How often is the diagnosis of the permanent vegetative state incorrect?

A review of the evidence.

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Competing interests.

I am not infrequently asked to assess people in a prolonged state of unconsciousness, and in some cases I am paid for this work specifically.

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Abstract.

Background Some research suggests that 40% of people in the vegetative state are misdiagnosed. This review investigates the frequency, nature and causes of reported misdiagnosis of patients in the vegetative state, focusing on the nature of the error.

Method. A systematic review of all relevant literature, using references from key papers identified. Data summarised in tables.

Results. Five clinical studies of rate of misdiagnosis in practice were identified, encompassing 236 patients in the vegetative state of whom 80 (34%) were reclassified has having some awareness, often minimal. The studies often included patients in the recovery phase after acute injury, and were poorly reported. Five systematic reviews of signs and technologically-based neurophysiological tests were identified, and they showed that most studies were small, lacked accurate or important details, and were subject to bias. Studies were not replicated. Many signs and tests did not differ between people in the vegetative and minimally conscious state, and those that did were unable to diagnose an individual patient. The few single case reports suggest that failure to ensure an accurate diagnosis of the underlying neurological damage and dysfunction could, rarely, lead to significant misdiagnosis usually in patients who had brain-stem damage with little thalamic or cortical damage.

Conclusions. Significant misdiagnosis of awareness, with an apparently 'vegetative' patient having good awareness, is rare. Careful neurological assessment of the cause and routine measurement of awareness using the Coma Recovery Scale- Revised should further reduce mistakes.

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Introduction.

"*Despite rigorous clinical assessment, many patients in the vegetative state are misdiagnosed.*" [1] "*The rate of misdiagnosis of VS (41%) is roughly equivalent to rates reported in the U.S. and U.K*" [2] Those reading these statements often assume that the misdiagnosed 'unaware' patients are fully aware and 'locked in'. Relatives become distressed, and people involved in making decisions - doctors, lawyers and others - lose confidence in their ability and the ability of others to make a diagnosis. This paper reviews the (limited) evidence on the nature and extent of presumed misdiagnoses, discusses how they arise, and recommends how clinical decisions should be approached.

The context.

This paper is concerned with determining the level of awareness of people with a prolonged disorder of consciousness - an unconscious state that:

- has persisted for over one to four weeks [3] [4];
- is caused by brain damage, and
- is not a coma induced for medical reasons.

Decisions about starting or stopping treatment in this group of patients, lacking the mental capacity to decide, are made by the treating team. Until recently, in England and Wales at least, there was a legal imperative to distinguish the vegetative state [5] from the minimally conscious state [6]. Legally the former had no interests, and thus treatment was futile and could be stopped without considering best interests, whereas the latter required consideration of Best Interests [7]. The distinction is difficult, being based on an artificial boundary [8][9], leading to clinical and legal debate around the evaluation of awareness [8].

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Some claim that technologically-based investigations may help detect awareness [10]. Although scientific investigations into prolonged disorders of consciousness may increase our understanding of the neurophysiological and neuroanatomical basis of consciousness, few studies have been replicated. The validity of both imaging and electroencephalographic techniques in detecting awareness are not yet agreed [8][11][12].

The evidence: clinical diagnosis

The evidence used in this article comes from a systematic search in Medline titles and abstracts for 'misdiagnosis' and 'vegetative' and similar terms, and tracking references found (see Appendix one).

Table one shows the four clinical studies referred to by authors claiming a high misdiagnosis rate [2][13 - 15] and an additional more recent one [16]. The notable findings are that:

- there are only five studies, encompassing a total of 236 patients initially diagnosed as being in the vegetative state; 80 (34%) were reclassified as having some awareness, usually minimal;
- three of the five studies are over 20 years old, when diagnostic methods and expertise were still developing;
- many of the patients studied were in the recovery phase of their condition;
- the descriptions and details given about patients and about diagnostic criteria are usually limited, insufficient to allow critical evaluation of the study;
- bias in reporting is apparent; for example the 'misdiagnosis' rate of people believed to be minimally conscious but diagnosed as being in the vegetative state is not given [15]

Table one

Misdiagnosis of vegetative state.

The evidence: signs and tests.

