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CHAPTER 22

Different beliefs about pain perception in the vegetative and minimally conscious states: a European survey of medical and paramedical professionals ☆

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Abstract: Pain management in severely brain-damaged patients constitutes a clinical and ethical stake. At the bedside, assessing the presence of pain and suffering is challenging due to both patients' physical condition and inherent limitations of clinical assessment. Neuroimaging studies support the existence of distinct cerebral responses to noxious stimulation in brain death, vegetative state, and minimally conscious state. We here provide results from a European survey on 2059 medical and paramedical professionals' beliefs on possible pain perception in patients with disorders of consciousness. To the question ''Do you think that patients in a vegetative state can feel pain?,'' 68% of the interviewed paramedical caregivers ($n = 538$) and 56% of medical doctors ($n = 1166$) answered ''yes'' (no data on exact profession in 17% of total sample). Logistic regression analysis showed that paramedical professionals, religious caregivers, and older caregivers reported more often that vegetative patients may experience pain. Following professional background, religion was the highest predictor of caregivers' opinion: 64% of religious ($n = 1009$; 850 Christians) versus 52% of nonreligious respondents ($n = 830$) answered positively (missing data on religion in 11% of total sample). To the question ''Do you think that patients in a minimally conscious state can feel pain?'' nearly all interviewed caregivers answered ''yes'' (96% of the medical doctors and 97% of the paramedical caregivers). Women and religious caregivers reported more often that minimally conscious patients may experience pain. These results are discussed in terms of existing definitions of pain and suffering, the remaining uncertainty on the clinical assessment of pain as a subjective first-person experience and recent functional neuroimaging findings on nociceptive processing in disorders of

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consciousness. In our view, more research is needed to increase our understanding of residual sensation in vegetative and minimally conscious patients and to propose evidence-based medical guidelines for the management of possible pain perception and suffering in these vulnerable patient populations.

Keywords: pain; brain injury; disorders of consciousness; survey; neuroimaging; ethics; end-of-life; vegetative state

Introduction

The International Association for the Study of Pain (IASP, 1994) defines pain as ''an unpleasant sensory and emotional experience associated with real or potential tissue damage.'' As stressed by the IASP, the inability to communicate verbally does not negate the possibility that an individual is experiencing pain and is in need of appropriate pain-relieving treatment. Pain may also be reported in the absence of tissue damage or any likely pathophysiological cause; usually this happens for psychological reasons. Activity induced in the nociceptor and nociceptive pathways by a noxious stimulus is not pain, which is always a psychological state, even though pain most often has a proximate physical cause. Pain is a subjective first-person experience with both physical and affective aspects (Kupers et al., 2005). It is a sensation in a part or parts of the body, which is, always unpleasant and, therefore, an emotional experience. Pain and suffering are not interchangeable constructs. However, the concept of suffering is surprisingly ill defined and given relatively little attention in medicine. A person might experience significant pain-related suffering from a relatively low-level noxious stimulation if she or he believes the implications are ominous, interminable, and beyond their control (Turk and Wilson, 2009). Cassell (1991) defined suffering as ''the state of severe distress associated with events that threaten the intactness of the person.'' Pain by itself does not seem to be sufficient to cause suffering; rather it seems that the person's interpretation of the symptoms is crucial. We will here consider (as expressed by the Multi-Society Task Force on PVS, 1994) that pain and suffering refer to the unpleasant experiences that occur in response to stimulation of peripheral nociceptive receptors and their peripheral and central afferent pathways or that they may emanate endogenously from the depths of human self-perception.

The management of pain and suffering in disorders of consciousness (DOCs) is challenging because, by definition, patients in a vegetative state (VS) or minimally conscious state (MCS) cannot verbally or nonverbally communicate their feelings or experiences (e.g., McQuillen, 1991; Bernat, 2006; Laureys and Boly, 2007). The VS is a condition of preserved wakefulness contrasted with absent voluntary interaction with the environment (Jennett and Plum, 1972). The MCS was only recently defined (Giacino et al., 2002) and is characterized by discernible but fluctuating signs of awareness without consistent communication with the environment. How can we know if patients in VS or in MCS feel pain or suffering? The perceptions of pain and suffering are conscious experiences: the wakeful unconsciousness of vegetative patients, by definition, precludes these experiences. Of course, there is a theoretical problem to evaluate the subjective experience of pain (and any other conscious perception or thought) in another person. At the patient's bedside, we are limited to evaluate the behavioral responsiveness to pain. If patients never show any sign of voluntary movement in response to noxious stimuli it will be concluded they do not experience pain. They may, however, be aroused by noxious stimuli by opening their eyes if they are closed, quickening their breathing, increasing heart rate and blood pressure, and occasionally show grimace-like or crying-like behavior. As all these abilities are also seen in infants with anencephaly (The Medical Task Force on Anencephaly, 1990; Payne and Taylor, 1997) they are considered to be of subcortical origin and not necessarily reflecting conscious perception of pain. We also know from studies in general anesthesia that motor or

autonomic responses are no reliable indicators of consciousness (e.g., Halliburton, 1998).

