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PSYCHIATRIC MANAGEMENT OF PAIN (M CLARK, SECTION EDITOR)

The Perception of Pain and its Management in Disorders of Consciousness

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Abstract One of the most controversial issues in the management of patients in a vegetative state or a minimally conscious state concerns their hypothetical capacity to continue to experience pain despite an apparent absence of self- and environmental awareness. Recent functional neuroimaging studies have shown a greater perception of pain in patients in minimally conscious state compared with patients in vegetative state, suggesting the possible involvement of preserved cognitive mechanisms in the process of pain modulation in the former. In addition, a subgroup of patients might continue to experience some elementary emotional and affective feelings, as suggested by the reported activation of specific cerebral areas in response to situations, which commonly generate empathy. However, the available evidence is not sufficient to draw conclusions about the presence or absence of pain experience in patients with disorders of consciousness. Future studies should contribute to a better understanding of which central neural pathways are involved in the perception and modulation of pain in healthy subjects and in patients with severe brain injuries. Such studies should thus also improve our know-how about pain management in this particularly challenging group of patients.

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Introduction

Pain is a frequent component of physical disorders, including neurologic diseases. It can be present in an acute form or can become chronic, persisting despite the resolving of the pathologic condition, which originally generated it. The development of chronic pain is a maladaptive response of the organism, which through changes in structure and neurotransmission within the central or peripheral nervous system, brings about a 'centralization' of the pain, rendering it autonomous from the conditions, which set it off and making it a brain disease in itself [1]. Chronic pain is therefore a complex condition deriving from a deviant interaction of cognitive, emotional, and modulatory processes with patterns of sensory system activation [1]. In particular, emotional factors previously interpreted as mere reactions to pain are, in reality, to be considered an integral part of its modulation. Indeed the International Association for the Study of Pain states that pain is always to be considered a psychological state and that, as one of the many expressions of individual subjectivity, it is not measurable through mere objective signs [2, 3]. Moreover, psychological distress can exacerbate the perception of pain, cause it to become chronic, and complicate its management. This results in a vicious circle, in which pain causes psychological distress, which in turn contributes to the continuation of the pain itself. Pain, therefore, has 2 facets: it can be an alarm bell, warning of an underlying pathologic condition, or it can become a disorder in itself, persisting even when the original triggering pathology has been eradicated. Several studies recently investigated some aspects of the perception

of pain in patients with disorders of consciousness (DOCs) [4, 5, 6••]. Their findings are controversial and do not allow definitive conclusions to be drawn about the nature of the experience of pain in these patients. Nevertheless, the brain injuries underlying DOCs are so widespread and severe and lead to such serious impairment that it is legitimate to expect that such patients will have multiple sources of physical pain. Moreover, the clinical course of the above injuries is so long that one cannot exclude that forms of chronic and centralized pain, favored by maladaptive Central Nervous System (CNS) responses, may also develop and persist even when tissue damage has healed. Therefore, in patients with a DOC, pain-related symptoms and signs could indicate a syndrome within the syndrome, independently requiring proper identification and management.

The Pain Matrix

Nociception is not a synonym of pain. Nociception includes all the processes responsible for the reception of a peripheral painful stimulus and its centripetal transmission towards the subcortical and cortical structures through the ascending sensory system. Pain, on the other hand, is a multidimensional conscious experience, which is linked with the activity and interconnectivity of specific cortical and subcortical brain structures [7••]. From this perspective, pain can be considered as a complex behavior emerging from the flow and integration of information among a large number of neuronal assemblies [8]. The notion that nociception and pain are two separate experiences is also supported by the fact that there can be pain in the absence of nociception, for example in the phenomenon known as thalamic pain, or nociception in the absence of pain, for example in the case of autonomic responses evoked by nociception and not associated with a conscious experience of pain. Brain regions, which are implicated in the mediation of the pain experience, belong to what is known as the pain matrix. This extensive network, which has been widely investigated by means of functional neuroimaging, includes structures such as the primary (S1) and secondary (S2) somatosensory cortices, the insula, and the anterior cingulate cortex (ACC) [7••]. However, it is not clear whether or not the pain matrix should be considered a specific pain-processing network. Indeed, whether the activation of particular areas within the pain matrix represents a pain-specific neural signature or an epiphenomenon is a controversial question. Equally controversial is the evidence for the involvement of these structures in recognizing emotions that are being experienced by others, which is to say in generating conditions of empathy. Further doubts surround the notion that the pain neuromatrix can be divided into specialized substructures such as S1 and S2, belonging to the so-called lateral pain system or *somatosensory node* and responsible for the transmission of signals of physical pain, and the medial brain structures including the ACC, constituting the medial pain system or *affective node*, which is implicated in the affective dimension of pain [7••]. The evidence for [9–21] and against [22–28] the concept of the pain matrix as a specific pain-processing network is summarized in Table 1.

