to understand how pain becomes a conscious sensation, how consciousness modulates pain perception and behavior, and how pain affects consciousness in different states and disorders.

Pain and consciousness are correlated by the coordinated activation of multiple brain areas, commonly described as a "pain matrix". This is not a fixed arrangement of structures but rather a fluid system composed of several interacting networks that process different aspects of pain.

The Pain Matrix involves two main subsystems: the Lateral Neuronal Network (LNN) and the Medial Network (MN). The LNN encompasses S2 cortex (suprasylvian parietal operculum), lateral thalamus, with the posterior insula [42] encoding the sensory discriminative information; the MN encompasses anterior cingulate cortex (ACC) with the prefrontal cortex encoding affective-cognitive information [37]. Most of the spinothalamic afferent input reaches these areas, which are activated through direct thalamocortical connections [43], ensuring the bodily characteristics of physical pain.

In humans, the pain matrix responds consistently to noxious mechanical or thermal stimuli [44–46], with the LNN deputed to coding intensity and localization of pain inputs, and the MN related to the attentional (orienting and arousing) components of pain [43,44,47,48]

Also, the cerebellum [49] and motor areas (e.g., the striatum, cerebellum, and the supplementary motor area) [50] are involved in pain perception and processing.

The pain experience can be further modulated by internal states, including personal beliefs, emotions, and expectations, involving a "third-order" of regions (i.e., anterolateral and orbitofrontal, ventral tegmental and perigenual/limbic networks) linked to high-level cognition, affect and motivation [51,52].

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Then pain is not only the result of activity in sensory or associative brain areas. The continuous interaction of cited networks allows the encoding and integration in the memory system of pain experience [9,53,54].

7. Pain in DOC

Pain is a subjective experience, and its definition may vary from person to person. The International Association for the Study of Pain (IASP) approved a definition of pain in 1979, encompassing both the sensory and emotional dimensions of the experience and the association between tissue injury and pain [55]. The IASP modified its basic pain terminology in 2007, introducing new terms to describe the various aspects of pain [56]. However, the subjective nature of pain remains a fundamental aspect of the experience, and reporting on it becomes crucial, with the narrative approach being recommended to assess pain in subjects who can communicate (Table 2). Considering the current definition of pain, assessing it in non-communicative patients remains challenging [57].

Table 2. - Pain - terminology.

Term	**Definition of Pain**
Pain	An unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage.
Neuropathic Pain	Pain caused by a lesion or disease of the somatosensory system.
Central Neuropathic Pain	Neuropathic pain resulting from a lesion or disease of the central somatosensory nervous system.
Peripheral Neuropathic Pain	Neuropathic pain resulting from a lesion or disease of the peripheral somatosensory nervous system.
Nociceptive Pain	Pain that arises from actual or threatened damage to non-neural tissue and is due to the activation of nociceptors.
Nociplastic Pain	Pain that arises from altered nociception despite no clear evidence of actual or threatened tissue damage.
	Types of Pain Sensations:
Allodynia	Pain due to a stimulus that does not normally provoke pain.
Hyperalgesia	An increased response to a stimulus which is normally painful.
Hypoalgesia	Decreased sensitivity to painful stimuli.
Anesthesia dolorosa	Pain in an area or region which is anesthetic.
Dysesthesia	An unpleasant abnormal sensation, whether spontaneous or evoked.
Hyperesthesia	Increased sensitivity to stimulation, excluding the special senses.
Hyperpathia	A painful syndrome characterized by an abnormally painful reaction to a stimulus, especially a repetitive stimulus, as well as an increased threshold.
Hypoesthesia	Decreased sensitivity to stimulation, excluding the special senses.
Paresthesia	An abnormal sensation, whether spontaneous or evoked.
	Nerve-Related Terms:
Neuralgia	Pain in the distribution of a nerve or nerves.
Neuritis	Inflammation of a nerve or nerves.
Neuropathy	A disturbance of function or pathological change in a nerve.
Nociception	The neural process of encoding noxious stimuli.
Nociceptive Neuron	A neuron that is capable of detecting noxious stimuli.
Nociceptive Stimulus	A stimulus that is damaging or threatens damage to normal tissues.
Nociceptor	A receptor preferentially sensitive to a noxious stimulus or to a stimulus which would become noxious if prolonged.
Noxious Stimulus	A stimulus that is damaging to normal tissues.
	Pain Threshold and Tolerance:
Pain Threshold	The minimum intensity of a stimulus that is perceived as painful.