DOC patients classically are bed- or chair-bound and may suffer from spasticity, contractures, fractures, pressure sores, soft tissue ischemia, peripheral nerve injuries, complex regional pain syndrome, central pain syndromes, and post-surgical incisional pain (Schnakers and Zasler, 2007). Since they cannot communicate their potential painful state, the existence of pain is clinically inferred from observing their spontaneous behavior or their motor responses to noxious stimulation. Stereotyped responses (i.e., slow generalized flexion or extension of the upper and lower extremities), flexion withdrawal (i.e., withdrawal of the limb away from the point of the stimulation), and localization responses (i.e., the nonstimulated limb locates and makes contact with the stimulated body part at the point of stimulation) are linked to, respectively, brainstem, subcortical, or cortical activity (e.g., Stevens and Nyquist, 2006). No response after intense noxious stimulation reveals a deep stage of coma; stereotyped responses are considered as ''automatic'' unconscious reflexes, whereas localization of noxious stimulation is usually considered as indicative of conscious perception (Posner et al., 2007).

Repeated clinical examinations by trained and experienced examiners are paramount for the behavioral assessment of pain. To date, several scales are used for assessing pain in noncommunicative individuals with end-stage dementia, in newborns and in sedated intensive care patients, but no scale was developed to assess pain in DOCs (Schnakers et al., 2009b). We therefore recently proposed the Nociception Coma Scale as a standardized and validated tool measuring motor, verbal, and visual responses and facial expression in response to pain (Schnakers et al., 2009a). However, the absence of a behavioral response cannot be taken as an absolute proof of the absence of consciousness (McQuillen, 1991; Bernat, 1992) and inferring pain and suffering solely by observing behavioral responses may be misleading, especially in patients with extreme motor impairment or with fluctuating levels of vigilance (e.g., Majerus et al., 2005). Given these limitations of our bedside clinical assessment of pain in noncommunicative brain injured patients, inherent to the first-person subjective dimension of pain, we will next review the usefulness of functional neuroimaging methods in the study of pain and suffering in VS and MCS.

Neuroimaging of pain

Since brain responses are the final common pathway in behavioral responses to pain (unconscious and conscious), we believe that the application of functional imaging will allow us to study pain in an objective manner and to propose evidence-based guidelines on the use of analgesia and symptom management in DOCs (e.g., Borsook and Becerra, 2006; Laureys et al., 2006; Laureys and Boly, 2008). In healthy controls, studies with positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) have revealed that pain cannot be localized in an isolated ''pain centre'' but rather encompasses a neural circuitry, the pain ''neuromatrix'' (Jones et al., 1991; Peyron et al., 2000). More specifically, two distinct cerebral networks have been identified to be involved in pain perception: (i) a lateral pain system or sensory network, encompassing lateral thalamic nuclei, primary and secondary somatosensory, as well as posterior parietal cortices; and (ii) a medial pain system or affective network, which involves the medial thalamus, anterior cingulate, and prefrontal cortices; the insular cortices playing an intermediate role (Hofbauer et al., 2001). For example, increased activity in the insular and anterior cingulate cortices prior to painful stimulation has been linearly associated with increased painfulness (Boly et al., 2007). Inversely, a hypnotic-induced absence of activation in these areas was associated with reduced subjective pain reports (Vanhaudenhuyse et al., 2009). These and other studies are increasing our understanding of the neural correlates of the sensory and affective components of pain (e.g., see review in Kupers et al., 2005), but it should be noted that at present our understanding of suffering (i.e., distress associated with events that threaten the intactness of the person; Cassell, 1991) is very limited and barely studied.

