Disorders of consciousness: do state-of-the-art neuroimaging techniques shed new light on the brain-injured patient?

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Any illness in a loved one can be distressing for friends and relatives, yet there is something particularly challenging about issues affecting the brain. A variety of conditions from depression to dementia, from Creutzfeldt-Jakob disease to coma can leave the patient physically present whilst something of the person you previously knew is now hidden.

At least four distinct disorders of consciousness (DOCs) are associated with brain damage arising from trauma and/or shortage of oxygen (e.g. following cardiac arrest): coma, vegetative state, minimally conscious state and locked-in state (see Table 1). Several high profile cases, notably Tony Bland in the UK and Terri Schiavo in the USA, have prompted discussion regarding the ethics of withdrawing artificial nutrition and hydration (ANH) from patients in a long-term vegetative state, thereby hasten their death (e.g. Jennett, 1992; Keown, 2002; Annas, 2005). The current paper will not deal with the issue of withdrawal of ANH except tangentially; the focus here will be constrained to the role of emerging brain-imaging technologies in the diagnosis of DOCs.

Table 1: Principal characteristics of consciousness disorders
(adapted from Kobylarz and Schiff, 2004)

Condition / Characteristic	*Unresponsive patients*		*Minimally responsive patients*	
	Coma	**Vegetative state**	**Minimally conscious state**	**Locked-in state**
Cyclic arousal	×	✓	✓	✓
Command following	×	×	✓?	✓
Purposeful movement	×	×	✓?	×
Functional communication	×	×	×	✓

Abbreviations: × = absent, ✓ = present, ✓?= inconsistently present

Significant advances in understanding of DOCs have occurred during the early part of this century. Given the evolution of both the definitions of various conditions and recent developments in the technologies that are offering insight into (non)functioning of the mind, it is necessary to introduce the salient disorders and also the scientific approaches under discussion.

Dissecting disorders of consciousness

Consciousness itself has been tricky to define; however it is generally considered to have two major components; wakefulness (arousal) and awareness (of self and environment). Each of the four states described differs in the combination of wakefulness and awareness exhibited by patients.

Coma: Aside from brain death, the lowest level of brain activity is manifest by those in a comatose state. A coma is an absence of both arousal and awareness (Laureys *et al*, 2004). A patient may exist in such a condition for many years, though most commonly they become more wakeful within about a month and thereafter can be considered to have transferred to one of the other states.

Vegetative state: Unlike coma, patient in the vegetative state (VS) exhibits cycles of sleep and wakefulness, during which their eyes will open. They may perform a range of other behaviours, including yawning, grimacing or uttering sounds but in a random and unpredictable manner. The original term *persistent* vegetative state was coined by Jennett and Plum (1972), but a second term *permanent* vegetative state was later added in recognition of the fact that some patients appeared to be immutably in this condition. A patient is considered to have moved from persistent to permanent vegetative state 3 months after non-traumatic or 12 months after traumatic brain injury (Multi-Society Task Force on PVS, 1994a and 1994b). Although intended as a helpful distinction, many clinicians are uncomfortable with both vegetative states have the same acronym, PVS. There is thus an increasing trend to speak simply of patients being in VS, and to draw the distinction instead as being between VS and MCS, the minimally conscious state.

Minimally conscious state: Growing recognition that a sub-population of brain injured patients demonstrate "inconsistent but discernable evidence of consciousness" (Giacino *et al*, 2002: p349) led to introduction of MCS as a distinct category. A patient in MCS may intermittently follow simple commands, respond by making gestures, smile or cry appropriately, or similarly demonstrate a transient awareness (Bernat, 2006).

Locked-in state: Finally, reference must also be made to the locked-in state. A suffer is both awake and aware but other damage renders them quadriplegic and anarthric; they cannot convey their awareness to the world except via minute movement of, for example, an eye or eyelid (Laureys *et al*, 2004). The locked-in state is not strictly a disorder of *consciousness*, and is included here solely to complete the spectrum of conditions that may result from brain injury.

Brain-visualisation technologies

Whilst it is generally advantageous for the brain to be protected within the cranium, this arrangement becomes problematic when examination of a malfunctioning brain is required. Nevertheless, a variety of neurophysiological and neuroimaging techniques offer the capacity to probe inside the head in a non-invasive manner. To understand the experiments described below, it is necessary briefly to introduce neurophysiological methods such are electroencephalography (EEG) and event-related potentials (ERP), and neuroimaging methods, including computed tomography (CT) scans, positron emission tomography (PET), magnetic resonance imaging (MRI) and more recently functional MRI (fMRI).