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Pain Tolerance Level	The maximum level of pain which a subject is prepared to tolerate.
	Sensitization:
Sensitization	An increased response to stimulation.
Central Sensitization	Increased responsiveness of nociceptive neurons in the central nervous system to their normal or subthreshold afferent input.

Disorders of Consciousness (DOC) encompass a range of pathologies that affect a patient's ability to interact with their surroundings, resulting from both traumatic and non-traumatic causes. Consciousness is generally defined as the brain's capacity to perceive oneself and the environment, which requires adequate arousal (wakefulness) and awareness of content (sensory, cognitive, and affective experiences) [58,59]. These components are referred to as the level and content of consciousness.

Following an acquired brain injury, two possible conditions may arise: Vegetative State/Unresponsive Wakefulness Syndrome (VS/UWS) or Minimally Conscious State (MCS). VS/UWS is characterized by spontaneous eye-opening and an absence of consciousness, with only residual reflexive responses to external stimuli [60]. On the other hand, MCS presents minimal yet discernible non-reflex behaviors in response to various stimuli, although these responses may be inconsistent [60].

Clinical assessments of these conditions rely on consensus and behavioral scales, such as the Coma Recovery Scale–Revised (CRS-R), to determine the severity and extent of the disorder [60,61].

Pain can be present during both the acute phase and the subsequent intensive rehabilitation period in patients with brain injuries [62], resulting from various factors such as skin lesions, surgical wounds, neuropathic pain, and injuries of different types. Additionally, pain may arise from nursing maneuvers and devices used during hospitalization. In the rehabilitation and chronic phases, pain can be caused by peripheral nerve lesions, central pain, spasticity, joint limitations, bedsores, paraosteoarthropathy, constipation, and post-traumatic headaches [63,64]. Central nervous system damage may also lead to chronic pain, such as thalamic pain [65–67].

These conditions can lead to changes in pain processing in the central nervous system and to Complex Regional Pain Syndrome (CPRS), a neuropathic pain disorder characterized by various clinical features [68]. The underlying mechanism of CPRS is multifactorial, involving abnormal neuronal transmission, autonomic dysregulation, and central sensitization. The pro-inflammatory and immunological response further contributes to peripheral sensitization and alteration of the sympathetic nervous system [68].

Painful symptoms may interfere with rehabilitation processes, limiting or delaying their effectiveness [62]. Thus, it is crucial to implement appropriate early interventions to prevent secondary damage and pain-related functional limitations, such as bedsores or muscle-tendon retraction.

8. Pain treatment in DOC

There is no consensus on the appropriate pharmacological treatment of pain in patients with DOC[69]. Medication should typically be given when there are clear behavioral indications of pain. Precise dosing of pharmacotherapy is crucial to prevent interference with the evaluation and therapy strategy for recovering consciousness.

Also, if the strategy's efficiency is still debatable and yet to be proven through large-scale studies, the World Health Organization (WHO) proposes the WHO analgesic ladder, a pain management strategy developed in 1986 to provide adequate pain relief for cancer patients [70]. The ladder consists of three steps, with each step providing increasing levels of pain management options. The first step is for mild pain and involves the use of non-opioid analgesics such as NSAIDs or acetaminophen with or without adjuvants. The second step is for moderate pain and involves the use of weak opioids such as hydrocodone, codeine, or tramadol, with or without non-opioid analgesics and with or without adjuvants. The third step is for severe and persistent pain and involves the use of potent

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opioids such as morphine, methadone, fentanyl, oxycodone, buprenorphine, tapentadol, hydromorphone, or oxymorphone, with or without non-opioid analgesics and with or without adjuvants.

