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Misdiagnosis as an ethical and scientific challenge

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Abstract

Difficulties of behavioral assessment of consciousness. An astonishingly high rate of misdiagnosis between vegetative state/unresponsive wakefulness syndrome and minimally conscious state has been detected. This raises the issue of the adequacy of the consciousness' assessment in patients with disorders of consciousness. The behavioral assessment of consciousness could be not able to detect covert awareness, which is increasingly identified by the instrumental assessment.

Ancillary methods. Neurotechnology, particularly neuroimaging, provides relevant data concerning the neurological underlying condition of patients with DOCs, but the instrumental approach has still to assess some technical issues.

Ethical considerations. A correct diagnosis of a DOC is not only an instrumental issue, but also an ethically relevant demand to the scientific community. Finally, an integration between behavioral and instrumental assessments seems to be the most adequate strategy in order to decrease the rate of misdiagnosis.

Key words
• bioethics
• coma
• diagnostics

INTRODUCTION

New findings in neuroscientific investigation of disorders of consciousness (DOCs) are increasingly leading to two results, one theoretical and one practical:

- the development of new diagnostic tools;
- the development of new therapeutic strategies.

The impact of these results is so relevant to suggest a real paradigm shift in the DOCs' understanding and treatment [1].

The emerging data potentially raising more therapeutic consequences is the evidence that some severely brain damaged patients preserve residual cortical processing even in the absence of behavioral signs of consciousness. This possible dissociation between neurological state and behavioral evidence suggests the clinicians to be cautious in their claims about the consciousness of patients with vegetative state/unresponsive wakefulness syndrome (VS/UWS) [2-4].

In fact several studies have shown an astonishingly high rate of misdiagnosis between VS/UWS and minimally conscious state (MCS), estimated between 30% and 40% [5, 6, 2]. One of the reasons of such a high rate of wrong diagnosis is the use of nonstandardized consensus-based diagnostic techniques in DOCs [7]. This implies that the use of systematized scoring systems, whose introduction uncovered a lot of misdiagnoses, is mandatory. Anyhow, owing to the possible dissociation between behavior and related neurological condition, even the use of standardized behavioral scales may be not sufficient to avoid wrong diagnosis. A complementation of behavioral assessment with instrumental assessment of consciousness seems the most promising strategy to reduce the high rate of misdiagnosis.

This paper aims at:

- outlining the high rate of misdiagnosis of DOCs emerging from the difficulties of the behavioral assessment of consciousness;
- outlining prospects and limitations of the instrumental assessment of consciousness, particularly its impact on the clinical management of patients with DOCs;
- summarizing the ethical issues arising from the misdiagnosis between VS/UWS and MCS.

The fundamental idea of the paper is the necessity to integrate behavioral and instrumental assessment of consciousness in patients with DOCs.

DIFFICULTIES OF BEHAVIORAL ASSESSMENT OF CONSCIOUSNESS

The bedside assessment of consciousness is very challenging and risky. Within the main factors potentially affecting the accuracy of behavioral assessment of consciousness there are [8-10]:

- the presence of underlying deficits in communication by patients;
- locked-in syndrome;
- paralysis and akinesia;
- aphasia;
- tracheotomy;
- the use of sedatives;

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- cortical deafness or blindness;
- limited attentional capacities of patients.

Furthermore, it is clinically very challenging to disentangle reflex behavior, which characterizes VS/UWS patients, from intermittent voluntary behavior, characteristic of MCS patients [1].

Thus a systematization of behavioral assessment scales grounded on a comparative system has been necessary. The American Congress of Rehabilitation Medicine performed a systematic, evidence-based review of behavioral assessment scales for DOCs and provided evidence-based recommendations for clinical use founded on content validity (*i.e.*, enclosing diagnostic criteria), reliability, diagnostic validity, and ability to predict functional outcomes [11].

The review shows that "the Coma Recovery Scale-Revised (CRS-R), Sensory Stimulation Assessment Measure (SSAM), Wessex Head Injury Matrix (WHIM), Western Neuro Sensory Stimulation Profile (WNSSP), Sensory Modality Assessment Technique (SMART), Disorders of Consciousness Scale (DOCS), and Coma/Near-Coma Scale (CNC) have acceptable standardized administration and scoring procedures. The CRS-R has excellent content validity and is the only scale to address all Aspen Workgroup criteria. The SMART, SSAM, WHIM, and WNSSP demonstrate good content validity, containing items that could distinguish persons who are in a vegetative state, are in a minimally conscious state (MCS), or have emerged from MCS. The Full Outline of UnResponsiveness Score (FOUR), WNSSP, CRS-R, Comprehensive Levels of Consciousness Scale (CLOCS), and Innsbruck Coma Scale (INNS) showed substantial evidence of internal consistency. The FOUR and the CRS-R showed substantial evidence of good reliability. Evidence of diagnostic validity and prognostic validity in brain injury survivor samples had very high levels of potential bias because of methodological issues such as lack of rater masking".

