

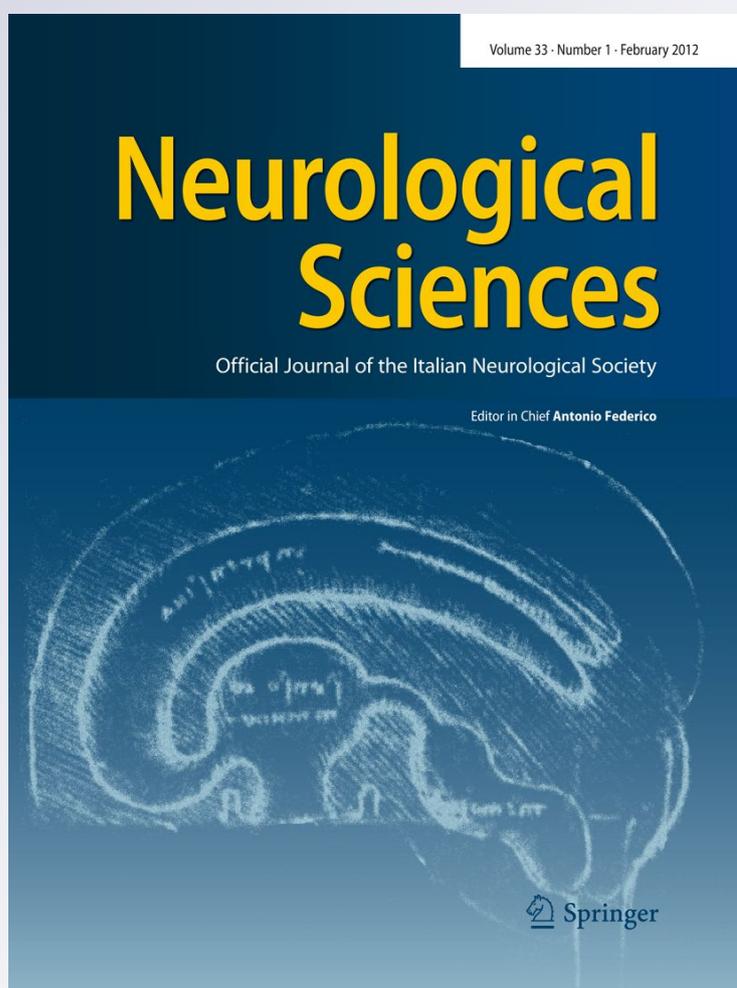
Persistent vegetative state: an ethical reappraisal

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Abstract New knowledge from scientific research on vegetative state (VS) and its consequences in clinical practice are reviewed. The ambiguity of the concept of consciousness and the difficult issue of its moral significance are then examined. The Authors stress the need for longitudinal prognostic studies, the promotion of an expert widespread use of standardized behavioural scales, and recommend that the ethical debate about VS rely upon the widest consensus of the scientific community.

Keywords Vegetative state · Functional neuroimaging · Consciousness theories · Disability evaluation · Ethics · End-of-life treatments

Introduction

For many years research on persistent vegetative state (PVS) has been at a standstill and both in the scientific and bioethical literature, PVS was usually regarded as a clinical picture resulting from the dissociation between a functioning brainstem and a non-functioning or even destroyed cortex. On the basis of this idea the concept of (neo) cortical death was proposed, both in scientific [1] and bioethical papers. This concept was endorsed by the Bioethics and Palliative Care in Neurology Study Group of the Italian Neurological Society in its first document on PVS [2] (but this statement was subsequently modified in a paper issued in 2002 [3]).

However, from the early 1990s, many researchers showed that the diagnosis of PVS was often fallacious [4–6]. Moreover, a host of cases not entirely corresponding

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to the usual criteria of PVS were reported: for instance, “fragments of behaviour” were observed in patients otherwise classified as PVS [7].

During the late 1990s, the Aspen Conference encompassing, among others, neurologists and rehabilitation specialists, suggested to create a new category of patients, the minimally conscious state (MCS [8]), in which some meaningful responses to external stimuli are observed, albeit inconsistently.

