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International Journal of Clinical Therapeutics and Diagnosis (IJCTD)
ISSN 2332-2926

The Impact of Contemporary Neurotechnology on Diagnosing and Treating Patients with Disorders of Consciousness - A Review

Review Article

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Abstract

Disorders of consciousness, especially Vegetative State, are assessed from a theoretical (historical and ethical) and empirical (neuroscientific) points of view, through a review of the most relevant recent literature.

Both the potentiality of neuroscientific investigation and the limitations of its clinical (diagnostic and prognos- tic) application are underlined, showing the urgency of a collaboration between science, law and ethics in order to define the most appropriate nosography and to ensure the best therapy to patients with disorders of con- sciousness.

Keywords: Bioethics; Disorders of Consciousness; Unresponsive Wakefulness Syndrome; Vegetative State.

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Received: August 10, 2013
Accepted: August 31, 2013
Published: September 02, 2013

Citation: Farisco M, Petrini C (2013) The Impact of Contemporary Neurotechnology on Diagnosing and Treating Patients with Disorders of Consciousness - A Review. Int J Clin Ther Diagn. 1(2), 12-19. **doi:** http://dx.doi.org/10.19070/2332-2926-130003

Introduction

Disorders of consciousness (DOCs) include different severe brain injuries which are assessed through specif- ic diagnostic criteria, mainly by accurate clinical behav- ioral scales (e.g., Coma Recovery scale-revised, Sensory Modality Assessment and Rehabilitation Technique, Full Outline of Unresponsiveness, Glasgow Coma Scale). The data emerging from such assessment at the bedside could and should be confirmed by new medical technologies, especially electrophysiology and functional neuroimaging. To date through the combi- nation of behavioral and instrumental assessments of consciousness it is possible to distinguish the following severe brain damages or DOCs:

1.Coma
2.Vegetative state (VS) or post-coma unresponsive- ness (PCU) or unresponsive wakefulness syndrome (UWS) [1]
3. Minimally conscious state (MCS), recently sub-cat- egorized in MCS+ and MCS-
4. Locked-in syndrome.

The new neurotechnological clinical tools are increas- ingly showing the limitation of the assessment of re- sidual consciousness of patients with DOCs at the bedside, because the underlying neurological condition is often too difficult or even impossible to understand from the behavior. Does this mean that in the case of patients with DOCs the instrumental assessment of consciousness will completely replace the behavioral assessment? How would this hypothetical replacement affect the diagnosis, the management and the therapy of such patients? An overview of the most recent sci- entific studies, particularly regarding vegetative state, could help us to underline both the opportunity and the issues emerging from neurotechnologies applied to patients with DOCs and to point out the possible con- sequences for a new nosography.

Historical Perspective

The term "coma" derives from the ancient Greek κόμη ("hair"). In Latin ("coma"), as well as in ancient Greek, the term indicates a state of sleep from which one may not wake up.

The word is used by Hippocrates (460 BC – 370 BC) in his "Corpus" and by Galen (129 AD – 199/217 AD). After these and other historical testimonies in the Greek and Roman age, the notion was rarely men- tioned in the literature up to the Seventeenth century [2].

In 1672 Thomas Willis mentioned coma, lethargy, carus (deprivation of sense) and apoplexy in "De ani- ma brutorum".

During the Eighteen century, the term "coma" is re- current. For example, Herman Boeherhaave (1668- 1738), in his authoritative lectures, compared disorders of consciousness to sleep and studied intoxications and other possible causes of coma. In the same peri- od, François Boissier Sauvages de la Croix (1706-1767) classified "comate" and several conditions of sound sleep as one class among a series of disabilities.

In the Nineteenth century, with the improvement of medical knowledge, many causes of coma were de- scribed [3]. Physical examinations and a series of ob- servations were used for the

diagnosis.

In 1899 W. Rosenblath, in the "Archives of Medicine", described the "Low-Level Neurological State" giving the example of a several traumatic brain injury oc- curred to a young acrobate [4].

