Pain and Disorders of Consciousness Patients

Subjects: Clinical Neurology

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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.

pain nociception disorders of consciousness consciousness

1. Introduction

Pain is a universal response to harmful stimuli, and is a fundamental aspect of the evolutionary process in living organisms [1][2]. 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 behaviors 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. 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 [7]. The IASP modified its basic pain terminology in 2007, introducing new terms to describe the various aspects of pain [8]. 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 (**Figure 1**, **Table 2**). Considering the current definition of pain, assessing it in non-communicative patients remains challenging [9].

- Pain is defined as an unpleasant sensory and emotional experience linked with actual or potential tissue damage.
- Different types of pain include neuropathic pain (caused by a lesion or disease of the somatosensory system), nociceptive pain (arising from actual or threatened damage to non-neural tissue), and nociplastic pain (resulting from altered nociception without evidence of actual or threatened tissue damage). Neuropathic pain can be further divided into central and peripheral, depending on the location of the lesion or disease.
- Various pain sensations include allodynia (pain due to normally non-painful stimuli), hyperalgesia (increased response to a painful stimulus), hypoalgesia (decreased sensitivity to painful stimuli), and dysesthesia (an unpleasant abnormal sensation), among others.
- Some nerve-related terms include neuralgia (pain in the distribution of a nerve), neuritis (inflammation of a nerve), and neuropathy (a functional disturbance or pathological change in a nerve).
- Pain threshold is the minimum intensity of a stimulus perceived as painful, while pain tolerance level is the maximum level of pain a person can tolerate.
- Sensitization refers to an increased response to stimulation. If this occurs in the central nervous system's nociceptive neurons, it is termed central sensitization.

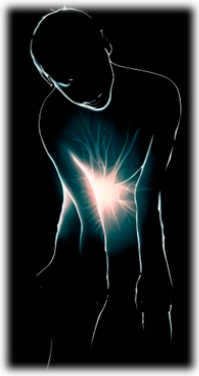

Figure 1. Overview of various terminologies related to pain.

Table 2. Classification and Description of Pain Types and Associated 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.

Term	Definition of Pain
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.
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.

eract 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) [10][11]. 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 [12]. On the other hand,

MCS presents minimal yet discernible non-reflex behaviors in response to various stimuli, although these responses may be inconsistent [12].

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 [12][13].

Pain can be present during both the acute phase and the subsequent intensive rehabilitation period in patients with brain injuries [14]. This may result 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. During 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 [15][16]. Central nervous system damage may also lead to chronic pain, such as thalamic pain [17][18][19].

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 [20]. 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 [20].

Painful symptoms may interfere with rehabilitation processes, limiting or delaying their effectiveness [14]. 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.

3. Pain Treatment in DOC

There is no consensus on the appropriate pharmacological treatment of pain in patients with DOC [21]. 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.

Moreover, 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 [22]. 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 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 [23] and may hinder cognitive recovery and attention [21][24]. The optimal drug dosage could preserve the patient's arousal and consciousness, reducing the risk of misdiagnosis [25][26]. Different approaches are suggested in the presence of suspected symptomatic, mild, moderate, or neuropathic pain. In the case of managing pain with symptoms, the principles of proportionality and gradualness are considered, given their interactions 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 [21][27]. In cases of suspected mild pain, administering aspirin, paracetamol, or nonsteroidal anti-inflammatory drugs is suggested [28]. For moderate or neuropathic pain, it is recommended to use high-dose aspirin or paracetamol, oral NSAIDs, and GABAergic agents [14][21][29][30]. Finally, for suspected severe pain the use of mixed agonists/antagonists, partial agonist opioids, parenteral opioids, antidepressants, anticonvulsants, and atypical agents is usually suggested [14][21][31][32].

Since around 89% of DOC patients are characterized by spasticity [33], which is associated with pain and other symptoms (i.e., increased hypertonia, altered sensorimotor control, and muscle spasms) [34], in cases of focal spasticity, or to treat severe or worsening cases, infiltration of botulinum [35][36] is suggested. For dystonia and diffuse spasticity, improvements were instead observed by administering intrathecal baclofen [37].

