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Abstract

Recently, a number of neuroimaging studies have been conducted, aimed at detecting signs of consciousness in patients with a diagnosis of vegetative or minimally conscious state. The contributions appeared during an ongoing international ethical and socio-legal debate, on the admissibility of decisions to withdraw artificial nutrition from vegetative patients, thereby allowing them to die. We argue that neuroimaging is more likely to contribute to medical diagnosis and decision making if two requirements are met. First, those studies inferred awareness from the neural correlates of cognitive processes that are assumed to involve consciousness. However, neural correlates of consciousness proper, as defined by current philosophy and neuroscience, are the only admissible non-behavioral signs of awareness. Second, in those studies patients attempted to answer medically irrelevant questions by modulating their cortical activity in imagery tasks. We suggest patients should instead be queried on matters relevant to their clinical condition and quality of life.

Keywords

Regulation of Medical Behavior, Medical Law and Ethics, Rights of Patients, Disorders of Consciousness, Neuroethics and Law & Neuroscience.

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1. Introduction

As a first approximation, consciousness in individuals may be represented as an unbroken line, with brain death at the one end, and full awareness at the other.1 Where a particular brain-damaged and consciousness-impaired patient stands in this line, is usually decided by means of diagnostic criteria. However, criteria are liable to shift, and diagnostic categories may change or disappear altogether, partly as a result of the evolution of the scientific-technical apparatus supporting medical practice. As uncertainty from various sources is likely to affect different stages of medical diagnosis and decision making, the inclusion of methods from experimental brain research may be deemed desirable to settle clinical cases that would remain ambiguous, if diagnosis was based on standard bedside protocols alone. Under what conditions can experimental methods be included in clinical assessments of disorders of consciousness? This question and related issues are the focus of the present paper.

Take the distinction between ‘minimally conscious state’ (MCS) and ‘vegetative state’ (VS). Both VS and MCS can only be brought about by life-saving medical intervention following brain injury. The diagnostic label VS was introduced after the use of resuscitation, artificial ventilation and intensive care technology had become widespread in most rich countries. Since the 1970s, it has became possible to restore heartbeat and support respiration mechanically. Some severely brain-damaged patients may regain the ability to breathe independently, and no longer need intensive care treatment. Those who fail to recover consciousness are said to be in a VS. This condition of wakefulness with partial arousal, though without apparent consciousness, may last for weeks and may be diagnosed as a persistent vegetative state (PVS). However, after recovering spontaneous respiration and intensive care independency, some patients may exhibit ‘partial, intermittent or inconsistent’ signs of consciousness before the VS can be considered persistent (Fins 2005). This condition has been described as MCS (Giacino et al. 2002).

As these patients would not meet the diagnostic criteria for the VS, the medical community felt it necessary to devise a new clinical category, the MCS. For this purpose, Giacino et al. (2002) carried out a systematic survey of 260 studies on disorders of consciousness, and reported that only 5 of these studies claimed to have differentiated, based on empirical observations, VS patients from patients showing some signs of consciousness. Giacino et al. concluded that there were insufficient data to establish evidence-based guidelines for diagnosing the MCS. Thus, they proposed to resort to a consensus-based set of criteria to define the MCS. They listed a number of behavioral signs they would take as indicative of the presence of minimal consciousness, including: the patient can follow simple commands, give gestural or verbal yes-or-no responses, utter intelligible words, or exhibit purposeful behavior like reaching for objects. Severely brain-damaged patients can be said to be in an MCS if they display at least one of these abilities (Bernat 2006).

The VS and MCS are typically diagnosed by a multi-disciplinary medical team. The team observes the patient’s appearance and his or her acts to detect signs of consciousness (Jennett 2009). In the United Kingdom, for instance, the clinical management of VS and MCS patients is regulated by the 2003 British College of Physicians (BCP) guidelines (Royal College of Physicians 2003). According to the BCP guidelines, family members can, with validity, request and obtain withdrawal of life-prolonging treatment from a VS patient whose condition is diagnosed as permanent. If the patient is in an MCS, requests to withdraw treatment made by family members have no legal validity.

Unfortunately, however, consciousness is hardly the kind of mental state that is reliably expressed in behavior: a patient that appears asleep may be only partly or not at all aware of himself or the environment, and a patient that appears awake may be utterly unconscious. This partial dissociation between wakefulness and awareness suggests that observing the patient’s behavior alone could well lead to underestimating the presence of consciousness, and therefore to making a PVS diagnosis more likely, leading to withdrawal decisions when the patient may still have some residual consciousness. This shows it is desirable to build diagnostic inference on a broader data base than behavioral evidence; hence the relevance of neurophysiological measures of brain activity, such as

[1]Hereafter, the terms ‘consciousness’ and ‘awareness’ will be used interchangeably (Libet 1999).

EEG and fMRI, and of testing paradigms from experimental neuroscience, to help determine the actual consciousness level in a brain damaged patient.

2. Experimental approaches to consciousness detection

2.1. What is a neural correlate of consciousness?

When behavioral signs of awareness are not available, the level and the content of consciousness may be inferred based on the presence and strength in a given pattern of brain activity of a neural correlate of consciousness (NCC). A neural system N is an NCC if the state of N correlates with states of consciousness (D1). These states can be conceived of as points in a 3-dimensional space, in which the dimensions are: (1) arousal state (ranging from deep sleep to full wakefulness)2, (2) level of consciousness; (3) content of consciousness. Importantly, this is not a homogeneous space: for instance, some of its portions are not accessible, such as being asleep and fully conscious, a state which does not seem to be attainable in principle. These dimensions are only partly independent (Chalmers 1998). For example, a particular stage of sleep (e.g., REM sleep) can be associated with varying degrees of awareness on different occasions. The key term in definition (D1) is 'correlation', which requires that some measurable variable in N, such as physiological activation level (e.g. BOLD responses in fMRI), co-varies with the state of consciousness, though not with anything else independently (Frith et al. 1999). The latter restriction implies that a candidate neural system is not an NCC if its activation levels correlate with states of consciousness and with some other factor, such as the cognitive or motor complexity of the experimental task, or the perceptual complexity of the stimulus; examples will be discussed below.