In the first decades of the Twentieth century the sub- ject was almost completely ignored in the medical lit- erature.

From the 1940s, several case reports were published. In 1940 E. Kretschmer coined the expression "apallic syndrome" ("Das Apallish Syndrome") [5] to describe the state intervening in case of loss of bihemispheric/ cortical functions with concurrent preservation of brain stem functions. The expression spread quickly and was adopted for a long time, thanks also to the noteworthy book "Das Traumatisch Apallische Syn- rome" by F. Gertensbrand [6]. The expressions "Kretschmer syndrome" and "neocortical death" were used as synonymous of "apallic syndrome". These ex- pressions, now abandoned, are not clinically correct: functional magnetic resonance has demonstrated neocortical areas active in subjects previously classified as in "neocortical death".

In 1963 M. Arnaud and colleagues used for the first time the expression "vegetative state" (in French: "vie vegetative") [7].

In 1972 D.H. Ingwar and A. Brun suggested to re- place the expression "apallic syndrome" with the ex- pression "dispallic syndrome" or "incomplete apallic syndrome", since clinical conditions of subjects in such state do not correspond exactly to the conditions caused by the absence of pallium.

The same year the Scottish neurosurgeon B. Jennet and the American neurologist F. Plum attempted to face the confusion in terminology and introduced the notion of "persistent vegetative state" to indicated subjects who come out from coma and remain in con-dition of "wakefulness without awareness" [8]. The expression "persistent vegetative state" had a world-wide diffusion. For some years, the French school con-tinued to prefer "vigilant coma" ("coma vigil"), but afterwards accepted the expression suggested by Jen-net and Plum. According to the Oxford English dic-tionary, "to vegetate" means to "live a merely physical life devoid of intellectual activity or social intercourse" and "vegetative" describes "an organic body capable of growth and development but devoid of sensation and thought". To lay public and media, however, it has a rather pejorative undertone and seems, incorrectly, to refer to patients as being vegetable-like. Therefore, the expression had an unintended denigrating conno-tation.

In 1980 F. Plum and J. B. Posner published the exten-sive study "Diagnosis of stupor and coma". The book united for the first time a theoretical understanding of the arousal system in the upper brain stem with clin-icopathologic case studies, and in doing so created the modern examination for coma that is based on the pa-tient's pupils, eye movements, and breathing patterns. In 1989 the American Academy of Neurology pub-lished the "Position statement: certain aspects of the care and management of profoundly and irreversibly paralyzed patients with retained consciousness and cognition. Report of the Ethics and Humanities Sub-commitee of the American Academy of Neurology" [9].

The description of "vegetative state" adopted by the American Academy of neurology is similar to the defi-nition adopted in 1994 by the The Multy-Society Task Force on PVS (MSTF). According to the MSTF "The vegetative state is a clinical condition of complete unawareness of the self and the environment, accom-panied by sleep-wake cycles, with either complete or partial preservation of hypothalamic and brain-stem autonomic functions. In addition, patients in a vegeta-tive state show no evidence of sustained, reproduc-ible, purposeful, or voluntary behavioral responses to visual, auditory, tactile, or noxious stimuli; show no evidence of language comprehension or expression; have bowel and bladder incontinence; and have vari-ably preserved cranial-nerve and spinal reflexes. We define persistent vegetative state as a vegetative state present one month after acute traumatic or nontrau-matic brain injury or lasting for at least one month in patients with degenerative or metabolic disorders or developmental malformations. The clinical course and outcome of a persistent vegetative state depend on its cause. Three categories of disorder can cause such a state: acute traumatic and nontraumatic brain injuries, degenerative and metabolic brain disorders, and severe congenital malformations of the nervous system" [10,11]. The notion of "persistent vegetative state" adopt-ed by the MSTF rouse much controversy both for clin-ical and ethical reasons. Nevertheless, it was adopted also by Ethics Committees: the same year the Medical Ethics Committee of the British Medical Association published the "BMA guidelines on treatment decisions for patients in a persistent vegetative state" [12].