Over the last 20 years many studies have investigated the ability of clinical signs and technologically-based physiological tests to detect and measure awareness. There have been at least five relevant systematic reviews [17-21], shown in table two.

Table two

These studies show that:

- many small studies investigating many different specific signs or tests have been undertaken using different designs and differing diagnostic criteria;
- statistical associations between level of awareness and performance on some tests or signs has been found, **but**
    - for many tests or signs either no association or inconsistent associations have been found
- no single test or sign has been shown to have acceptable sensitivity or specificity when trying to categorise a person's level of awareness, **although**
    - the rate of true and false positives and negatives is rarely given
- damage to and/or dysfunction of the thalamus is the most frequently localised dysfunction associated with a prolonged disorder of consciousness
- the quality of many studies is poor and a high risk of bias is common, **including**
    - publication bias with studies reporting 'misdiagnosis' being more likely to be published
- few studies are replicated.

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The evidence: misdiagnosed cases.

Collating evidence on individual misdiagnosed cases is difficult as they are rarely reported.

Some misdiagnoses arise from mis-interpretation of observations. People generally attribute agency to behaviour and events; in other words, most people talk and sometimes act as if there was a cause underlying an observed event or behaviour. An example is the case of Rom Houben where an international expert supported the proposition that a man who had been unaware for seven years in fact was aware [22][23]; it later became obvious that he was not [24]. More recently a man in a vegetative state was reported to have become minimally conscious after vagal nerve stimulation [25] and to have become 'more aware' [26]; in fact he died shortly after the procedure [27].

It is unknown how much mis-interpretation is driven by bias arising from hope and expectation, and how much is more deliberate, possibly in an attempt to frustrate a decision not wanted by the observer, being "*against the unit's philosophy of care*" [28].

Cases are also misdiagnosed because the person or team has not considered the underlying neurological damage and dysfunction. The central case in a book [29] on prolonged disorders of consciousness, Maggie, is described (and was diagnosed) as being in the vegetative state and later a minimally conscious state. However the MRI tractography on the front cover of the book and the detailed text in the book both make it clear that she had a vascular brain-stem infarction (stroke) and was in an extreme form of the locked-in syndrome. She was young and had no other brain damage and it was clinically probable that she was aware when awake. A case reported in another book had an inflammatory disorder that was also likely to recover and

would not necessarily leave someone unaware [30]. Three other reported cases illustrate how careful neurological diagnosis can alter the 'diagnosis of the vegetative state' [31].

A case known to me, diagnosed by a specialist service with a prolonged disorder of consciousness after a spinal cord injury and ascending myelitis, 'woke up' when given an anti-depressant; she had full mental capacity confirmed by several people. Her unresponsiveness arose from a combination of brain-stem damage, sufficient to leave her dependent on a ventilator, and severe depression.

Some case reports are actually reports of late recovery. This is not a failure of diagnosis; it is a 'failure' in prognosis. Although the limits of expected recovery are known, they are not and cannot be expected to be definitive in every case and there are credible but rare reports of limited recovery after the accepted limits [7][32][33].

Discussion.

Mistakes will inevitably be made when diagnosing people in the vegetative state; no diagnostic process in medicine can avoid mistakes. The important question is whether it is true that "*patients whose brains were previously thought vegetative or non-responsive but turn out – in up to 20 percent of cases – to be vibrantly alive,* " [34].

Some important points must be made about the evidence. The standard of reporting is often poor, lacking important information and/or with ambiguous statements. The time since onset is often not clear; the evidence used to confirm the level of unawareness is limited; the clinical and neurological data are limited; and, in group studies, useful tabulated data are often lacking. There is also an obvious bias towards 'proving' that an apparently unaware person is aware.

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With few exceptions, reports focus upon apparent misdiagnosis only one way; reports on the 'misdiagnosis' of the minimally conscious state when the person is actually in a vegetative state are notable by their absence. Publication bias is probable [20]. The evidential basis for reassigning the category of and/or the extent of awareness 'found' is rarely well described. These factors complicate evaluation of the validity and clinical significance of any conclusions.

It is possible that some papers have been missed. However, the main papers (Table one) that have specifically considered the clinical diagnosis did not identify any other studies and it is relatively unlikely that papers with strong evidence contrary to those mentioned have been missed.