Recent neuroimaging studies have shown that DOCs are characterized by distinct cerebral patterns in response to sensory stimulation (e.g., Laureys et al., 2004; Laureys, 2005a; Giacino et al., 2006; Schiff, 2007; Owen, 2008). In 15 VS patients, our group found no evidence of noxious stimulation-related downstream activation beyond primary somatosensory cortex (Laureys et al., 2002). More importantly, functional connectivity assessment showed that the observed cortical activation subsisted as an island, dissociated from the pain matrix and the higher-order cortices that are currently thought to be necessary for conscious awareness (as shown by studies on conscious perception in healthy controls and on loss of consciousness in sleep and anesthesia; e.g., Baars et al., 2003; Boveroux et al., 2008; Laureys, 2005b). However, another study reported additional activation of secondary somatosensory and insula cortices in VS patients (Kassubek et al., 2003), implying the possibility of affective experiences of pain.

In striking contrast to what we observed in VS, MCS patients showed activation in not only midbrain, thalamus, and primary somatosensory cortex but also in secondary somatosensory, insular, posterior parietal, and anterior cingulate cortices (Fig. 1). The spatial extent of the activation in MCS patients was comparable to controls and no brain region showed less activation in MCS as compared to healthy individuals. A functional connectivity assessment of insular cortex demonstrated its preserved connections with a large set of associative areas encompassing posterior parietal, motor and supplementary motor, striatum, and dorsolateral prefrontal and temporal associative cortices as observed in controls (Boly et al., 2005). These neuroimaging data show large differences in brain activation between VS and MCS patients, despite a similar bedside behavioral evaluation. In the next section, we report differences in healthcare workers' beliefs toward possible pain in DOCs.

Attitudes toward pain perception

To our knowledge, no data exist on the thoughts of physicians and paramedical personnel toward pain perception in patients in VS as compared to MCS. We here present results from a questionnaire survey on attitudes on DOCs, which was distributed during lectures at medical and scientific conferences and meetings ($n = 48$) within

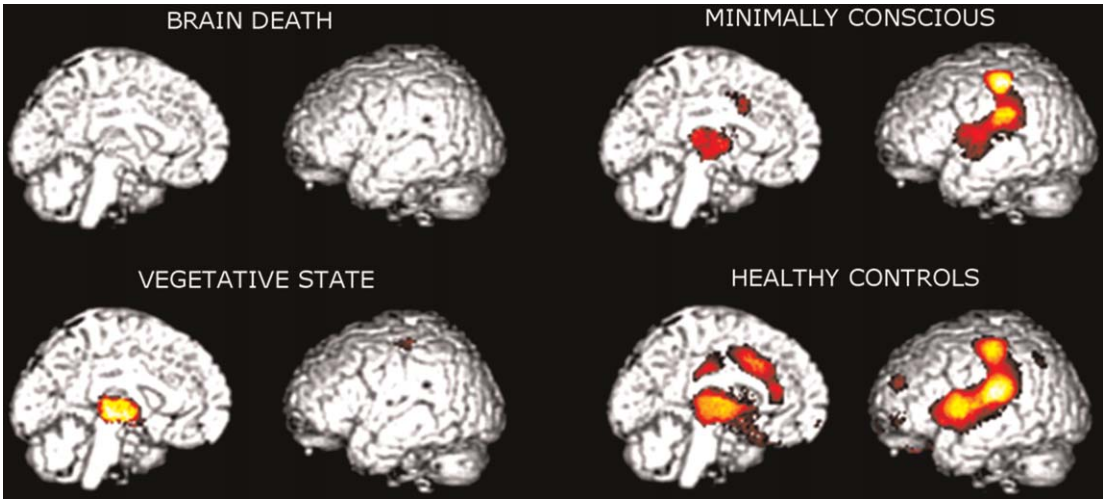

Fig. 1. Cerebral activation to noxious stimulation in brain death (adapted from Laureys, 2005a with permission), the VS (Laureys et al., 2002 with permission), and the MCS (Boly et al., 2008 with permission) as compared to healthy volunteers. Note: (i) the absence of activation in brain death; (ii) the preserved but low-level subcortical and primary cortical activation in the VS (the primary cortical activation was disconnected from the rest of the brain), and (iii) the near-normal activation in the minimally conscious state.

