Ethical Implications: Pain, Coma, and Related Disorders

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Glossary

Analgesic – Any member of the diverse group of drugs (colloquially known as painkillers) used to relieve pain (achieve analgesia). Analgesic drugs act in various ways on the peripheral and central nervous systems; they include paracetamol (acetaminophen), the nonsteroidal anti-inflammatory drugs (NSAIDs) such as the salicylates, narcotic drugs such as morphine, synthetic drugs with narcotic properties such as tramadol, and various others.

Functional neuroimaging – The use of neuroimaging technology to measure an aspect of brain function, often with a view to understanding the relationship between activity in certain brain areas and specific mental functions.

Hydranencephaly – A type of cephalic disorder. This is a rare condition in which the cerebral hemispheres are absent and replaced by sacs filled with cerebrospinal fluid.

Opiates – Named so because they are constituents or derivatives of constituents found in opium. The major biologically active opiates found in opium are morphine, codeine, thebaine, and papaverine.

Pain – Defined as an unpleasant sensory and emotional experience associated with real or potential tissue damage.

Primary somatosensory area – In the human cortex it is located in the postcentral gyrus (parietal lobe). It is the location of the primary somatosensory cortex, the main sensory receptive area for the sense of touch.

Sedative – A substance that depresses the central nervous system, resulting in calmness, relaxation, reduction of anxiety, sleepiness, and slowed breathing. At high doses or when they are abused, many of these drugs can cause unconsciousness (see hypnotic) and even death.

Thalamus – It constitutes the main part of the diencephalon. The thalamus is believed to both process and relay sensory information selectively to various parts of the cerebral cortex, as one thalamic point may reach one or several regions in the cortex.

Introduction

"Pain is defined as an unpleasant sensory and emotional experience associated with real or potential tissue damage." As this definition of the International Association of Pain Specialists points it out, pain is a subjective first-person experience. Pain assessment is directly based on the patient's verbal report. Pain scales were developed to be used by the patient himself as, for instance, the Visual Analogical Scale (VAS), one of the most used scales which allows to assess the intensity of pain in communicative patients. This method is inadequate for patients who cannot functionally communicate (verbally or nonverbally). Detecting and treating signs of pain represents an important medical and ethical stake especially in patients who are not communicative, as it is the case for many patients recovering from coma. Progress in acute neurocritical care has led to an increase in the number of patients surviving severe brain injury. Whereas some recover quickly, others take more time and pass through different states of unconsciousness (i.e., coma, vegetative state) before partially (i.e., minimally conscious state) or fully recovering awareness. In patients with an altered state of consciousness, it is necessary to

Encyclopedia of Consciousness (2009), vol. 1, pp. 243-250

use indirect means of assessments such as behavioral observation or physiological measurements. Responses such as facial expression, movements of the limbs, vocalizations and modification of heart rate or breathing is often considered to detect the presence of a painful experience. Numerous standardized pain scales were developed. The aim of this article is to (1) review the remnant brain activity evoked by noxious stimuli in altered states of consciousness, particularly in vegetative (VS) and minimally conscious (MCS) states; (2) discuss the problems encountered in pain assessment in these noncommunicative patients; and (3) review the ethical concerns as regards to their potential feeling of pain.

Pain Assessment in Noncommunicative Patients

Severely brain-injured patients are unable to communicate their feelings and possible pain experiences. Numerous pain scales were developed for assessing noncommunicative subjects such as newborns or demented elderly. However, few of these scales were properly validated. The most validated scales are the Neonatal Infant Pain Scale (NIPS) and the Faces, Legs, Activity, Cry, Consolability (FLACC) Pain Assessment Tool used for assessing pain in newborns (see Table 1). The Pain Assessment in Advanced Dementia Scale (PAINAD) and the Checklist of Nonverbal Pain Indicators (CNPI) are used for assessing pain in the demented elderly (see Table 1). These pain scales mainly include the observation of grimaces, cries, negative verbalizations, body movements, changes in breathing patterns, and consolability.