4. Pain and Consciousness in DOC

Pain treatment is a relevant aspect of the management of DOC patients. However, pain characteristics related to the presence/absence of behavioral responses, and the modifications observed in biomarkers during noxious stimuli, can provide information on the covert content of consciousness (**Table 2**).

Table 2. Common Signs and Characteristics Evaluated in Pain in DOC Patients.

Signs/Symptoms/Characteristics	Description	Evaluation in MCS Patients	Evaluation in VS/UWS Patients
Motor Response	Assessed in the NCS and NCS-R as part of the behavioral response to pain stimuli.	Higher-level responses, such as flexion or withdrawal.	Lower-level responses, such as abnormal posturing or none/flaccid.
Verbal Response	Evaluated in the NCS and NCS-R; factors such as crying, groaning, or intelligible verbalization are considered.	Higher-level responses, such as vocalization or intelligible verbalization.	Lower-level responses, such as groaning or no response. Necessary to consider lower responses due to tracheostomy conditions.

Signs/Symptoms/Characteristics	Description	Evaluation in MCS Patients	Evaluation in VS/UWS Patients
Facial Expression	Assessed as part of NCS and NCS-R, includes evaluation of reactions like grimacing.	More expressive, such as a cry or grimace.	Startled/oral reflexive movements or no response.
Visual Expression	Assessed as part of NCS, includes evaluation of reactions like fixation.	Higher-level responses, such as fixation and eye movements.	Startled or no response.
Pain Localization	Higher-level behavior indicative of pain as assessed by the NCS and NCS-R.	Observable.	Not observable.
Personalized Stimulation Reaction	Involves reactions to personalized stimuli, such as opening the hand, abducting the upper limbs, and mobilizing the head.	More demonstrated.	Less demonstrated.
Cardiac Frequency (Heart Rate Variability)	HRV can be used to assess autonomic responses to pain, such as increased sympathetic activity and reduced vagal modulation.	More stable HRV.	Increased sympathetic activity and reduced vagal modulation.
Galvanic Skin Response (GSR)	GSR measurements can indicate physiological responses to pain stimuli.	Trace conditioning was observed in healthy controls. No studies are present for MCS patients.	Can show trace conditioning to noxious stimuli.
Tracheostomy Condition	Pain assessment should consider lower cut-off values for tracheostomized patients due to lower verbal subscale scores.	Not applicable.	Lower cut-off values for nociception.
Spasticity	Severe spasticity can affect pain assessment in DOC patients.	Possible.	Possible. [38]

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necessary pressure to observe the behavioral response to the stimulus. The NCS consists of four subscales assessing motor, verbal, visual responses, and facial expression, allowing distinctions between reflexes (e.g., groaning or oral reflex movements) and higher-level behaviors (e.g., pain localization and crying 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) [39]. The absence of the visual subscale does not alter its sensitivity, maintaining the same clinometric property of the NCS [40], with higher total scores in MCS than in VS/UWS patients.

In a study on 64 patients, Chatelle and colleagues [39] observed that the total scores and subscores (motor, verbal, and facial) of the NCS were higher in noxious than non-noxious stimulation conditions. They identified an NCS cut-off value of four 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 from the ACC and NCS-R scores, indicating a correlation with pain processing [41]. Considering the NCS-R, Chatelle and colleagues proposed a cut-off value of two to differentiate nociception from pain [42]. However, in a retrospective study on the neural basis for pain experience based on the preservation of brain metabolism as assessed by FDG-PET, Bonin and colleagues, suggested a conservative NCS-R cut-off score of less than five to identify pain in these patients [43].

Concerning the modality with which to administer the nociceptive stimulus, Formisano et al. [44] 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 with simpler pressure applied to the fingernail bed.

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 injuries and multiple co-morbidities is needed [45].

In a recent study involving 70 VS/UWS patients, Cortese and colleagues [46] provided evidence to show 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 of ≥5 and ≥3 for the NCS-R, can predict positive outcomes with regard 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 they may have been intubated, making pain assessment more complex [33][47]. In patients with tracheostomy, it is necessary to consider lower cut-off values to distinguish nociception from pain because of lower verbal sub-scares in these patients [48].