The review suggests that the first step in the diagnostic process should focus on the cause, establishing that there:

- is known or plausible brain damage sufficient to be compatible with a prolonged disorder of consciousness; **and**
- are no treatable other factors causing or exacerbating the disturbed consciousness.

Although we do not know the structural or physiological basis of consciousness in detail, it is generally agreed that prolonged disorders of consciousness are associated with widespread damage of the cerebral cortices and deep brain nuclei especially the thalamus [35-38]. It is important to establish that such damage and potential dysfunction is likely. Failures in this step may underlie some of the more dramatic misdiagnoses. In particular patients left with minimal motor control due to extensive brain-stem damage but who, at the same time, have minimal damage to thalamic and cortical structures, are likely to have good awareness. The reports reviewed earlier illustrate this.

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It is also important to consider whether drugs may be reducing responsiveness. There is little published research, but most experts have seen a few cases of people in the minimally conscious state who improve considerably when unnecessary drugs are reduced. Sedating drugs should always be reduced and withdrawn if possible.

The second step is to measure awareness, and most apparent errors in diagnosis concern the categorisation of the level of awareness. Traditionally there have been two categories: the vegetative state and the minimally conscious state, itself sometimes divided into lower and upper levels [39]. However, the level of awareness is on a spectrum, and the categories are not only artificial but also are not possible to delineate unequivocally [8][9][17]. Some of the signs that are supposed to delineate one category from another have no validity [8].

Categorisation 'errors' arise in several ways. The distinction is sometimes based on individual signs such as visual pursuit, which has no validity as evidence of awareness [8]. Variation in signs [40] will also lead to a change in category.

Natural variability in level of responsiveness leads to a greater problem. The categories are referred to as '*states*', implying stability of a phenomenon - the "mode of existence of a system" [Oxford English Dictionary]. Many families, healthcare professionals and lawyers interpret the terms used to mean that the patient's level of responsiveness is fixed, unvarying in its nature. A moment's reflection will expose that this is illogical. Everyone has periods of unresponsiveness – being asleep – and when awake, alertness varies from high, when in a demanding situation, to low, when listening to a boring committee chair talking. We never refer to a person as being in

'*a state*', such as asleep, or alert, or day-dreaming, as a summary of their state of awareness over time.

People with a prolonged disorder of consciousness are no different; their responsiveness fluctuates throughout the day [41][42]. In a recent study on 123 patients with a prolonged disorder of consciousness assessed at least six times with the Coma Recovery Scale - Revised, the category allocated on the first assessment was changed after the next five in 44 (36%) people. The study only reported upward change, taking the highest level as the 'state' or correct category. Possibly the very rare cases with short episodes of a coherent response [8][43] arise from occasional more extreme fluctuations.

Third, changes in categorisation may arise from natural improvement over time, and reported 'errors' may simply arise because the actual level of responsiveness has improved between assessments. Rarely, and usually only after traumatic brain injury, patients may improve unexpectedly [2][32][33]. These are not misdiagnoses of level of awareness.

Thus, many if not the majority of misdiagnoses reported arise simply from the patient being moved across an artificial boundary, and often there will be no discernible other behavioural evidence of altered awareness. Some misdiagnoses are not mistakes, but simply a record of actual change.

Last, it is worth acknowledging that patients who have passed through a vegetative and minimally conscious state into full awareness first recover into a state of confusion and amnesia, and with other marked cognitive impairments such that, although aware of the immediate situation, they usually lack insight into their situation. If patients in the vegetative

state truly were internally fully aware ("*vibrantly alive*") then they would emerge from that state with better awareness, but this is not seen.

Clinical conclusions and recommendations.

Instances of a person being legitimately diagnosed as being in the vegetative state actually having reasonably full awareness may occur, but are rare. Most misdiagnoses have minor clinical significance, with a patient crossing an artificial boundary within a spectrum of responsiveness with minimal behavioural change. The evidence base is limited, often difficult to interpret, and subject to bias with few studies being replicated. The '40% misdiagnosis rate' misrepresents the data; the rate of clinically significant misdiagnosis is likely to be low.

