Persistent Vegetative State and Minimally Conscious State

A systematic review and meta-analysis of diagnostic procedures

Andreas Bender, Ralf J. Jox, Eva Grill, Andreas Straube, Dorothée Lulé

SUMMARY

Background: Acute brain damage can cause major disturbances of consciousness, ranging all the way to the persistent vegetative state (PVS), which is also known as "unresponsive wakefulness syndrome". PVS can be hard to distinguish from a state of minimal preserved consciousness ("minimally conscious state," MCS); the rate of misdiagnosis is high and has been estimated at 37–43%. In contrast, PVS is easily distinguished from brain death. We discuss the various diagnostic techniques that can be used to determine whether a patient is minimally conscious or in a persistent vegetative state.

Methods: This article is based on a systematic review of pertinent literature and on a quantitative meta-analysis of the sensitivity and specificity of new diagnostic methods for the minimally conscious state.

Results: We identified and evaluated 20 clinical studies involving a total of 906 patients with either PVS or MCS. The reported sensitivities and specificities of the various techniques used to diagnose MCS vary widely. The sensitivity and specificity of functional MRI-based techniques are 44% and 67%, respectively (with corresponding 95% confidence intervals of 19%–72% and 55%–77%); those of quantitative EEG are 90% and 80%, respectively (95% CI, 69%–97% and 66%–90%). EEG, event-related potentials, and imaging studies can also aid in prognostication. Contrary to prior assumptions, 10% to 24% of patients in PVS can regain consciousness, sometimes years after the event, but only with marked functional impairment.

Conclusions: The basic diagnostic evaluation for differentiating PVS from MCS consists of a standardized clinical examination. In the future, modern diagnostic techniques may help identify patients who are in a subclinical minimally conscious state.

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An estimated 1500–5000 patients in a persistent vegetative state are now living in Germany (1). This condition is defined as one without any clinical evidence for psychologically interpretable contact between the patient and the outside world, despite phases of wakefulness in which the patient’s eyes are open (2). The treatment of vegetative patients is a major interdisciplinary challenge for all persons involved, ranging from the staff of the intensive care unit to the family physicians and specialists providing chronic care.

Recent prospective observational studies and innovative electrophysiological and imaging techniques have extended our knowledge about the diagnosis and prognosis of patients with severely impaired consciousness after acute brain damage. We systematically review and evaluate these findings in this article.

Diagnosis

The persistent vegetative state – a clinical diagnostic challenge

A severe impairment of consciousness after an acute brain injury typically first manifests itself as coma: a state in which the patient does not open his or her eyes even on very vigorous stimulation and displays no evidence of psychologically interpretable contact with the outside world, even after the discontinuation of analgesic and/or sedating drugs that might impair consciousness (2). In patients who are particularly severely affected, coma can undergo a transition to a state in which the patient’s eyes are intermittently open (wakefulness), but there is nonetheless no evidence for an ability to make contact, or for awareness (Figure 1). This so-called persistent vegetative state (PVS) has also been variously designated as apallic syndrome, and, most recently, unresponsive wakefulness syndrome (3).

As soon as a patient manifests any type of reproducible behavior indicating conscious perception of the environment, he or she is no longer said to be vegetative, but, rather, in a minimally conscious state (MCS) (4). The authors of this article would prefer to designate both the persistent vegetative state and MCS as clinical syndromes; thus, the abbreviation MCS could be taken to stand for “minimally conscious syndrome” (rather than “state”). In any case, characteristic findings in MCS include basal, non-reflective behavior patterns such as visual fixation and ocular pursuit movements (use of a mirror during the examination; so-called “MCS minus”), or the ability to...
The diagnostic categorization of severely impaired consciousness. Two different aspects must be assessed: alertness (wakefulness) and awareness. The persistent vegetative state (PVS) is characterized by a lack of reproducible responses to the environment. As soon as simple responses to the environment are seen, the patient is said to be in a minimally conscious state (MCS). Functional communication (whether verbal or nonverbal) or functional use of objects indicates that the patient has emerged from the minimally conscious state. Patients will then often manifest a confusional or amnestic syndrome before regaining normal consciousness.