In 1996 a working group by the Royal College of Phy-sicians published the report "The permanent vegeta-tive state" in which it distinguished "persistent vegeta-tive state" from "continuous vegetative state" [13].

In 2010 the European Task Force on Disorders of Consciousness (ETFDC) has proposed to replace the name "Vegetative State", considered not appropri-ated given the clinical condition of the patient showed by instrumental assessment, with the "Unresponsive Wakefulness Syndrome" (UWF) [1].

Recent Findings From Contemporary Neuroscience

As the history of their investigation shows, DOCs are surely one of the most problematic and intriguing field of contemporary neuroscience: the astonishing progresses of their assessment during the last decades leave still unanswered important questions. This un-certainty has not only theoretical, but also clinical and medical consequences, so that neuroscientific uncer-tainty about DOCs, especially about VS, has relevant ethical and legal implications.

As recently outlined [14], to date we know quite a lot about the neuropathology underlying VS but our un-derstanding is incomplete. VS can be clinically defined as wakefulness without awareness: the definition by MSTF states that VS patients show no evidence of sus-tained, reproducible, purposeful, or voluntary behav-ioral responses to visual, auditory, tactile, or noxious stimuli; show no evidence of language comprehension or expression; have bowel and bladder incontinence; and have variably preserved cranial-nerve and spinal reflexes [10,11].

This definition has been followed by many other documents. A significant synthesis of the different approaches to VS is the cited Royal College of Physicians definition, according to which VS is a clinical condition of unawareness of self and environment in which the patient breathes spontaneously, has a stable circulation, and shows cycles of eye closure and opening which may simulate sleep and waking [13].

From these definitions three characteristics of VS emerge: cycles of eye opening and closing, giving the appearance of sleep-wake cycles; complete lack of self- and environment-awareness; complete or partial preservation of hypothalamic and brain stem autonomic functions.

35 years after the definition by MSTF, the ETFDC has recently proposed the new label "Unresponsive Wakefulness Syndrome". According to the ETFDC the main reason to propose a new name for VS is the persistent, even if unintended, negative connotation of the expression "vegetative state".

The reason for choosing the name VS was to refer to the preserved vegetative nervous functioning (e.g., sleep-wake cycles, respiration, digestion or thermoregulation). Yet the definition of such patients as vegetative has not been universally accepted in these years [15,16 ,17]. As a result the discussion is open about the appropriateness of the term [18].

Another problematic point is the use of "state", that, according to ETFDC, risks to suggest chronicity, while a vegetative state may become chronic (lasting for decades) or may remain a transitory condition on the way to further recovery [1,19].

For these reasons the Aspen Neurobehavioral Conference Workgroup has recently proposed the definition of Minimally Conscious State (MCS) to denote the clinical condition of patients recovering from VS and showing more than reflex motor behavior but failing to show functional communication or object use [20]. Furthermore the clinical condition of MCS has been recently subcategorized on the basis of the complexity of patients' behavior. More specifically MCS+ shows command following, intelligible verbalization or gestural or verbal yes/no responses; MCS- shows minimal behavioral interaction with non-reflex movements such as: orientation of noxious stimuli, pursuit eye movements in direct response to moving or salient stimuli; movements or affective behaviors in appropriate response to relevant environmental stimuli [21].

Some have criticized the introduction of MCS because both VS and MCS patients are hopelessly brain dam-aged [22]. Yet recent findings show difference in neural response to external stimuli [23,24,25] and in progno-sis [26,27].