Pain Perception and Assessment in Patients with Disorders of Consciousness

Disorders of consciousness (DOCs) include coma, vegetative state (VS), and minimally conscious state (MCS). Patients in a coma lack both wakefulness and awareness: they have closed eyes and a variable response to verbal or nociceptive stimuli depending on how deep the state of coma is [29]. Patients in VS lack awareness despite preserved, or recovered, wakefulness: they show cycles of eye closure and eye opening as in sleep and waking, but they cannot interact with their surroundings due to a complete loss of self- and environmental awareness [30]. Patients in MCS show fluctuating, erratic and non-reproducible purposeful behaviors, which indicate that they

Table 1 Main evidence for and against the concept of the pain matrix as a specific pain-processing network, as suggested by Iannetti and Mouraux [7••]

	Studies
Pros	
Reported activation of the pain matrix structures following painful stimulations	Garcia-Larrea 2003 Bushnell 2005
Strong correlation between the magnitude of pain matrix activation and the intensity of subjective pain perception	Derbyshire 1997 Coghill 1999 Tölle 1999 Iannetti 2005 Rainville 2002 Porro 2003
Modulation of the magnitude of pain matrix response by factors, which also modulate pain intensity	Rainville 1997 Hofbauer 2001
Description of painful sensations evoked by epileptic seizures involving pain matrix structures (ie, insula)	Isnard 2000 Charlesworth 2009
Description of painful sensations evoked by direct electrical stimulation of various areas of the pain matrix through implanted electrodes	Ostrowsky 2002
Cons	
Unsuccessful recognition of spatially segregated areas preferentially involved in the processing of nociceptive stimuli	Kenshalo 2000
Scattered distribution in space of supposed nociceptive-specific neurons and response of these neurons also to stimuli belonging to other sensory modalities	Dong 1994 Kenshalo 1995 Hutchison 1999 Wall 1995
Activation of the pain matrix also by non-nociceptive inputs	Kunde 1993 Lui 2008

have partially recovered their state of consciousness or at least that a minimum degree of recovery is imminent [31]. Moreover, some patients in MCS show specific behaviors, including the recovered awareness of how common objects should be handled (glass, spoon, comb) and the appearance of communication efforts, which may herald a forthcoming recovery of consciousness [31].

Despite the above definitions, in daily clinical practice it is extremely difficult to discern different states of consciousness and their transitions. To a nonexpert outside observer these patients can appear to be extremely similar and all equally behaviorally unresponsive. This perceived similarity is due to the fluctuating nature of behaviors, which are interpreted as meaningful. The rate of misdiagnosis is therefore extremely high, especially when isolated clinical impressions take the place of repeated and rigorous neurologic examinations [32].

From all this it is evident just how difficult it is to gauge and characterize the experience of pain in patients with a DOC. However, the lack of expression of pain and difficulty in observing or measuring it must not be used to testify in favor of the hypothesis that patients with a DOC are incapable of feeling pain. In fact, although there are no definitive data concerning this, one is inclined to think that these patients can experience at least the physical dimension of pain: that they can feel, for example, the discomfort induced by spasticity or by the interruption of nutrition or hydration and the bodily disturbance caused by recurring infections. On the other hand, it is improbable that they can feel distress in response to bad news or sorrow regarding their own situation and that of their families. Such distress, in fact, is closely entwined with the integrity of the cognitive functions of the individual. In other words, if the patient is not aware of himself and of the surrounding environment, if he is not able to locate himself in a time and place, if he does not have a historical memory of his past and the capacity to imagine his future, it is extremely unlikely that he can experience distress or sorrow in relation to a given situation. In support of this there is the aforementioned proposed separation between the lateral pain system or *somatosensory node* and the medial pain system or *affective node* [7••]. In healthy subjects, these two systems are intertwined, as is suggested by the fact that physical pain often leads to emotional distress and vice versa, to the point that it is difficult to discern one from the other. It may be that this communication between pathways has been interrupted in patients in VS but is partially recovered in patients in MCS, who seem to show a more complete perception of pain [4, 5, 6••].

Behavioral Scales for the Assessment of Pain in Patients with DOCs

In daily clinical practice, different scales can be used to evaluate response to pain in patients with a DOC [33, 34, 35, 36••, 37]. These include both non pain-specific and pain-specific scales. The former, such as the Glasgow Coma Scale (GCS), the Coma Recovery Scale—Revised (CRS-R), and the Full Outline of UnResponsiveness (FOUR) score, are designed for a multidimensional evaluation of the state of consciousness of the patient and only marginally identify the patient's response to painful stimuli [33, 34, 35]. In fact, following noxious stimulation, the presence or absence of nociception is inferred through motor responses such as stereotypical responses, flexion/withdrawal, and localization responses [36••]. The Glasgow Coma Scale (GCS) is composed of 3 tests exploring eye, verbal, and motor responses, respectively (Table 2). The eye response test evaluates whether the patient opens his eyes following the administering of a verbal or a painful stimulus. The motor response test can be used to ascertain whether the patient responds to painful stimuli either through purposeful movements towards the source of pain (localization to pain), attempts to withdraw from pain (flexion/withdrawal from pain), or abnormal flexor or extensor posturing [33]. The Coma Recovery Scale Revised (CRS-R) is the most sensitive and reliable tool for recognizing consciousness transitions and is the only scale able to distinguish between VS and MCS [34, 38, 39]. It is divided into 6 subscales addressing auditory, visual, motor, oromotor,

Table 2 Glasgow Coma Scale (GCS)

Score	response
Eye opening	
4	Opens eyes spontaneously
3	Opens eyes in response to speech
2	*Opens eyes in response to painful stimulations*
1	Does not open eyes in response to any stimulation
Motor response	
6	Follows commands
5	*Makes localized movement in response to painful stimulation*
4	*Makes non purposeful movements in response to painful stimulation* (withdraws from pain)
3	*Flexes upper extremities / extends lower extremities in response to painful stimulation*
2	*Extends all extremities in response to painful stimulation*
1	*Makes no response to noxious stimuli*
Verbal response	
5	Is oriented to person, place and time
4	Converses, may be confused
3	Replies with inappropriate words
2	Makes incomprehensible sounds
1	Makes no response