Electroencephalography and event-related potentials: EEG measures electromagnetic activity in the brain via a series of electrodes on the outside of the head. Under normal circumstances, EEG measures a large amount of electrical activity occurring simultaneously making it extremely difficult to pick out any particular process (Taylor and Baldeweg, 2002). In order to detect brain activity associated with a specific trigger or event, it is necessary to have a large number of recordings and to take an average. Averaging of multiple measurements means that most signals from random brain activity should cancel each other out, allowing information relating to the particular event, the ERP, to be revealed. ERP has the advantage over neuroimaging techniques that it can measure responses on a much shorter timescale, typically a few milliseconds (as opposed to seconds for MRI). However the requirement for averaging of many recordings to 'unmask' the event-related signal is a constant weakness with this approach.

Computed (Axial) Tomography: CT (or CAT) scans are a means of obtaining structural information about any part of the body, including the brain. A large series of 2D X-ray scans are combined to generate a 3D image.

Magnetic Resonance Imaging: A later development that CT, MRI also provides anatomical insight, with the advantage that no ionising radiation is involved. A cylindrical magnet around the patient's head creates a controlled magnetic field which causes protons within the body to align. Strong radio waves are then passed through the body and knock the protons out of alignment. When the radio waves are stopped the protons return to their original position, emitting energy. This energy is detected and converted into an image.

Although CT and MRI provide invaluable information about the *structure* of the brain, the real breakthrough for assessment of DOCs has come with techniques that offer insight into brain *function*. The ability to see which areas of the brain are active during an event, or in response to an instruction, allows assessment of cognition. The most valuable approaches in this regard are PET and fMRI.

Positron Emission Tomography: PET is a process involving use of radioactive tracer molecules. In the context of neurological investigation, labelled compounds are usually ^{15}O-water, to measure changes in regional cerebral blood flow (rCBF) and ^{18}F-fluorodeoxyglucose (FDG), a particularly useful indicator of metabolic activity (Miller, 2006). As the isotopes decay they emit sub-atomic positrons; when a positron collides with an electron, this leads to release of gamma rays which can be monitored with a suitable detector.

The use of PET for brain imaging rests on the assumption that areas of high radioactivity in the brain correlate with areas of high metabolic activity which, in turn, is a proxy for neuronal activity. Since PET itself only facilitates localisation of tracer, it must be used in conjunction with other approaches such as CT or MRI to determine the structural location of the signal.

functional Magnetic Resonance Imaging: fMRI involves tracking blood oxygen level dependent (BOLD) changes, on the assumption that oxygen consumption is a reliable indicator of neuronal activity. Oxygen is transferred around the body attached to iron in haemoglobin. The magnetic signal from the iron is different depending upon whether or not it has oxygen bound; it is this distinction that is exploited in fMRI.

Insights from new approaches: some key experiments

During the last decade, a number of remarkable 'activation studies' have brought into doubt aspects of our understanding of disorders of consciousness *per se* and particularly the impression that recovery from VS is not possible. PET, and particularly fMRI, have allowed investigators to interact directly with the mind of a patient whose body may not be able to indicate, by movement or verbal response, that they are indeed aware. Brain imaging can offer a mechanism by which awareness can be demonstrated.

Two studies in the late 1990s used PET to demonstrate activation in the brains of VS patients in response to, in one case, the patient's mother telling him a story, compared with response to non-word sounds (de Jong *et al*, 1997) and, in the other, being shown pictures of familiar faces versus unfamiliar faces (Menon *et al*, 1998).

Another patient confirmed by two neurologists to be in VS 10 months after cardiac arrest, exhibited greater brain activity in response to his own name than other names and silent control (Staffen *et al*, 2006). The authors are sanguine about the interpretation of this data, noting that recognition of one's name is a relatively basic form of language recognition. They also caution against generalisations based on an individual patient. Nevertheless, the experiment stands in a corpus of increasing evidence of retained awareness in some patients with cognitive disorders.

In an electrophysiological study, Laureys and coworkers used ERP to examine the response of 15 brain-injured patients (5 VS, 6 MCS and 4 'locked-in') to their own and alternative names (Perrin *et al*, 2006). All locked-in, all MCS and 3 out of 5 VS patients exhibited brain activity in response to their own but not other names.