Thus the differentiation between VS and MCS is clini-cally very important, both for diagnosis and prognosis, so that a big problem of misdiagnosis exists [28,29,30], despite the publication of guidelines about the diagno-sis of VS and the definition of clinical criteria for MCS [30]. According to Grosseries et al. [31], this problem of misdiagnosis illustrates the need for standardized 'consciousness-scale'. Regarding this point, in a recent milestone paper, the American Congress of Rehabilita-tion Medicine conducted a systematic, evidence-based review of behavioral assessment scales for disorders of consciousness and provided evidence-based recom-mendations for clinical use founded on content validity (i.e., enclosing diagnostic criteria), reliability, diagnostic validity, and ability to predict functional outcomes [32]. Yet recent neuroscientific findings suggest the need for motor-independent signs of awareness derived directly from brain signals.

From the above summarized studies we can conclude that recent neuroscientific findings suggest to clini-cians to be very careful in their conclusions about the awareness of patients with DOCs [14,33-38]. Besides these consequences for diagnosis, re-cent advancements in neuroscience have an increasing impact on treatment. Particularly "the existing thera-peutic nihilism in the field of DOC is currently get-ting challenged by recent data supporting that some DOC patients could benefit from some rehabilitative interventions (surgical, pharmacologic, or behavioral)" [39]. Furthermore recent new findings have challenged the classical temporal boundaries of irreversibility [40], even if at present the possible positive effects of clini-cal interventions are not evidence-based nor generally accepted by medical community [41].

It is possible that patients with DOCs preserve some neural activities related not only to wakefulness but somehow to awareness as well, although in very low degree and disconnected ways. This is particularly rel-evant for the question of misdiagnosis which is mainly caused by the difficulty to behaviorally assess con-sciousness (empirical limit). Moreover the possibility to retain in some way awareness in patients with DOCs is also related to a conceptual problem in establishing "lack of awareness" (theoretical limit): absence of evi-dence (of awareness) is taken as evidence of absence (of awareness) [14,[42,43].

For the above reasons the ETFDC has proposed to change the label VS in UWS. This name refers to pa-tients that show a number of clinical signs (hence the use of syndrome) of unresponsiveness (meaning they fail to show non-reflex behavior or command follow-ing) in the presence of wakefulness (meaning they open their eyes spontaneously or upon stimulation) [1]. Other names were rejected: coma vigil was considered a contradiction in terminis, while a-pallic syndrome was considered not appropriated, given that such patients retain some (merely primary) cortical activities [45,46].

The definition by the ETFDC, starting from new neu-roscientific findings, focuses on the behavioral assess-ment of consciousness, underlying both what is lack (Unresponsive) and what is present (Wakefulness). The main concern of this changing is to give the possibility to be acknowledged to patients recovering from coma as having even minimal signs of consciousness. Re-cent neuroscientific developments, in fact, show that such patients, even if unable to recover any voluntary responsiveness, may retain or recover other signs of types of consciousness [47]. The aim of the ETFDC is to give a neutral tool to physicians in order to describe the clinical condition of patients with DOCs as objec-tively as possible.

Starting from the theoretical progresses related to neu-roscientific investigation, the main interest of the UWS definition is a practical one: improve the management and the standard of care of patients in such a state. The premise is that if we cannot change the negative connotation of the term VS it is better to replace it.

Besides the importance to increase the collaboration between clinical practice and neuroscience, the ET-FDC also stresses the need to develop new, more ef-ficacious behavioral scales to assess consciousness and the importance to identify objective paraclinical signs confirming the clinical detection of consciousness. What is happening is that the broad definition of VS/ UWS as wakefulness without awareness is increasing-ly under question because of the new neuroscientific findings. Particularly a consistent lack of metabolic activity in the widespread network of polymodal as-sociative cortices (located in the frontal and parietal lobes of the brain) that are involved in the cognitive processing of sensory information was identified in VS/UWS through neu-

roimaging. Thus the VS/UWS is characterized by the lack of connections between this frontoparietal network and deeper centers in the brain, notably the thalamus [48]. For these reasons in VS/UWS we can have a survival of islands of cortex - capable of supporting minimal cortical activity - that are not part of a coherent cortico-thalamo-cortical system, and this isolated brain activity seems to be not sufficient to support awareness and probably neither to support sensible perception [18,49,50]. Neverthe-less recent findings have showed that some VS/UWS patients have a surprising capacity of learning through classical conditioning [38]. Furthermore neuroimaging studies of VS/UWS showed a reduction in brain me-tabolism of 50% and a reduced basal resting state ac-tivity, while some levels of residual cognitive functions (such as processing of linguistic and self referential stimuli) are present in VS/UWS [51].