Items involving painful stimulations are rendered in italics

communication, and arousal processes with the lowest item on each subscale representing reflexive activity and the highest one representing cognitively mediated behaviors (Table 3). The FOUR score explores 4 components represented by eye response, motor response, brainstem reflexes, and respiration pattern (Table 4). Although not distinguishing between VS and MCS, this scale allows detecting preserved eye tracking and blinking to command, which are useful signs to avoid misdiagnoses between the VS and the Locked-in Syndrome (LIS) [35, 40, 41•]. However, the above scales identify the response to pain in patients with a DOC as part of a rapid evaluation of the state of general consciousness; they do not linger to form a more analytical characterization of the painful experience. On the other hand, a new pain-specific scale has recently been developed for patients with DOCs [36••]. This is the Nociception Coma Scale (NCS), which consists of 4 subscales assessing motor, verbal, visual, and facial responses to pain, with each subscore ranging from 0 to 3 [36••] (Table 5). The validity, inter-rater agreement, and sensitivity of the above scale have been tested in patients with DOCs and were judged as being good, suggesting that the NCS might be a sensitive behavioral tool for assessing nociception in these patients [36••]. Moreover, following the observation that the exclusion of the visual subscale increased the cut-off sensitivity of the whole scale, a revised version of the scale, without the visual subscore, has been proposed [37]. Nonetheless, although these clinical tools are essential for the rapid identification of behavioral signs in response to nociceptive stimuli, they do not provide information about the level of perception and processing of pain. The usefulness of neuroimaging and

Table 3 Coma Recovery Scale Revised (CRS-R)

Score	Response
Auditory function scale	
4	Consistent movement to command[b]
3	Reproducible movement to command[b]
2	Localization to sound
1	Auditory startle
0	None
Visual function scale	
5	Object recognition[b]
4	Object localization: reaching[b]
3	Visual pursuit[b]
2	Fixation[b]
1	Visual startle
0	None
Motor function scale	
6	Functional object use[a]
5	Automatic motor response[b]
4	Object manipulation[b]
3	*Localization to noxious stimulation*[b]
2	*Flexion withdrawal*
1	*Abnormal posturing*
0	*None/flaccid*
Oromotor/verbal function scale	
3	Intelligible verbalization[b]
2	Vocalization/oral movement
1	Oral reflexive movement
0	None
Communication scale	
2	Functional: accurate[a]
1	Nonfunctional: intentional[b]
0	None
Arousal scale	
3	Attention
2	Eye opening without stimulation
1	Eye opening with stimulation
0	Unarousable

Items involving painful stimulations are rendered in italics

[a] Denotes emergence from MCS

[b] Denotes MCS

Table 4 Full Outline of UnResponsiveness (FOUR) score

Score	Response
Eye response	
4	Eyelids open or opened, tracking, or blinking to command
3	Eyelids open but not tracking
2	Eyelids closed but open to loud voice
1	*Eyelids closed but open to pain*
0	*Eyelids remain closed with pain*
Motor response	
4	Thumbs-up, fist, or peace sign
3	*Localizing to pain*
2	*Flexion response to pain*
1	*Extension response to pain*
0	*No response to pain or generalized myoclonus status*
Brainstem reflexes	
4	Pupil and corneal reflexes present
3	One pupil wide and fixed
2	Pupil or corneal reflexes absent
1	Pupil and corneal reflexes absent
0	Absent pupil, corneal, and cough reflex
Respiration	
4	Not intubated, regular breathing pattern
3	Not intubated, Cheyne-Stokes breathing pattern
2	Not intubated, irregular breathing
1	Breathes above ventilator rate
0	Breathes at ventilator rate or apnea

Items involving painful stimulations are rendered in italics

Table 5 Nociception Coma Scale

Score	Item	Response
Motor response		
3	Localization to noxious stimulation	The non-stimulated limb must locate and make contact with the stimulated body part at the point of stimulation.
2	Flexion withdrawal	There is isolated flexion withdrawal of at least one limb. The limb must move away from the point of stimulation.
1	Abnormal posturing	Slow, stereotyped flexion or extension of the upper and/or lower extremities occurs immediately after the stimulus is applied.
0	None/flaccid	There is no discernible movement following application of noxious stimulation, secondary to hypertonic or flaccid muscle tone.
Verbal response		
3	Intelligible verbalization	Production of words in response to noxious stimulation. Each verbalization must consist of at least 1 consonant-vowel-consonant (C-V-C) triad. For example, «aie » would not be acceptable, but «stop» or «that hurts» would.
2	Vocalization/oral movement	At least one episode of non-reflexive oral movement and/or vocalization in response to stimulation (such as «ah» or «aie »)
1	Groaning	Groans are observed not spontaneously but in response to noxious stimulation.
0	None	No response to any of the above.
Visual response		
3	Fixation	In response to noxious stimulation, eyes change from initial fixation point and refixate the examinator for more than 2 seconds.
2	Eyes movements	Anarchical eye movements in response to noxious stimulation.
1	Startle	Eyes opening or eyelids enlargement in response to noxious stimulation.
0	None	There are no discernible changes in response to noxious stimulation.
Facial expression		
3	Cry	Cries are observed not spontaneously but in response to noxious stimulation.
2	Grimace	Grimaces are observed not spontaneously but in response to noxious stimulation.
1	Oral reflexive movement/startle response	Clamping of jaws, tongue pumping, yawning, chewing movement.
0	None	There is no discernible facial expression following application of noxious stimulation.

neurophysiological techniques may contribute to a better understanding of the qualitative characteristics of the experience of pain in patients with DOCs and of the mechanisms underlying its perception and processing.