Some of these clinical parameters are observed during the behavioral assessment of patients in altered states of consciousness (see Table 2). The behavioral observation remains the gold standard to detect conscious perception in response to various stimuli such as auditory, visual, tactile, as well as noxious. Considering noxious stimulation, three types of motor responses to pain are usually considered: stereotypical responses (i.e., slow generalized flexion or extension of the upper and lower extremities), flexion withdrawal (i.e., the limb moves away from the point of stimulation), and localization responses (i.e., the nonstimulated limb must locate and make contact with the stimulated body part at the point of stimulation). These responses are respectively linked, based on current understanding and theory, to brainstem, subcortical or cortical activity, respectively. Localization response to pain is the only motor response considered indicative of conscious perception. Clinically, these behaviors are studied by applying pressure to the fingernail, to the temporomandibular joint, the supraorbital nerve, or to the ear. For instance, the Glasgow Coma Scale, which is the most used coma scale in the world, uses the pressure to the fingernail. The literature nevertheless suggests that pressure of the finger nail bed with a pencil as was first proposed by Teasdale and Jennett (1974) falsely lowers the level of responsiveness. No study has assessed which stimulation is the more efficient to elicit localization of pain. Determining which stimulation is the most powerful to detect signs of conscious perception is a real challenge. Indeed, previous studies showed a high rate of misdiagnosis (37%–43%) among patients diagnosed as being in VS underlying the difficulty to detect signs of consciousness. Moreover, various rates of misdiagnosis were observed according to the scale used for the behavioral assessment. As these scales used different noxious stimulations,

Table 1 Selection of behavioral scales which assess acute pain in noncommunicative patients

Population	*Behavioral scale*
Infants	NIPS: Neonatal Infant Pain Scale FLACC: Faces, Legs, Activity, Cry, Consolability Observational Tool PIPP: Premature Infant Pain Profile CRIES CHEOPS: Children's Hospital of Eastern Ontario Pain Scale
Demented elderly	PAINAD: Pain Assessment In Advanced Dementia CNPI: Checklist of Nonverbal Pain Indicators DOLOPLUS 2 ADD: The Assessment of Discomfort in Dementia Protocol PACSLAC : Pain Assessment Checklist for Seniors with Limited Ability to Communicate

Adapted from Schnakers C and Zaster ND (2007) Pain assessment and management in disorders of consciousness. *Current Opinion Neurol*, 20, 620–626.

Table 2 Behavioral coma scales with assessment of pain

Scale name	*Clinical assessment*
Glasgow Coma Scale	Encompasses three components: eye (E), verbal (V), and motor (M) response to external stimuli. Procedure: As regards to motor responses, pressure is applied to the fingernail bed with a pencil resulting in either flexion or extension at the elbow. If flexion is observed, stimulation is then applied to the head and neck and to the trunk to test for localization. Number of stimulations: Not explicitly mentioned. Quotation: Best response observed ranging from M1 to M6.
Coma Recovery Scale – Revised	Includes auditory, visual, motor, verbal, communication, and arousal subscales. Procedure: A deep pressure applied to the nail beds of each extremity. Number of stimulations: Two times each side. Quotation: considered as present if behavior is observed two out of four times.
Full Outline of Unresponsiveness	Consists of four components (eye, motor, brainstem, and respiration) with a maximal score of four. The motor component combines decorticate and withdrawal flexion responses. Procedure: The painful stimulus is applied to the temporomandibular joint or supraorbital nerve. Number of stimulations: Not explicitly mentioned. Quotation: Best response observed.
Coma/Near-Coma Scale	Assesses responses to auditory, visual, verbal, tactile, olfactory, threat, and noxious stimulation. Procedure: Two stimuli are used to assess response to pain: (1) firm pinch on finger tip; (2) robust ear pinch/pull. Number of stimulations: Three times each side. Quotation: Score of 0–4 according to the number and the type of response observed.

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further studies could assess which of these simulations is the more interesting in the detection of conscious perception and, therefore, in the detection of pain.

Some coma scales also study grimaces but none in response to noxious stimulation. Even if grimacing is considered as a pain indicator, for instance, in pain assessment scales employed in demented elderly, the Multi Society Task Force on PVS did not consider it as a necessary sign of conscious perception. Patients showing no sign of consciousness except grimaces to noxious stimuli can therefore be diagnosed as being in VS. However, clinical data considering the proportion of VS patients only showing this behavior are warranted. Moreover, until now, no functional neuroimaging study has investigated the neural processing of pain in these patients as previous studies did not involve patients presenting grimaces in response to pain. Additional research is needed to better understand the brain processing underlying this apparent indicator of painful experience. Similarly to grimaces, other parameters such as vocalization and verbalization or, less often, changes in breathing rate are part of some behavioral consciousness scales but never in response to pain. Finally, the consolability (i.e., number of tactile or auditory stimulations needed to reassure the stimulated patient) is not considered in any known coma scale.