Thus the issue of VS/UWS patients' consciousness is very problematic. Albeit we accept they do not retain awareness, recent findings suggest that a more basic form of consciousness, called "affective conscious-ness" [52], could be active in such patients, even if the higher substrates of the mind, especially the neocor-tex, are damaged [53]. If this is true, VS/WS patients could continue to feel some sort of emotional expe-riences: subcortical brain structures could be able to generate unreflective affective states and basic experi-ences [54,55]. Is the term "Vegetative State" really able to express such a complex medical condition? Could the label "Unresponsive Wakefulness Syndrome" re-ally help us to solve such a complexity? Only time will tell us if this proposal succeeds, but it surely outlines the urgency to develop a new nosography of VS/UWS taking into account that complexity.

Particularly relevant is the progress in the instrumen-tal assessment of consciousness: for instance, given the big difficulties to rightly diagnose VS/UWS and MCS, neuroimaging experiments have tried to define accurate biomarkers of consciousness level in VS/UWS and MCS [56]. To date Neuroimaging and elec-trophysiological measures can […] identify signs of awareness inaccessible to clinical examination, which permit a better understanding of the mechanisms of human consciousness and improve our care of DOC patients [57]. Particularly functional neuroimaging and electrophysiology increasingly show residual cogni-tive processing in some non responsive patients [22,58,59,60]. For instance, in 2006, Adrian Owen in col-laboration with the research team of Steven Laureys scanned patients with a diagnosis of vegetative state asking them to perform a mental imagery task, like playing tennis or moving around the home: "In one exceptional VS patient, task specific activation was observed, unequivocally demonstrating consciousness in the absence of behavioral signs of consciousness. Interestingly, the patient subsequently recovered" [57]. For this type of patients, clearly not definable as VS, has been proposed the definition of "functional locked-in syndrome, emphasizing the dissociation be-tween their extreme behavioral motor dysfunction and the identifiied preserved higher cognitive functions as shown by functional imaging techniques" [21].

From the aforementioned case another potential use of neurotechnology emerges, which may allow us to implement a form of communication with patients with DOCs, so that "neuroimaging instruments in some exceptional cases of motor-deprived non-com-municating DOC patients may be used as a means to establish a reliable communication code" [58,51].

Some neuroscientists think that it is not so far the time when real-time fMRI communication or evoked po-tential brain computer interfaces will allow us to as-sess crucial clinical and ethical issues in patients with DOCs, such as pain and discomfort perception[22]. To date EEG based communication devices, the BCI, are being developed as a more practical, transportable and cheaper alternative to fMRI for communicating with DOC patients.

Important results have also been obtained from neu-romaging measurement of brain activity in VS/UWS patients after specific commands: a partially-preserved brain activity has been detected [59] not attributable to automatic recruitment of the areas of interest so that the patients in question can be considered conscious [59].

Of note is that the patient 6 months later recovered visual pursuit of a mirror indicating her transition to MCS [60]. In this case the most important aspect to take into account is that the instrumental assessment of consciousness preceded the behavioral output.