The same researchers recently used repeated ERP of an apparently comatose woman to allow for her reclassification as 'locked-in' and thereby move her to a rehabilitation programme (Schnakers *et al*, 2009). In this particular study, they instructed her not only to respond to her own name but also to one additional name of her choosing from a list of 7 alternatives. Each of the 8 names (her own, her chosen name and the 6 others) was repeated 15 times in a random order. As well as internal averaging, her results were compared with those of 4 healthy control subjects. Reproducible response to an additional name confirms that this process involved comprehension of auditory instruction and thereby discounts any suggestion that recognition of one's own name is an automated process.

An fMRI study of 14 patients with a variety of DOCs (7 VS, 5 MCS and 2 recently emerged from MCS but severely handicapped) examined their response to a hierachical series of audio prompts (Coleman *et al*, 2007). The test commences with rudimentary Sound Perception (i.e. distinguish speech or noise versus silence), progress onto Speech Perception (i.e. genuine speech versus signal noise) and latterly Speech Comprehension (e.g. contrasting responses to ambiguous and unambiguous sentences). Only 4 of the VS patients did not manifest some evidence of advanced speech processing, further supporting the case that at least some patients diagnosed as being in VS retain element of cognitive function.

In a particularly exciting fMRI study, a young woman fulfilling the clinical criteria for VS, nevertheless demonstrated both an ability to understand spoken commands and to trigger brain activity in response (Owen *et al*, 2006). Initially, the researchers worked through a series of increasingly discriminatory auditory tasks (as per Coleman *et al* (2007) above). They report that the patient's brain was activated in response to sentences containing ambiguous words (e.g. creek/creak, ceiling/sealing) in a manner consistent with healthy volunteers undergoing the same test.

Even more remarkably, the patient was given verbal cues about two mental images to generate in response to particular instructions, and to rest in between. She was asked to imagine either that she was playing tennis or that she was walking through her home. These scenarios were selected because prior work with normal volunteers had consistently shown activation of distinguishable areas of the brain. In response to the prompts, the patient showed an equivalent activation pattern.

Furthermore, in response to initial criticism that the observed brain activity may have been an automatic, that is non-conscious, response to the words 'tennis' and 'house', the authors showed that healthy volunteers did not exhibit the same pattern when challenged by sentences containing those words but without specific instruction to imagine performing the task (Owen *et al*, 2007a).

Elsewhere the researchers have additionally argued the patient's responses to relevant prompts was sustained for longer than would have occurred in an unconscious response, only finishing when she was instructed to rest (Owen *et al*, 2007b). The possibility that the response seen was automatic is rendered even more unlikely by a separate study in which healthy volunteers receiving even relatively minor anaesthesia had significant difficulty performing sentence comprehension tasks (Davis *et al*, 2007).

Ethical implications of the new approaches: some key issues

Although evidence for retention of awareness in some patients in VS or other DOCs seems striking, there are a number of ethical issues arising from these observations. These include questions regarding diagnosis, access to imaging services, and the clinical consequences of revelations about the consciousness of patients.

Diagnosis: firstly, questions have been raised about the interpretation of neuroimaging data, with some critics questioning whether apparent detection of 'normal' brain activation in VS patients truly correlates with conscious awareness. As documented above, a growing body of carefully conducted research suggests that, at the very least, some of the observed responses are genuine.

Russell Poldrack, a UCLA psychologist, worries that some fMRI findings are being over-interpreted. "The field has sometimes permitted itself," he states, "to believe that patterns of BOLD activity reveal more than it is possible to measure given the method's spatial and temporal sampling" (Van Horn and Poldrack, 2009: p1).

Poldrack has particular concern about 'reverse inference' experiments, studies in which researchers work backwards from detection of activity in the brain to infer a particular cognitive process has occurred (Poldrack, 2006; 2008). Poldrack's ire is especially directed at psychologists who fish for signals in the brain and then draw behavioural inferences. Asking a patient to imagine playing tennis or walking through their home are technically examples of 'reverse inference' but these trials have been well conducted and well controlled and have not been identified as flawed.

Secondly, if reports of consciousness in VS and MCS patients are genuine, how widespread a phenomena is retention (or recovery) of awareness? The visual nature of the data, coupled with the tantalising promise of being able to see into the secret world of another individual, have led to widespread media coverage of neuroimaging experiments. This may leave the wrong impression that these results are the norm, which is a concern to some observers. "A bias may be creeping into public thought" comments Eelco Wijdicks from the Mayo Clinic. "If we believe the media, we are either at the verge of a neurorehabilitation breakthrough or we are fooling ourselves and our patient's loved ones" (Wijdicks, 2007: p251). It certainly seems likely that the amazing accounts of recovery are currently the exceptions rather than the rule, but their existence at all may have profound implications for care (see below).

