SECTION 3

Clinical Conditions (Pathology) Affecting Pain and Consciousness

Pain Processing in Psychiatric and Neurological Disorders Affecting Consciousness

CHAPTER 10

Pain and Nociception in Disorders of Consciousness

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PAIN ASSESSMENT IN NONCOMMUNICATING PATIENTS

Pain is utterly personal and intimate. Officially, it has been defined as the "unpleasant sensory and emotional experience associated with real or potential tissue damage" [30]. Currently, we know that pain results from an interaction between the sensory characteristics of a stimulus and the state of the nervous system based on past experiences and emotional processes of the body at the time of stimulation [35]. Thus, healthy subjects might experience significant pain-related suffering from a relatively low-level noxious stimulation if they believe the implications are ominous, interminable, and beyond their control.

As with other conscious experiences, pain needs to be communicated in order to be assigned to a person. In cases of severely brain-injured noncommunicating patients, conscious perception of pain is classically inferred from motor responses to noxious stimulation. This is because by definition neither patients in an unresponsive wakefulness syndrome (also known as the vegetative state, VS/UWS [37]) nor patients in a minimally conscious state (MCS [23]) are able to functionally communicate their experiences. Indeed, patients in VS/UWS are in a condition of preserved wakefulness with absent voluntary interaction with the environment. Patients in MCS show discernible but fluctuating signs of awareness but also remain unable to functionally communicate with their surroundings [23]. It is therefore impossible for them to express their own feelings or to use any usual scale (such as the Visual Analog Scale) to report the presence of pain and its intensity. Interestingly, the International Association for the Study of Pain states the inability to verbally communicate does not negate the possibility that an individual is experiencing pain and is in need of appropriate pain-relieving treatment. As pain and suffering can also be

present in the absence of noxious stimulation [41], how can one know whether patients in VS/UWS or in MCS experience pain?

In a recent survey around Europe, 2059 medical and paramedical professionals expressed their beliefs on possible pain perception in patients with disorders of consciousness. To the question "Do you think that patients in a minimally conscious state can feel pain?" almost all interviewed caregivers (96% of the medical doctors and 97% of the paramedical caregivers) answered positively. To the question "Do you think that patients in a vegetative state can feel pain?" 68% of the interviewed paramedical caregivers and 56% of medical doctors endorsed the statement. Interestingly, religion correlated most with health care professionals' opinions [16]. Since nearly half of the interviewed doctors express that VS/UWS patients do not feel pain, they could be expected to act accordingly by, for instance, not providing analgesic medication in these patients. These issues become even more important in cases when VS/UWS patients are agreed to be withdrawn from life-supporting treatment, such as artificial nutrition and hydration [14]. In these cases, VS/UWS patients can be left without administration of opioids or other analgesic drugs during their dying process on the grounds that they are not able to suffer from hunger and thirst [18]. More recently, we showed that health care providers' beliefs on possible pain perception in patients in VS/UWS indeed influences opinions on end of life [15]. Specifically, respondents who considered VS/UWS patients as able to feel pain supported less the withdrawal of life-sustaining therapy. For MCS, withdrawing life-supporting treatment was denied by most respondents, independently on the status of pain perception in these patients [15]. Such data show that research on attitudes of health care providers bring forth important questions about the relationship of research to clinical guidelines, the discrepancies of attitudes between health care providers and the complex relationship between pain perception and attitudes toward life-sustaining treatments. Ethical questions like these illustrate the need for closer attention to perspectives in research and in clinical care within the development of consensual approaches and guidelines, the need to understand practice variability and to minimize its impact on families, and the careful interpretation of recent neuroimaging findings and their consequences on withdrawal of life support [13].

PAIN PROCESSING IN DISORDERS OF CONSCIOUSNESS: FINDINGS FROM NEUROIMAGING AND ELECTROPHYSIOLOGICAL STUDIES

The International Association for the Study of Pain defines nociception is "an actually or potentially tissue damaging event transduced and encoded by nociceptors" [41]. The activation of peripheral nociceptors can produce pain, but nociception is not

pain, which is a conscious experience. Additionally, the activation of nociceptors can trigger reflexive and autonomic responses without necessarily generating a conscious experience of pain [27, 64]. While nociception is usually necessary for pain perception [41], pain can also occur in the absence of nociception [19].

Supporting these definitions, neuroimaging studies suggest that nociception and pain are mediated by different cortical networks, together forming the "pain matrix" [29]. The transmission of nociceptive information will be transmitted from the thalamus to the cortical nociceptive network encompassing the primary and secondary somatosensory cortices, as well as the posterior insula, the so-called lateral network participating in the sensory–discriminative aspects of pain processing [40, 48]. It has been suggested that the activation of this network is not sufficient to generate the conscious experience of pain which necessitates the cingulate, anterior insula, and prefrontal cortices, the so-called medial network, which is involved in the motivational-affective and cognitive-evaluative aspects of pain processing [60].