The accurate diagnosis of a patient’s state of consciousness—in particular, the differentiation of PVS from MCS—remains a major challenge in routine clinical care. The rate of misdiagnosis in this area has been estimated at 37%–43%: in other words, many patients are wrongly diagnosed as apallic, even though careful evaluation would in fact disclose clear evidence for MCS (5). Frequent clinical misdiagnosis is a serious matter, because even minimally conscious patients might suffer emotionally from the lack of personal attention that results when their state is not properly recognized, and because the incorrect assignment of a poor prognosis could even result in the premature termination of life-sustaining care.

Neither the Glasgow Coma Scale (GCS) nor the Coma Remission Scale (Koma Remissions Skala, KRS, a scale widely used in Germany) enables a clear, operationalized distinction between PVS and MCS (6). An internationally established instrument for this purpose is the revised Coma Recovery Scale (CRS-R), which contains an ordinal scale ranging from zero (deepest possible coma) to 23 points (awake and fully capable of contact) and permits a clear differentiation of PVS from MCS and from the successful emergence from MCS to a still higher level of consciousness (www.coma.ulg.ac.be/medical/chronic.html) (6).

**New methods for the detection of preserved minimal consciousness**

The high rate of clinical misdiagnosis has led to intensified efforts to develop technical methods for identifying patients who are in a minimally conscious state. It must be pointed out at the outset that our assessment of diagnostic techniques is limited by a basic methodological difficulty: the sensitivity and specificity of any diagnostic test can only be judged in reference to a gold standard. Thus, the authors take the CRS-R to be the diagnostic gold standard for the differentiation of PVS from MCS, in order to judge, for example, what percentage of patients fulfilling the CRS-R criteria for PVS turn out to have a negative result on an fMRI or FDG-PET study (fMRI = functional magnetic resonance imaging; FDG-PET = 18F-fluorodeoxyglucose positron emission tomography). Yet one cannot be absolutely sure that a patient is in a persistent vegetative state even if the CRS-R implies that this is so. All clinical tests require the patient to make an appropriate, visible movement when presented with a task, e.g., “Follow my finger with your eyes.” In the absence of such a movement, it is concluded that the patient is not conscious, i.e., that he or she is indeed in a vegetative state.

Yet it remains conceivable that a patient might be conscious but still unable to activate his or her motor system in order to comply (visibly) with the task. Therefore, when we try to assess a diagnostic technique, we face the problem of being unable to say for certain whether a test result is truly or falsely negative (or positive). Nor can it be assumed that visual fixation alone is always an expression of preserved minimal consciousness, even though the CRS-R operationalization in fact takes it to be so.

**Methods**

This article is based on a systematic review of pertinent literature and on a quantitative meta-analysis of the sensitivity and specificity of new diagnostic methods for the minimally conscious state. (For an extensive description of methods, see eBox, eTable, and eFigure.)

**Results**

Our systematic review of the literature revealed 20 clinical studies including a total of 470 MCS patients and 436 PVS patients (Table 1). The most commonly used techniques were:

- functional magnetic resonance imaging (fMRI),
- quantitative EEG methods (qEEG; automated analysis of EEG characteristics, including an electrophysiological assessment of sleep architecture),
- event-related potential (ERP) recording.
For each of the diagnostic techniques that were represented in three or more of the individual studies that we assessed (fMRI, ERP, qEEG), we performed a pooled meta-analysis with bivariate random-effect modeling (Figure 2).

The qEEG methods for the automated diagnosis of MCS had the highest sensitivity (90%, with 95% CI 69%–97%) as well as relatively high specificity (80%, with 95% CI 66%–90%). fMRI and ERP-based techniques were much less sensitive for the detection of MCS, with respective sensitivity values of 44% (95% CI, 19%–72%) and 59% (95% CI, 26%–85%).

**Discussion**

Our meta-analysis shows that modern diagnostic techniques can already make a major contribution to the diagnostic assessment of MCS. EEG-based techniques (including an analysis of sleep patterns, connectivity, power, etc.) seem to be supported by the best available evidence. Moreover, these techniques have the advantage that they can be performed continuously over a relatively long period of time and can thus overcome the problem of having to assess a fluctuating condition at a small number of discrete times.