Pain Perception in DOCs: Contributions from Neuroimaging

Recently, positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) have gained a central role in identifying specific cortical activation patterns associated with painful stimulation in patients with DOCs. The first findings came from a PET study, which demonstrated increased neuronal activity in the midbrain, contralateral thalamus, and primary somatosensory cortex (S1) in patients in VS after the administration of nociceptive stimuli [42]. However, the activation of the primary somatosensory cortex was not associated with that of higher-order associative cortices [42]. This was interpreted as a sign of a possible functional disconnection and isolation of S1 from the other cerebral areas normally engaged during experiences of somatosensory perception [42]. This conclusion was also in line with evidence from previous lesion studies, which had demonstrated how the functioning of the higher-order associative cortices was indispensable for the conscious processing of somatosensory stimuli [43]. Divergent results came from another PET study, which reported a pattern of pain-induced activation not confined to the S1 but also involving the secondary somatosensory cortex (S2), the cingulate cortex contralateral to the stimulus and the posterior insula ipsilateral to the stimulus [44]. Contrary to what was observed in the previous study, this activation pattern suggested that a residual pain-related cerebral network might somehow be preserved in patients in VS [44]. A successive study identified specific cortical patterns in response to pain in patients in VS or MCS, respectively [4]. In line with some previous evidence, patients in a VS showed isolated activation of the S1, which was dissociated from higher-order associative cortices. The patients in MCS, on the other hand, had a close to normal activation pattern also involving the higher-order associative cortices [4]. Similar results were found in a later study, which confirmed that more widespread activation within the pain matrix can be seen in patients in MCS compared with patients in VS and that the functional connectivity between S1 and higher-order associative cortices is preserved in the MCS but not in VS [5]. Finally, more recent fMRI studies explored the activation of the affective subsystem of the pain matrix in patients in VS by investigating the pattern of cortical activation while the patient was exposed to pain-related sounds as crying [6••]. More than one-half of the patients were reported to presumably respond to the pain cries of other people, as demonstrated by the similarity between their activation pattern and that commonly observed in healthy subjects [6••]. With some variability between patients, the activation pattern was brain-wide, in that it included

both pain matrix regions and structures not normally involved in pain perception such as the cerebellum. Although these are extremely interesting results, further studies will be necessary to be able to conclude that such activation patterns represent a 'neural signature' of preserved empathy in patients in VS or MCS.

Pain Perception in DOCs: Contributions from Clinical Neurophysiology

The response to painful stimulation in patients with DOCs has also been investigated using neurophysiological techniques. The neurophysiological approach, unlike the previously described one, aims to explore the perception of pain in patients in VS or MCS, especially as a predictive index of a hypothetical recovery. In this respect, recent studies have shown that the presence of middle latency evoked potentials elicited by painful electrical stimulation is a strong predictor of a good outcome in patients with DOCs [45]. Moreover, painful electrical stimulation has been reported to improve the predictive value of somatosensory-evoked potentials and fMRI with respect to outcomes [46]. Similarly, painful stimulation may increase the ability of EEG nonlinear analyses to identify the patients with the best chances for consciousness recovery [47]. Finally, signs of residual pain processing have recently been recognized in patients in VS through the detection of laser evoked responses [48•]. The appearance of such responses was strongly influenced by the intensity of the stimulation, suggesting that the salience of the stimulus affects its perception in unconscious patients [48•]. All these data suggest that the neurophysiological evaluation of pain responses in patients with DOCs may complement clinical assessment in the prediction of prognosis. Moreover, the absence of specific pain-related neurophysiological patterns might be used as a negative prognostic indicator with respect to consciousness recovery.

What Kind of Pain?