The primary recommendation is to move from categorisation to clinical measurement of awareness, for example by the routine use of the Coma Recovery Scale - Revised [44] in people remaining in a prolonged disorder of consciousness. It is the most well documented measure [45-47] and has the great advantage that it is relatively short and can be undertaken by anyone with appropriate training and experience. The Wessex Head Injury Matrix is a reasonable but less good alternative [48].

Second, a proper clinical evaluation of the neurological basis for the observed clinical state is vital. This should:

- establish that the patient's thalamus and cortices are likely to have severe general damage, **and should exclude**:
    - primary brain-stem damage **without** thalamic and hemisphere damage;
    - any other plausible or likely treatable cause.
- ensure that sedating medication is minimised as far as possible, **especially**

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- when routine observations suggest intermittent but credible high-level responses

Last, clinical decisions should be made on the basis of a person's best interests [3], not the categorisation of awareness. The important clinical features include current actual behaviour and experience, and prognosis [49]. Routine observations, supported by structured observations, should be used to build a picture of someone's situation in terms of the frequency and quality of behaviours and, if assessable, experiences; these should be judged against known or assumed values, attitudes and beliefs concerning the decision to be made.

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Table one

Clinical reports on diagnostic accuracy.

Paper	Population and method	Results	Comment
Tresch et al, 1991 [12]	Four nursing homes in United States surveyed for residents in vegetative state (VS); all those identified by care staff assessed fully.	62/1611 patients identified as being in vegetative state; 11 (18%) had signs of awareness (two had improved between time of identification on admission and review)	Many aetiologies, not just acute damage. Most were long-standing. Diagnostic expertise of identifying staff unknown.
Childs et al, 1993 [13]	Patients referred from acute hospital to rehabilitation service with diagnosis (at time of referral) of vegetative state.	49 admissions, 18 (37%) had signs of awareness. One was two years after onset; the remainder were in the acute phase.	All acute brain damage, most traumatic. Time since onset not given in detail, but many within three months of onset. Diagnostic expertise of referring team unknown.

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Andrews et al, 1996 [14]	Patients referred to specialist unit from acute and other sources, with diagnosis at referral of vegetative state.	40 admissions; 16 (40%) had some evidence of awareness. 9/16 were within 12 months of onset at admission.	Many of the patients could have improved after referral. Diagnostic expertise of referring team unknown.
Schnakers et al, 2009 [2]	Patients being assessed in a specialist centre. Team clinical diagnosis (vegetative v minimally conscious) compared with Coma Recovery Scale revised (CRS-R) diagnosis	103 patients, all acute onset aetiology, 46% in acute phase: 44 clinically in VS, 18 (44%) were diagnosed as MCS using CRS-R. Eight of the 18 were reclassified purely on basis of visual fixation or pursuit.	Did not present data on (a) 'misdiagnosis' rate if within or outside expected recovery, or (b) rate of 'misdiagnosis' of MCS, classified as VS by CRS-R score.
Van Erp et al, 2015 [15]	National survey of residential care including hospitals in Netherlands for people with prolonged disorder of consciousness. 53 identified by care team as in VS	41 diagnosed as in vegetative state by treating doctor: external assessor found MCS- in 11 (27%), MCS+ in 4 (10%) and two (5%) to be conscious. 6 of 11 MCS had visual pursuit; 5 had localisation, or reflex behaviour	41% misdiagnosis rate, but MCS- could be unaware as signs not necessarily evidence of awareness. Time since onset not given for the 'misdiagnosed' group.

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CRS-R	Coma Recovery Scale - Revised
MCS	Minimally Conscious State (MCS- & MCS+ = gradations in MCS)
VS	Vegetative State

Table two

Systematic reviews of studies investigating awareness in people with prolonged disorders of consciousness.

Paper	Subject	Results	Comment
Liberati et al, 2014 [17]	Studies comparing any test or sign in patients in vegetative state with patients in minimally conscious state.	23 studies: measures included behaviour, EEG, PET, fMRI. many different active and passive paradigms. 47 statistical comparisons made, 24 were not significant.	Unable to find any clear distinction between vegetative and minimally conscious state.
Hannawi et al 2015 [18]	Resting brain activity on imaging: fMRI, PET, SPECT. Patients with disordered consciousness: VS 43%, MCS 23%, coma 24%	36 studies, 687 patients. No statistically significant differences between VS and MCS patients. Meta-analysis (13 studies) showed consistently reduced activity in bilateral medial dorsal nucleus of thalamus, left cingulate, precuneus, middle frontal and medial temporal gyri.	Did not find any evidence to allow use of these techniques to help distinguish vegetative from minimally conscious state.
Bender et al, 2015 [19]	Quantitative meta-analysis of sensitivity and specificity of new	20 studies; 470 MCS and 436 VS patients: fMRI (8); FDG-PET (1); TMS/EEG (2); ERP (3); eye tracking	Methodological variation between studies made analysis