The conclusion of the review is that a more or less significant reservation is necessary for the use of any behavioral scale to assess consciousness in patients with DOCs. Of course the different scales have different rates, that is different abilities to detect residual consciousness. The CRS-R is rated as the best scale which can be used with minor reservation; moderate reservations are suggested for the SMART, WNSSP, SSAM, WHIM, and DOCS; major reservation for the CNC, while the FOUR, INNS, Glasgow-Liege Coma Scale, Swedish Reaction Level Scale-1985, Loewenstein Communication Scale, and CLOCS are not recommended, at least for this time.

The reservation to use behavioral scales in the assessment of consciousness suggests their insufficiency for an objective diagnosis. The same standardization of the behavioral scales caused at the same time the improvement of the diagnosis and the revelation of several cases of misdiagnosis. The point is that the behavioral assessment of consciousness is affected by an inner limitation: it is not possible to ascertain what happens in the brain from the external behavior, especially in the case of DOCs for which a dissociation may exists between neurological condition and behavior.

It is necessary to see over visibility, and this is increasingly possible through neurotechnology [12]. In conclusion, for a more accurate diagnosis it is recommendable to integrate the behavioral assessment with ancillary technological methods of diagnosis.

ANCILLARY METHODS

Neurotechnology, particularly neuroimaging, provides relevant data concerning the neurological underlying condition of patients with DOCs going beyond the dissociation between neurology and behavior.

Neuroimaging studies have been recently used to assess patients' responses to specific external stimuli (*i.e.*, command following). Particularly, the assessment of consciousness and the new form of communication allowed by functional Magnetic Resonance Imaging (fMRI) [13] suggest a new diagnostic class, the so called 'functional locked-in syndrome'. This condition is used to underlie the state of patients who preserve higher cognitive function (such as imagining to play tennis or to walk in their house), but are affected by an extreme behavioral motor dysfunction [14, 15].

The introduction of the category of functional locked-in syndrome, such as the suggested use of UWS, is an example of the increasing impact of neurotechnology on the diagnosis and the nosology of DOCs. The most relevant impact of neurotechnology on clinical practice is the need for a new nosography. It is relevant that many studies regarding VS/UWS were published prior to the formal recognition of the diagnostic criteria of MCS, so that it is not possible to exclude that the studied patients were in MCS instead of VS/UWS. It raises the practical/clinical problem to properly manage patients with DOCs, as well as the theoretical issues of the validity and accuracy of our actual knowledge.

The study of consciousness at rest is a particularly promising application of neuroimaging technology [16]. Particularly 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 at rest than during attention-demanding tasks. This default mode network is considered to be involved in self-related processes [17]. It is relevant that resting state connectivity disappears in brain death and shows a non-linear disintegration in pseudocoma or locked-in syndrome as compared to minimally conscious or relative to unconscious states (VS/UWS or coma). This means that monitoring the resting state connectivity through neuroimaging can be a new, potentially very accurate tool for better diagnosing and managing patients with DOCs [18-21].

The spontaneous fMRI activity patterns can serve as a useful diagnostic tool in DOCs. Of course, there are limits and limitations in the fMRI assessment of consciousness, particularly the fact that, 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 particular brain region able to ac-

tivate and process sensory stimulation. Furthermore, the non activation during passive fMRI paradigms may be consequent to peripheral sensory systems' impairments (*e.g.*, deafness). Notwithstanding such limitations, as stressed by Soddu *et al.*, "resting-state fMRI acquisitions are easy to perform (*i.e.*, do not need auditory, visual or somatosensory stimulation equipment in the fMRI environment) and could have a potentially broader and faster translation into clinical practice" [18]. This does not mean that the clinical application of resting state analysis is simple nor unproblematic. In fact, there are technical problems still to assess, such as spatial normalization, movement correction and how to properly assess strongly asymmetric brains in DOC.

The resting state study can be included in the attempts to answer to the need for motor-independent signs of awareness derived directly from brain signals [22]. A promising preliminary study showed the potential of resting state structural study to define the prognosis of DOCs and to differentiate between VS/UWS and MCS [23].

Even 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, but in practice the application of functional neuroimaging to patients with DOCs is often difficult and ambiguous with respect to resolving diagnostic uncertainty. For instance the mental activities required for detecting and monitoring awareness raise a problem of feasibility of consciousness assessment. Electrophysiological and neuroimaging protocols have been developed to probe for signs of awareness even in patients completely unable to move. The main problem is that the mental imagery tasks used for MRI detection of consciousness require high-order cognitive abilities such as comprehending or carrying out instructions and can be very demanding for many brain-injured patients. On the contrary event-related EEG potentials elicited by simpler sensory stimulations involve lower cognitive resources. It would be useful to develop more sensitive methods of detection independent from the subject's ability to comprehend or carry out instructions [24].