Actually an increasing correlation between neuro-technologies and clinical management of patient with DOCs is already ongoing: Although […] functional neuroimaging cannot confiirm a diagnosis of vegetative state, it is increasingly clear that functional neuroimag-ing can be used to rule out a diagnosis of vegetative state and may even yield information about prognosis. Indeed, limited data on prognosis show that quanti-tative measurements of brain activity—in particular, activations beyond primary sensory cortices—are positively correlated with recovery from the vegetative state [14]. Furthermore clinical observation may be supported also by electroencephalography (EEG) [61]. These neuroscientific technologies are increasingly used to investigate patients with DOCs at rest. Particu-larly PET and fMRI identified the so called "default mode network", a set of areas (posterior cingulated/ precuneus, anterior cingulated/mesio-frontal cortex, temporo-parietal junctions) which are more active in at rest than during attention-demanding tasks. This default mode network is considered to be involved in self-related processes [58]. Regarding DOCs, it is rel-evant that resting state connectivity was shown to dis-appear in brain death […] and to show a non-linear disintegration in pseudocoma or locked-in syndrome as compared to minimally conscious or relative to un-conscious states (VS/UWS or coma).

To assess the consciousness of patients with DOCs through fMRI of resting state may allow us to over-come the conceptual limit of a fMRI approach to consciousness: given the lack of a full understanding of the neural correlates of consciousness, even a near-to-normal activation in response to passive stimulation cannot be taken as proof of preserved awareness, but only as the manifestation of the activation of a par-ticular brain region able to activate and process sensory stimulation. Furthermore, the non activation during passive fMRI paradigms may be consequent to periph-eral sensory systems' impairments (e.g., deafness). On the contrary Resting-state fMRI acquisitions are easy to perform (i.e., do not need auditory, visual or soma-tosensory stimulation equipment in the fMRI environ-ment) and could have a potentially broader and faster translation into clinical practice [62].

Generally speaking the problem with the electrophysi-ological and neuroimaging assessment of conscious-ness is that the mental imagery tasks used or MRI de-tection of consciousness require high-order cognitive abilities and can be very demanding for many brain-injured patients. On the contrary event-related EEG potentials elicited by simpler sensory stimulations in-volve lower cognitive resources [47].

Starting from the assumption that consciousness is ef-fective connectivity of the thalamocortical area, it is possible to test its presence through transcranial mag-netic stimulation (TMS) and to read the relative EEG results.

Nosography of Docs as an Ethical Problem

To develop an appropriated nosography of DOCs, particularly of VS/UWS, is not only a scientific, but also an ethical issue, as clearly shown by three institu-tional Australian documents which preceded the scien-tific definition by ETFDC.

The definition of "Post Coma Unresponsiveness" (PCU) has been proposed in three documents by the Australian Government, National Health and Medical Research Council: *Diagnostic Framework concerning Post-co-ma unresponsiveness or Vegetative state (2003), Ethical Guide-lines for the Care of People in Post-Coma Unresponsiveness (Vegetative State) or a Minimally Responsive State (2008), Post-Coma Unresponsiveness and Minimally Responsive State. A guide for families and carers of people with profound brain damage (Guide for families) (2008)*. In these documents PCU is suggested at the same time as a synonymous and an alternative to the commonly used VS.

The *Diagnostic Framework* (2004) describes PCU as fol-lows: Post-coma unresponsiveness (VS) encompasses clinical states that follow emergence from coma in which there is apparently complete lack of purpose-ful responsiveness, with preservation of sleep-wake cycles and cardio-respiratory function, and partial or complete preservation of hypothalamic and brain-stem autonomic (vegetative) functions. Post-coma un-responsiveness (VS) is a manifestation of severe brain damage [63]. Although this label has the advantage to avoid the use of a temporal criterion, like persistent or permanent, its meaning seems to be too much large and it may produce a confusion between vegetative state and cerebral death.

In the document of 2003 it was also written that there are three main reasons to prefer PCU to VS: It use-fully excludes unresponsive states that do not follow a period of coma, such as the terminal stages of Alzhei-mer's disease, or the unresponsiveness seen in devel-opmental abnormalities such as anencephaly; it avoids the potentially pejorative term vegetative; and it has no time-based qualifiers—that is, it could apply as soon as emergence from coma occurs and for as long as the patient remains unresponsive [63].