Interestingly, Cortese and colleagues [49] showed the possibility of observing trace conditioning in VS/UWS patients without any behavioral responses to nociceptive stimuli. The study measured the Galvanic Skin Response (GRS) and Heart Rate Variability (HRV) to assess responses to nociceptive stimuli in 13 healthy subjects and 37 VS/UWS

patients. Eight VS/UWS, which all showed trace conditioning to the noxious stimulus, were diagnosed as MCS within one month.

In the context of autonomic responses to pain, Heart Rate Variability (HRV) emerges as a valuable marker for assessing nociceptive responses in cases of experimentally induced pain. Enhanced parasympathetic activity has been associated with better self-regulation capacities and increased pain inhibition capacity [50]. In a study conducted by Tobalbini and colleagues, involving 24 patients diagnosed with disorders of consciousness (DOC), it was observed that nociceptive stimuli could lead to changes in autonomic function. This change was characterized by increased sympathetic activity and reduced vagal modulation [51]. In two separate studies—one involving 21 DOC patients, including 11 with UWS/VS [52], and the other involving 24 DOC patients, including 12 with UWS/VS [51]—a reduction in cardiac complexity (i.e., HRV entropy) was noted in UWS/VS patients during exposure to noxious stimuli. Additionally, in an EEG-based study involving 21 DOC patients, pain stimulation was linked with a higher parietal response in the delta frequency band, lower activation in the left frontal region, and increased Galvanic Skin Response (GSR) and Heart Rate [53].

References

1. McGrath, P.A. Psychological Aspects of Pain Perception. Arch. Oral Biol. 1994, 39, 55S–62S.
2. Walters, E.T.; Williams, A.C.D.C. Evolution of Mechanisms and Behaviour Important for Pain. Philos. Trans. R. Soc. B Biol. Sci. 2019, 374, 20190275.
3. Sneddon, L.U. Comparative Physiology of Nociception and Pain. Physiology 2018, 33, 63–73.
4. Damasio, A.; Carvalho, G.B. The Nature of Feelings: Evolutionary and Neurobiological Origins. Nat. Rev. Neurosci. 2013, 14, 143–152.
5. Nesse, R.M.; Schulkin, J. An Evolutionary Medicine Perspective on Pain and Its Disorders. Philos. Trans. R. Soc. Lond. B Biol. Sci. 2019, 374, 20190288.
6. Hunt, T. The Middle Way of Evolution. Commun. Integr. Biol. 2012, 5, 408–421.
7. Ilana, E. Pain Terms: A List with Definitions and Notes on Usage. Recommended by the IASP Subcommittee on Taxonomy. Pain 1979, 6, 249.
8. Loeser, J.D.; Treede, R.D. The Kyoto Protocol of IASP Basic Pain Terminology. Pain 2008, 137, 473–477.
9. Riganello, F.; Soddu, A.; Tonin, P. Addressing Pain for a Proper Rehabilitation Process in Patients With Severe Disorders of Consciousness. Front. Pharmacol. 2021, 12, 9.
10. Giacino, J.T.; Schnakers, C.; Rodriguez-Moreno, D.; Kalmar, K.; Schiff, N.; Hirsch, J. Behavioral Assessment in Patients with Disorders of Consciousness: Gold Standard or Fool's Gold? Prog. Brain Res. 2009, 177, 33–48.