To summarize, existing coma scales do not specifically assess possible pain perception in noncommunicative patients recovering from coma. This is why we have recently developed a scale to assess pain in severely brain-injured patients, the Coma Pain Scale (CPS). This scale consists in the observation of motor, verbal, and visual responses, facial expression, and pain anticipation. In a previous version, the CPS also included the subscale 'breathing,' which was excluded considering the difficulty in assessing this parameter without appropriate monitoring devices. Each subscale of the CPS is scored from 0 to 3 according to the response complexity (the total score is 15). A pilot study was performed in 24 severely brain-injured patients (63 ± 14 years, 15 men, 10 traumatic, 8 chronic) diagnosed as VS ($n = 11$) or MCS ($n = 13$). The results showed a good correlation between the CPS and other validated pain scales such as the PAINAD, the CNPI, the NIPS, and the FLACC, suggesting that, in parallel to other scales, the CPS assessed pain. However, on the contrary to these pain scales, the CPS scores were significantly different according to clinical entity (i.e., VS and MCS), suggesting that the CPS is better adapted for the assessment of pain in patients recovering from coma. Finally, a good interrater agreement was observed. The CPS seems therefore to be a promising tool for assessing pain in severely brain-injured patients in altered states of consciousness. Further investigations are undergoing and the obtained results will need to be compared with functional neuroimaging data.

Pain Processing in Coma and Related Disorders

It is known that pain is mediated by a widely distributed cerebral network. The neural correlates of pain involve the lateral and medial pain systems. The lateral pain system includes the lateral thalamus, primary and secondary somatosensory cortex (SI and SII), parietal operculum, and insula. The medial pain system involves the medial thalamus, anterior cingulated cortex, amygdala, hippocampus, hypothalamus, locus coeruleus, and periaqueductal gray matter.

In fact, the emergence of pain perception is composed by sensory–discriminative, cognitive–evaluative, and motivational–affective central systems. Indeed, the thalamus (which participates to the increase of arousal following a noxious stimulation) and midbrain (more exactly, periaqueductal matter) are thought to be involved in the modulation of reflex responses to pain stimulus. Primary and secondary somatosensory cortex participate to the sensory–discriminative aspects of pain processing, whereas cingulate, insula, orbitofrontal, and medial prefrontal cortices are considered to be involved in the affective aspect of pain processing. Moreover, interconnectivity between the periaqueductal matter and orbitofrontal cortex may be key to cognitive–emotional responses associated with pain. Additionally, a recent study of Boly *et al.* showed that activity in the anterior cingulate cortex and insula just before pain stimulation can increase pain perception.

Recently, residual central pain processing existing in altered states of consciousness such as VS and MCS was investigated by the use of functional neuroimaging. Laureys *et al.* compared cerebral activation to high-intensity noxious electrical stimulation of the median nerve at the wrist in 15 VS patients (12 nontraumatic, mean time postinsult was 1 month) and 15 healthy volunteers. Noxious stimulation activated contralateral thalamus, midbrain, and primary somatosensory cortex in every vegetative patient, possibly suggesting a partially preserved sensory–discriminative pain processing. Kassubek *et al.*, who used a similar methodology in 7 VS patients (all anoxic, mean time postinsult was 1.5 years), confirmed the activation in primary somatosensory cortex but also found an activation in secondary somatosensory, insular, and anterior cingulate cortices, which is considered critical in the affective and cognitive processing of pain. However, brain connectivity studies conducted by Laureys *et al.* showed that primary somatosensory cortex was functionally disconnected from secondary somatosensory, bilateral posterior parietal, premotor, polysensory superior temporal, prefrontal cortices, as well as from anterior cingulate cortex. The observed primary cortex activation is therefore suggested to be isolated from higher-order associative cortical activity considered crucial in the conscious perception of the stimuli as well as from areas involved in the affective and cognitive pain processing. Finally, in brain death, noxious stimuli do not lead to any neural activation whatsoever (see Figure 1).

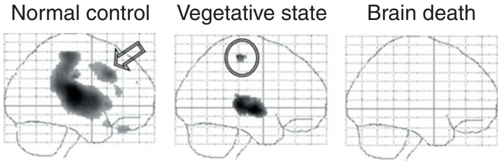

Figure 1 Painful stimuli activate a widespread network of cortical areas encompassing the anterior cingulate cortex considered to be involved in the affective component of pain perception (arrow). Patients in a vegetative state not only show subcortical activation (i.e., brainstem and thalamus) but also of primary somatosensory cortex (circle). However, this area is disconnected from the rest of the gray matter and is hence considered to be insufficient to lead to conscious perception of pain. In brain death, noxious stimuli do not lead to any neural activation whatsoever. Adapted by permission from Macmillan Publishers Ltd: [Nature Reviews Neuroscience] (Laureys *et al.*, 2005), copyright (2005).