The sources of pain in patients with DOCs are certainly multiple. It can be presumed that various experiences of pain accompany the patient from the acute phase of intubation, through the stages of resuscitation, to the chronic phase, which is generally dominated by a series of complications associated with a prolonged period of being bedridden and with the total dependence for all activities of daily life. In this last phase, pain may arise from the presence of spasticity, osteomata, and pressure ulcers and from the use of medical devices such as the urinary catheter, the central venous catheter, the nasogastric tube, or the percutaneous endoscopic gastrostomy, which, over time, can create physical discomfort for the patient. The constant necessity of bronchoaspiration and the need for frequent haemochemical analyses further increase the global discomfort of these patients. Furthermore, the possibility cannot be excluded that they might also suffer from headache, especially where there is a history of headaches prior to the severe brain injury, although the data concerning this is scarce and controversial due to the obvious difficulties in recognizing such pain in non-communicative patients [49]. Neuropathic pain can also be present as a consequence of a concomitant spinal injury or due to nutritional deficiencies or critical illness polyneuropathy [50]. Post-surgical pain may also occur in the case of recent neurosurgical procedures and in some circumstances this may become chronic [51]. Indeed, in a chronic condition such as VS it is likely that a peripheral pain becomes independent from the initial peripheral triggers just persisting as a centralized pain. Moreover, given the extent of cerebral lesions, which can be observed in severely brain-injured patients, it cannot be excluded that some of them may also experience central pain. In fact, in most cases these patients present a mosaic of lesions, which can involve the cortex, subcortical white matter, basal ganglia, brainstem, and cerebellum. In recognition of this it has been recently proposed considering VS no longer as a unique syndrome but as the result of the concurrence of different subsyndromes, each with its own clinical manifestation through a variable combination of symptoms and signs, which might be pyramidal, extrapyramidal, cerebellar, sensory, or indicative of brainstem damage [52]. It is to be expected that such a mosaic of strategic lesions might also manifest itself through symptoms of central pain, which may in turn be associated with signs of paroxysmal sympathetic hyperactivity in what is known as a sympathetic storm [53]. Finally, although it is impossible to obtain reliable data concerning this, we must bear in mind the possibility that these patients may also have depression or anxiety disorders, either remaining from a pre-existing psychiatric condition or as a reaction to their present state. In fact, as suggested by the most recent evidence from brain neuroimaging, the apparent lack of awareness of the environment in behaviorally unresponsive patients does not necessarily indicate a lack of self-awareness. It could be argued that self-awareness may be preserved more than it is commonly deemed and that self-experiences are progressively eroded by persistent disturbances in consciousness, affect, and expression, as in depersonalization disorders and psychotic syndromes [54]. Therefore, the assessment of self-awareness and the detection of hypothetical pain experiences in patients with DOCs should also take into account all the psychological and emotional implications of their deranged and alienating condition.

Doubts, Controversies, and Future Directions

The main dilemma we have to face when addressing the issue of pain in patients with DOCs is whether the patient

experiences pain in terms of both perception and suffering, or whether the experience is confined to the field of perception without entering the realm of consciousness. Several authors have dwelled upon the controversial question of whether specific fMRI and PET patterns may be an indirect testimony of preserved awareness in these patients or whether, on the contrary, they simply document retained modular function in the absence of the integrative processes necessary for consciousness [55–57]. Observations made in other types of patients would seem to support the second hypothesis. For example, preserved activation of the striate cortex has been recorded in cortically blind patients, despite their visual capacity being obviously compromised following a bilateral stroke [55]. This suggests that the isolated activation of an area, which up to now has carried out a particular function cannot be considered either a surrogate or proof of the conservation of that same function. In fact, according to the latest theories on brain complexity and interconnectivity, the isolated activity of single cerebral areas, in the absence of a continuous flow of information among relay centers, does not warrant the recovery of the original functions [58••, 59–62]. In other words, in order to map the *geography of consciousness* in the brain, as with the *geography of pain*, we must not only consider the stations where the information arrives, or should arrive, but also the multiple connections, which underlie the exchanges of information necessary for the formation of an integrated and multidimensional experience. Future developments should therefore be based on an integrated approach, considering the data available from neuroimaging and neurophysiological studies along with the growing evidence about the nature of brain network organization. This may enable the unraveling of the brain circuits underlying consciousness as well as the mechanisms of pain perception both in healthy subjects and in brain-injured patients.

Guidelines for Pain Management in Patients with DOCs and Ethical Issues

The Multi-Society Task Force on PVS first addressed the issue of pain in patients with DOCs in 1994 [30, 63]. On that occasion it declared that pain perception and suffering are conscious experiences and that unconsciousness, by definition, precludes them [63]. Contextually it was noted that patients in VS can experience only subcortical forms of pain, which generate mere reflex responses. These include monosynaptic reflex responses occurring at the spinal cord level, thalamic responses, and subcortical nociceptive responses, which may cause grimace-like or crying-like behaviors as a result of synaptic connections between the thalamus and the limbic system [63]. At that time no specific recommendations were made for the treatment of pain of any type. Furthermore, referring to the possibility of withdrawal of artificial nutrition and hydration in cases judged irreversible, it was imprudently stressed that patients in a persistent VS cannot experience thirst or hunger [63]. A more prudent approach was later adopted by the Royal College of Physicians in UK who, as well as advising against the use of the terms 'persistent' and 'permanent' in the definition of VS, recommended that any decision on the level and nature of treatments should be the result of dialogue between the physicians and the family, taking account also of the patient's own views when known, whether these were formally recorded in a written document (an advance directive) or not [64]. In the same spirit and considering the uncertainties surrounding the matter, several scientists have recently proposed treating pain in all vegetative and minimally conscious patients, guided by a precautionary principle [65, 66]. However, further controversies concern the possibility that the use of sedatives and analgesics might render even more difficult the already challenging assessment of consciousness in these patients, with the risk of underestimating any subtle signs of recovery [67•]. At the same time, extreme pain left untreated could contribute to masking the behavioral responsiveness of patients who are in fact on the road to recovery [67•]. In addition, over the years no definitive answer has yet been found to the question of whether the withdrawal of artificial nutrition and hydration in patients in VS might cause pain or not. On this matter, the American Society for Parenteral and Enteral Nutrition, in the A.S.P.E.N. ethics position paper, established that decisions regarding artificial nutrition and hydration should be based on evidence-based medicine, best practice and clinical experience, and that decisions regarding their withdrawal should take into account a benefit-risk-burden analysis [68]. This analysis should consider the possibility that the withdrawal might cause pain in patients in VS or MCS, at least until this possibility is not reasonably and scientifically excluded [68].