The true leap forward of PVS research was made after the turn of the century, when the new neurophysiological and neuroimaging techniques were introduced.

New knowledge from scientific research

The major research groups in this field, in Liège and Cambridge, had resort to the most advanced techniques of neuroimaging [positron emission tomography (PET); functional magnetic resonance imaging (fMRI)] and of electrophysiology, [event-related potentials (ERPs) magnetoencephalography (MEG)].

The first result of this research was the demonstration (through PET) that in many patients in PVS sensory stimuli (auditory, visual, somatosensory) evoke a metabolic response in the primary projection areas like in normal subjects, but—differently from the latter—metabolic activation does not spread in the associative cortical areas, where sensory information is processed and where conscious processing may take place. This showed that the old idea of a non-functioning cortex is mistaken.

At the same time, through electrophysiological techniques, researchers were able to demonstrate that in some PVS patients sensory stimulation can also evoke the so-called long-latency potentials, originating from associative areas. In some cases a response was obtained only with meaningful stimuli (such as the patient's own name).

PET can demonstrate instant metabolic activity of the nervous system, but it cannot provide information about metabolic changes over time as fMRI can do. In 2006, Owen [9] achieved a real breakthrough in this field using fMRI. In one experiment two paradigms have been discovered [10] in healthy volunteers: these are two mental imagery tasks characterized by two different and consistent patterns of activation of cortical areas which are easy to recognize in fMRI scans. A young woman in PVS was asked to perform the tasks 5 months after head injury and, in spite of a clinical diagnosis conform with standardized scales of PVS, she responded to the verbal commands (“imagine playing tennis”, and “imagine going through the rooms of your home”) very similar to the healthy subjects.

Owen concluded that “this patient retained the ability to understand spoken commands... Moreover, her decision to

cooperate with the authors by imaging particular tasks when asked to do so represents a clear act of Intention.” These statements were criticized by some scholars arguing that these responses could be “automatic”: an instance of a general phenomenon known in neuropsychology as “priming” (the implicit memory effect in which exposure to a stimulus, even if not consciously perceived, influences response to a subsequent stimulus). However, in the recent paper by Monti [11] who is working in the Cambridge group himself, a very impressive case was described (n. 23). A patient, initially diagnosed as in PVS and studied 60 months after the brain trauma, was not only able to respond to the paradigms, previously described in the same way as healthy volunteers, but also to code one of them as “yes” and the other as “no”. Thus, the patient was able to answer simple questions concerning his family and the answers were verified and proved to be true. This was all performed without any behavioural responses. However, at the time of scanning, thorough retesting at the bedside showed reproducible but highly fluctuating and inconsistent signs of awareness (see the supplementary appendix of the paper). These findings are consistent with the diagnosis of MCS. This extraordinary experiment shows that a real process of communication has taken place demonstrating evidence of mental activity. In this case no criticism appears justified. In the same article, a series of 54 cases is reported (23 in PVS and 31 in MCS). Two PVS and three MCS patients had fMRI responses similar to those described in the 2006 paper. So, it seems as if approximately 10% of PVS/MCS patients show at least “fragments” of mental activity. These positive results have been obtained only in traumatic brain injury (TBI) which is not surprising, since TBI causes multiple, widespread, patchy lesions especially in white matter but always sparing some “islands” of brain tissue.

Notably a closer look at the data presented by Monti et al. reveals that out of 31 MCS patients only one was able to modulate his brain activity in response to the imagery task. This negative finding highlights a very low sensitivity of the fMRI active paradigm, since almost all the subjects (97%) which were clearly responsive at the bedside turned out to be unresponsive in the scanner. This extremely low sensitivity may be due to the fact that the imagery task is not designed for patients with severe brain injury and hence it represents a significant challenge for them. In fact there may be cases, such as in aphasia, akinetic mutism, catatonic depression, or diffuse dopaminergic lesions in which a patient, although aware, may not be able to understand or may not be willing to respond. Moreover, because of frequent movement artefacts and because of possible alterations in the normal coupling of the hemodynamics and neuronal firing [12], acquiring and interpreting fMRI data is especially difficult in patients with disorders of

consciousness (DOC) 2006 [13] and imagery task studies have not been successful to distinguish between PVS and MCS.