There is now accumulating evidence that at least part of the activation of the "pain matrix" would not reflect activity that is specific for nociception or the perception of pain but would rather be involved in multimodal processing of saliency [44, 54]. Another hypothesis is that this "salience" (nonspecific) network within the pain matrix interacts with nociceptive-specific networks of the pain matrix such as the posterior insula, to generate a pain sensation attributable to the own body [20]. Although there is still no clear interpretation of the pain matrix in humans, looking at brain responses to pain could constitute a highly useful tool to help improve and objectify our understanding of pain perception in severely brain-injured patients who are unable to communicate.

For example, a study investigating the processing of noxious stimuli in 15 patients in a VS/UWS by using H_2O positron-emission tomography (PET) imaging reported an increase in metabolism in midbrain, contralateral thalamus, and primary somatosensory cortex in response to a potentially painful electrical stimulation applied to the median nerve of the wrist [38]. Additionally, primary somatosensory cortex was functionally disconnected from associative areas (i.e., secondary somatosensory cortex, bilateral posterior parietal, premotor, polysensory superior temporal, and prefrontal cortices) as compared to 15 healthy controls. These findings suggest that in patients in VS/UWS the activation of the primary cortex was isolated from higher-order associative cortices, reducing the probability that a potentially painful stimulus could be experienced in an integrated and conscious manner. Later on, it was shown that patients in MCS had a brain activation similar to healthy controls in response to noxious stimuli, encompassing not only midbrain, thalamus, and primary somatosensory cortex, but also secondary somatosensory cortex, insular, posterior parietal, as well as the posterior part of the anterior cingulate cortex [4]. This broader pattern of activation observed in the associative cortices areas and, particularly, in the anterior cingulate cortex and insula, suggests that patients in a

MCS have the ability to process the unpleasant aspect of painful stimuli [60]. Similar results were reported in a recent functional MRI study where the brain of patients with disorder of consciousness (DOC) was scanned under a resting condition [12]. Among other systems, the analysis also focused on the salience network, which encompasses mainly bilateral insula and anterior cingulate cortex [59] and which has been involved in conflict monitoring, information integration, response selection, interoceptive processes [49, 66], and the emotional counterpart of pain [60]. For the salience network, a positive correlation between clinical scores measuring the level of consciousness and part of the anterior cingulate cortex was found (Fig. 10-1). Such results could account for the preserved capacities of some patients to orient their attentional resources toward environmental salient stimuli, such as noxious stimulation, corroborating previous PET data [4]. They also relate to the issue of patients experiencing spontaneous pain in the absence of external stimulation, or experiencing pain elicited by non-noxious stimuli such as neuropathic pain, which can be caused by brain damage or dysfunction [33].

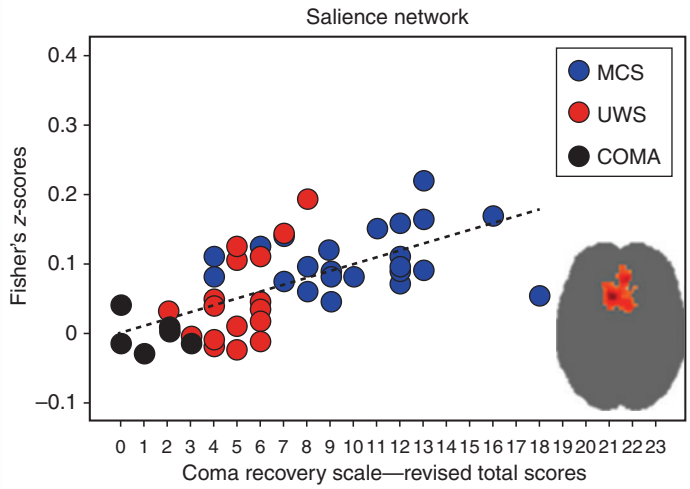

FIGURE 10-1 Potential pain perception can be studied in patients with disorders of consciousness during resting state, in the absence of external stimulation. Here, the level of consciousness in noncommunicating patients in minimally conscious state (MCS), vegetative state/unresponsive wakefulness syndrome (VS/UWS), and coma positively correlated with functional connectivity in the anterior cingulate cortex of the salience network, which has been implicated in the attentional and emotional aspects of pain. Although the subjective-emotional counterpart cannot be directly measured with this approach, these results could account for the preserved capacities of some patients to orient their attentional resources toward environmental salient stimuli, such as noxious stimulation. (Adapted from Demertzi et al. [12].)

Other studies conducted in patients in a VS/UWS showed different results. Kassubek et al. [32] studied seven anoxic patients in a VS/UWS, reporting a more widespread activity than what was reported in Laureys et al. [38] in the posterior insula/secondary somatosensory cortex, postcentral gyrus/primary somatosensory cortex, midcingulate cortex contralateral to the stimulus, and posterior insula ipsilateral to the stimulus. More recently, de Tommaso et al. [17] used nociceptive-specific laser-evoked potentials known to be related to cortical generators, such as the anterior cingulate cortex, and have reported a response (although with a longer latency) in three patients in a VS/UWS. Finally, two other studies reported an activation of both the sensory and affective pain networks (i.e., anterior cingulate cortex and/or insula) in 30% of patients in a VS/UWS in response to noxious stimulation [42] as well as pain cries [42, 68].