11. Laureys, S.; Celesia, G.G.; Cohadon, F.; Lavrijsen, J.; León-Carrión, J.; Sannita, W.G.; Sazbon, L.; Schmutzhard, E.; Wild, K.R.V.; Zeman, A.; et al. Unresponsive Wakefulness Syndrome: A New Name for the Vegetative State or Apallic Syndrome. BMC Med. 2010, 8, 68.
12. Giacino, J.T.; Katz, D.I.; Schiff, N.D.; Whyte, J.; Ashman, E.J.; Ashwal, S.; Barbano, R.; Hammond, F.M.; Laureys, S.; Ling, G.S.F.; et al. Practice Guideline Update Recommendations Summary: Disorders of Consciousness: Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology; the American Congress of Rehabilitation Medicine; and the National Institute on Disability, Independent Living, and Rehabilitation Research. Arch. Phys. Med. Rehabil. 2018, 99, 1699–1709.
13. Giacino, J.T.; Kalmar, K.; Whyte, J. The JFK Coma Recovery Scale-Revised: Measurement Characteristics and Diagnostic Utility1. Arch. Phys. Med. Rehabil. 2004, 85, 2020–2029.
14. Schnakers, C.; Zasler, N. Assessment and Management of Pain in Patients With Disorders of Consciousness. PM&R 2015, 7, S270–S277.
15. Bexkens, R.; Washburn, F.J.; Eygendaal, D.; van den Bekerom, M.P.J.; Oh, L.S. Effectiveness of Reduction Maneuvers in the Treatment of Nursemaid's Elbow: A Systematic Review and Meta-Analysis. Am. J. Emerg. Med. 2017, 35, 159–163.
16. Ivanhoe, C.B.; Hartman, E.T. Clinical Caveats on Medical Assessment and Treatment of Pain after TBI. J. Head Trauma Rehabil. 2004, 19, 29–39.
17. Irvine, K.A.; Clark, J.D. Chronic Pain After Traumatic Brain Injury: Pathophysiology and Pain Mechanisms. Pain Med. 2018, 19, 1315–1333.
18. Munivenkatappa, A.; Agrawal, A. Role of Thalamus in Recovery of Traumatic Brain Injury. J. Neurosci. Rural Pract 2016, 7, S76–S79.
19. Sherman, K.B.; Goldberg, M.; Bell, K.R. Traumatic Brain Injury and Pain. Phys. Med. Rehabil. Clin. N. Am. 2006, 17, 473–490.
20. Guthmiller, K.B.; Varacallo, M. Complex Regional Pain Syndrome. In StatPearls; StatPearls Publishing: Treasure Island, FL, USA, 2020.
21. Bartolo, M.; Chiò, A.; Ferrari, S.; Tassorelli, C.; Tamburin, S.; Avenali, M.; Azicnuda, E.; Calvo, A.; Caraceni, A.T.; Defazio, G.; et al. Assessing and Treating Pain in Movement Disorders, Amyotrophic Lateral Sclerosis, Severe Acquired Brain Injury, Disorders of Consciousness, Dementia, Oncology and Neuroinfectivology. Eur. J. Phys. Rehabil. Med. 2016, 52, 14.
22. Anekar, A.A.; Cascella, M. WHO Analgesic Ladder. In StatPearls; StatPearls Publishing: Treasure Island, FL, USA, 2023.
23. Brown, E.N.; Pavone, K.J.; Naranjo, M. Multimodal General Anesthesia: Theory and Practice. Anesth. Analg. 2018, 127, 1246–1258.