Special mention can be made here of a methodologically sound prospective study of a group of more than 120 patients with both fMRI and FDG-PET (7). FDG-PET enabled the correct classification of the patients’ state of consciousness in 85% of cases (95% CI: 77%–90%). FDG-PET is a quantitative measurement of cerebral glucose metabolism; it enables conclusions to be drawn about the metabolic activities of specific brain regions that are considered essential for consciousness, e.g., the so-called default mode network (DMN) (Figure 3).

**Consciousness only in the scanner?**

At present, the distinction between PVS and MCS is susceptible to the basic problem that the clinical standard used (the CRS-R) may not be sensitive enough to identify all patients who are in MCS. In fact, current research suggests that 10% to 24% of the patients who are unambiguously judged to be in a persistent vegetative state on clinical grounds (and who thus do not belong to the 37% to 43% of clinically misdiagnosed patients) actually show clear evidence in fMRI or EEG of understanding and being able to follow commands.

**TABLE 1**

<table>
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<tr>
<th>Technique</th>
<th>Paradigm/method*1</th>
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<th>MCS patients</th>
<th>Quality*2</th>
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*1In some studies, multiple methods were used; for brevity, only the main method is named here.

*2Overall quality assessment of studies of diagnostic evaluative methods, based on QUADAS scores (for details, cf. eBox, eTable, eFigure).

PVS = persistent vegetative state; MCS = minimally conscious state; fMRI = functional magnetic resonance imaging; FDG-PET = 18F-fluorodeoxyglucose positron emission tomography; TMS/EEG = combined transcranial magnetic stimulation and electroencephalography; ERP = event-related cognitive potentials; EMG = electromyography; qEEG = quantitative EEG.
fMRI can be used to identify patients in whom, for example, the instruction to imagine carrying out certain movements (motor imagery)—e.g., ”Imagine you are on a tennis court and are hitting the ball”—is followed by activation of the same task-specific brain areas as in normal control subjects (10, 27).

EEG-based imagery techniques have yielded similar results. For example, a high-resolution EEG (HD-EEG; 64–256 electrodes) can be recorded while the patient is instructed to make a fist, or to wiggle his/her toes, upon hearing a particular tone. The EEG signal is then analyzed for changes in bioelectric brain activity occurring regularly in a suitable region of the brain (e.g., in the motor hand area, in the case of making a fist) at the proper temporal interval after the signal (tone). This is called event-related desynchronization (28).

10% to 24% of the PVS patients were, in fact, able to perform the task, in both the fMRI-based and the EEG-based studies. Thus, although these patients had been correctly given the diagnosis of PVS according to the currently accepted criteria, testing with more advanced techniques indicated that they had some degree of preserved consciousness (10, 28).

Both of these techniques are methodologically highly demanding, particularly with respect to the statistical evaluation incorporated in them, and a degree of controversy still surrounds them (29). How can one judge whether the new methods really provide evidence for preserved consciousness, rather than merely artefacts or erroneous interpretations? To answer this question, one would have to study a cohort of PVS patients with fMRI and EEG over the long term, asking the ones who later go on to regain communicative abilities whether they remember the study and the tasks they were asked to perform. As a practical matter, this would be very hard to do, as nearly all patients who recover from PVS or MCS have persistent amnesia for the period in which their consciousness was impaired (c2).

Yet there is nonetheless an important piece of evidence for the validity of such methods. One PVS patient being studied with fMRI was able to answer five of six autobiographical questions correctly by
imagining himself to be playing tennis as a means of answering “yes,” and by imagining himself to be taking a tour of an apartment as a means of answering “no” (10).