Although some criticism has been addressed to definition (D1), none of it seems conclusive. For example, Noë & Thompson (2004) refer to (D1) and to similar claims as to the 'matching content doctrine'. They see that "the first task of the neuroscience of consciousness is to uncover the neural representational systems whose contents systematically match the contents of consciousness", and they proceed to discard this position, arguing that there is no experimental evidence that the neural states that correlate with conscious perceptual experience match, in a one-to-one 'isomorphic' fashion, the content of awareness. While probably correct, this does not seem to undermine (D1), as it unduly restricts one of the terms of the correlation to conscious content. In (D1), indeed, correlations can be established with each of the three dimensions in which consciousness is seen to vary, and not just with content.

Supposing we restricted (D1) to conscious content for the sake of the argument, Noë and Thompson's criticism would seem to misfire, as correlations of the kind involved in the definition of NCCs do not entail a representational isomorphism between the contents of awareness and those of the neural substrate. For one, the concept of representation at the neural level is formidably hard to pin down. A phenomenal NCC, i.e., an NCC in which the relevant dimension is content, can be defined as the minimal neural basis for the content of an experience, such as that which differs between the experiences of red and green (Block 2005). Any states of N that show a double dissociation in cortical responses induced by any two experiences which differ in content, and that do not vary with anything else independently, can be considered as phenomenal NCCs. This makes the idea of isomorphism or 'systematic match' dispensable, and seems to salvage (D1) from Noë and Thompson's criticism. We agree with them that "to suppose that there were no isomorphism would be tantamount to the supposition that there was no intelligible connection (beyond brute correlation) between the experience and the neural locus in question", but we take 'brute correlations' of the right sort as sufficient for the purposes of uncovering NCCs.

The definition framework (D1) can be enriched with several elements. The first (E1) is a distinction between phenomenal consciousness (P-consciousness) and access consciousness (A-

[2]Above we noted that wakefulness and consciousness are distinct phenomena, thus it would now seem mistaken to include arousal states in the definition of NCC. However, arousal and awareness are only partly independent, as will be emphasized again in this paper, and the difficulty involved in tearing the two apart in some key cases (e.g., one cannot be fully aware unless one is awake) appears to justify the present choice (Chalmers 1998).

consciousness) (Block 2005). P-consciousness follows the above definition of awareness of different perceptual contents or qualia, such as redness or greenness. A-consciousness includes informational content, which is made available to the brain's supra-modal systems, like language, reasoning, decision making, and so forth. Crucially, Block argues, the two domains are not co-extensive: there are P-contents that contain too little information to become A-conscious, and A-contents that lack the subjective qualia feel associated with P-consciousness. Thus, there can be disjoint NCCs of A- and P-consciousness.

The second element (E2) is the distinction between detection and awareness. As has been observed by Libet (1999) as well as others, detection (of weak signals, color differences etc.) must not be confused with awareness, for the former can occur without the latter (Libet et al. 1991). Relatively complex behaviors that involve detection can be initiated in the absence of either A- or P-consciousness, as is suggested by experimental work (Libet et al. 1983). A substantial amount of cognitive processing can occur outside awareness and still influence behavior: examples include semantic priming (Dehaene et al. 1995; see below), binocular rivalry, motor control (e.g., corrective movements), and blindsight (Weiskrantz et al. 1974; for discussion, see Rees & Frith 2007). It is therefore mandatory to exercise extra care when inferences based on brain activity are drawn. A neural correlate of a cognitive process that may involve consciousness, or that usually implies consciousness, but does not necessarily do so, is not an NCC. We will see an example of this below.

Finally, the third element (E3) is a differentiation between the kinds of cortical architectures that support NCCs. Crick & Koch (1998) discuss three families of accounts: (T1) theories in which awareness arises out of the activity of restricted cortical areas or networks; (T2) models in which consciousness is viewed as the result of the activity of specific types of neurons, which may be either distributed across the brain or localized in a particular area; the latter possibility may make (T1) and (T2) indistinguishable, while the former would be consistent with (T3) theories in which consciousness is rather a global phenomenon, emerging from the integrated activity of large-scale brain networks (Greenfield 1995), in which activity in sensory areas is driven by the frontal cortex through top-down attentional amplification (Dehaene & Naccache 2001). NCCs are bound to appear as very different entities, depending on which of these three families (if any) delivers a most successful theory of consciousness.

How does the refined notion of NCC relate to current attempts to determine whether severely brain-injured and unresponsive patients possess any degree of awareness? Below we offer an answer to this question, discussing a restricted yet representative sample of recent experiments using electrophysiology (EEG) and neuroimaging (fMRI).3

2.2. Electrophysiology and disorders of consciousness

Event-related potentials (ERPs) are brain signals obtained averaging over a large number of segments of the EEG trace, where each segment is time locked to the onset of a stimulus event from one experimental condition. Using this method, Schnakers et al. (2008) tested 22 brain-injured patients diagnosed as being in a VS (N=8) or in an MCS (N=15). Patients were shown sequences of proper nouns that contained either the patient's own name or unfamiliar names, in an active and a passive condition. In the active condition, patients were asked to count all occurrences of their name, or of another name. In response to their own name, MCS patients showed the same P3 wave in ERPs as healthy controls; the P3 was larger in the active counting condition. No such ERP response was observed in VS patients. The authors argue that "active evoked-related potentials paradigms may permit detection of voluntary brain function in patients with severe brain damage who present with a disorder of consciousness", and conclude that their method is "sufficient to detect voluntary and therefore conscious brain activity".