To date, apart from these speculations, no specific recommendations on the management of pain in patients with DOCs are available. As a result, in daily clinical practice, physicians end up making decisions on the basis of what their common sense suggests, taking into consideration, above all, the general state of the patient, the possibility of recovery, and the expectations of the patient's family. Herein lies the extreme usefulness of innovative neuroimaging and neurophysiological approaches which, through a better comprehension of the processes underlying pain perception in these patients, may pave the way for the development of evidence-based guidelines for pain management.

Conclusions

Functional neuroimaging and neurophysiological studies are certainly providing new evidence about the perception of pain in patients with DOCs. It is important to bear in mind,

however, that a patient in MCS has a widespread brain injury and that the patient's behavior does not at all resemble that of a healthy subject, even when the activation of the respective cerebral areas in response to specific stimuli can seem to overlap. Therefore, although techniques of functional neuroimaging are a precious tool for the progress of research in this field and for the future drawing up of evidence-based guidelines for pain management, we must not forget that the visible cerebral condition of *feeling* is a different thing from the *sensation of feeling*, just as an observed pattern of cerebral processing of nociceptive stimuli is different from the subjective experience of pain. In conclusion, it is likely that there is indeed an increasing degree of pain perception as a patient rises through the spectrum of DOCs, as suggested by functional imaging studies. However, this does not allow the conclusion that patients in VS are incapable of feeling pain. The possibility cannot be excluded that they may feel pain in a way that escapes currently used definitions and is difficult to track using neuroimaging. Therefore, any possible pain remains a symptom to be identified and properly treated.

Compliance with Ethics Guidelines

Conflict of Interest Francesca Pistoia declares that she has no conflict of interest. Simona Sacco declares that she has no conflict of interest. Marco Sarà declares that he has no conflict of interest. Antonio Carolei declares that he has no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:

- • Of importance
- •• Of major importance

1. Borsook D. Neurological diseases and pain. Brain. 2012;135:320–44.
2. Pain terms: a list with definitions and notes on usage. Recommended by the IASP Subcommittee on Taxonomy. Pain. 1979;6:249.
3. Loeser JD, Treede RD. The Kyoto protocol of IASP Basic Pain Terminology. Pain. 2008;137:473–7.
4. Boly M, Faymonville ME, Peigneux P, Lambermont B, Damas F, Luxen A, et al. Cerebral processing of auditory and noxious stimuli in severely brain injured patients: differences between VS and MCS. Neuropsychol Rehabil. 2005;15:283–9.
5. Boly M, Faymonville ME, Schnakers C, Peigneux P, Lambermont B, Phillips C, et al. Perception of pain in the minimally conscious state with PET activation: an observational study. Lancet Neurol. 2008;7:1013–20.
6. •• Yu T, Lang S, Vogel D, Markl A, Müller F, Kotchoubey B. Patients with unresponsive wakefulness syndrome respond to the pain cries of other people. Neurology. 2013;80:345–52. *This reference is of importance as it highlights the presence of residual empathy-related responses in apparently unconscious patients*.
7. •• Iannetti GD, Mouraux A. From the neuromatrix to the pain matrix (and back). Exp Brain Res. 2010;205:1–12. *This review is extremely interesting as it summarizes main evidence pro and against the concept of pain matrix in recent studies*.
8. Tracey I. Nociceptive processing in the human brain. Curr Opin Neurobiol. 2005;15:478–87.
9. Garcia-Larrea L, Frot M, Valeriani M. Brain generators of laser-evoked potentials: from dipoles to functional significance. Neurophysiol Clin. 2003;33:279–92.
10. Bushnell MC, Apkarian AV. Representation of pain in the brain. In: McMahon S, Koltzenburg M, editors. Textbook of pain. 5th ed. Philadelphia: Churchill Livingstone; 2005. p. 267–89.
11. Derbyshire SW, Jones AK, Gyulai F, Clark S, Townsend D, Firestone LL. Pain processing during 3 levels of noxious stimulation produces differential patterns of central activity. Pain. 1997;73:431–45.
12. Coghill RC, Sang CN, Maisog JM, Iadarola MJ. Pain intensity processing within the human brain: a bilateral, distributed mechanism. J Neurophysiol. 1999;82:1934–43.
13. Tölle TR, Kaufmann T, Siessmeier T, Lautenbacher S, Berthele A, Munz F, et al. Region-specific encoding of sensory and affective components of pain in the human brain: a positron emission tomography correlation analysis. Ann Neurol. 1999;45:40–7.
14. Iannetti GD, Zambreanu L, Cruccu G, Tracey I. Operculoinsular cortex encodes pain intensity at the earliest stages of cortical processing as indicated by amplitude of laser-evoked potentials in humans. Neuroscience. 2005;131:199–208.
15. Rainville P. Brain mechanisms of pain affect and pain modulation. Curr Opin Neurobiol. 2002;12:195–204.
16. Porro CA. Functional imaging and pain: behavior, perception, and modulation. Neuroscientist. 2003;9:354–69.
17. Rainville P, Duncan GH, Price DD, Carrier B, Bushnell MC. Pain affect encoded in human anterior cingulate but not somatosensory cortex. Science. 1997;277:968–71.
18. Hofbauer RK, Rainville P, Duncan GH, Bushnell MC. Cortical representation of the sensory dimension of pain. J Neurophysiol. 2001;86:402–11.
19. Isnard J, Guénot M, Ostrowsky K, Sindou M, Mauguière F. The role of the insular cortex in temporal lobe epilepsy. Ann Neurol. 2000;48:614–23.
20. Charlesworth G, Soryal I, Smith S, Sisodiya SM. Acute, localised paroxysmal pain as the initial manifestation of focal seizures: a case report and a brief review of the literature. Pain. 2009;141:300–5.
21. Ostrowsky K, Magnin M, Ryvlin P, Isnard J, Guenot M, Mauguière F. Representation of pain and somatic sensation in the human insula: a study of responses to direct electrical cortical stimulation. Cereb Cortex. 2002;12:376–85.
22. Kenshalo DR, Iwata K, Sholas M, Thomas DA. Response properties and organization of nociceptive neurons in area 1 of monkey primary somatosensory cortex. J Neurophysiol. 2000;84:719–29.
23. Dong WK, Chudler EH, Sugiyama K, Roberts VJ, Hayashi T. Somatosensory, multisensory, and task-related neurons in cortical area 7b (PF) of unanesthetized monkeys. J Neurophysiol. 1994;72:542–64.
24. Kenshalo DR, Douglass DK. The role of the cerebral cortex in the experience of pain. In: Bromm B, Desmedt JE, editors. Pain and the brain: from nociception to cognition. New York.: Raven Press; 1995. p. 21–34.
25. Hutchison WD, Davis KD, Lozano AM, Tasker RR, Dostrovsky JO. Pain-related neurons in the human cingulate cortex. Nat Neurosci. 1999;2:403–5.
26. Wall PD. Independent mechanisms converge on pain. Nat Med. 1995;1:740–1.