The cerebral activation to pain is different in MCS patients. Boly *et al.* showed brain activation similar to controls in response to noxious stimuli in five patients in a MCS. This activation involved the anterior cingulate area, which suggests that the patients could perceive the unpleasant aspect of painful stimulation. Even if other studies are needed to confirm these results, this study suggests a sufficient cortical integration for conscious perception and hence a conscious pain experience in MCS patients. Further studies will need to investigate the level of pain perception in these patients. Indeed, many cognitive components such as long-term memory (particularly, the ability to remember previous pain experiences) play a role in the experience of pain. Few studies have investigated the residual cognitive functioning in altered states of consciousness. Recently, Owen and coworkers showed a brain activation similar to controls in a severely brain-injured patient who was instructed to imagine herself playing tennis or going for a walk in her home. As semantic as well as autobiographical information encoded in long-term memory were needed to perform this task, this result suggests that some high-level cognitive treatment could be preserved in patients recovering from coma, even in the presence of low behavioral levels (this patient exclusively showed brief visual fixation).

Ethical Considerations

As discussed, neuroimaging data seem to indicate a brain activation to pain in MCS similar to controls, involving the anterior cingulate cortex. The data suggest that these MCS patients could perceive pain. On the contrary, VS patients showed a functionally disconnected brain activity, suggesting the absence of an integrated pain perception. Considering these results, adequate analgesic treatment has to be provided in MCS patients. The issue is much more complicated in VS patients. Given the high rate of misdiagnosis (37%–42%), if we decide not to administer analgesic treatment in the presence of a potential painful experience (e.g., contractures or fractures), there is a real probability for not treating a patient erroneously diagnosed and, hence, for not treating a patient who perceives pain. As regards to the ethical principles of beneficence and nonmaleficence, clinicians want to be certain that an individual is not suffering when making clinical decisions about treatment or the end of treatment. Therefore, medical staff has to provide pain treatment and comfort to all patients, even noncommunicative patients diagnosed as being in a VS.

In a medicolegal context, the question may be different as the patient has to be categorized as perceiving or not perceiving pain. However, as pain is a subjective first-person experience mediated in part by beliefs or emotions, we cannot be sure whether patients in an altered state of consciousness perceive pain or not. In our view, considering the current levels of clinical and scientific uncertainty, pain treatment should be considered in all patients in a VS or MCS. However, current clinical guidelines do not share this view and do not propose the use of analgesics in VS. For instance, Terry Schiavo died from dehydration without administration of opiates as she was diagnosed as VS by the High Court's experts.

On the contrary, a systematic use of analgesics in VS could have undesirable sedative effects leading to an underestimation of the state of consciousness. Under-use of analgesics could however also lead to an underestimation of consciousness. Indeed, the presence of intense pain may diminish already trifling cognitive and motor abilities and could, then, lead to diagnostic error. Adequately assessing and monitoring pain and pain therapy hence represents a real clinical challenge.

In our view, much more research is needed in order to propose evidence-based guidelines. But such researches represent major ethical challenges. For some scientists noxious stimuli cannot be applied to patients unable to give informed consent. Monitoring pain in severely brain damaged patients represents such an important humane, affective, and social problem that it warrants further study to better understand the underlying cerebral dysfunction of VS and MCS. In fact, to exclude investigations of residual perception of pain in these patients would be ethically unwarrantable. We propose an ethical framework balancing on patients' protection and inclusion in research protocols and medical advances.

Conclusions

VS and MCS patients can, by definition, not communicate their feelings and possible pain perception. Behavioral coma scales developed for assessing the consciousness level of severely brain-injured patients integrate some parameters used for detecting pain perception in noncommunicative patients. These scales are nevertheless not sufficient for specifically assessing pain in VS or MCS patients. Moreover, some of the studied parameters such as physiological changes are not sufficient to discern a conscious painful experience. Indeed, studies in general anesthesia showed that autonomic measurements (i.e., heart rate, respiratory frequency, blood pressure, pupillary diameter, and skin conductance) are not reliable indicators of pain. Future studies should hence focus on methodologies for adapted pain assessment relevant to this patient population. A standardized and validated behavioral pain scale for altered states of consciousness will allow (1) at a scientific level, to better specify the behavioral pattern of VS patients (e.g., prevalence of grimaces) and to determine the possible prognostic value of these behaviors and (2) at a clinical level, to monitor pain treatment in order to avoid sedative effects as well as under-uses of analgesics.