[3]These studies were selected based on the novelty of the reported findings and on the prominence of the journals in which they appeared (i.e., Science, The New England Journal of Medicine and Neurology). These two factors seem to us a reasonable proxy for the impact these studies can have on the scientific and medical community, as well as on the media and on public opinion.

Brushing aside some methodological details, what matters here is the use of the following inference scheme: the patient complies with the task instructions and counts the occurrences of a name; these two processes are assumed, without an argument or evidence of sorts, (1) to actually occur, and (2) to be voluntary in all instances; the second assumption is that anything voluntary must be conscious; from which the authors infer it followed that counting nouns was a conscious act, and that the P3 was an NCC, or a reliable consciousness detector in this context. However, this inference scheme – which occurs in slightly modified versions in the literature, as will be seen later on – is not valid. First, some restrictions: if the observed P3 was a true NCC, it would be a correlate of A-consciousness (E1), and it would rather fit the global theory of consciousness (T3). However, the key problem here lies in the idea that counting is a conscious process, regardless of whether it is characterized as being 'active' or 'voluntary'. In this particular task, in which patients are unable to report the outcome of their counting acts, hence experimenters cannot assess whether patients actually counted, either correctly or at all, counting may involve little more than the detection of a recurring sound pattern in the input. And if detection can occur without awareness (E2), the P3 would not be a genuine NCC, but merely a neural correlate of detection. Indeed, it has been suggested (Sommer et al. 1998) that the P3 wave is the reflection of an automatic frequency detector that is not (always) under voluntary control, and that may (Dehaene et al. 2001) or may not (Bernat et al. 2001) be A-conscious. It is based only on the previous diagnosis of MCS, in which one can suppose counting, in these patients, to be conscious. Hence, if a P3 was found in some VS patients (Perrin et al. 2006), it would not follow that their counting acts are voluntary or conscious, for (1) counting in these patients might require simply an involuntary change-repetition detection below awareness, and (2) the P3 is not an NCC. We conclude that the P3 component in ERPs is not a reliable diagnostic instrument in disorders of consciousness, especially combined with a task such as counting, which, as in other high-level cognitive processes, requires some kind of behavioral output in order to determine whether at all, and how, the patient complied with the instructions. We shall return to this important issue later on.

A more sophisticated, but no less problematic, electrophysiological approach is described by Boly et al. (2011). Their background theory belongs to the family (T3) of global models of consciousness, in which awareness of a given stimulus (P-consciousness) arises out of the integration of activity from (1) a bottom-up stream from sensory systems to higher-level frontal cortices, and (2) a top-down stream from frontal areas back into sensory regions (Laureys et al. 2000; Boly et al. 2004). The additional hypothesis, grounded in previous studies by the same group (Garrido et al. 2007), is that the early, exogenous components of the ERP waveform reflect bottom-up processing, whereas later, endogenous components index top-down processing. The authors used an 'oddball' paradigm in which a sequence of identical auditory tones is interrupted by a novel deviant tone (i.e., the oddball), which becomes a standard through repetition; the sequence is in turn interrupted by a novel deviant, and so on. The authors report that both early and late ERPs, including the P3, were seen in healthy volunteers and MCS patients, whereas VP patients displayed only the earlier ERP responses, and hence no P3; see however King et al. (2011) for technical comments on these responses. The proposed dynamic causal models (DCM) of the EEG data, purportedly showing that only VS patients exhibit impaired top-down connectivity, do shift the focus of what is a relevant NCC from single ERPs to large-scale network connectivity. However, this more sophisticated approach is based upon the reconstruction of source activity underlying ERP components: if the P3 does not count as an NCC because it can also be elicited by subliminal stimuli (Reuter et al. 1989; Shevrin 2001), then it would seem that its DCM source and connectivity reconstruction (i.e., a mathematical transformation of the same data, plus several assumptions) cannot be an NCC either. This holds as well for ERP responses later than the P3, including the N400 modulated by semantic priming (Kiefer 2002; more below), that are predicted by Garrido et al. (2007) to involve top-down processing.

Suppose, however, one could remove ERPs from the picture. The question would remain whether some kind of large-scale brain connectivity pattern can count as an NCC (T3), and whether unawareness can be inferred from the lack of integrity in that pattern. ERP waves such as the P3 and N400 would be produced by that network, but a one-to-many ERP-to-function relationship would apply, such that the presence or absence of any particular ERP component could not be taken to reflect the presence or absence of consciousness. The MCS and the VS would be understood as 'disconnection syndromes', with varying degrees of severity. This view has some appeal, especially if contrasted with alternative notions. As argued by Laureys (2005), the lesional approach has failed to establish a specific brain area or a restricted network that, according to the family of theories (T1), would support consciousness; metabolic levels are similarly not explanatory, as though consciousness would be equal to supra-threshold activity throughout the cortex, as in some (T3) theories. However, the disconnection syndrome approach itself raises several problems. First, not any large-scale disconnection would do: there exist cases of severe lesions in fronto-temporal white matter pathways that result in cognitive deficits, though not necessarily in diminished awareness (see Catani & Mesulam 2008a, 2008b). Is "widespread functional disconnection across the corticothalamic system" (Schiff 2006), or equivalently a "metabolic dysfunction of a widespread cortical network" (Laureys 2005), still a disconnection in some meaningful sense? Unless the disconnectionist account of MCS and VS is made more precise, and more readily falsifiable, one is led to take large portions of the brain ("medial and lateral prefrontal cortices and parietal multimodal associative areas", Laureys 2005) as a substrate for NCCs, which apparently violates a key aspect of (D1): the physiological activation levels of the NCC must co-vary with the state of consciousness, but not with anything else. It is to be expected that activation in a frontal, prefrontal and parietal brain network would vary with a number of cognitive processes that may or may not involve consciousness.