Thirdly, as the significance of fMRI and PET have increased, it has become all the more important that robust and consistent standards of testing are put in place. As noted above (in regard to the work of Owen and colleagues), an agreed series of auditory and/or visual stimuli of increasing discrimination should be employed, alongside appropriate controls. Standardisation of magnetic field strength, regions of the brain to map and statistical tools for analysis ought also to be pursued (Fins *et al*, 2008).

Access: if it becomes established that neuroimaging is a useful tool in assessment of patients suffering with DOCs, the issue of equivalent access to imaging services will become important. At present few centres have the appropriate equipment and expertise to conduct neuroimaging (Schiff, 2007). If patients with DOCs are to be treated justly, then ways to increase availability to this form of evaluation must be sought.

This raises a related issue, namely consent for involvement in research and treatment. Individuals with DOCs are clearly unable to provide informed consent before their involvement. In some instances permission has been granted by legally-appointed advocates. However, despite this, there are examples of funding bodies, ethics committees and journal editorial boards have rejecting studies of this type on the basis that the research subjects had not provided informed consent (Laureys *et al*, 2004; Fins *et al*, 2008).

Clinical response to revelation of consciousness: Detection of awareness in patients previously considered unresponsive must have more than academic interest. It therefore follows that there will be clinical consequences if someone is shown to be aware. At the very least, management of their circumstances must make greater account of their psychological as well as their physical needs. However, this is not without its own difficulties since, for example, provision of analgesics to control pain may also lead to undesired sedation and underestimation of consciousness (Fins *et al*, 2008).

Should caring for patients with some awareness extend to prioritising attempts to hasten emergence from their state of reduced consciousness? Alongside findings of awareness in patients diagnosed as being in MCS or VS, there have separately been reports of the role of pharmaceutical intervention (e.g. Brefel-Courbon *et al*, 2007) and deep brain stimulation (Schiff *et al*, 2007) in bringing about more sustained awareness.

There are two groups in addition to the 'aware' DOC patient for whom the impact of these observations also needs to be considered. One is relatives of such patients; a whole range of emotions may be triggered in the close kin of those exhibiting unanticipated awareness and, indeed, in those patients who do *not* show signs of improvement.

This leads onto the second group affected, namely other patients with DOCs. Although personally excited by accounts of patient recovery, some practitioners are left with ethical dilemmas about the treatment of other patients. As a leading bioethicist, with an active interest in this field, has observed "if some vegetative patients can get better and respond, does that undermine the entire right to die?" (Fins, 2009: p9).

This, in turn, raises another interesting dilemma for the clinician. Suppose that having established two-way communication with the patient via brain imaging they indicate a wish to be aided in terminating their life, for example by withdrawal of artificial nutrition and hydration – how should the doctor then respond? If withdrawal of ANH was feasible when the patient's wishes were not known is it ruled out now that they can confirm that course of action?

Conclusions

Although some observers (e.g. Fins *et al*, 2008) have argued that patients in the major studies documented above must have been misdiagnosed, I do not believe that this diminishes the relevance of their stories. Correctly or incorrectly, the fact remains that several neurologists using standard criteria diagnosed VS. There is every possibility, therefore, that other patients correctly or incorrectly diagnosed as being in VS may recover.

It is important to recognise that classification of a patient as being in VS rests upon *absence* of response. In consequence there is always the risk of someone inappropriately being labelled as vegetative. Owen and colleagues (e.g. Owen and Coleman, 2008a; 2008b) are frequently at pains to stress that inability to detect consciousness does not mean that the patient is not conscious. A non-response may, for example, result from the patient being asleep during the trial or the test not working for technical reasons.

The possibility of subsequent recovery from head injury must also not be discounted. For example, dramatic recovery of a patient from MCS some 19 years after trauma has been associated with regrowth of axons within the brain (Voss *et al*, 2006).

At present it is fair to assume that the majority of patients diagnosed in long-term VS will not recuperate (Schiff, 2007). Nevertheless a growing body of carefully conducted data demonstrates that our understanding of disorders of consciousness remains far from complete and under such circumstances patients in these conditions should be afforded as much care as possible under the expectation that they may recover.

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