Prognosis and course
For many years, the prevailing view of prognosis in PVS was that a patient had no realistic chance of regaining consciousness if he or she was still vegetative 12 months after a traumatic brain injury or 3 months after non-traumatic, e.g., hypoxic, brain damage (30). Recent evidence suggests that this rule must be modified somewhat, although a PVS of traumatic origin still seems to have a better prognosis, in general, than one of non-traumatic origin. In one study, a group of 50 patients who had been in a persistent vegetative state for at least six months when the study began were followed prospectively for two years. 10% of patients regained minimal consciousness, and a further 14% regained more than minimal consciousness (31). Most of the patients who emerged from a vegetative state and regained the capability for contact with the outside world did so only after a delay of more than one year. This was true whether the underlying brain injury was of traumatic or non-traumatic origin.

Aside from a traumatic etiology, lower age is also associated with a better prognosis for emerging from a vegetative state into minimal consciousness. In the study just mentioned, the patients with a more favorable course were much younger than those who stayed vegetative (age 32 ± 12 versus 54 ± 12 years, p = 0.001). All patients that regained consciousness still had major functional impairments and remained permanently dependent on nursing support (31, 32).

Another prospective observational study has been initiated to assess the outcome of long-term treatment of severely affected patients in Germany (the KOPF-register study, supported by the ZNS – Hannelore Kohl Foundation) (33). This currently ongoing study has already revealed that consciousness can be regained after even longer delays than are generally expected, and that the early prognostic indicators currently in use—e.g., the absence of cortical somatosensory evoked potentials (SEP)—do not enable the definitive prediction of a poor outcome in individual cases, and especially not in head trauma patients (33, 34).

The new methods of assessing consciousness that were described above can also yield important clues to prognosis. FDG-PET correctly predicts the outcome at 1 year in 74% of patients who are in the subacute (weeks) or chronic (months/years) phase of the persistent vegetative state or the minimally conscious state (7). In another study, event-related potentials induced with a semantic paradigm were measured in 92 vegetative or minimally conscious patients in early neurologic rehabilitation (35). In as many as 80% of patients, N400 analysis enabled accurate prediction of whether they would ever regain functional communicative ability over the long term.

Varying definitions of a “good outcome” are now in use among physicians assessing the prognosis of patients who are comatose after an acute brain injury. The spectrum ranges all the way from a mere regaining of consciousness to full independence with no more than mild impairment. From the outside perspective of (some) physicians and family members, anything less than the regaining of a fully independent lifestyle might not seem worthwhile, yet some very severely physically impaired patients who have regained the ability to communicate do indeed state that they enjoy a good quality of life (36).
The significance of these new developments for routine care

The modern diagnostic techniques discussed above have not replaced the standardized clinical examination, with the use of established scales, as the basis of patient assessment. All of them are still far from being established as routine diagnostic tests. Some major methodological questions remain unanswered:

- Which techniques, paradigms, and analytical methods should be applied?
- Which patients are most suitable for study – those in the acute, subacute, or chronic phase?
- How informative are the findings?

Aside from FDG-PET, which is now a standard technique in many nuclear medicine departments, these techniques are currently available only in specialized centers for use in clinical studies. Financial reimbursement for the time- and labor-intensive data analysis that they require is also problematic, and one may ask whether the amount of knowledge obtained actually justifies the necessary expense. Moreover, when a study with a very new technique yields a result apparently implying consciousness, even though the patient is ostensibly unresponsive, this may be emotionally unsettling for everyone involved, and especially for the patient’s family (37).

The findings of the present meta-analysis are also liable to the methodological objection that some techniques were assessed in pooled fashion even though they employed very different paradigms and cutoff values for the diagnosis of the minimally conscious state. The grouped sensitivities and specificities calculated in this way should thus be considered no more than rough estimates.

The ethical dimension

Patients with chronically impaired consciousness are among the most vulnerable patients of all, as they cannot express themselves and can thus easily become the victims of other persons’ interests. Therapeutic decision-making for such patients is a major challenge, in view of the uncertainties about their state of consciousness, prognosis, and personal desires (38).

These patients often could not survive without intensive treatment by nurses and doctors, e.g., respiratory support and the giving of antibiotics. Such measures do not bear an automatic legitimation; at every point along the patient’s course, they should be provided if and only if they are ethically and legally justified. The readiness to treat patients with impaired consciousness with all necessary means of nursing and medical support now varies from one country to another (39).