While these findings suggest a residual ability to perceive pain in VS/UWS, the last study also reported, in a parallel analysis, that the connectivity within the whole pain network was significantly impaired as compared with patients in a MCS [34]. Even though this supports an altered perception in patients in a VS/UWS, the activation of the affective pain network might denote the presence of residual pain perception in some of those patients. Moreover, these findings need to be interpreted with caution as many of the "pain matrix" components have been shown to be not specific to pain [43, 44, 54].

Taken together, these studies support the need for clinicians for a daily management of potential pain in every patient with DOC, independently of their clinical diagnosis at the bedside, which might be erroneous [58]. In this context, the development of tools to appropriately assess and treat pain in those patients is necessary.

BEHAVIORAL ASSESSMENT OF PAIN IN DISORDER OF CONSCIOUSNESS

Several scales have been developed and validated to detect pain in noncommunicating patients, such as newborns, patients with dementia (see chapter in this volume), AQ1 and sedated/intubated patients. For example, the COMFORT scale has been developed for use in young sedated patients between 0 and 3 years old [63]. It includes the observation of respiratory and motor responses, cardiac frequency, blood pressure, facial expression, agitation, and level of awakening. Each parameter is scored from 1 to 5. The total score ranges from 8 to 40, with a score between 17 and 26 indicating appropriate sedation level. To our knowledge, this is currently the sole scale that assesses oversedation, comfort, and distress in newborns and young children in intensive care. The Behavioral Pain Scale (BPS [47]) and the Critical Care Pain Observation Tool (CCPOT [22]) have been developed for noncommunicating and sedated adult patients in intensive care. The BPS assesses facial expression, movements of the

upper limbs, and the compliance to mechanical ventilation in intubated adults. Each parameter is scored from 1 to 4. The total score ranges from 4 to 12. The CCPOT includes the facial expression, body movements, muscle tension, and compliance with the ventilator/vocalization. Its total score ranges from 0 to 8. Several studies have shown the reliability and validity of these scales for use in intensive care adult patients [3, 53]. Additionally, a recent study also suggested that the CCPOT would be more sensitive to pain than the BPS when comparing score changes between a non-painful and a painful condition [53]. Recently, a new scale has also been proposed for ventilated critically ill, noncommunicating patients, the "scale of behavior indicators of pain" (Escala de Conductas Indicadoras de Dolor: ESCID). A good concurrent validity with the BPS and a good internal consistency of the scale were reported in a previous study [36].

AQ2

Nevertheless, only a few scales have been developed to assess pain in patients with DOC until recently [57]. Among them, the Nociception Coma Scale (NCS [57]) was developed in 2010 to specifically assess nociception and pain in patients with DOC in acute and chronic setting. The NCS is based on preexisting pain scales validated in noncommunicating patients with advanced dementia and newborns. The first version of the scale consisted of four subscales assessing motor, verbal, visual responses, and facial expression. Initially, breathing responses were also assessed but later discarded due to the difficulty to objectively assess breathing patterns in patients not benefiting from respiratory monitoring devices [56]. In addition, previous studies have shown that physiological parameters seem insufficiently sensitive for pain assessment [21, 26]. Stress, medication, medical complications, and brain lesions affecting autonomic functions can influence these parameters and bias the assessment as well.

A first study including 48 patients from intensive care, neurology/neurosurgery units, rehabilitation centers, and nursing homes reported a good interrater reliability and good concurrent validity for the NCS total scores and subscores when compared to other scale developed for noncommunicating patients (e.g., the neonatal infant pain scale [39], the pain assessment in advanced dementia scale [65]). A second study on 64 patients investigated the sensitivity of the NCS by comparing NCS scores observed at rest, in response to a non-noxious stimulus (i.e., tap on the shoulders) and a noxious stimulus (i.e., nail bed pressure [9]). Results showed that NCS total scores as well as motor, verbal, and facial subscores were significantly higher in response to a noxious stimulus than at rest or in response to a non-noxious stimulus, reflecting the good sensitivity of the scale. However, no difference could be observed between noxious and non-noxious conditions for the visual subscores, suggesting that this subscale was not specific to nociception. A modified version of the scale excluding the visual subscale, the nociception coma scale—revised (NCS-R, see Table 10-1) [9], was therefore proposed.

The NCS-R is meant to be administered in all patients who are in a VS/UWS or in a MCS, especially those who present a documented potential pain (e.g., polytraumatic

TABLE 10-1 The Nociception Coma Scale—Revised

Motor Responses

3—Localization to painful stimulation

2—Flexion withdrawal

1—Abnormal posturing

0—None/flaccid

Verbal Responses

3—Verbalization (intelligible)

2—Vocalization

1—Groaning

0—None

Facial Responses

3—Cry

2—Grimace

1—Oral reflexive movement/startle response

0—None

injuries, decubitus ulcers, severe spasticity, wounds, or arthralgia). A particular attention should be given to patients with spasticity as it is a frequent condition in chronic DOC. Indeed, a recent study showed that 89% (58/65) of patients who were in a chronic DOC demonstrated signs of spasticity (modified Ashworth Scale, MAS $\geq$ 1), including 60% (39/65) qualified with severe spasticity (MAS $\geq$ 3). In addition, the severity of spasticity was correlated to NCS-R scores (i.e., likely to reflect nociception or pain), highlighting the importance of pain management in noncommunicating patients after severe brain injury [62].