It is essential to consider that inadequate pain control may impair intentional behavioral responses, whereas excessive treatment, using high doses of opioids to decrease pain, could negatively interfere with arousal[71] and may hinder cognitive recovery and attention [69,72]. The optimal drug dosage could preserve the patient's arousal and consciousness, reducing the risk of misdiagnosis [73,74]. Different approaches are suggested in the presence of suspected symptomatic, mild, moderate, or neuropathic pain. In the case of pain with symptoms, the management considers the principles of proportionality and gradualness, considering its interaction with current therapies. In this case, treatment approaches typically involve the use of aspirin, paracetamol, nonsteroidal anti-inflammatory drugs, opioids, and γ-aminobutyric acid (GABA)-ergic agents [69,75]. In case of suspected mild pain, administering aspirin, paracetamol, or nonsteroidal anti-inflammatory drugs is suggested [76]. For moderate or neuropathic pain, it is recommended to use high-dose aspirin or paracetamol, oral NSAIDs, and GABAergic agents[62,69,77,78]. Finally, for suspected severe pain the use of mixed agonists/antagonists, partial agonist opioids, parenteral opioids, antidepressants, anticonvulsants, and atypical agents is usually suggested [62,69,79,80].

Again, since around 89% of DOC patients are characterized by spasticity [81] associated to pain and other symptoms (i.e., increased hypertonia and altered sensorimotor control and muscle spasms) [82], in case of focal spasticity, or to treat severe or worsening cases, infiltration of botulinum [83,84] is suggested. For dystonia and diffuse spasticity, improvements were instead observed by administering intrathecal baclofen [85].

9. Pain and Consciousness in DOC

Pain treatment is a relevant aspect of the management of DOC patients. However, pain's characteristics related to the presence/absence of behavioral response and the modifications observed in biomarkers to noxious stimuli can provide information on the covert content of consciousness.

The Nociception Coma Scale (NCS) has been developed to assess pain in DOC patients [86]. A fingernail pressure to the four limbs gives the nociceptive stimulus, applied generally using an algometer to quantify the necessary pressure to observe the behavioral response to the stimulus. The NCS consists of four subscales assessing motor, verbal and visual responses, and facial expression, allowing for disentangling reflex (e.g., groaning or oral reflex movements) from higher-level behaviors (e.g., pain localization and cry or intelligible verbalization). Since the visual subscale does not show significant changes between a noxious and a non-noxious condition, NCS was recently substituted by its revised version (NCS-R) [87]. The absence of the visual subscale does not alter its sensitivity, maintaining the same clinometric property of the NCS [88], with higher total score in MCS than in VS/UWS patients.

Chatelle and colleagues [87], in a study on 64 patients, observed that the total scores and subscores (motor, verbal and facial) of the NCS were higher for the noxious than the non-noxious stimulation conditions, identified an NCS cut-off value of 4 that distinguished the patients who received a noxious stimulation from those who received a non-noxious stimulation.

A successive neuroimaging study in DOC with fluorodeoxyglucose (FDG)-PET showed positive correlations between brain activity in ACC and NCS-R scores, indicating a correlation with pain processing [89]. Considering the NCS-R, Chatelle and colleagues proposed a cut-off of 2 to differentiate nociception from pain [90]. However, Bonin and colleagues, in a retrospective study on the neural basis for pain experience based on the preservation of brain metabolism as assessed by FDG-PET, suggested a conservative NCS-R cut-off score ≥5 to identify pain in these patients [91].

About the modality to administer the nociceptive stimulus, Formisano et al. [92] proposed the use of NCS(-R) with personalized stimulations (for example, opening the hand, abducting the upper limbs and mobilizing the head), which may cause different reactions compared to simpler pressure applied to the fingernail bed.

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Again, a multicentric study involving 40 healthy volunteers and 60 DOC patients found that VS/UWS and MCS patients had lower pressure pain thresholds than healthy participants, suggesting further research on possible pain hypersensitivity in patients with severe brain injury and multiple co-morbidities [93].

In a recent study involving 70 VS/UWS patients, Cortese and colleagues [94] showed evidence that an accurate assessment of pain could predict changes in consciousness level with an accuracy of 84% when using the NCS and 72% when adopting the NCS-R. The results indicated that a change in behavioral response following a nociceptive stimulation, with a total score for the NCS ≥5 and for the NCS-R ≥3, can predict the positive outcome to the condition of MCS.