2.3. Neuroimaging and disorders of consciousness

In the previous section we have highlighted some of the limitations to the use of electrophysiology as a diagnostic tool in disorders of consciousness. We argued that diagnosis would require one to be able to determine whether a reliable NCC is present, has deteriorated or is absent in a given patient or group. We have also seen that none of the putative ERP markers of voluntary or conscious processing used in the literature sample reviewed above (Schnakers et al. 2008; Boly et al. 2011) satisfies the requirements set by definition (D1) of NCC. There is no evidence that any known ERP component, including the P3, co-varies systematically with awareness and with nothing else independently. Therefore, no known ERP wave currently counts as an NCC. No dependent measure (e.g., effective connectivity from DCM) derived from ERPs can identify an NCC either. Another limitation of electrophysiology is the kind of theories of consciousness to which it necessarily connects. Because the EEG is recorded at the subject's scalp, there is no unique solution to the problem of reconstructing the underlying cortical sources; hence EEG is said to have poor spatial resolution, and cannot be used to test the more localizationist (T1) or single-neuron-type (T2) of theories of consciousness, but only larger-scale models (T3) and complexity-based models (Tononi & Edelman 1998; Tononi & Koch 2008). fMRI data seem more relevant for (T1) theories, and may provide stronger NCC candidates, based on (T3) accounts, than ERPs.

Owen and co-workers conducted a set of fMRI studies on MCS and VS patients (see Owen et al. 2006; 2007a; Monti et al. 2010a among others). In Owen et al. (2006), furthermore, the goal of using experimental neurophysiology tools in a clinical setting is clarified to a degree: "we hypothesized that this technique [fMRI] also may provide a means for detecting conscious awareness in patients who are assumed to be vegetative yet retain cognitive abilities that have evaded detection using standard clinical methods." In a recent study by Monti et al. (2010a), 54 patients were tested in an fMRI experiment, of whom 31 had been diagnosed in MCS and 23 in VS by an interdisciplinary medical team, based 'on the patients' appearance and acts'. The subjects (both patients and healthy volunteers) had to perform tasks of motor and spatial imagery in the MRI scanner: each subject was asked to picture himself while walking into his home (spatial imagery), and while playing tennis (motor imagery). In 5 patients (4 in VS and 1 in MCS) the fMRI scans revealed activation of neocortical networks associated with orientation and navigation in space (parietal cortex and parahippocampal gyrus)4 and movement (motor cortex), similar to the activation of healthy

[4]In Monti et al. (2010a), the spatial imagery task activated only the parahippocampal gyrus in 4 of the 5 patients. In the patient described by Owen et al. (2006), the same task also activated parietal and premotor areas. These discrepancies have not been discussed by the authors, and neither has the possibility that the spatial and motor imagery tasks, due to the

volunteers. The authors argue that “these results show that a small proportion of patients in a VS or MCS have brain activation reflecting some awareness and cognition.”

In a related previous study, Owen et al. (2006) report the case of a 23-year-old brain-injured patient who had been diagnosed in a VS, but had fMRI responses similar to healthy controls in a passive language comprehension task, as well as in the same spatial and motor imagery tasks described above. Importantly, while in Owen et al. (2006) patients were just asked to imagine navigating through their home or playing tennis, in Monti et al. (2010a) these two kinds of imagery were elicited in order to receive yes-or-no answers from all healthy controls, and from one patient, to questions that pertained to their personal lives: e.g., to the query ‘Do you have any brothers?’ the subject had to respond doing motor imagery if the answer was ‘yes’, and doing spatial imagery if it was ‘no’. This shift suggests two uses of brain imaging: Owen et al. (2006) adopt fMRI scans as a diagnostic tool, i.e., as evidence that, assuming the modulation of brain activity is a willful relevant response to external stimuli, patients are conscious, and therefore any VS patient that shows such pattern must be re-diagnosed in an MCS; Monti et al. (2010a) instead also use fMRI as a tool to communicate with subjects, albeit in a form limited by the kinds of questions that were asked (verifiable queries) and by the kind of answers that could be obtained (yes-or-no). It is this two-fold use of brain imaging, as a diagnostic and as a communicative tool, that raises a number of thought-provoking and pressing questions, which shall keep us occupied for the remainder of this paper.

The interpretation of the data, offered by Owen, Monti and colleagues, has been criticized by several parties. Some have remarked that the activations reported in these studies could have been entirely automatic and unconscious, and that the experimental design leaves no room for a distinction between a patient’s being unconscious and his being unwilling or unable to attend to the task instructions (Nachev & Husain 2007). Others have asked what the evidence is that patients interpreted the verbal stimuli as instructions rather than as indicative sentences, such that the observed fMRI activations would be involuntary and unconscious (Greenberg 2007). Although Owen, Monti and collaborators have responded to these critiques, neither their original paper, nor the commentaries, address what seems to us to be the key issue, that the motor, temporal and parietal activations reported by their studies are not NCCs, and would not be so even if the potential conflicting evidence highlighted by the critics were assumed or shown to be insubstantial. Our argument is, once again, that a pattern of BOLD responses that correlate independently with other cognitive processes than consciousness – as is the case with motor, temporal and parietal activations, which do vary at least with spatial and motor imagery – is not an NCC as defined by (D1). These fMRI activations are neural correlates of motor and spatial imagery, not of A- or P-consciousness.