Any information about preexisting pain (e.g., osteoarthritis, rheumatoid arthritis) is helpful before starting using the scale. The NCS-R should be scored at rest and during cares in order to observe the spontaneous responses presented by the patient (preferably assessed with eyes opened) before the potentially painful care and/or stimulating a potentially painful area. Behavioral responses observed before and during the care and/or stimulation will be scored according to the NCS-R guidelines. Spontaneous behaviors at rest can also be taken into considerations. However, these responses could be unrelated to pain (e.g., pathologic activation of subcortical areas leading to constant but not appropriate cries [45]) and should therefore be replicated in a pain-related condition (i.e., mobilization/palpation). The highest scores obtained for each subscale are summed to obtain a total score ranging from 0 to 9. In case of a documented cause of potential pain, the NCS-R should be administered before and after analgesic treatment.

It is essential to assess simultaneously the patient's level of consciousness in order to avoid overmedication. Indeed, it is likely that the administration of sedating analgesics will decrease the presence of pain behaviors but also the patient's responsiveness as those medications may have an impact on alertness and vigilance in patients with severe brain injury. On the other hand, the presence of untreated pain could reduce already limited attentional resources, and prevent the patient from interacting with his or her surroundings and showing sign of consciousness. Indeed, a recent study reported an improvement of consciousness when administering analgesic treatment to a brain-injured patient suffering from severe spasticity [62]. A good balance remains therefore to be found between undertreatment and overtreatment by revising pain treatment regularly. Considerations should be given to nonsedating medications or to medications with reversible effects whenever there is question of medication effects versus ongoing deterioration of neurological status.

In this context, the NCS-R may constitute a helpful instrument for monitoring pain behavior on a daily basis. In the absence of documented conditions likely to produce pain, a sudden increase of the NCS-R total score independent from an improvement in the level of consciousness can alert the clinician of the potential presence of pain/underlying medical complication. Additional investigations may then be performed to identify its origin/localization (e.g., by using mobilization/palpation/CT scan).

In a recent study looking at the clinical validity of the scale, 39 patients with potentially painful conditions (e.g., due to fractures or spasticity) were assessed during nursing cares before and after the administration of an analgesic treatment tailored to each patient's clinical status [8]. The Glasgow coma scale (GCS) was also used before and during treatment in order to observe fluctuations in consciousness. A decrease in the NCS-R total scores and subscores was reported during treatment when compared to the scores observed before treatment. Interestingly, no difference between the GCS total scores obtained before versus during treatment was observed suggesting a good balance between decrease in pain and preserved level of consciousness. More precisely, 20 patients showed a decrease in the NCS-R scores with no decrease of the level of consciousness (i.e., GCS scores). Finally, 5 of these 20 patients showed higher signs of consciousness (i.e., increase in GCS scores) following the analgesic treatment as compared with before, suggesting that the presence of pain may have compromised the ability of the patient to respond at bedside (also see reference [62]). The fact that 59% of the patients included in the study (23 of 39) did not have any analgesic treatment prior to the assessment also underlines the crucial need for an appropriate management of pain in this population.

The COMFORT, the BPS, the CCPOT, and the ESCID were first developed for patients in the acute setting (including sedation and ventilation), and all of the scales presented here include observation of the motor response and facial expression. However, studies quantifying facial expression (i.e., grimace) in patients with DOC are currently lacking. This is even more of a problem in case of severe

spasticity [62] or oral response limited by trachea/anarthria, where the use of motor or verbal responses may be limited and facial expression is sometimes the only remaining communicative means that can be used in this population. Even if grimacing is considered as an indicator of pain, the Multi-Society Task Force on PVS did not consider it as a necessary sign of conscious perception as they can occur reflexively through subcortical pathways in the thalamus and limbic system [45]. Patients showing no sign of consciousness except grimaces to nociceptive stimuli can therefore be diagnosed as being in VS/UWS. Nevertheless, very few studies have investigated such behavior in conscious (MCS) versus nonconscious (VS/UWS) patients. Recently, Schnakers et al. [55] investigated the frequency of grimace in DOC. They reported that grimaces were more frequently displayed in response to nociceptive stimuli than in response to non-nociceptive stimuli in both MCS and VS/UWS patients (i.e., 48% vs. 4% for VS/UWS and 65% vs. 3% for MCS, respectively). However, grimace to pain was not observed more frequently in MCS than in VS/UWS patients.

A recent neuroimaging study investigated the correlation between the NCS-R score and brain areas involved in the "pain matrix" network [10]. Using 18-fluorodeoxyglucose PET scan, a significant correlation was observed between NCS-R total scores and brain metabolism in the posterior part of the anterior cingulate cortex. Those results suggest that the NCS-R is at least partially related to the activity in one cortical area involved in pain processing and hence may constitute an appropriate behavioral tool to assess, monitor, and treat nociception and pain in noncommunicating patients with DOC. However, as highlighted earlier, what is crucial to lead to a fully conscious experience of pain is more the connectivity between different areas involved in pain processing than the cingulate area alone, which are not necessarily specific to pain processing. Therefore, these results should be interpreted with caution and cannot be used to affirm that the NCS-R is a sensitive tool to assess subjective pain and not only nociception.