Europe (data were collected by SL, AD, MAB, AV, MAB, and DL between June 2007 and April 2009). Participation to the survey was voluntary and anonymous. Participants were first introduced to the clinical definitions of DOCs and were then asked to provide 'yes' or 'no' answers to 16 questions related to consciousness, VS, MCS, and locked-in syndrome. We here report the replies obtained in European medical and paramedical professionals to the questions ''Do you think that patients in a vegetative state can feel pain?'' and ''Do you think that patients in a minimally conscious state can feel pain?'' — the questions related to consciousness and the brain have been reported elsewhere (Demertzi et al., 2009). Recorded demographic data included age, gender, nationality, profession, and religious beliefs. Nationalities were categorized into three geographical regions based on previous classification criteria (Sprung et al., 2003): Northern (Denmark, Estonia, Finland, Lithuania, Netherlands, Norway, Poland, Russia, Sweden, United Kingdom), Central (Austria, Belgium, Czech Republic, Germany, Hungary, Luxembourg, Moldavia, Romania, Serbia, Slovakia, Slovenia, Switzerland), and Southern Europe (Bulgaria, Croatia, Cyprus, France, FYROM, Greece, Italy, Portugal, Spain, Turkey). Statistical analyses were performed using SPSS v.16.0 software packages. Multiple logistic regression (stepwise backward; i.e., independent variables are removed from the equation at consecutive steps; entry, $p = 0.05$ and removal, $p = 0.1$) was used to assess associations between obtained answers to the two questions and age, gender, profession, region, and religiosity. Chi-square tests assessed differences within categorical variables. Results were considered significant at $p < 0.05$ (two-sided).

The study sample included 2059 medical and paramedical professionals coming from 32 European countries (see Table 1 for demographic data). As a whole, the sampled participants replied more often that MCS patients could feel pain than that VS patients could feel pain ($\chi^2(1) = 7.9$, $p < 0.001$). Participants' opinions were much more consistent for pain perception in MCS (96% of the total sample considered MCS patients can feel pain), while responses were much more discordant for VS (59% considered vegetative patients could feel pain). Paramedical caregivers ($n = 538$) replied more often that patients in a VS could feel pain than did medical doctors ($n = 1166$) (68% versus 56%; $\chi^2(1) = 23.07$, $p < 0.001$; Fig. 2a). Following professional background, religion was the highest predictor of caregivers' opinion: 64% of religious ($n = 1009$; 94% Christians) versus 52% of nonreligious respondents ($n = 830$) answered positively (see Fig. 3a). There was no effect of religion practice (317 were practicing and 664 were not practicing their religion) on attitudes toward pain perception in the VS ($\chi^2(1) = 0.261$, $p = 0.609$). Logistic regression analysis showed that paramedical professionals, religious caregivers, and older caregivers reported more often that vegetative patients may experience pain (Table 2). To the question ''Do you think that patients in a minimally conscious state can feel pain?'' nearly all interviewed caregivers answered ''yes'' (96% of the medical doctors and 97% of the paramedical caregivers; Fig. 2b). Logistic regression analysis showed that women and religious caregivers reported more often that minimally conscious patients may experience pain. For attitudes on pain in MCS, the difference between medical

Table 1. Demographic characteristics of the study sample ($n = 2059$)

Age, mean ± SD (range), years	43 ± 12 (18–83)
Gender, no. (%)	
Women	993 (47%)
Men	962 (48%)
Missing	104 (5%)
Respondents by geographical region, no. (%)	
Northern Europe	283 (13%)
Central Europe	1011 (49%)
Southern Europe	470 (24%)
Missing	295 (14%)
Profession, no. (%)	
Medical professionals	1196 (58%)
Paramedical professionals	548 (27%)
Missing	315 (15%)
Religiosity, no. (%)	
Religious respondents	1033 (50%)
Non-religious respondents	849 (41%)
Missing	177 (9%)