Owen, Monti and colleagues seem, however, to be employing a different strategy to the one we have considered so far. The observed neural correlates of motor and spatial imagery appear to be modulated at will by the subject, depending on what the experimenters ask the subject to imagine, and on the exact question to be answered. The inference scheme discussed earlier on comes back again into play: if something is under voluntary control, then it is conscious. Responding to the criticism that motor and spatial imagery could be automatic and therefore unconscious (Nachev & Husain 2007; Greenberg 2007), Owen et al. (2007b) indeed write: “the argument that our stimuli may have automatically elicited the responses that we reported in our patient is supported neither by a direct test of this hypothesis nor by relevant literature in this area. The most parsimonious explanation therefore remains that this patient was consciously aware and purposefully following the instructions given to her, despite her diagnosis of vegetative state.” Is this ‘most parsimonious explanation’ grounded in empirical data? How complex or deep can automatic unconscious neural processing be?

Dehaene et al. (1995) tested healthy subjects using a masked prime (an integer between 1 and 9) and a visible target numeral, which could be denoted either by an Arabic number or a word. The task was to decide whether the target numeral was smaller or larger than 5. In some trials, the prime was congruent with the target, i.e., both numbers fell on the same side of 5; in other trials it was incongruent, with one number being smaller than 5 and the other larger than 5. They found a

(Contd.)

movement component that they share, might activate a common subset of premotor or supplementary motor areas in some patients.

behavioral priming effect, where subjects responded more slowly in incongruent trials than in congruent trials. ERPs confirmed the effect of the invisible mask on processing the target: P3 responses were slower in incongruent trials; moreover, lateralized readiness potentials (LRPs), measured over motor cortex, were more negative in incongruent trials, reflecting covert motor priming; finally, motor activation was also revealed using fMRI. These data show that participants would unconsciously apply the task instructions to the prime, categorize it as smaller or larger than 5, and prepare a motor response. Unconscious brain activity is not restricted to sensory regions, but extends to motor regions too: "a large amount of cerebral processing, including perception, semantic categorization and task execution, can be performed in the absence of consciousness." Importantly, this does not prove that the brain activations in MCS and VS patients were automatic and unconscious; it does however raise the possibility that they could have been, which suggests that a genuine NCC must be sought, if experimental approaches using fMRI are to have any diagnostic value.

Even leaving NCCs aside, there is more methodological trouble connected with the work of Monti et al. (2010a). One striking finding of their experiment is that, of the 31 patients with an MCS diagnosis, 30 did not show any sign of awareness (imagery) when tested with fMRI. This fact is remarkable, considering that what differentiates VS and MCS is the presence of some such signs. We would like to advance two interpretations of this finding. One interpretation draws upon the attitude of doctors, who may be conservative when applying diagnostic labels to brain-damaged patients, and may tend to avoid using the label VS because of its implications for end-of-life decisions. In the UK, for instance, treatment in PVS patients can be lawfully withdrawn upon request by a legal representative (Royal College of Physicians 2003). The second interpretation is that at least some of these 30 patients actually were in an MCS, but the fMRI study failed to establish their consciousness level at the moment of testing. If correct, this may represent a surprisingly high false-negative rate of prediction of MCS. Whatever the origin of this null effect, or of these 30 null effects, this line of thinking appears to have far-reaching consequences: no patient could ever be diagnosed VS based on this kind of fMRI research, unless the fMRI test was used in combination with, and, in cases of conflict, subordinately to, standard bedside protocols. The exclusive use of fMRI would result, paradoxically, in increased diagnostic uncertainty, at least in that fMRI studies can disconfirm the diagnosis of MCS, but cannot support a new diagnosis of VS (Nachev & Hacker 2010). This points to a clear limitation in the uses of fMRI as a diagnostic tool. Future work may produce ways around this problem. One solution is to move beyond single-session fMRI, which seems incompatible with diagnostic criteria for MCS, where the 'partial, intermittent or inconsistent' nature of awareness in this condition is emphasized. Therefore, if at all possible and ethically acceptable (more below), testing patients multiple times may reduce the rate of false positives (i.e., VS patients displaying signs of awareness) and false negatives (i.e., MCS patients showing no such signs).

3. Clinical and ethical implications and non-implications

3.1. Turning neuroscience experiments into diagnostic tools

It has been repeatedly suggested that VS patients are very frequently the victim of misdiagnoses. This claim is used to emphasize the need for research aimed at developing new diagnostic tools for detecting consciousness. Owen and colleagues (Owen et al. 2006; 2007a; Coleman et al. 2009; Monti et al. 2010a), as well as other authors in the field (Fischer & Appelbaum 2010; Johnson 2010; Bosco et al. 2010; Tshibanda et al. 2010), state that approximately 40% of VS patients are misdiagnosed (i.e., are not in fact in VS)5, but do not substantiate this notion other than by making reference to the same three studies (Andrews et al. 1996; Childs et al. 1993; Schnakers et al. 2009). However, none of these establishes conclusive evidence that high rates of misdiagnosis occur. Two studies appeared in the early and mid-1990s and seem now outdated because of the technological and scientific development that has taken place in the past 15 years, and due to changes in regulation that have shifted the criteria

[5] This claim is also repeated outside scientific publications, in contexts that may be more accessible to medical and nursing staff, and to the lay public, such as on the internet pages of Siemens United Kingdom (Cogito ergo sum. Healthcare News. 02 July 2010).

by which the VS is diagnosed. The third study is more recent and we shall discuss it in some detail (Schnakers et al. 2009).