However, it is crucial to consider the patient's clinical condition in the pain assessment. DOC patients could have developed severe spasticity or been intubated, making pain assessment more complex [81,95]. In patients with tracheostomy, it is necessary to consider lower cut-off values to distinguish nociception from pain because of lowers verbal sub-scares in these patients [96].

Interestingly, Cortese and colleagues [97] showed the possibility of observing the trace conditioning in VS/UWS patients without any behavioral responses to nociceptive stimuli. The study measured Galvanic Skin Response (GRS) and Heart Rate Variability to assess responses to nociceptive stimuli in 13 healthy subjects and 37 VS/UWS patients. Eight VS/UWS, which all showed a trace conditioning to the noxious stimulus, were diagnosed as MCS within one month.

5. Conclusions

Pain is a complex and subjective experience that involves various brain networks. Assessing pain in patients with disorders of consciousness is particularly challenging, and clinicians must rely on careful observations and behavioral scales to determine the presence and intensity of pain.

As multidimensional experience, pain is distinct from nociception and involves salience and arousal responses throughout the body and in overlapping brain circuits. Analysis of autonomic nervous system activity was suggested as a surrogate measure of salience and arousal to improve the accuracy and specificity of functional neuroimaging analyses and help to overcome current difficulties in assessing pain-specific responses in the brain[98].

Pain has well-established effects on attention. Research has shown that the effects of acute and chronic pain on attention are different, suggesting that different models need to be developed to understand these phenomena[99].

The aversive experience called "pain" results from the coordinated activation of multiple brain areas (pain matrix), which progresses rapidly to the recruitment of anterior insular and fronto-parietal networks, and finally to the activation of perigenual, posterior cingulate, and hippocampal structures. During the initial second following a stimulus, the interaction between sensory and high-level networks intensifies, potentially playing a key role for access to consciousness. [100]. A possible model suggests that various brain networks facilitate pain processing transitions from unconscious sensorimotor and limbic reactions to conscious awareness. This process, which integrates personal memories and self-awareness, occurs only during alert states. However, even unconscious individuals may form implicit memories from repeated pain exposure[100].

Recognizing pain, as opposed to just a nociceptive response, in patients who are unable to communicate it is of great significance. Pain is a distressing experience that can negatively impact a patient's quality of life. Identifying and managing pain can provide significant relief and improve overall patient well-being. Pain responses can provide valuable insights into a patient's condition. In patients with disorders of consciousness, the presence of pain might indicate residual or covert consciousness, influencing prognostic considerations and care plans.

The ethical considerations involved in this context are also substantial[101]. In DOC patients, difficulties in accurately predicting an individual's ability to experience pain and distress pose significant obstacles when trying to offer sufficient pain relief, even when employing verified pain assessment tools[102].

The appropriate pharmacological treatment of pain in these patients is still under debate [69]. Clinicians should consider the potential side effects of medication and its impact on consciousness

and cognitive recovery when determining the appropriate pharmacological treatment of pain in DOC patients.

The NCS and NCS-R are the used behavioral scales to assess pain in DOC patients, providing subscales that allow for disentangling reflexes from higher-level behaviors, allowing the differentiation between nociception and pain [86,87]. Additionally, personalized stimulation protocols that induce different responses may be used to enhance pain assessment accuracy [92]. Recent studies have shown that an accurate pain assessment might predict changes in the level of consciousness in DOC patients with a high degree of accuracy [94]. Furthermore, the presence or absence of behavioral responses to nociceptive stimuli and modifications observed in biomarkers can help differentiate nociception from pain and identify covert content of consciousness in patients diagnosed as VS/UWS [97].

Future research should focus on enhancing neuroimaging techniques and developing advanced pain assessment tools for improved detection and differentiation of pain in patients with disorders of consciousness. There is also a significant need to optimize pharmacological treatments that consider the cognitive recovery of these patients, alongside investigating the long-term effects of repeated pain exposure.

A multidisciplinary approach is advisable to manage pain effectively in DOC patients and to optimize their recovery process. Through an accurate assessment, changes in pain response may predict changes in the level of consciousness, further highlighting the importance of ongoing pain management in these patients.

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