Thus, before fMRI active paradigms may be included in the diagnostic battery for DOC, some problems should be solved. For instance, it would be useful to implement and validate the same paradigm using EEG recording in order to reduce the impact of artefacts and the fMRI logistic/economic hurdles (actually some work is being done in this direction). Neuroimaging techniques associated with passive paradigms, without any tasks, may offer a more reliable assessment. Recent MRI and fMRI measurements aiming at studying anatomical [14] and functional connectivity [15] within the thalamocortical system of brain injured patients have shown a good potential in discriminating patients with different levels of consciousness. These techniques, based on diffusion tensor imaging or on analysis of resting state connectivity in default mode network, do not require the patient's participation which involves faster and simpler acquisition protocols.

Some months after Monti's paper, Estraneo et al. [16] published the results of a prospective study on 50 patients in a vegetative state of different origin (TBI, anoxic, and posthemorrhagic) followed for a mean of 25.7 months from onset (5 of them for more than 4 years) and evaluated only by means of validated scales (Coma recovery scale-revised and disability scale rating scale). Twenty percent showed late recovery of responsiveness (later than 1 year post onset in TBI patients and later than 3 months in the other patients) and 12% further progressed to consciousness. Late recovery significantly correlated with younger age and was relatively more frequent in TBI patients. Functional abilities were severely impaired in all patients.

What are the consequences in clinical practice?

Although the reports by Owen and Monti do not provide sufficient evidence to include fMRI in clinical practice, they clearly demonstrate that a subset of non-responsive patients may retain some mental activity. Similarly, Estraneo's clinical study supports the need of a deep revision of prognosis in DOC. Altogether, these findings are bound to affect clinical practice in many ways.

First of all, a thorough clinical examination of the patients extended over a certain time is mandatory and this examination must be performed by means of standardized scales, such as the JFK Coma Recovery Scale-R [17]. The clinical exam must be supported by neurophysiological studies (EEG, sleep EEG, short latency and possibly ERPs); imaging is equally mandatory, at best by MRI. When possible, advanced techniques like PET and fMRI could be used, but it should be kept in mind that, at present,

they remain research tools and should be used with caution for clinical practice.

Prognosis is very difficult. The prognostic criteria of the Multi-Society Task Force (1994) [18] are still roughly valid, but the temporal limit for recovery of consciousness (12 months for traumatic, three for non-traumatic PVS) cannot be viewed as absolute. Prognosis have to be tailored to the individual case, taking into consideration aetiology (traumatic vs. non traumatic, not rarely superimposed), size and number of the lesions, close observation and a program of stimulation appropriate for the individual; moreover, a longer period of follow-up may be necessary.

In our country, two different working groups established by the Italian Ministry of Health, the first one in 2000 (Gruppo di lavoro su nutrizione e idratazione artificiale in soggetti con irreversibile perdita di coscienza, presided by Fabrizio Oleari, http://www.istitutobioetica.org/documenti/salute/parere_idratazione.htm) and the second in 2008 [19], issued two very different position papers on the heated debates concerning the case of Eluana Englaro. The first one stated the possibility to withdraw any treatment in the patient in PVS, once the diagnosis of permanent VS was reached by a medical expert committee. The second paper did a review of the relevant scientific literature (much developed after 2000) and did not reach a conclusion on the reliability of the prognosis, while stressing uncertainty and suggesting to cancel the very term of permanent (i.e., irreversible) VS.

We think that, in spite of the undeniable difficulties in making a prognosis, we are requested to adopt a clear position and communicate this to the relatives while explaining the margin of error (as in any medical prognosis).