For such treatment to be considered legitimate in Germany, it must be medically indicated (note that, according to the German Medical Association, the indication may vary from case to case and is the physician’s responsibility to judge), and consent must be obtained from the patient’s guardian or proxy (often a relative); according to current law, persons with impaired consciousness are not competent to consent to medical treatment, even if they are found capable of rudimentary communication through a brain-computer interface (40). The honest and understandable provision of information by a physician is a precondition for valid decision-making about consent to medical treatment. The patient’s advance-care directive or orally expressed views about treatment (if available) or the patient’s presumed wishes need to be taken into account (37).

### TABLE 2

| Recommendations for formulating treatment indications and for determining the patient’s presumed wishes |
|-------------------------------------------------|-------------------------------------------------|
| **Major questions** | **Procedure for answering questions** |
| Formulation of indications for treatment by medical professionals | – What treatment goal can be stably achieved if the patient’s further rehabilitation takes the best possible course? |
| | – How likely is this goal to be achieved? |
| | – In what time frame can this goal be achieved? |
| | – What risks and stresses for the patient are associated with the present illness and the process of rehabilitation? |
| | – What is the patient’s current quality of life, and how would it be likely to evolve in the course of further rehabilitation? |
| | – interdisciplinary and multiprofessional team discussions |
| | – consideration of evidence-based predictors of clinical course |
| | – special tests for prognostication, if indicated |
| | – making clear that the formulation of indications always involves value judgments |
| | – critical reassessment of indications over the course of treatment |

Discussion with patient proxy or guardian (relatives) about the patient’s wishes

| – Does the treatment goal correspond to a condition that the patient has called acceptable, or would consider acceptable, for himself/herself? |
| – Are the likelihood of achieving this goal and the time frame in which it might be achieved acceptable for the patient? |
| – From the patient’s point of view, does the goal of treatment outweigh the risks and stresses associated with it? |
| – How does the patient’s proxy or guardian (relatives) rate the patient’s current quality of life? |
| –honest, empathic imparting of understandable information |
| – In the absence of a legally responsible proxy or guardian, a court judgment may need to be obtained. |
| – Ask about a living will or advance care directive; if available, such documents need to be interpreted meticulously, in cooperation with patient representatives and relatives. |
| – If a relevant document of this type is not available, ask about any prior expressions by the patient as to what should be done in a situation of the current type, and about the patient’s presumed wishes. |
An orientation toward therapeutic goals can be very helpful in making ethically sound, emotionally beneficial, and socially acceptable decisions about treatment (Table 2). The important goals of treatment extend beyond the mere prolongation of life and include the regaining of an ability to communicate or the achievement of a certain degree of independence in everyday life. Controversy now surrounds the question whether the mere regaining of consciousness, without any ability to communicate, could ever be a reasonable goal of treatment (e3). The value of consciousness would seem to be derived precisely from its enabling communication, social participation, and other life activities beyond the plain fact of awareness. Moreover, consciousness may often be accompanied by negative experiences such as pain or emotional suffering, which, if the individual cannot communicate, may be difficult to recognize and to alleviate.

KEY MESSAGES

- 37% to 43% of patients who receive the diagnosis of a persistent vegetative state can be demonstrated by careful, standardized clinical examination on the basis of the Coma Recovery Scale (CRS-R) to have at least minimally preserved consciousness.
- Some patients can regain consciousness after years of being in a vegetative state, albeit with major, persistent physical impairment.
- Technical methods, particularly those based on 18F-fluorodeoxyglucose positron emission tomography (FDG-PET) and quantitative EEG, can be useful aids to the determination of a patient’s state of consciousness.
- FDG-PET and event-related cognitive potential recording are useful for long-term prognostication.
- Modern technical studies including functional magnetic resonance imaging can identify patients with clinically occult consciousness.

Conflict of interest statement

PD Dr. Bender received an honorarium from the Covidien company for lecturing at a stroke symposium.

PD Dr. Jox has served as a paid expert consultant for Elsevier in a matter related to the topic of this article.

The remaining authors state that they have no conflict of interest.