In the same document the essential features of PCU are described as follows:

• long periods of wakefulness without responsive-ness.

• roving eyes, sometimes briefly tracking a moving object.
• spastic limbs, with withdrawal in response to pain, and often grasp or grope reflex in the hands.
• no words uttered or mouthed, no commands obeyed.
• no purposeful emotional responses — frowning, crying, tears, smile-like movements and laughter may occur but are divorced from appropriate stim-uli.

The *Ethical Guidelines* of Australian Government devel-op a vocabulary of several disorders of consciousness and aim to promote the best interests of these vulner-able people. They define coma as a state of presumed profound unconsciousness from which the person cannot be roused when examined. Coma is not brain death; some brain function remains, and some or all may be recoverable [64].

Consequently the PCU is a state or condition in which a person has emerged from coma to the extent that he or she is observed to have sleep/wake cycles over a period of time but no purposeful responses to stimuli. Responsiveness may gradually return in some people, leading to MRS [Minimally Responsive State] or even better, although improvement may be very slow. Some recovery may be achievable but full recovery is highly improbable [64]. Interestingly the Ethical Guidelines of 2008 prefers the words "person" rather than patient.

The Australian institutional documents use the term "Minimally responsive state (MRS)" rather than "mini-mally conscious state". This condition may arise when a person has emerged from coma or PCU. There is a minimal level of purposeful response, with discernible but inconsistent evidence of consciousness. Cognitive-ly mediated behavior occurs often enough or for long enough to distinguish it from reflex behavior, and the more complex the response, the easier it is to make this distinction [64].

The *Diagnostic Framework* concerning *Post-coma unrespon-siveness or Vegetative state* [63] underlines that PCU must be diagnosed primarily through clinical examination. The National Health and Medical Research Council recognizes the value of imaging technologies in diag-nostic process but at the same time outlines their limi-tation: structural, functional and electrophysiological tests could establish the site and extent of brain injury, but no "gold standard test" is available.

The *Ethical Guidelines* [64] of Australian Government consider more carefully neuroscientific studies with neuroimaging technology [37,[65]. If the Diagnostic *Framework* [63] recognized that there are many diffi culties in diagnosing PCU and distinguishing it from MRS, the *Ethical Guidelines* [64] specifies that it is dif-ficult to be certain that a person who has sleep/wake cycles is not responding at all, and it is not possible to be certain that the person is unaware, or what level of awareness he or she might experience. In MRS, there may be a delay between a stimulus (e.g., touch, light, movement, a voice) and any response, and responses may be ambiguous and difficult to identify.

About diagnosis and prognosis, the Ethical Guidelines specify that accurate diagnosis of PCU and MRS of-ten takes many weeks or longer. Confident diagnosis needs to be distinguished from the provisional findings of a single clinical examination – when, for example, a person emerging from coma may be observed to be in PCU or MRS. Similarly, the prognosis for a person with a diagnosis of PCU or MRS becomes clearer only over many weeks or months [64]. From a clinical and ethical points of view, the Australian Ethical Guidelines underlines that the research evidence is very limited and difficult to interpret. Furthermore, it is essential the periodic clinical reassessment in the long term, in relationship to the gradual and slow change of clinical condition. According to this document, the chances of improvement decreases with the increase of timeless. This evaluation has only a probabilistic and not abso-lute value, because life expectancy is difficult to pre-dict. Finally, according to the Australian Document of 2008, the general and specialist medical care are to be assured to people in PCU or MRS, including antibiot-ics and palliative care.

The abovementioned Australian documents shows at the same

time the importance to include neuroscien-tific findings in the ethical assessment of DOCs and to clear the limitation of the instrumental assessment of consciousness. Relevant ethical, social and legal issues arise from the potential inclusion of neurotechnology in the clinical examination and treatment: for instance, the allocation of economic resources, related to the fact that neuroimaging is not available in all places and in all circumstances; the competence of the medical staff who has to interpret the data; the time factor, that is the need to repeat the assessment of conscious-ness in different time and in different conditions; the balance between the instrumental and the behavioral assessment of consciousness.