The ambiguity of the concept of consciousness

We have stated that Monti's experiment is convincing and it has demonstrated the possibility of persistent mental activity in some PVS/MCS patients. This demonstration has been reached by what many researchers have identified as instrumental "surrogates" of behaviour. Of course, in natural science no real alternative to a behavioural approach to consciousness is given, but the philosophical problem of the definition of this inherently ambiguous concept remains open. One big problem is that the word "consciousness" is used with different meanings in different contexts, such as common language, science, and philosophy.

In daily life we recognize others as conscious if they can communicate their own experiences verbally or by means of their behaviour either spontaneous or in response to external stimuli. Medicine works in a similar and even more rigorous way. There is another way to approach

consciousness and that is when each of us experiences it through introspection (a “private” way by definition).

Several theories of consciousness have been proposed. For the purpose of the present reappraisal we refer to the model proposed by Block [20]. He has argued that consciousness is a hybrid concept covering several components. He calls phenomenal or P-consciousness (P), the “private” component of the human experience, for which he suggests an openly weak, circular definition: it is “what it is like to have it”, with a clear reference to a famous paper by Nagel [21]. The second component, according to Block, is access or A-consciousness (A). It encapsulates the tasks involved in cognition, representation and the control of behaviour. Block recognizes that A is a composite concept that includes many elements, among which reportability, even though not the most important, is generally the most practical lead to A.

P and A are distinct and not superimposable but interacting with one another. In ordinary life, they dissociate only in rare circumstances; there are situations in which A is more extended than P and other in which the opposite is true (for instance, when we perform learnt, quasi-automated activities). In pathological conditions, this kind of dissociation is probably much more frequent.

A third component of consciousness is reflective- or self-consciousness, the capacity of anyone to think of oneself as an entity over time.

If we accept Block’s suggestion, we may ask ourselves what Owen’s and Monti’s experiments really demonstrate. As previously mentioned, the first experiment has been criticized because it could have been explained as automated activity, external both to P and A. Monti’s experiment overcomes this objection, as it implies an act of volition and this is a good signal of A. This kind of consciousness is probably rare in PVS/MCS, since only one such case has been found so far. However, P-consciousness could be present and not be accessible to us, meaning that the patient is unable to communicate and, if in pain, unable to report it.

In fact some PET experiments have shown that painful stimuli activate thalamic nuclei and the primary sensory cortex in many PVS and MCS patients; in MCS (and in some PVS) subjects many associative areas (the so-called pain matrix, in which the experience of pain probably arises) are also involved. Boly and Faymonville [22] maintains that the distinction between the two groups is blurred and thinks that the possibility that vegetative patients experience pain is not excluded. In Block’s terms, as we cannot exclude that (at least some) PVS subjects could be P-conscious, it is not unlikely that they are able to suffer. Given this new data, the Italian Ministry of Health Working Group (already quoted) gives a recommendation on which we agree: the use of analgesics in DOC patients

when a painful experience can be expected, for concomitant painful diseases or manoeuvres.

The moral significance of consciousness

At this point some questions arise: What does it mean for the relatives of a PVS patient—e.g., 14 months post onset—to be informed that, notwithstanding the absence of behavioural response, cortical responses to verbal stimuli can be evoked? Is it a merely instrumental response or does it imply that the subject is conscious?

Instrumental responses could be a good prognostic sign if related to an imminent awakening, but we cannot state it on the basis of current scientific knowledge. Furthermore, how should an instrumental response influence end-of-life decision making?

This leads us to the difficult issue of the moral significance of consciousness as Kahane and Savulescu [23] have phrased it.

Mental life is generally viewed as intrinsically endowed with moral value and both the public and researchers, seem to share the idea that from the very fact of being conscious unequivocal moral consequences are to follow. We think that this position is controversial especially because, in principle no ethical inference (for instance the duty to support life without any limit) can be drawn from an empirical fact (the fact of being conscious). Moral prescription must be above all based on the interests (the well-being) of the involved individuals. This is not to say that consciousness (and its level) is not relevant to moral reasoning, but simply that no straightforward inference can be drawn from it.