Schnakers et al. (2009) propose the adoption of a behavioral scoring system (named CRS-R or Coma Recovery Scale Revised) to detect consciousness, after the patient starts breathing spontaneously. CRS-R lists a number of signs in the patient's appearance and acts, which may indicate the presence of consciousness: can the patient hear or see, can she move, talk or communicate with others? A conventional score is assigned to each sign observed. If the total score is above a certain threshold, the patient is labeled MCS. Using the CRS-R, the condition of 103 severely consciousness-impaired patients was re-assessed by Schnakers et al. (2009). The patients in the sample had previously been assigned a diagnosis (VS, MCS or uncertain) by a medical team, based on behavioral observations but without a scoring system (i.e., a 'clinical consensus diagnosis'). The use of the CRS-R led to re-labeling a substantial percentage (41%) of the patients as MCS, whose 'clinical consensus diagnosis' was VS. The conclusion reached by the authors is that, typically, about 40% of patients labeled VS are in fact MCS. Necessarily, this conclusion assumes that the use of the CRS-R scoring system adds reliability to the diagnosis. However, there is no independent evidence for this assumption, and no separate evaluation of CRS-R against an alternative scoring system or another method of diagnosis. Importantly, the mere fact that the use of the CSR-R leads to the classification more patients in the MCS group is no proof of its reliability.

Could methods from experimental neuroscience, such as those described above, contribute to diagnosis by providing the kind of low-level physiological evidence that is required to assess the level of awareness in brain-injured patients? As has been argued by Giacino et al. (2006), turning experiments into diagnostic tools may indeed aid in differential diagnosis, prognostic assessment, identification of pathophysiologic mechanisms, and possibly restoration of function. There is no question that progress can be made along these lines. However, we have painted a rather bleak picture of the present state of affairs, arguing that methodological obstacles prevent even the most advanced neurophysiological experiments from being turned into diagnostic tools in a straightforward manner, e.g. by applying an established laboratory paradigm and some standard dependent measure (say, auditory oddball stimuli and the P3 wave) to a different population (MCS and VS patients). Based on our critique, we would like to suggest at least three ways in which the use of EEG and fMRI in a clinical setting may be refined and improved to suit the needs of medical diagnostics.

First, we propose that whenever the phrase 'consciousness detection' is used, there should be a qualification of what is meant by 'consciousness'. This seems a trivial point, but it is often enough ignored, presumably to avoid intricate or idle philosophical and neuroscientific discussions. Nonetheless, conceptual clarity is in this case imperative, if only because of the ethical and legal implications that a decision to re-diagnose a patient (e.g., from MCS to VS, or vice versa) may have. Conceptual specificity may also invite neuroscientists, medical doctors, ethicists and philosophers to consider whether an increase in one form of consciousness, rather than another (e.g., A-consciousness instead of mere P-consciousness, or self-consciousness in addition to either A- or P-consciousness), should be seen as an improvement in the patient's condition, or something that would make the MCS more desirable than the VS (more on this later). Here the distinction made by Block (2005) between A-consciousness and P-consciousness may be useful, and in its seeming coarseness already shows that the studies we have considered above are in some relevant respect incommensurable: the EEG study by Boly et al. (2011), assuming it taps into awareness and not merely into detection, seems more relevant for P-consciousness, i.e., sensory awareness of auditory qualia; in contrast, the fMRI studies by Owen et al. (2006) and Monti et al. (2010a) show brain responses that may suggest the presence of A-consciousness in some MCS and VS patients, that is, the broadcasting of sensory information (i.e., the verbal instructions) to the appropriate brain regions to perform the two imagery tasks. In order for neurophysiological studies to be comparable, and in order for us to decide whether they may serve as either complementary or alternative diagnostic methods, it is desirable that preliminary conceptual clarification is carried out to establish at least what kinds of consciousness one aims to detect (Lycan 1996). This bears on the issue of the cross-validation of diagnoses: if one does not know whether two or more studies produce NCCs of the same form of consciousness (and whether these are the same as the forms of consciousness revealed by other criteria, e.g. behavioral bedside tests), one would be unable to tell whether their results contradict or support each other (if the same forms of consciousness are studied across experiments), or whether instead their results could be consistent regardless (if different experiments deal with different forms of consciousness).

The second recommendation we intend to issue is the following: once the exact form of consciousness one aims to detect has been specified, an experiment, or a series of experiments, should be designed, with the purpose of revealing a neural correlate of that particular form of consciousness, that is, an NCC as defined by (D1) above. There is no need to remind the reader why an NCC is superior in this context to a neural correlate of some cognitive process, such as motor or spatial imagery, which, be it voluntary or not, must be assumed, perhaps mistakenly, to require consciousness. The obvious difficulty is that, in severely brain-damaged patients, the level of consciousness cannot be assessed behaviorally as is done in standard psychophysiological studies on humans or animals, and systems like the CRS-R may be of limited use when the resulting score has to be correlated with some physiological parameters. But we do not take this to be an insurmountable difficulty. So far as one or more reliable NCCs can be attested in healthy humans, through the application of correlational psychophysiological methods, the same NCCs could then be sought in MCS and VS patients using the same stimulation protocols and the same physiological dependent measures. The unavailability of behavioral output (say, buttons being pressed depending on the intensity of the perceived stimulus) would not undermine the inference that, if (1) a patient and a healthy individual are shown the same stimuli, (2) the healthy subject shows an NCC correlating with above-threshold consciousness, and (3) the patient shows the same NCC, then that patient consciously perceives or processes the stimuli above that threshold, i.e., presumably perception or processing are as conscious as they are in healthy individuals. Most real-life applications of this scheme will be considerably more complicated, but we believe the NCC-based approach may be about the only scientifically sound way to go; if there is some agreement within and between the philosophy and neuroscience communities, it lies in the belief that NCCs are definable and measurable in vivo. As far as P-consciousness is concerned, one could try to test whether MC and VS patients show NCCs in the visual system, as these seem to be better-understood than putative NCCs in some other sensory domain (Crick & Koch 1995, 1998; Rees et al. 2002), and arguably they are more tractable than supposed NCCs in high-level non-sensory domains, such as imagery or language as involved in the studies by Owen, Monti and colleagues.