Future studies should better investigate the presence of target behaviors (e.g., grimaces) in the detection and treatment of pain in this population. It would also be useful to conduct more studies comparing changes in the scores when analgesics/potential pain condition is administered in a double-blind placebo/control study, in order to control that the observed changes were only associated with the treatment/condition. Finally, there is an urgent need for a better understanding of response to analgesic treatment in this population for short and long-term pain management.

FUTURE PERSPECTIVES

The presence of pain in patients with DOC is a real challenge to clinicians. Several studies have investigated whether these patients are able to process pain in a conscious manner, including subjective suffering [4, 38, 42]. Clinicians who deal with DOC patients should therefore be concerned about nociception, regardless of the

patient's subjective experience. The presence of nociception may also help caregivers to detect medical complications, such as undiagnosed fractures, kidney stones, urinary tract infection. In this context, a method assessing the presence of nociception through behavioral (e.g., facial grimaces, moaning, restless movement) and/or physiologic (e.g., rise in heart rate or blood pressure, dilation of pupils) responses should not rely on the patient's state of consciousness.

Behavioral response to nociception is complex, and includes autonomic and reflexive responses generally displayed in various ways by VS/UWS and MCS patients (i.e., facial grimacing, moaning, producing tears, increases in tonic posturing, and thrashing limb movements [45]). Currently, the NCS-R is the only measure of nociception and pain developed specifically for patients with DOC and which has been validated. However, this tool may have limitations for use to accurately assess solely nociception in this population. First, the highest number of points that can be scored depends on the patient's state of consciousness (i.e., localization to pain, appropriate cries, and intelligible verbalization). Second, it has a relatively small point range, particularly for responses that are considered as being reflexes, and therefore of interest for assessing nociception. In this context, it may be useful to develop a measurement tool with a wider range of items to maximize sensitivity to the intensity of nociception, taking into account the limited examination time. Finally, clinicians using the NCS-R should be careful when interpreting the findings as "agitation," which may be confounded with a recovery of consciousness. Indeed, patients beginning to regain consciousness can display new spontaneous responses and agitated behaviors that may involve facial grimacing, moaning, or limb movements, for example [2], which would increase the scores observed at the NCS-R. While it is believed that the presence of nociceptive stimuli can prompt outbursts of agitation, it is also believed that agitation can appear as a primary syndrome related to brain injury, in the absence of noxious stimulation. For that reason, repetitive assessments in different condition (no noxious vs. noxious) are needed to be able to better define the presence of pain and the potential source.

In addition to behavioral responses, physiological responses to pain (e.g., heart rate, respiration, pupil dilation) are other indicators that may be of interest for assessing pain in DOC. Following a painful stimulation, breathing becomes irregular or faster, blood pressure and heart rate increase, and oxygen saturation decreases. These indicators are included in some of the validated scales for noncommunicative patients such as the COMFORT. In research, intracranial pressure, skin conductance, and heart rate are the most used indicators [28]. Some studies suggested that changes in the heart rate were associated with the subjective pain unpleasantness but not with the pain intensity [50, 51] or could be used as an indicator of inadequate analgesia [31]. On the other hand, other studies reported that vital signs (heart rate, respiration) did not correlate significantly with self-reports of pain or

unpleasantness and should thus not be used as indicators of pain in the nonverbal critically ill [21, 22, 24, 52].

Pupil response to pain (noradrenergic circuits) is a complex sympathetically mediated response that involves defensive supraspinal processing in the central autonomic network [6, 7, 46], and it is associated with conscious processing [67] and subjective pain in healthy volunteers. However, few studies have been investigating pupil response in brain injured patients [61] and little is known about the variety of centrally acting drugs with potential anticholinergic or sympathomimetic effects.

Finally, in hospitalized patients, a variation of vital responses can be observed following homeostatic changes and certain medications, leading experts to recommend avoiding the use of these measures as pain indicators [1, 25]. These measures may also be disturbed by factors other than pain, such as stress, restlessness, hunger, and should therefore, if used, always be interpreted with caution [52].

Even though it is crucial to have tools for detecting and treating acute pain, another challenge in the future will be to better understand and manage neuropathic pain in patients with DOC. This would include the development or adaptation of existing scales currently validated for assessing acute pain. Indeed, it has been shown that the prevalence of chronic pain is high after a traumatic brain injury (as 50% of patients with mild to moderate injury report recurrent headaches) or after a nontraumatic brain injury (as thalamic or cortical stroke may lead to chronic pain), as well as in presence of recurrent bedsores, severe spasticity or uncomfortable deformities [5]. Future work will hopefully aim at developing guidelines regarding the type of treatment to implement in order to manage and treat pain/nociception in patients with DOC.