As regards to neuroimaging, on the contrary to MCS, VS does not suggest an integrated cortical pain processing. However, there are still some debates regarding whether conscious perception of pain may be mediated by subcortical areas. Indeed, a subcortical system comprising the basal ganglia, medial and midline thalamic nuclei, substantia nigra, ventral tegmental area, superior colliculi, midbrain, and pontine reticular formation has been proposed by Merker and coworkers as sufficient to mediate the organization of consciousness. Consistent with this theory, the responses to noxious stimulation of children with hydranencephaly seem sometimes purposeful and similar to those of intact children. Preterm neonates or adolescents with cortical parenchymal injury mount biobehavioral responses to pain that are indistinguishable from those of normal controls. This suggests that the mechanisms of conscious sensory perception are not entirely dependent on cortical activity. However, most neuroscientific studies point to a key role of cortico-cortical and thalamo-cortical interaction in the emergence of conscious experiences. This interaction seems to be absent in VS patients. Therefore, the question of whether pain perception and suffering are present in patients with an altered state of consciousness has certainly to be further investigated in noncommunicative VS and MCS patients.

Finally, in our view, as regards to our current scientific knowledge on brain processing in altered states of consciousness, the possibility of pain perception should be considered in all patients recovering from coma. In the future, researches integrating behavioral and neuroimaging data will be warranted to establish clear guidelines for treating pain in these patients and therefore to increase the quality of life or of the end of life in this challenging noncommunicative population.

Acknowledgments

This research was funded by the Belgian National Funds for Scientific Research (FNRS), European Commission, James McDonnell Foundation, Mind Science Foundation, French Speaking Community Concerted Research Action, Fondation Médicale Reine Elisabeth, and University of Liège.

See also: Animal Consciousness.

Suggested Readings

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Biographical Sketch

Caroline Schnakers graduated as a neuropsychologist from the University of Liège in 2003. Dr Schnakers joined the Coma Science Group in 2002. She has expertise in the behavioral assessment of consciousness levels in severely brain-injured patients. She validated the French version of the Coma Recovery Scale – Revised and employs in electrophysiological methods (more exactly, electroencephalogram and cognitive evoked potentials) investigating its potential in the detection of early signs of consciousness in coma survivors. She received her doctorate in psychological sciences in 2008 and is involved in the Belgian federal network for the care of VS and MCS patients. She has recently developed a freely available DVD for educational purposes on the diagnosis and assessment of chronic disorders of consciousness. Dr Schnakers is supported by the 'Fonds Léon Fredericq,' The European Commission and the Belgian National Funds for Scientific Research (FNRS).

Marie-Elisabeth Faymonville graduated as a medical doctor medicine from the University of Liège (UL) in 1977. She specialized in anesthesia-intensive care in 1981 and obtained in 1983, a PhD in clinical sciences. She developed in 1992 a new technique in anesthesia: hypnosedation. Her scientific approach allowed to promote hypnosis as a clinical tool, which is particularly interesting in modern medicine (especially, in chronic pain and in palliative care). Her research activity is focused on the investigation of the neuroanatomic mechanisms of different states of consciousness, including hypnosis. Since 2004, she has been leading the Pain Clinic and the Palliative Care Unit of the University Hospital of Liège.

Steven Laureys is a senior research associate at the Belgian National Fund of Scientific Research (FNRS) and Clinical Professor head of clinics at the Department of Neurology of the Liège University Hospital. In 1993, he graduated as a medical doctor from the Vrije Universiteit Brussels, Belgium. While specializing in neurology he took up a research career and obtained his MSc in pharmaceutical medicine, working on pain and stroke using *in vivo* microdialysis and diffusion MRI in the rat (1997). Drawn by functional neuroimaging, he moved to the Cyclotron Research Center at the University of Liège, Belgium, where he obtained his PhD (2000) by studying residual brain function in coma, vegetative, minimally conscious, and locked-in states. He is board certified in neurology (1998) and in palliative and end-of-life medicine (2004). He is a recipient of the William James Prize (2004) from the Association for the Scientific Study of Consciousness (ASSC) and the Cognitive Neuroscience Society (CNS) Young Investigator Award (2007). He recently published *The Boundaries of Consciousness* (Elsevier, 2005) and The Neurology of Consciousness (Academic Press 2008). He nowadays leads the Coma Science Group at the Cyclotron Research Centre at the University of Liège, Belgium.