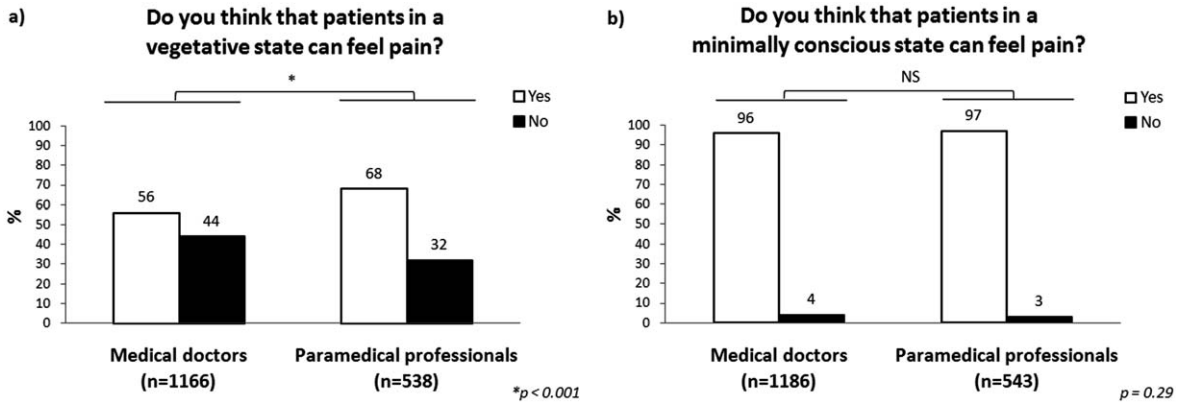

Fig. 2. Attitudes toward pain perception in the vegetative and the minimally conscious as expressed by European medical and paramedical professionals.

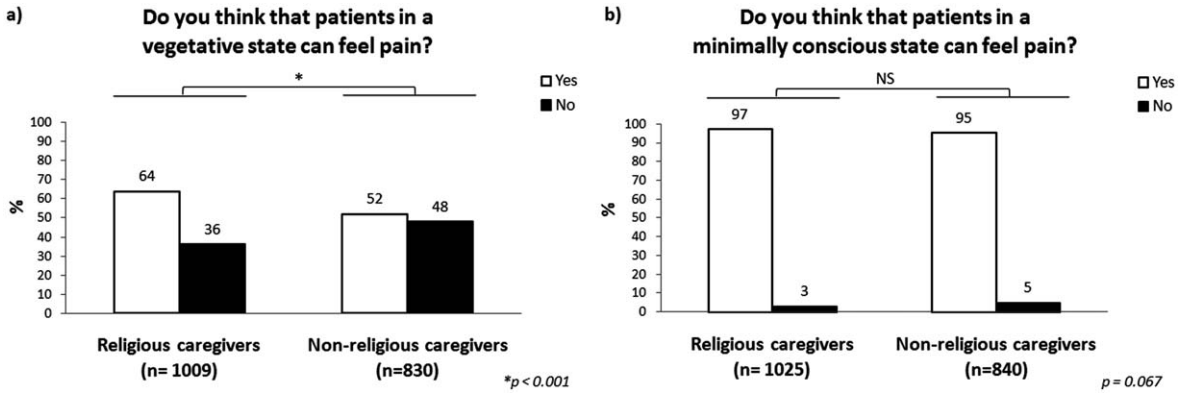

Fig. 3. The effect of religion on attitudes toward pain perception in patients with DOCs.

and paramedical professionals was not significant ($\chi^2(1) = 1.07$, $p = 0.295$).

According to our survey, healthcare workers have different beliefs about possible pain perception in MCS as compared to VS patients. This finding implies that, despite the recent introduction of MCS (Giacino et al., 2002), the medical community regards MCS and VS as two separate clinical entities characterized by different pain perception profiles. The major differences in physicians' beliefs about pain in VS as compared to MCS are supported by results from the functional neuroimaging data discussed above (Laureys et al., 2002; Boly et al., 2008). However, our survey showed that a high proportion of medical doctors (56%) and paramedical professionals (68%) considered that VS patients feel pain. The observed differences in viewpoint depending on professional background might be related to many factors including differences in proximity to the patient, time spent at the bedside, sensibilities, and education. Previous American studies reported a smaller minority of physicians holding these views. Payne et al. (1996) surveyed 170 physicians from the American Academy of Neurology and 150 from the American Medical Directors Association and reported that only 30% believed VS patients experience pain (they found no differences between academic and non-academic physicians). Similarly, an unpublished survey by the American Neurological Association reported that 31% of its members

Table 2. Logistic regression results on participants' characteristics (age, gender, region, professional background, religiosity) and ''Yes'' versus ''No'' answers to the questions on pain perception in VS and MCS

Question predictors	Odds ratio[a]	95% Confidence interval		*p*-value
Do VS patients feel pain?[b]				
Age	1.01	1.00	1.02	0.05
Women	1.25	0.99	1.58	0.06
Northern Europe	1			
Central Europe	0.81	0.58	1.14	0.24
Southern Europe	1.1	0.76	1.6	0.6
Paramedical professionals	1.56	1.2	2	<0.001
Religious respondents	1.37	1.1	1.7	0.004
Do MCS patients feel pain?[c]				
Women	2.38	1.33	4.26	0.003
Religious respondents	1.83	1.05	3.18	0.031