CONCLUSIONS

In both acute and chronic stages of DOC following a severe brain injury, several conditions are likely to induce pain, especially during care and mobilization [11]. The possibility of preserved pain perception capacities highlighted by neuroimaging studies in patients in a MCS and in some patients in a VS/UWS supports the idea that these individuals need analgesic treatment and monitoring. The NCS-R is the first tool developed to assess nociception and pain in patients with DOC in both acute and chronic stage. It is based on a rapid, standardized, and sensitive scale, which can be easily implemented in acute and subacute units for assessing acute pain. Other scales also showed their interest for assessing sedated and or intubated patients in the intensive care setting. Additional investigations are needed to develop a complete battery of valid and sensitive measures for clinicians to efficiently detect and treat nociception and pain (both acute and neuropathic pain) in patients with severe brain injury. Finally, clinical guidelines regarding prevention and treatments of pain in DOC need to be developed.

REFERENCES

1. Barr J, Fraser GL, Puntillo K, Ely EW, Gelinas C, Dasta JF, Davidson JE, Devlin JW, Kress JP, Joffe AM, et al. Clinical practice guidelines for the management of pain, agitation, and delirium in adult patients in the intensive care unit. Crit Care Med 2013;41(1):263–306.
2. Bogner JA, Corrigan JD, Fugate L, Mysiw WJ, Clinchot D. Role of agitation in prediction of outcomes after traumatic brain injury. Am J Phys Med Rehabil 2001;80(9):636–44.
3. Boitor M, Fiola JL, Gelinas C. Validation of the critical-care pain observation tool and vital signs in relation to the sensory and affective components of pain during mediastinal tube removal in postoperative cardiac surgery intensive care unit adults. J Cardiovasc Nurs 2015; Epub Mar 30.
4. Boly M, Faymonville ME, Schnakers C, Peigneux P, Lambermont B, Phillips C, Lancellotti P, Luxen A, Lamy M, Moonen G, et al. Perception of pain in the minimally conscious state with PET activation: an observational study. Lancet Neurol 2008;7(11):1013–20.
5. Borsook D. Neurological diseases and pain. Brain 2012;135(Pt 2):320–44.
6. Chapman CR, Bradshaw DH, Donaldson GW, Jacobson RC, Nakamura Y. Central noradrenergic mechanisms and the acute stress response during painful stimulation. J Psychopharmacol 2014;28(12):1135–42.
7. Chapman CR, Oka S, Bradshaw DH, Jacobson RC, Donaldson GW. Phasic pupil dilation response to noxious stimulation in normal volunteers: relationship to brain evoked potentials and pain report. Psychophysiology 1999;36(1):44–52.
8. Chatelle C, De Val MD, Catano A, Chaskis C, Seeldrayers P, Laureys S, Biston P, Schnakers C. Is the nociception coma scale-revised a useful clinical tool for managing pain in patients with disorders of consciousness? Clin J Pain 2015; Epub May 28.
9. 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(12):1233–7.
10. Chatelle C, Thibaut A, Bruno MA, 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(2):149–52.
11. Chatelle C, Thibaut A, Whyte J, De Val MD, Laureys S, Schnakers C. Pain issues in disorders of consciousness. Brain Inj 2014;28(9):1202–8.
12. Demertzi A, Antonopoulos G, Heine L, Voss HU, Crone JS, de Los Angeles C, Bahri MA, Di Perri R, Gomez F, Vanhaudenhuyse A, et al. Intrinsic functional connectivity differentiates minimally conscious from unresponsive patients. Brain 2015;138:2619–31.

13. Demertzi A, Jox RJ, Racine E, Laureys S. A European survey on attitudes towards pain and end-of-life issues in locked-in syndrome. Brain Inj 2014;28(9):1209–15.

14. Demertzi A, Ledoux D, Bruno M-A, Vanhaudenhuyse A, Gosseries O, Soddu A, Schnakers C, Moonen G, Laureys S. Attitudes towards end-of-life issues in disorders of consciousness: a European survey. J Neurol 2011;258(6):1058–65.

15. Demertzi A, Racine E, Bruno M-A, Ledoux D, Gosseries O, Vanhaudenhuyse A, Thonnard M, Soddu A, Moonen G, Laureys S. Pain perception in disorders of consciousness: neuroscience, clinical care, and ethics in dialogue. Neuroethics 2013;6(1):37–50.

16. Demertzi A, Schnakers C, Ledoux D, Chatelle C, Bruno M-A, Vanhaudenhuyse A, Boly M, Moonen G, Laureys S. Different beliefs about pain perception in the vegetative and minimally conscious states: a European survey of medical and paramedical professionals. Prog Brain Res 2009;177:329–38.

17. de Tommaso M, Navarro J, Ricci K, Lorenzo M, Lanzillotti C, Colonna F, Resta M, Lancioni G, Livrea P. Pain in prolonged disorders of consciousness: laser evoked potentials findings in patients with vegetative and minimally conscious states. Brain Inj 2013;27(7–8):962–72.

18. Fins JJ. Affirming the right to care, preserving the right to die: disorders of consciousness and neuroethics after Schiavo. Palliat Support Care 2006;4(2):169–78.

19. Flor H, Nikolajsen L, Staehelin Jensen T. Phantom limb pain: a case of maladaptive CNS plasticity? Nat Rev Neurosci 2006;7(11):873–81.