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REFERENCES


ORIGINAL ARTICLE

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eREFERENCES


**eBOX**

**Detailed presentation of methods**

Our systematic review of the literature included all pertinent articles in German or English that were available online on PubMed up to 30 June 2014. The precise PubMed search syntax with MeSH subheadings was: (prognosis OR diagnosis) AND ("persistent vegetative state" OR "unresponsive wakefulness"). Inclusion criteria for the purposes of this article were as follows:

- study on the diagnosis of PVS ("persistent vegetative state") or MCS ("minimally conscious state") with technical methods
- use of an established, standardized clinical method for the differentiation of PVS and MCS
- at least 5 patients per group
- sufficient data to calculate sensitivity and specificity of the method for PVS and MCS

In a first screening step, the 1025 unselected PubMed hits were judged for possible inclusion by a reading of their titles and abstracts; all but 84 were excluded. These were then subjected to a more rigorous screening employing the full text of each article, which was carried out independently by two of the authors (AB and DL) according to the inclusion criteria. Initially divergent assessments were eliminated by agreement of the two assessors. As a result, 28 studies were included in the qualitative analysis and 20 in the quantitative analysis. The details of study selection are shown in a PRISMA flow diagram in the eFigure. Only studies on the differential diagnosis of PVS and MCS were quantitatively evaluated.

Sensitivity and specificity for the diagnoses of PVS and MCS were taken as measures of the quality of the diagnostic techniques under study and were calculated with 95% confidence intervals (95% CI) for each. For the purpose of this meta-analysis, the CRS-R was taken as the clinical gold standard for the determination of true versus false positive and negative findings for PVS and MCS. As usual, sensitivity was defined as (true positives) / (true positives + false negatives), and specificity as (true negatives) / (true negatives + false positives).

To take account of the dependence of sensitivity and specificity, as recommended by the Cochrane Collaboration for the meta-analysis of diagnostic studies (e4), the data from individual studies were grouped together with bivariate random-effect modeling (e5). The analysis was carried out with the aid of the MetaDAS macro in SAS 9.3 (Cary, NC) (e6). The Forest plots were also generated with SAS 9.3. RevMan 5.3 (Review Manager Software; The Nordic Cochrane Centre, Copenhagen, Denmark) was used to calculate the sensitivities and specificities in individual studies.

The quality of the included studies was evaluated with the Quality Assessment of Diagnostic Accuracy Studies (QUADAS) tool, as recommended by the Cochrane Collaboration. Other limitations of the study quality not covered by the QUADAS tool were additionally assessed by one of the authors (AB), and each study was given an overall quality rating of low, middle, high, or unclear (Table 1 and eTable).

Studies on prognostication in coma patients (e.g., with evoked potentials), as defined by the Glasgow Coma Scale (GCS) and without further subcategorization into PVS and MCS, were not considered. For this topic, the reader is referred to published reviews (e9) on early prognostication.
eFIGURE

Articles identified by PubMed search: 1025

Articles included after screening of titles and abstracts: 84

Full text checked for inclusion criteria: 84

Articles included in qualitative analysis: 28

Articles included in quantitative analysis: 20

Articles excluded after screening of titles and abstracts (941), because of:
- different subject: 447
- only case reports: 43
- no information about diagnosis or prognosis: 451

Full text articles excluded (56) because of:
- lack of a standardized diagnostic evaluation for PVS/MCS: 10
- fewer than 5 patients: 21
- no information about calculation of sensitivity/specificity: 25

PRISMA flowchart of the literature search
PVS = persistent vegetative state; MCS = minimally conscious state
## eTABLE

### Quality assessment of the included studies with the QUADAS tool*1

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*1 From (e7) and (e8).

*2 The overall assessments of study quality were performed semi-quantitatively by one of the authors (AB) on the basis of individual answers to the 11 QUADAS questions.

*3 The MRI device was changed to another one with greater field strength in the course of the study due to long recruitment time.

*4 Change of method during the study.

*5 Low number of cases per group.

*6 Two EEG systems with different numbers of electrodes were used. x = criterion fulfilled; - = criterion not fulfilled; ? = unclear or insufficient information.