The methodology of neuroimaging investigation of patients with DOCs may affect also the diagnostic accuracy of the instrumental assessment of the patients. There is a real risk of instrumental bias in the assessment of consciousness of patients with DOCs. For instance, in quantitative positron emission tomography (PET) studies many assumptions determinate the absolute value of cerebral metabolic rates, and there is not a consensus in cases of cerebral pathology. Furthermore the variability of corrector factors, such as the lumped constant, in cerebrally damaged brains, or metabolically inactive spaces of the brain, may artificially lower the calculated cerebral metabolism.

Like metabolic studies, even functional studies (such as $H_2{}^{15}O$-PET, fMRI or magnetoencephalography) raise relevant methodological issues: the coupling of neural activity and local hemodynamics, which is essential for these studies, in brain damaged patients is different than healthy people, so that the interpretation of data is very difficult. Moreover the choice of the appropriate experiment (for instance auditory or visual) is crucial, as well as the right complexity of the investigation, which must be complex enough to study the cognitive processes of interest but not so complex to overload the cognitive capacities of the patient. Other relevant practical problems potentially leading to misdiagnosis are the frequent episodes of low arousal and sleep in patients with DOCs. Even spontaneous movements during the scan may compromise the interpretation of functional neuroimaging data. Finally, some co-occurring pathologies, like gross hydrocephalus or focal pathology, may complicate the fitting of functional to structural imaging data.

These difficulties do not mean that neurotechnological assessment is not feasible or not adequate, but that it is necessary to properly manage it in order to obtain reliable data. Furthermore the possible uncertainty raising from instrumental assessment suggests as a proper strategy the integration with the behavioral assessment.

ETHICAL CONSIDERATIONS

A correct diagnosis of a DOC is not only an instrumental issue, but also an ethically relevant demand to the scientific community.

One of the reasons for the ethical relevance of a right diagnosis between VS/UWS and MCS is their different prognosis: the prognosis of the latter is better than the prognosis of the former [25-28]. To not adequately diagnose a patient with DOC could imply to not properly manage and care him, with the consequent not respecting his right to be cared and of his relatives' and/or his legal representative's right to be adequately informed.

Another ethically relevant reason for developing an adequate diagnostic tool for patients with DOCs, particularly for properly discriminating between VS/UWS and MCS, is the potential for pain perception and suffering in the two states: it seems reasonable to assume that MCS patients can feel pain and can suffer, while VS/UWS patients cannot. This may affect the decision regarding clinical treatment, particularly for the use of analgesia and painkillers [29]. A wrong diagnosis may cause a wrong use of analgesic treatment with potentially negative effects for patients: if the patient is in VS/UWS and is wrongly diagnosed as in MCS the use of painkillers may reduce the residual awareness of the patients and so leading to diagnostic difficulties; if the patient is in MCS and is wrongly diagnosed as in VS/UWS the clinician may decide to not use painkiller while they should be recommendable.

Finally, the decisions regarding a possible withdrawal of life sustaining treatments can be different for VS/UWS and MCS patients, so that a correct diagnosis is crucial for a properly informed decision.

Another socially and ethically relevant phenomenon is the increasing request for new diagnostic and therapeutic strategies from the family of patients with DOCs. In fact, to date some of these new procedures remain investigational [30]. Beside the fact that to date most of them have not been translated from the laboratory to the clinics, some emerging results are still partial and waiting for being confirmed. Further studies are necessary on this point. The investigational nature of

diagnostic and therapeutic strategies requires the clinicians to be aware in their conclusion regarding patients' residual consciousness. Furthermore, the necessity of specific informed consent and adequate information regarding the experimental procedures emerges.

Another relevant point is that the costs of such technologies may be very high, rising the ethical problems of the individual access to them and of the resources' allocation.

Shortcomings in the media coverage of neuroscientific information lead the risk of unrealistic expectations by families and surrogate decision makers [31, 32]. This issue is socially and ethically relevant: the clinicians have the duty to explain the diagnostic potential and limitations of the instrumental assessment of consciousness [30].

CONCLUSION

To date consciousness cannot be objectively measured and assessed. Even an instrumental estimation of consciousness requires an interpretation of several clinical signs.

In order to avoid a sort of relativism and to develop the quantification and standardization of the consciousness' assessment many scoring systems have been developed [33]. The main problem is that, since there is not a gold standard, criterion validity and diagnostic value of the different scoring system cannot be quantified [34]. For this reason imaging-based diagnostic methods are a recommendable complement of behaviorally based assessment in order to avoid diagnostic errors. Complementation is not substitution: the instrumental assessment is not free of problems of management, analysis and interpretation, so that it cannot completely replace the standardized clinical assessment.

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Conflict of interest statement

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