20. Garcia-Larrea L, Peyron R. Pain matrices and neuropathic pain matrices: a review. Pain 2013;154(suppl 1):S29–S43.

21. Gélinas C, Arbour C. Behavioral and physiologic indicators during a nociceptive procedure in conscious and unconscious mechanically ventilated adults: similar or different? J Crit Care 2009;24(4):628.e7–17.

22. Gelinas C, Johnston C. Pain assessment in the critically ill ventilated adult: validation of the Critical-Care Pain Observation Tool and physiologic indicators. Clin J Pain 2007;23(6):497–505.

23. Giacino J, Ashwal S, Childs N, Cranford R, Jennett B, Katz D, Kelly J, Rosenberg J, Whyte J, Zafonte R. The minimally conscious state: definition and diagnostic criteria. Neurology 2002;58(3):349–53.

24. Halliburton JR. Awareness during general anesthesia: new technology for an old problem. CRNA 1998;9(2):39–43.

25. Herr K, Coyne PJ, Key T, Manworen R, McCaffery M, Merkel S, Kelly JP, Wild L. Pain assessment in the nonverbal patient: position statement with clinical practice recommendations. Pain Manag Nurs 2006;7(2):44–52.

26. Herr K, Coyne PJ, McCaffery M, Manworren R, Merkel S. Pain assessment in the patient unable to self-report: position statement with clinical practice recommendations. Pain Manag Nurs 2011;12(4):230–50.

27. Hofbauer RK, Fiset P, Plourde G, Backman SB, Bushnell MC. Dose-dependent effects of propofol on the central processing of thermal pain. Anesthesiology 2004;100(2):386–94.

28. Hummel P, van Dijk M. Pain assessment: current status and challenges. Semin Fetal Neonatal Med 2006;11:237–45.

29. Ingvar M. Pain and functional imaging. Philos Trans R Soc Lond B Biol Sci 1999;354(1387):1347–58.

30. International Association for the Study of Pain. Classification of chronic pain: descriptions of chronic pain syndromes and definitions of pain terms. Task force on taxonomy. Seattle, WA: IASP Press; 1994.

31. Jeanne M, Logier R, De Jonckheere J, Tavernier B. Heart rate variability during total intravenous anesthesia: effects of nociception and analgesia. Auton Neurosci 2009;147(1–2):91–6.

32. Kassubek J, Juengling FD, Elsa T, Spreerc J, Herpersa M, Krauseb T, Moserb E, Lücking CH. Activation of a residual cortical network during painful stimulation in long-term postanoxic vegetative state: a $^{15}O–H_2O$ PET study. J Neurol Sci 2003;212:85–91.

33. Kim CE, Kim YK, Chung G, Jeong JM, Lee DS, Kim J, Kim SJ. Large-scale plastic changes of the brain network in an animal model of neuropathic pain. Neuroimage 2014;98:203–15.

34. Kotchoubey B, Merz S, Lang S, Markl A, Muller F, Yu T, Schwarzbauer C. Global functional connectivity reveals highly significant differences between the vegetative and the minimally conscious state. J Neurol 2013;260(4):975–83.

35. Kupers R. Is the placebo powerless? N Engl J Med 2001;345(17):1278–9.

36. Latorre Marco I, Solis Muñoz M, Falero Ruiz T, Larrasquitu Sanchez A, Romay Perez AB, Millan Santos I. Validation of the scale of behavior indicators of pain (ESCID) in critically ill, non-communicative patients under mechanical ventilation: results of the ESCID scale [in Spanish]. Enferm Intensiva 2011;22(1):3–12.

37. Laureys S, Celesia GG, Cohadon F, Lavrijsen J, Leon-Carrion J, Sannita WG, Sazbon L, Schmutzhard E, von Wild KR, Zeman A, Dolce G. Unresponsive wakefulness syndrome: a new name for the vegetative state or apallic syndrome. BMC Med 2010;8:68.

38. Laureys S, Faymonville M, Peigneux P, Damas P, Lambermont B, Del Fiore G, Degueldre C, Aerts J, Luxen A, Franck G. Cortical processing of noxious somatosensory stimuli in the persistent vegetative state. Neuroimage 2002;17(2):732–41.

39. Lawrence J, Alcock D, McGrath P, Kay J, MacMurray SB, Dulberg C. The development of a tool to assess neonatal pain. Neonatal Netw 1993;12(6):59–66.

40. Lockwood PL, Iannetti GD, Haggard P. Transcranial magnetic stimulation over human secondary somatosensory cortex disrupts perception of pain intensity. Cortex 2012;49(8):2201–9.

41. Loeser JD, Treede RD. The Kyoto protocol of IASP basic pain terminology. Pain 2008;137(3):473–77.

42. Markl A, Yu T, Vogel D, Muller F, Kotchoubey B, Lang S. Brain processing of pain in patients with unresponsive wakefulness syndrome. Brain Behav 2013;3(2):95–103.

43. Moulton EA, Pendse G, Becerra LR, Borsook D. BOLD responses in somatosensory cortices better reflect heat sensation than pain. J Neurosci 2012;32(17):6024–31.