27. Kunde V, Treede RD. Topography of middle-latency somatosensory evoked potentials following painful laser stimuli and non-painful electrical stimuli. Electroencephalogr Clin Neurophysiol. 1993;88: 280–9.
28. Lui F, Duzzi D, Corradini M, Serafini M, Baraldi P, Porro CA. Touch or pain? Spatio-temporal patterns of cortical fMRI activity following brief mechanical stimuli. Pain. 2008;138:362–74.
29. Plum F, Posner JB. The diagnosis of stupor and coma. Contemp Neurol Ser. 1972;10:1–286.
30. The Multi-Society Task Force on PVS. Medical aspects of the persistent vegetative state: first of two parts. N Engl J Med. 1994;330: 1499–508.
31. Giacino JT, Ashwal S, Childs N, et al. The minimally conscious state: definition and diagnostic criteria. Neurology. 2002;58:349–53.
32. Schnakers C, Vanhaudenhuyse A, Giacino J, Ventura M, Boly M, Majerus S, et al. Diagnostic accuracy of the vegetative and minimally conscious state: clinical consensus vs standardized neurobehavioral assessment. BMC Neurol. 2009;9:35.
33. Teasdale G, Jennett B. Assessment of coma and impaired consciousness. A practical scale. Lancet. 1974;2:81–4.
34. Giacino JT, Kalmar K, Whyte J. The JFK Coma Recovery Scale-Revised: measurement characteristics and diagnostic utility. Arch Phys Med Rehabil. 2004;85:2020–9.
35. Wijdicks EF, Bamlet WR, Maramattom BV, Manno EM, McClelland RL. Validation of a new coma scale: the FOUR score. Ann Neurol. 2005;58:585–93.
36 •• Schnakers C, Chatelle C, Vanhaudenhuyse A, Majerus S, Ledoux D, Boly M, et al. The Nociception Coma Scale: a new tool to assess nociception in disorders of consciousness. Pain. 2010;148:215–9. *This paper is of importance as it describes the only available pain specific scale to be used in patients with DOCs*.
37. 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 Psychiatry. 2012;83:1233–7.
38. Lombardi F, Gatta G, Sacco S, Muratori A, Carolei A. The Italian version of the Coma Recovery Scale-Revised (CRS-R). Funct Neurol. 2007;22:47–61.
39. Sacco S, Altobelli E, Pistarini C, Cerone D, Cazzulani B, Carolei A. Validation of the Italian version of the Coma Recovery Scale-Revised (CRS-R). Brain Inj. 2011;25:488–95.
40. Marcati E, Ricci S, Casalena A, Toni D, Carolei A, Sacco S. Validation of the Italian version of a new coma scale: the FOUR score. Intern Emerg Med. 2012;7:145–52.
41.• Sarà M, Pistoia F. Defining consciousness: lessons from patients and modern techniques. J Neurotrauma. 2010;27:771–3. *This reference may help physicians to recognize the main causes of diagnostic error in patients with DOCs*.
42. Laureys S, Faymonville ME, Peigneux P, Damas P, Lambermont B, Del Fiore G, et al. Cortical processing of noxious somatosensory stimuli in the persistent vegetative state. Neuroimage. 2002;17:732–41.
43. Caselli RJ. Ventrolateral and dorsomedial somatosensory association cortex damage produces distinct somesthetic syndromes in humans. Neurology. 1993;43:762–71.
44. Kassubek J, Juengling FD, Els T, Spreer J, Herpers M, Krause T, et al. Activation of a residual cortical network during painful stimulation in long-term postanoxic vegetative state: a 15O-H2O PET study. J Neurol Sci. 2003;212:85–91.
45. Zanatta P, Messerotti Benvenuti S, Baldanzi F, Bosco E. Pain-related middle-latency somatosensory evoked potentials in the prognosis of post anoxic coma: a preliminary report. Minerva Anestesiol. 2012;78:749–56.
46. Zanatta P, Messerotti Benvenuti S, Baldanzi F, Bendini M, Saccavini M, Tamari W, et al. Pain-related somatosensory evoked potentials and functional brain magnetic resonance in the evaluation of neurologic recovery after cardiac arrest: a case study of 3 patients. Scand J Trauma Resusc Emerg Med. 2012;20:22.
47. Wu DY, Cai G, Yuan Y, Liu L, Li GQ, Song WQ, et al. Application of nonlinear dynamics analysis in assessing unconsciousness: a preliminary study. Clin Neurophysiol. 2011;122:490–8.