Block’s analysis can offer some useful cues to clinicians. If we resort to this scheme in the description of the clinical situations, we may think that:

- (a) most PVS patients are (probably) lacking both of P- and A-consciousness;
- (b) some of them and most, if not all, of MCS patients could be only P-conscious and consequently suffer, though unable to communicate it;
- (c) a minority of MCS patients could have an A-consciousness, as in the famous case n. 23 described in the paper of Monti et al. (quoted). Unfortunately they do not have the capacity of communicating their experience. So we do not know how they experience it “from the inside”. Anyway, it is reasonable to think that, even if they are A-conscious, they do not have reflective consciousness or self-consciousness.

Different is the situation for patients with locked-in syndrome (LIS), who have full consciousness and are aware of themselves, as shown by the memorable report of

this state made by Jean-Dominic Bauby [24] in his famous book ‘The diving bell and the butterfly’.

Hence if we try to link the different situations which occur in chronic DOC and our duty toward them, we may tentatively highlight the following:

- (a) Individuals in a PVS, lacking consciousness, are unable to experience pleasure pain and wishes. Our moral duty to sustain their life is a difficult question open to discussion. In some countries, as the UK [25], artificial nutrition has been withdrawn even without advance directive. In most countries it can be done only if the subject had previously made a formal advance directive or if his/her can be reconstructed in a reasonably faithful manner, as with the Englaro case in Italy and as the Oleari Commission (quoted) suggested.
- (b) MCS and a few PVS patients, if endowed with P-consciousness alone (in other words, if they are sentient), are to be protected from pain and suffering, whereas the duty to prolong their lives can be considered questionable, as in the previous situation. In fact, they probably lack the capacity to have any wishes and projects for their future, but their capacity to experience present facts is preserved. As in the previous category, the moral problem is easy to solve if there are advance directives, whereas the answer is uncertain when there are not.
- (c) Some MCS subjects could have a higher level of consciousness; some of them could even have the capacity of being aware of themselves and to have wishes, including the wish to go on living; in these cases the duty to protect them, to prevent suffering and to sustain their lives is obvious.

LIS subjects, being fully conscious, are full moral agents, they can give valid directives concerning their condition and we have a strong duty to respect them.

Research: the need for longitudinal prognostic studies and future scenarios

Ethical concerns should be raised about the participation of DOC patients in functional neuroimaging studies that may require invasive procedures and have no therapeutic purpose. By definition, DOC patients are very vulnerable, deserve special procedural protections, and cannot give informed consent, which is obtained from family or legal representatives according to the country. Ethical committee decisions should balance between medical research and protection of the patients and their relatives, who could be exposed to a relevant psychological burden (as in the case of a research aiming at exploring their loved one's assumed

mental life). Every effort should be made to protect the wishes and directives of DOC patients legally.

Research on PVS and MCS is attracting public attention because of its more sensational features, as the persistence of some mental activity in rare cases, the (exceedingly rare) late recovery and, moreover, the possibility that some patients are not really in PVS, but in a complete LIS, recognizable only by means of an expert behavioural examination supported by neurophysiological and fMRI investigations.

We hope that the researchers in this field promote prospective studies aimed at evaluating the prognostic significance of the cortical metabolic responses. One of the challenges of efficacy of treatment options is related to the extent and heterogeneity of these conditions and this approach can be seminal for future therapeutic studies.

In addition, functional neuroimaging could even become a communication tool in DOC. Notwithstanding the particularly dramatic context, this could help the patient also to enhance his autonomy.

In the meantime, we recommend not creating false hopes among relatives of PVS patients by explaining that neuroimaging results remain, at present, investigational. The ethical debate over PVS should not be contaminated by rumour but should rely upon the widest consensus of the scientific community.

On the other hand, we believe that even now the assessment of DOC patients could be improved promoting a widespread use of standardized neurobehavioural scales (Seel et al. [26]) reducing the discontinuity in the assessment between acute and rehabilitative phase and overcoming the heterogeneity of care facilities and of clinical-instrumental assessment.

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