[a]For the continuous variables, the odds ratio equals the relative change in the odds ratio when the variable is increased by one unit.
[b]Stepwise backward (Step 1).
[c]Stepwise backward (Step 4).

were ''uncertain'' about whether VS patients could experience pain (31%) and suffering (26%) (Daroff, 1990). Tresch et al. (1991) found that only 22% of the relatives of patients in VS believed that their relative could experience pain and suffering. We can only speculate about possible explanations for the seemingly increased proportion of physicians considering that VS patients feel pain. It maybe that the recent publication of the diagnostic criteria for the MCS (Giacino et al., 2002) or the highly mediatized report of a VS patient ''playing tennis in her head'' (Owen et al., 2006) may have changed physicians opinions. In addition, cultural and religious differences could underlie the observed discrepancies between our European study and the older American surveys.

Physician and caregivers' opinions on patients' pain perception was significantly influenced by religious beliefs. We have previously shown that personal philosophical convictions are of major influence on our views on the relationship between consciousness and the brain (Demertzi et al., 2009). Such personal beliefs have also been shown to weight on physicians' clinical decisions (e.g., see Jennett, 2002). In line with our findings on the influence of religion and age on beliefs on pain perception in VS, other studies on, for example, end-of-life decisions in intensive care patients have shown that older and more experienced doctors and doctors with religious convictions (i.e., Christians) more often refused to opt for treatment limitations (Christakis and Asch, 1995; Sprung et al., 2003).

Considering our results on varying beliefs about pain perception in DOCs, physicians and healthcare workers' views on pain and symptom management may also be affected. Since nearly half of the interviewed doctors express that VS 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 patients are agreed to be withdrawn from life-supporting treatment, such as artificial nutrition and hydration. In these cases (e.g., Terri Schiavo) patients may be left without administration of opioids or other analgesic drugs during their dying process (Fins, 2006; Laureys, 2005a) on the grounds that they are deployed from experiencing suffering from hunger and thirst (Ahronheim and Gasner, 1990). In light of an incomplete picture of pain perception in VS patients, the existing risk for misdiagnosis (Andrews et al., 1996; Childs et al., 1993; Schnakers et al., 2009c), the inconclusive drug-related effects in DOCs (Demertzi et al., 2008) and the limitations in interpreting neuroimaging results (Poldrack, 2008;

Laureys and Boly, 2007), pain prophylaxis and treatment have been proposed for all patients suffering from DOCs (Schnakers and Zasler, 2007; Schnakers et al., 2009b).

The reported discrepancies in opinions about pain perception in VS patients may also be related to the absence of a unanimously accepted definition of pain and suffering. The Multi-Society Task Force on PVS (1994) considered that grimace-like or crying-like behaviors are not likely to reflect conscious awareness of pain or suffering ''unless they are consistent, sustained, and definitive in nature.'' They differentiated between pain and nociception, in that the latter is merely a response to noxious stimulation that can be present without conscious awareness and stated that nociceptive stimulation may elicit unconscious postural responses, as well as other motor, autonomic, and endocrinologic reflexive responses without evoking the experience of pain and suffering if the brain has lost its capacity for self-awareness (Multi-Society Task Force on PVS, 1994). The IASP (1994) definition of pain also refers to cognitive and affective properties of pain, stressing the importance of subjectivity and environmental influences in the experience of pain. Some authors support the view that pain can be regarded as any response to a noxious stimulus (e.g., see Anand and Craig, 1996) — but it is clear that not just any reaction to changes in the environment can be considered as conscious (e.g., brain-death-associated reflexes and automatisms; Laureys, 2005a; Jain and DeGeorgia, 2005). Others have hypothesized, based on observations from children with hydrancephaly (Shewmon et al., 1999) newborns (Anand and Hickey, 1987) and fetuses (Derbyshire, 2008), that midbrain structures may mediate consciousness, supporting the claim that cortical activity is not necessary for conscious perception (Merker, 2007).

In conclusion, our survey shows clear differences in medical professionals' beliefs on pain perception in VS patients as compared to MCS patients. Nearly all respondents considered that MCS patients can feel pain and medical doctors and paramedical professionals largely concur. In contrast, the beliefs on pain perception in VS patients were much more divided. Paramedical professionals, religious participants, and older caregivers reported more often that VS patients may experience pain. In light of many controversies around pain (and hence pain management) in VS and MCS patients, an increase in scientific evidence is essential to enhance our understanding and to permit the development of adapted standards of care and improved clinical guidelines for these challenging and vulnerable noncommunicative patients with DOCs.

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