44. Mouraux A, Diukova A, Lee MC, Wise RG, Iannetti GD. A multisensory investigation of the functional significance of the "pain matrix." Neuroimage 2011;54(3):2237–49.

45. The Multi-Society Task Force on PVS. Medical aspects of the persistent vegetative state. N Engl J Med 1994;330(21):1499–508.

46. Oka S, Chapman CR, Kim B, Nakajima I, Shimizu O, Oi Y. Pupil dilation response to noxious stimulation: effect of varying nitrous oxide concentration. Clin Neurophysiol 2007;118(9):2016–24.

47. Payen JF, Bru O, Bosson JL, Lagrasta A, Novel E, Deschaux L, Lavagne P, Jacquot C. Assessing pain in critically ill sedated patients using a behavioral pain scale. Crit Care Med 2001;29(12):2258–63.

48. Ploner M, Gross J, Timmermann L, Schnitzler A. Cortical representation of first and second pain sensation in humans. Proc Natl Acad Sci U S A 2002;99(19):12444–8.

49. Ploner M, Lee MC, Wiech K, Bingel U, Tracey I. Prestimulus functional connectivity determines pain perception in humans. Proc Natl Acad Sci U S A 2010;107(1):355–60.

50. Rainville P, Bao QVH, Chrétien P. Pain-related emotions modulate experimental pain perception and autonomic responses. Pain 2005;118(3):306–18.

51. Rainville P, Carrier B, Hofbauer RK, Bushnell MC, Duncan GH. Dissociation of sensory and affective dimensions of pain using hypnotic modulation. Pain 1999;82:159–71.

52. Ranger M, Johnston CC, Anand KJS. Current controversies regarding pain assessment in neonates. Semin Perinatol 2007;31:283–8.

53. Rijkenberg S, Stilma W, Endeman H, Bosman RJ, Oudemans-van Straaten HM. Pain measurement in mechanically ventilated critically ill patients: Behavioral Pain Scale versus Critical-Care Pain Observation Tool. J Crit Care 2015;30(1):167–72.

54. Ronga I, Valentini E, Mouraux A, Iannetti GD. Novelty is not enough: laser-evoked potentials are determined by stimulus saliency, not absolute novelty. J Neurophysiol 2013;109(3):692–701.

55. Schnakers C, Chatelle C, Demertzi A, Majerus S, Laureys S. What about pain in disorders of consciousness? AAPS J 2012;14(3):437–44.

56. Schnakers C, Chatelle C, Majerus S, Gosseries O, De Val M, Laureys S. Assessment and detection of pain in noncommunicative severely brain-injured patients. Expert Rev Neurother 2010;10(11):1725–31.

57. Schnakers C, Chatelle C, Vanhaudenhuyse A, Majerus S, Ledoux D, Boly M, Bruno MA, Boveroux P, Demertzi A, Moonen G, Laureys S. The Nociception Coma Scale: a new tool to assess nociception in disorders of consciousness. Pain 2010;148(2):215–9.

58. Schnakers C, Vanhaudenhuyse A, Giacino J, Ventura M, Boly M, Majerus S, Moonen G, Laureys S. Diagnostic accuracy of the vegetative and minimally conscious state: clinical consensus versus standardized neurobehavioral assessment. BMC Neurol 2009;9(1):35.

59. Seeley WW, Menon V, Schatzberg AF, Keller J, Glover GH, Kenna H, Reiss AL, Greicius MD. Dissociable intrinsic connectivity networks for salience processing and executive control. J Neurosci 2007;27(9):2349–56.

60. Shackman AJ, Salomons TV, Slagter HA, Fox AS, Winter JJ, Davidson RJ. The integration of negative affect, pain and cognitive control in the cingulate cortex. Nat Rev Neurosci 2011;12(3):154–67.

61. Stoll J, Chatelle C, Carter O, Koch C, Laureys S, Einhauser W. Pupil responses allow communication in locked-in syndrome patients. Curr Biol 2013;23(15):R647–R648.

62. Thibaut 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;51:389–97.

63. van Dijk M, Peters WB, van Deventer P, Tibboel D. The COMFORT behavior scale: a tool for assessing pain and sedation in infants. Am J Nurs 2005;105(1):33–35, 37.

64. Wall PD, McMahon SB, Koltzenburg M. Wall and Melzack's textbook of pain. Philadelphia, PA: Elsevier/Churchill Livingstone; 2006.

65. Warden V, Hurley AC, Volicer L. Development and psychometric evaluation of the Pain Assessment in Advanced Dementia (PAINAD) scale. J Am Med Dir Assoc 2003;4(1):9–15.

66. Wiech K, Lin CS, Brodersen KH, Bingel U, Ploner M, Tracey I. Anterior insula integrates information about salience into perceptual decisions about pain. J Neurosci 2010;30(48):16324–31.

67. Yang LL, Niemann CU, Larson MD. Mechanism of pupillary reflex dilation in awake volunteers and in organ donors. Anesthesiology 2003;99(6):1281–6.

68. Yu T, Lang S, Vogel D, Markl A, Muller F, Kotchoubey B. Patients with unresponsive wakefulness syndrome respond to the pain cries of other people. Neurology 2013;80(4):345–52.

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