The third recommendation is a practical way of getting around what appear to be surprisingly high rates of false negatives in fMRI data, i.e., of MCS patients not showing the expected activations, as we have seen earlier on. One easy solution is to test the same patients repeatedly, on different days and possibly at different times of the day, to control for altered sleep-wake cycles. This would be the safest approach methodologically. However, it may raise ethical concerns, to which we shall return below.

We have so far discussed some of the conditions under which experiments based on neurophysiological techniques could be used as diagnostic tools in disorders of consciousness. Above, we have argued that at least the fMRI study by Monti et al. (2010a) suggests a rather different application of brain imaging technology: as a means to communicate with some patients. This issue is addressed below.

3.2. Breaking communicative barriers: brain scans as behavior

Based on medical practice in many western countries, patients are considered to have emerged from an MCS only when they are able to 'reliably and consistently' communicate, using language or some other means (Fins 2005; Schiff 2006). One question is to what extent the ability to communicate can be spared despite impaired motor function (e.g., of the vocal tract). There are reasons to suppose that patients can recover the ability to form communicative intentions and share thoughts and feelings before they regain the motor and cognitive machinery that is necessary to communicate in the physical world. If that is so, a communicative barrier can be said to exist, which could be overcome if patients were trained to modulate some other physiological response than muscle tension to convey their thoughts and feelings. The fMRI study by Monti et al. (2010a) has been taken to show that patients can voluntarily modulate their brain responses, by activating motor cortices when motor imagery was agreed to stand for, say, a 'yes' response to the experimenter's question, and by performing spatial imagery and activating parietal cortices in case of a negative response. There is no doubt that, if indeed these patients were awake, conscious and able to modulate their brain responses as intended, their fMRI activations would count as communicative behavior.

But what is behavior, and what is the use of calling BOLD responses 'behavior'? Importantly, in the UK, the VS and the MCS are currently diagnosed according to 'behavioral criteria', in accordance with the BCP guidelines (Royal College of Physicians 2003). Monti and collaborators (Monti et al. 2010b, 2010c, 2010d) suggest that fMRI-based testing can be 'diagnostically relevant' under the BCP guidelines currently in force; they write: "one must allow for brain activations to be considered as a form of behavior, albeit nonmotoric". We could see the effort of Monti and colleagues as an attempt to introduce fMRI in standard diagnostic procedures for severe impairments of consciousness, without a reform of the BCP guidelines currently in force. This could be done only if, indeed, fMRI activations could be filed under 'behavior'. So let us assume they can.

Monti et al. (2010a) say that their fMRI paradigm could be used to ask patients "if they are feeling any pain, and this information could be useful in determining whether analgesic agents should be administered". It is unknown whether these authors have made any attempt in that direction. The issue here is not so much that VS patients who undergo such research typically cannot provide informed consent to participate, in one or multiple MRI sessions, and that consent is given by a representative seems acceptable (Karlawish 2003; Laureys et al. 2004). The problem is rather that questions relevant for the medical condition of the patient appear not to have been asked in any these studies. Although information to that effect seems to be missing in the relevant paper contributions, we do not see why the fMRI paradigm, as it is, would not allow asking questions that could bear on pain and medical treatment, much in the same way as the patients were asked whether they have any brothers, whether their father's name is Thomas, or other biographic questions (Monti et al. 2010a). However, one can imagine what may prevent patients from answering questions about whether they feel any pain in a truthful and therefore informative way, as well as experimenters from being able to interpret the answers. The paradigms used by Owen and colleagues hinge on questions being verifiable, but they do not require that all questions be of that kind. Thus, it remains unclear why these (Owen et al. 2006; 2007a; Monti et al. 2010a) and other experiments (Di et al. 2009; Staffen et al. 2006) published so far, used, or reported to have used, exclusively questions that are irrelevant to the clinical condition of the patient.

Our present point adds to the set of ethical constraints discussed by Fins et al. (2008). Based on discussions at the conference on 'Ethics, Neuroimaging, and Limited States of Consciousness' at Stanford University in 2007, these authors identify three clusters of issues which, if properly and thoroughly addressed, may allow imaging methods to "mature into useful clinical tools for the diagnosis and treatment of those with disorders of consciousness": (1) clinical translation, (2) research challenges, and (3) patient consent. Above we have argued that clinical translation can occur only if certain conditions on experimental paradigms are met, first and foremost a focus on NCCs as diagnostic markers of one or another form of spared consciousness. As for research challenges, Fins and collaborators rightly argue that studies on the 'pain matrix' (i.e., the brain network underlying the conscious perception of bodily pain) are of the greatest importance (Laureys et al. 2002). However, note that this would require again (1) a definition of what kind of consciousness is involved in pain perception, and (2) a corroboration of positive findings, i.e., that a certain patient shows activation of the pain matrix and thus feels pain, with a demonstration of an NCC in that patient. Nonetheless, as the authors also notice, ethical considerations limit the kind and intensity of noxious stimuli that may be applied to these patients, whose consent moreover cannot be collected. It is precisely this kind of ethical consideration that shows the importance of future attempts to collect information on pain states directly from patients, also using fMRI as a means to communicate with them.

On the other hand, this would not completely solve the consent issue. Informed consent remains unavailable in severely brain-damaged and consciousness-impaired patients. Although we agree that the inability to provide consent should not, in itself, be seen as a prohibition against research participation, these patients and their family members seem more exposed than others to abuse. First, surrogate authorization, which is the customary procedural safeguard in these cases, may arguably not be valid if patients indeed turn out to have enough spared cognitive function to understand the relevant information about the study, and to provide consent themselves. Severe or total paralysis is not a sufficient ground to avoid trying to elicit consent via non-standard means, including fMRI.6 As Fins et al. (2008) also remark – and this point is underscored or at least implied by all fMRI experiments reviewed above – the ethical challenge is “to include these subjects, as they are able, in the consent or assent process, recognizing that subjects may reveal a greater capability to engage with the investigative team.” Thus, should the suitability of fMRI as a communicative tool be confirmed in future research, it would seem ethically appropriate to (1) try to elicit informed consent from the patients, and (2) ask – following some verifiable control questions – whether the patient feels any painful sensation, or suffers otherwise, as well as other queries relevant to their clinical condition and to medical and ethical decision making.