24. Fins, J.J.; Illes, J.; Bernat, J.L.; Hirsch, J.; Laureys, S.; Murphy, E. Neuroimaging and Disorders of Consciousness: Envisioning an Ethical Research Agenda. Am. J. Bioeth. 2008, 8, 3–12.
25. Lanzillo, B.; Loreto, V.; Calabrese, C.; Estraneo, A.; Moretta, P.; Trojano, L. Does Pain Relief Influence Recovery of Consciousness? A Case Report of a Patient Treated with Ziconotide. Eur. J. Phys. Rehabil. Med. 2016, 52, 4.
26. Whyte, J.; Poulsen, I.; Ni, P.; Eskildsen, M.; Guldager, R. Development of a Measure of Nociception for Patients With Severe Brain Injury. Clin. J. Pain 2020, 36, 281–288.
27. Mura, E.; Pistoia, F.; Sara, M.; Sacco, S.; Carolei, A.; Govoni, S. Pharmacological Modulation of the State of Awareness in Patients with Disorders of Consciousness: An Overview. CPD 2013, 999, 5–6.
28. Schnakers, C.; Zasler, N.D. Pain Assessment and Management in Disorders of Consciousness. Curr. Opin. Neurol. 2007, 20, 620–626.
29. Czuczwar, S.J.; Patsalos, P.N. The New Generation of GABA Enhancers: Potential in the Treatment of Epilepsy. CNS Drugs 2001, 15, 339–350.
30. Enna, S.J.; McCarson, K.E. The Role of GABA in the Mediation and Perception of Pain. In Advances in Pharmacology; Elsevier: Amsterdam, The Netherlands, 2006; Volume 54, pp. 1–27. ISBN 978-0-12-032957-1.
31. Adams, R.S.; Corrigan, J.D.; Dams-O'Connor, K. Opioid Use among Individuals with Traumatic Brain Injury: A Perfect Storm? J. Neurotrauma 2020, 37, 211–216.
32. Seal, K.H.; Bertenthal, D.; Barnes, D.E.; Byers, A.L.; Gibson, C.J.; Rife, T.L.; Yaffe, K. Traumatic Brain Injury and Receipt of Prescription Opioid Therapy for Chronic Pain in Iraq and Afghanistan Veterans: Do Clinical Practice Guidelines Matter? J. Pain 2018, 19, 931–941.
33. Thibaut, F.A.; Chatelle, C.; Wannez, S.; Deltombe, T.; Stender, J.; Schnakers, C.; Laureys, S.; Gosseries, O. Spasticity in Disorders of Consciousness: A Behavioral Study. Eur. J. Phys. Rehabil. Med. 2015, 51, 389–397.
34. Burke, D.; Wissel, J.; Donnan, G.A. Pathophysiology of Spasticity in Stroke. Neurology 2013, 80, S20–S26.
35. Childers, M.K.; Brashear, A.; Jozefczyk, P.; Reding, M.; Alexander, D.; Good, D.; Walcott, J.M.; Jenkins, S.W.; Turkel, C.; Molloy, P.T. Dose-Dependent Response to Intramuscular Botulinum Toxin Type A for Upper-Limb Spasticity in Patients after a Stroke. Arch. Phys. Med. Rehabil. 2004, 85, 1063–1069.
36. Verplancke, D.; Snape, S.; Salisbury, C.F.; Jones, P.W.; Ward, A.B. A Randomized Controlled Trial of Botulinum Toxin on Lower Limb Spasticity Following Acute Acquired Severe Brain Injury. Clin. Rehabil. 2005, 19, 117–125.