As recently outlined by Laureys and Schiff [66] neuro-scientists and clinicians have to face an emerging need for motor-independent signs of awareness derived directly from brain signals. Yet a clinical and ethical

problem derive from the fact that in absence of motor responsiveness functional neuroimaging in principle is a more direct and objective tool to measure residual cognition in severely brain-damaged patients, while in practice the application of functional neuroimaging to patients with docs is often difficult and ambiguous with respect to resolving diagnostic uncertainty. This difficulty and this ambiguity, from which a diagnostic and therapeutic uncertainty arises, have important ethi-cal implications, regarding for instance the rightness of the diagnosis and the allocation of resources to im-plement the diagnosis. The fundamental point to take into account is that to date the uncertainty of the be-havioral assessment of consciousness in patients with DOCs is not eliminated by instrumental assessment but often replaced by another form of uncertainty. For instance it is important to note that a negative result in an instrumental assessment of consciousness cannot be assumed as a proof of the absence of conscious-ness, while, on the other hand, positive results are in-formative and assumable as proof of consciousness. The interpretation of positive and negative result is part of the general problem of translating the instru-mental findings "from the bench to the bedside", and for this translation well defined ethical frameworks are necessary [66].

Furthermore a relevant clinical issue emerges, that is assessing the potential prognostic value of the neuro-imaging technique. Important ethical issues are related to this point. First of all the shifting models of recov-ery, diagnosis and prognosis which are consequence of the new discoveries could require a reframe of the ethical models as well [67,68]. For this reason it is necessary that policies for patients with disorders of consciousness keep up with the times, that is with the neuroscientific discoveries and related applications.

Further ethical and social issues arise from the increas-ing requests for new diagnostic tools by the family of patients with DOCs [69]. Particularly, relevant ethical issues emerge from the risk of unrealistic expectations by family and surrogate decisionmakers.

Ethically relevant are also the possible shortcomings and misunderstandings about the use and the value of neuroimaging: Jox et al. outline that the neuroimaging techniques are rarely or poorly explained, and the ca-pabilities of neuroimaging are often misunderstood in media coverage, in the sense that they are assumed as real picture of the brain conferring a high authority to scientific explanations in the eyes of the public.

The abovementioned concerns confirm at the same time the necessity to start from neurotechnology for a new nosography of DOCs and to clearly outline its intrinsic limitation.

Conclusion

The relevant progresses in the neuroscientific un-derstanding of consciousness and related disorders suggest a new nosography focused on a behavioral approach supported by neurothecnology. As exem-plified by the analyzed Australian documents, current guidelines should include the new neurotechnologies as a source of information for more appropriated di-agnosis and prognosis of DOCs, but they should also outline the limitation of the clinical feasibility of such technologies. Relevant ethical, social and legal issues arise from the potential inclusion of instrumental assessment of consciousness in the clinical examination and treatment.

A relevant issue emerging from contemporary neu-rotechnology applied to DOCs is the feasibility of an appropriated nosography. Particularly, given the ex-traordinary complexity of the neural correlates of con-sciousness, the relation between them and the linguis-tic categories we use in their description raises several issues as regards to our knowledge and its impact on our practice: how much arbitrary is the nosography we use? Is it really able to express both the knowledge and the uncertainty of contemporary neuroscience?

These and other related issues deserves more attention in order to define a more appropriated interaction be-tween medicine and neurotechnology.

Authors Contribution

The authors contributed equally to the manuscript

Acknowledgements

This article has been written as a part of the project "Nosographic revision of vegetative states: application of behavioral analysis methods in the study of sub-jects in coma and vegetative state" granted by Italian Minister of Health and developed by Italian National Institute of Health (Istituto Superiore di Sanità).

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