3.3. Is there a relation between consciousness and quality of life?

In several contributions by Owen’s group (Owen et al., 2006; 2007; Monti et al. 2010a) the transition from the VS to the MCS is called an ‘improvement’ and ‘progress’. Indeed, the whole debate on consciousness-impaired patients seems to involve the unquestioned assumption that some consciousness is better than no consciousness (Farah 2008). However, we think this unconvincing, and not only because a definition of ‘consciousness’ is consistently missing in all studies. For example, would an increase in one’s phenomenal awareness be desirable, if it leads to enhanced acuity in pain perception, everything else being equal? But even leaving these thorny issues aside, the ethical issue remains. We believe the point of view to adopt is that of a patient and his family. Would anyone prefer to be utterly unconscious, or rather partially aware while being severely cognitively impaired, extremely confused, and hardly able to communicate? Which of these two states would anyone find more acceptable for a family member? We expect that even an informal survey would reveal individual differences: some would opt for complete unconsciousness, others would prefer some consciousness to none at all, and others still would find both conditions equally undesirable (Kahane & Savulescu 2009).

Patients who emerge from the VS and the MCS are still consciousness-impaired and suffer from multiple severe handicaps (Bekinschtein et al. 2005). Society, doctors, patients and their families are faced with a hard ethical question: which developments in the patient’s condition should be viewed as improvements? In one account, which we tend to favor, an improvement is a change of the patient’s condition that leads to an increase in the patient’s well-being and quality of life. Owen, Monti and colleagues argue that fMRI could “assay how much cognition may remain, whether consciousness is preserved, and maybe even yield answers concerning their quality of life.” However, there is no obvious relation between consciousness and quality of life: as we remarked above, a patient who retains or regains the ability to experience painful sensations would suffer, and thus enjoy a lesser quality of life, unlike a patient who lacks that ability.

We suggest that the presence of consciousness is ethically and legally relevant in the decision-making process over the administration of life-prolonging medical treatment only if the patient is able, at least to some extent, to participate in the decision, by communicating his feelings about his own condition and his wishes regarding medical treatment and further prolongation of his life. The presence of consciousness, in some form, above a certain threshold, may not in itself be a sufficient reason to keep a patient alive, although a decision to treat could always be made in individual cases (Griffiths et al. 2008). The ability to answer simple questions correctly, or to tell one’s own name or the name of a loved one (Monti et al. 2010c; Di et al. 2009), as would be revealed by the activation of particular cortical regions (Owen et al. 2006; Monti et al. 2010a), would fail to meet that standard, for it does not imply that the patient is capable in a cognitive and moral sense to answer questions bearing on his condition and on medical treatment.

[6]There is a paradox connected with this practice: a patient would have to undergo fMRI prior to and in order to provide consent for the actual study; obviously, however, consent cannot be elicited and obtained for this preliminary fMRI session prior to its execution. Though imperfect, we take this to be an ethically more acceptable situation than one in which no consent at all is elicited or obtained.

Our considerations do not imply that the lives of patients whose consciousness and ability to communicate do not reach a certain threshold are of no or lesser value, or that ways of establishing a meaningful contact with patients should not be investigated. Quite the contrary, we have provided a set of recommendations for using EEG and fMRI activations as diagnostic and as communicative tools in disorders of consciousness. However, and equally importantly, we have argued that, even if EEG and fMRI were applied within the boundaries of all the relevant conceptual and methodological conditions listed above, physiological experiments would not provide conclusive grounds for ethical decisions, because there is no transparent way to map changes in consciousness level into a scale of values that would determine whether that change is morally acceptable.

4. Some conclusions

Here, we have aimed to expose and discuss certain assumptions and open issues that permeate current research on severe impairments of consciousness. We think it crucial to carry out such analysis as these issues spread to the public perception of the MCS and VS (Racine et al. 2008). Furthermore, should EEG and fMRI become part of standard clinical protocols in the future, it is only fair to remind ourselves that the patient's right to bodily integrity and personal dignity may be compromised by further medical treatment (Johnson 2011), and that, moreover, bodily integrity and personal dignity can be of higher value than the presence of (or the prospects for a future re-acquisition of) minimal consciousness, however defined, and possibly of higher value than survival itself.

We believe that research, which would help patients, families, doctors and society in decisions over the administration of life-prolonging treatment to consciousness-impaired patients, need not involve the development of advanced imaging tools, if their main goal is restricted to detecting minimal signs of consciousness. This may have intrinsic scientific value (Fins 2003), but as we have stated above any such effort is fraught with conceptual and methodological problems: (1) of what forms of consciousness, and according to what measures (Seth et al. 2008), has a change in consciousness level been detected?; and (2) is the observed pattern of activity in EEG or fMRI a genuine neural correlate of consciousness (NCC)?; finally, (3) can brain activations from partly conscious patients (as based on the consciousness-detection procedure) be used to obtain the patient's consent and to inquire whether he is feeling pain, or whether he can participate, with doctors and the family, in decision making? While experimental research along the lines of Monti et al. (2010a) grapples with these questions, it seems equally urgent to gather statistical data by means of large-scale, multi-center, longitudinal studies, on the variables affecting the patients' likelihood of recovering consciousness and at least part of their motor functioning. Some such variables are already known, the patient's age, for example (Owen et al. 2006). Brain imaging may have a very important role to play in this kind of inquiry, leading to more information on the relations between the type and location of brain lesions, and long-term recovery outcome (Fins 2003; Coleman et al. 2009).

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