48. • De Tommaso M, Navarro J, Ricci K, Lorenzo M, Lanzillotti C, Colonna F, et al. Pain in prolonged disorders of consciousness: laser evoked potentials findings in patients with vegetative and minimally conscious states. Brain Inj. 2013;27:962–72. *This neurophysiological study is of relevance as it investigates whether the salience of a painful stimulus may affect its perception in unconscious patients*.
49. Formisano R, Bivona U, Catani S, D'Ippolito M, Buzzi MG. Post-traumatic headache: facts and doubts. J Headache Pain. 2009;10: 145–52.
50. Celik C, Ucan H, Alemdaroglu E, Oktay F. Critical illness polyneuropathy: a case report. Neuro Rehabil. 2011;29:229–32.
51. Shipton EA. The transition from acute to chronic postsurgical pain. Anesth Intensive Care. 2011;39:824–36.
52. Pistoia F, Sarà M, Sacco S, Carolei A. Vegetative states and minimally conscious states revisited: a Russian doll approach. Brain Inj. 2013;27:1330–1.
53. Levy ER, McVeigh U, Ramsay AM. Paroxysmal sympathetic hyperactivity (sympathetic storm) in a patient with permanent vegetative state. J Palliat Med. 2011;14:1355–7.
54. Sass LA. Self-disturbance and schizophrenia: structure, specificity, pathogenesis (current issues, new directions). Schizophr Res. 2013.
55. Celesia GG, Sannita WG. Can patients in vegetative state experience pain and have conscious awareness? Neurology. 2013;80:328–9.
56. Rees G, Edwards S. Is pain in the brain? Nat Clin Pract Neurol. 2009;5:76–7.
57. Sarà M, Pistoia F, Cernera G, Sacco S. The consciousness dilemma: feel or feel of feeling? Arch Neurol. 2008;65:418.
58. •• Fingelkurts AA, Fingelkurts AA, Bagnato S, Boccagni C, Galardi G. Toward operational architectonics of consciousness: basic evidence from patients with severe cerebral injuries. Cogn Process. 2012;13:111–31. *This paper is extremely interesting as it focuses on brain complexity and interconnectivity as prerequisites for the consciousness experience*.
59. Rosanova M, Gosseries O, Casarotto S, Boly M, Casali AG, Bruno MA, et al. Recovery of cortical effective connectivity and recovery of consciousness in vegetative patients. Brain. 2012;135:1308–20.
60. Sarà M, Pistoia F. Complexity loss in physiological time series of patients in a vegetative state. Nonlinear Dyn Psychol Life Sci. 2010;14:1–13.
61. Sarà M, Pistoia F, Pasqualetti P, Sebastiano F, Onorati P, Rossini PM. Functional isolation within the cerebral cortex in the vegetative state: a nonlinear method to predict clinical outcomes. Neurorehabil Neural Repair. 2011;25:35–42.
62. Sarà M, Sebastiano F, Sacco S, et al. Heart rate nonlinear dynamics in patients with persistent vegetative state: a preliminary report. Brain Inj. 2008;22:33–7.
63. The Multi-Society Task Force on PVS. Medical aspects of the persistent vegetative state (2). N Engl J Med. 1994;330:1572–9.
64. [No authors listed]. The permanent vegetative state. Review by a working group convened by the Royal College of Physicians and endorsed by the Conference of Medical Royal Colleges and their faculties of the United Kingdom. J R Coll Physicians Lond. 1996;30: 119–21.
65. Schnakers C, Zasler ND. Pain assessment and management in disorders of consciousness. Curr Opin Neurol. 2007;20:620–6.
66. Panksepp J, Fuchs T, Garcia VA, Lesiak A. Does any aspect of mind survive brain damage that typically leads to a persistent vegetative state? Ethical considerations. Philos Ethics Humanit Med. 2007;2:32.

67. • Fins JJ, Illes J, Bernat JL, Hirsch J, Laureys S, Murphy E. Neuroimaging and disorders of consciousness: envisioning an ethical research agenda. Am J Bioeth. 2008;8:3–12. *This reference is of importance as it addresses the main ethical issues we have to face when treating patients with DOCs*.

68. Barrocas A, Geppert C, Durfee SM, Maillet JO, Monturo C, Mueller C, et al. A.S.P.E.N. Ethics Position Paper Task Force. A.S.P.E.N. Board of Directors; American Society for Parenteral and Enteral Nutrition. A.S.P.E.N. ethics position paper. Nutr Clin Pract. 2010;25:672–9.