	diagnostic methods for the minimally conscious state. Patients in VS or MCS, at least 10 patients, clinically diagnosed (e.g. using CRS-R)	(1); EMG (1); qEEG (5). Four high quality studies, five middle, 11 unclear. Meta-analysis (3+ studies) of diagnosis of MCS: qEEG 90% sensitive, 80% specific; fMRI and ERP much lower sensitivity (44%) and specificity (59%)	less robust. Shows limited clinical utility at an individual level
Kondziella et al, 2015 [20]	Relative utility of active or passive paradigms using fMRI or EEG when detecting covert awareness in people in MCS or VS following acute brain injury. Consciousness measured by CRS-R or other standard measure	37 studies, 1041 patients. MCS patients more likely than VS patients to have positive findings suggesting awareness. Passive paradigms more likely to be positive than active ones. EEG and fMRI rates similar. 8% to 14% VS patients show wilful changes in active paradigms. Individuals may be positive on active and negative on passive paradigms. High risk of bias in most studies.	Conclusions are difficult because (a) high risk of bias towards publishing 'positive' findings and (b) lack of absolute standard to compare with and (c) questions about validity of positive finding as evidence of awareness.
Zhang et al, 2017 [21]	Correlation between diffusion tensor imaging (DTI) and level of awareness in people with TBI. Consciousness	16 studies, 701 patients. Strong (r = 0.69) correlation between DTI in Corpus Callosum and	Did not study distinction between VS and MCS. Correlation not sufficient for

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	measured by standard assessment (e.g. CRS-R, GCS)	reasonable correlation in Internal Capsule and conscious levels.	diagnostic separation in an individual.

CRS-R	Coma Recovery Scale - Revised
DTI	Diffusion Tensor Imaging
EEG	Electroencephalogram
EMG	Electromyography
ERP	Event Related Potentials
FDG-PET	18fluorodeoxyglucose positron emission tomography
fMRI	Functional Magnetic Resonance Imaging (of the brain)
GCS	Glasgow Coma Scale
MCS	Minimally Conscious State
PET	Positron Emission Tomography
qEEE	Quantitative Electroencephalography
TBI	Traumatic Brain Injury

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TMS Transcranial Magnetic Stimulation

VS Vegetative State

Appendix

Search strategy used

This appendix describes the approach used to identify papers.

Clinical studies

Clinical studies that compared

- the classification of a patient by a clinical team either
    - with a second clinical assessment by a more expert team, or
    - with a second clinical means of establishing the diagnosis
- were identified from one search and then following references from those studies.

The search strategy (on 20th November 2017) in Medline, titles and abstracts, was:

- vegetative AND state AND diagnosis AND (mistake OR error OR misdiagnosis)

The search returns 28 papers, and the three studies identified on the search were:

- Andrews et al, 1986 [15]
- Schnackers et al, 2009 [2]
- van Erp et al, 2015 [16]

The last two papers were identified from the references, and both are referred to in the Andrews paper:

- Tresch et al, 1991 [13]
- Childs et al, 1993 [14]

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Signs and tests

These were found through repeated searches using a variety of terms, and no single strategy identifies more than three of the five studies. That strategy (used on 20th November 2017) was:

- review AND (vegetative OR minimally conscious) AND (consciousness OR awareness)

This strategy returned 131 papers and the three identified as relevant were:

- Bender et al, 2015 [19]
- Hannawi et al, 2015 [18]
- Kondziella et al, 2016 [20]

One of the remaining two was known to me from previous research [8]:

- Liberati et al, 2014 [17]

The last was identified by chance through Google:

- Zhang et al, 2017 [21]

Case reports:

These were identified through searching using Google, and also through Medline but were found through repeated searching with no clear successful strategy.