37. Pistoia, F.; Sacco, S.; Sarà, M.; Franceschini, M.; Carolei, A. Intrathecal Baclofen: Effects on Spasticity, Pain, and Consciousness in Disorders of Consciousness and Locked-in Syndrome. Curr. Pain Headache Rep. 2015, 19, 466.
38. Schnakers, C.; Chatelle, C.; Vanhaudenhuyse, A.; Majerus, S.; Ledoux, D.; Boly, M.; Bruno, M.-A.; Boveroux, P.; Demertzi, A.; Moonen, G.; et al. The Nociception Coma Scale: A New Tool to Assess Nociception in Disorders of Consciousness. Pain 2010, 148, 215–219.
39. Chatelle, C.; Majerus, S.; Whyte, J.; Laureys, S.; Schnakers, C. A Sensitive Scale to Assess Nociceptive Pain in Patients with Disorders of Consciousness. J. Neurol. Neurosurg. Psychiatr. 2012, 83, 1233–1237.
40. Vink, P.; Lucas, C.; Maaskant, J.M.; van Erp, W.S.; Lindeboom, R.; Vermeulen, H. Clinimetric Properties of the Nociception Coma Scale (-Revised): A Systematic Review. Eur. J. Pain 2017, 21, 1463–1474.
41. Chatelle, C.; Thibaut, A.; Bruno, M.-A.; Boly, M.; Bernard, C.; Hustinx, R.; Schnakers, C.; Laureys, S. Nociception Coma Scale–Revised Scores Correlate With Metabolism in the Anterior Cingulate Cortex. Neurorehabil. Neural Repair. 2014, 28, 149–152.
42. Chatelle, C.; Hauger, S.L.; Martial, C.; Becker, F.; Eifert, B.; Boering, D.; Giacino, J.T.; Laureys, S.; Løvstad, M.; Maurer-Karattup, P. Assessment of Nociception and Pain in Participants in an Unresponsive or Minimally Conscious State After Acquired Brain Injury: The Relation Between the Coma Recovery Scale–Revised and the Nociception Coma Scale–Revised. Arch. Phys. Med. Rehabil. 2018, 99, 1755–1762.
43. Bonin, E.A.C.; Lejeune, N.; Thibaut, A.; Cassol, H.; Antonopoulos, G.; Wannez, S.; Martial, C.; Schnakers, C.; Laureys, S.; Chatelle, C. Nociception Coma Scale-Revised Allows to Identify Patients With Preserved Neural Basis for Pain Experience. J. Pain 2020, 21, 742–750.
44. Formisano, R.; Contrada, M.; Aloisi, M.; Ferri, G.; Schiattone, S.; Iosa, M.; Buzzi, M.G. Nociception Coma Scale with Personalized Painful Stimulation versus Standard Stimulus in Non-Communicative Patients with Disorders of Consciousness. Neuropsychol. Rehabil. 2020, 30, 1893–1904.
45. Sattin, D.; Schnakers, C.; Pagani, M.; Arenare, F.; Devalle, G.; Giunco, F.; Guizzetti, G.; Lanfranchi, M.; Giovannetti, A.M.; Covelli, V.; et al. Evidence of Altered Pressure Pain Thresholds in Persons with Disorders of Consciousness as Measured by the Nociception Coma Scale–Italian Version. Neuropsychol. Rehabil. 2018, 28, 1295–1310.
46. Cortese, M.D.; Arcuri, F.; Nemirovsky, I.E.; Lucca, L.F.; Tonin, P.; Soddu, A.; Riganello, F. Nociceptive Response Is a Possible Marker of Evolution in the Level of Consciousness in Unresponsive Wakefulness Syndrome Patients. Front. Neurosci. 2021, 15, 771505.

47. Garuti, G.; Reverberi, C.; Briganti, A.; Massobrio, M.; Lombardi, F.; Lusuardi, M. Swallowing Disorders in Tracheostomised Patients: A Multidisciplinary/Multiprofessional Approach in Decannulation Protocols. Multidiscip. Respir. Med. 2014, 9, 36.
48. Lejeune, N.; Thibaut, A.; Martens, G.; Martial, C.; Wannez, S.; Laureys, S.; Chatelle, C. Can the Nociception Coma Scale-Revised Be Used in Patients With a Tracheostomy? Arch. Phys. Med. Rehabil. 2020, 101, 1064–1067.
49. Cortese, D.; Riganello, F.; Arcuri, F.; Lucca, L.; Tonin, P.; Schnakers, C.; Laureys, S. The Trace Conditional Learning of the Noxious Stimulus in UWS Patients and Its Prognostic Value in a GSR and HRV Entropy Study. Front. Hum. Neurosci. 2020, 14, 97.
50. Forte, G.; Troisi, G.; Pazzaglia, M.; Pascalis, V.D.; Casagrande, M. Heart Rate Variability and Pain: A Systematic Review. Brain Sci. 2022, 12, 153.
51. Tobaldini, E.; Toschi-Dias, E.; Trimarchi, P.D.; Brena, N.; Comanducci, A.; Casarotto, S.; Montano, N.; Devalle, G. Cardiac Autonomic Responses to Nociceptive Stimuli in Patients with Chronic Disorders of Consciousness. Clin. Neurophysiol. 2018, 129, 1083–1089.
52. Riganello, F.; Chatelle, C.; Schnakers, C.; Laureys, S. Heart Rate Variability as an Indicator of Nociceptive Pain in Disorders of Consciousness? J. Pain Symptom Manag. 2018, 57, 47–56.
53. Venturella, I.; Crivelli, D.; Fossati, M.; Fiorillo, F.; Balconi, M. EEG and Autonomic Responses to Nociceptive Stimulation in Disorders of Consciousness. J. Clin. Neurosci. 2019, 60, 101–106.